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# Genome-wide association studies of late-onset cardiovascular disease

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## Abstract

Human genetics is a powerful tool for discovering causal mediators of human disease and physiology. Cardiovascular diseases with late onset in the lifecourse have historically not been considered genetic diseases, but in recent years the contribution of a heritable factor has been established. More importantly, over the last decade genome-wide association studies (GWASs) have identified many loci associated with late-onset cardiovascular diseases including coronary artery disease, carotid artery disease, ischemic stroke, aortic aneurysm, peripheral vascular disease, atrial fibrillation, valvular disease and correlates of myocardial function. Here we review findings from GWASs considered statistically robust with regard to multiple testing ($p<5\times10^{-8}$) for late-onset cardiovascular diseases and traits. Although for only a handful of the 92 genetic loci described here have the mechanisms underlying disease association been established, new and previously unsuspected pathways have been implicated for several conditions. Examples include a role for NO signaling in myocardial repolarization and sudden cardiac death and a role for the protein sortilin in lipid metabolism and coronary artery disease. Genetic loci with multiple trait associations have also provided novel biological insights. For example, of the 46 genetic loci associated with coronary artery disease, only 16 are also associated with conventional risk factors for cardiovascular disease whereas the remaining two thirds may reflect novel pathways. Much work remains to functionally characterize genetic loci and for clinical utility, but accruing insights



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into the biological basis of cardiovascular aging in human populations promise to point to novel therapeutic and preventive strategies.

## 1. Introduction

Over the 20th century, cardiovascular diseases have replaced infectious and nutritional disease as the leading cause of death globally[1], and are leading causes of hospitalization in western countries. Such diseases typically display a late onset in the lifecourse, and are associated with both mortality and greatly impaired quality of life in the elderly.

Much effort has been invested in the development of preventive as well as novel therapeutic strategies for cardiovascular disease, notably for coronary artery disease, stroke, aortic aneurysmal disease, heart failure, atrial fibrillation and valvular disease, to facilitate healthful aging. Unfortunately, more than 90% of compounds that enter clinical trials fail to demonstrate sufficient safety and efficacy to gain regulatory approval, in large part due to limited predictive value of preclinical models of disease.[2, 3] For aging-related disease, it is particularly difficult to create animal models that faithfully recapitulate human aging, as assessment of aging in animal models over extended time is often not feasible, as in studies of the degeneration of aortic valves or development of impaired myocardial relaxation with aging.

Recently, human genetics has emerged as an unbiased tool to identify novel molecular targets in late-onset human diseases, as inherited differences in protein abundance or function can identify potential therapeutic effects that may respond favorably to pharmacological modulation.[2] Recent examples of the success of this strategy within the cardiovascular field have been the rise of *PCSK9* and *APOC3* inhibitors, potent cholesterol- and triglyceride-lowering medications developed after loss-of-function mutations in these genes were shown to confer lowering of cholesterol and triglycerides, respectively, and protection against coronary artery disease.[4, 5]

The recent progress and reduced costs of genotyping methods with arrays and next generation resequencing technologies have facilitated studies of genetic variation on a genome-wide scale. Particular success in terms of number of identified genetic loci has been observed with studies of common variants across the entire genome, termed genome-wide association studies (GWAS).[6]

The major cardiovascular diseases with a late onset in life have not traditionally been considered to be heritable, in contrast to diseases with early onset such as familial hypercholesterolemia, long QT syndrome or hypertrophic cardiomyopathy where familial aggregation was noted as early as in the 19th century. However, in recent years population-based studies have established a modest heritable component to the major cardiovascular diseases as well as many intermediate traits, motivating molecular genetic analyses of these diseases. [7–13] Genetic methods used to study early-onset Mendelian diseases, notably linkage analysis, have largely been unsuccessful in identifying variants associated with common disease, whereas GWAS has been highly successful. Importantly, even though large sample sizes are required in GWAS to detect comparatively modest genetic effects, the

identification of novel genetic associations can improve our understanding of the pathophysiology of human disease and provide novel drug targets, with potentially much stronger effects on the fundamental molecular process. Therefore, GWAS have been applied to all the major cardiovascular diseases as well as for longevity and a multitude of intermediate phenotypes for cardiovascular disease, such as plasma lipids, blood pressure and myocardial repolarization.[14, 15]

Importantly, GWAS have highlighted the importance of cardiovascular disease for aging and death. For example, the genetic locus most robustly associated with longevity is located at the ApoE gene. This locus has been associated both with coronary artery disease and dementia, highlighting amongst other things the importance of cardiovascular health for longevity.[16–19] In addition, polygenic scores based on genetic variants associated with cardiovascular disease are associated with longevity. (Smith JG, unpublished)

In this overview, we outline the central concepts of genome-wide association studies, describe findings from GWAS of aging-related cardiovascular phenotypes and diseases, and close with a discussion about the next steps to drawing biologic insights and potential drug targets from identified genetic loci. Most important to the cardiovascular disease spectrum at the population-level are atherosclerotic changes in the coronary and carotid circulations, as well as myocardial disease including heart failure and cardiac arrhythmia each of which is discussed in a separate section. The clinical utility of genetic loci established as determinants of cardiovascular disease is currently limited due to comparatively modest effects and the multifactorial nature of these diseases, and is briefly discussed in a final section.

## 2. Genome-Wide Association Studies (GWAS): a primer

The simple principle of GWAS entails the genotyping of hundreds of thousands of genetic variants and comparison of allele distributions between cases with a disease and controls without the disease.[20] Such studies became feasible with the development of highly-multiplexed genotyping arrays, sequencing of the human genome, and the recognition that the most common form of genetic variation is single nucleotide polymorphisms (SNPs) which are relatively correlated over sizable genetic distances in the general population.[6] The majority of common variation can therefore be assayed by genotyping of a few hundred thousand SNPs. The first studies were published in 2005–2007, using microarray methods for genotyping.[21–29] In more recent years, lower costs and increasing availability of next-generation resequencing have made even larger scale genotyping feasible. To achieve adequate sample sizes to detect modest genetic effects at sufficiently stringent p-value thresholds, meta-analysis of multiple studies is typically required; many recent studies include hundreds of thousands of study subjects. However, even with large sample sizes, statistical power to detect true associations is limited in these studies.

Human genetic association studies had been plagued by non-reproducibility of findings since the 1980s, in large part due to lax statistical criteria for assessing significance.[30, 31] With the introduction of GWAS, the genetics community therefore from an early stage recommended strict criteria to account for multiple testing, with an individual p-value of $p <$

$5\times10^{-8}$ considered significant, called “genome-wide significance”, corresponding to a Bonferroni correction for the estimated one million effective individual common variant tests across the genome, after accounting for correlation among neighboring variants.[32, 33] In this overview, we focus on findings that reach this stringent level of statistical significance.

To date, over 2000 common genetic variants have been associated with disease and been deposited in GWAS catalogs, such as that available at http://www.genome.gov/gwastudies. [14] Several general insights have emerged from the first waves of GWAS. First, most genetic effects for common variants are typically small and inversely related to allele frequency. Many loci with small impact contribute to the genetic basis of most complex phenotypes with >100 loci identified for traits with studies of hundreds of thousands of cases. Estimates indicate that many more additional loci of similar or smaller effects have yet to be identified, collectively accounting for substantial proportions of disease risk.[34]

## 3. Vascular traits

With increasing age, arterial walls typically undergo gradual stiffening, thickening, accumulation of atherosclerotic plaques and deposition of calcium. Such structural changes as vascular thickness, calcification, plaque composition and pulse wave velocity can be measured using ultrasound or computed tomography. Functional assessment of vasodilator capacity can be assessed by flow-mediated dilatation. Several such markers of cardiovascular aging have been examined in GWAS.

For pulse wave velocity, a marker of vascular stiffness, several GWASs have been performed [35, 36], identifying associations with a variant in a gene desert on chromosome 14q32 and a missense variant in the *COL4A1* gene (Table 1). The gene *COL4A1* encodes an alpha-subunit of collagen type 4, a major structural component of basement membranes. Rare mutations in this gene have also been linked to hereditary angiopathy, providing additional support for a role in vascular structure.[37] Both loci have also been linked to coronary artery disease (see section 4), although the specific variants associated with the two traits are uncorrelated ($r^2$ between SNPs ~0).

A consequence of increasing vascular stiffness is an increase in blood pressure (SBP, DBP, MAP), often to the point (>140/90) that anti-hypertensive therapies are warranted to reduce cardiovascular complications. Extensive efforts have been invested in GWASs of blood pressure, a complex trait with multiple determinants beyond vascular stiffness, including endocrine and autonomic factors, which have been thoroughly reviewed elsewhere (Kosova G, manuscript under revision with Nature Reviews Genetics). Notable among the blood pressure GWASs is the dramatic enrichment of loci containing genes involved in the production and signaling of natriuretic peptides and nitric oxide, systems that converge on the production of intracellular cyclic guanosine monophosphate leading to natriuresis and vasodilation.

The buildup of atherosclerotic plaque leads to different manifestations in different vascular beds. Most important are coronary disease (section 4), carotid disease (section 5) and lower limb arterial disease. A related disease process is aneurysmal dilation of large arteries, most

commonly the abdominal aorta. Studies have suggested some shared genetic susceptibility among these four disease manifestations, as well as differences.[38] Loci identified in GWAS for these diseases are summarized in Tables 1–3.

Arterial disease in the lower limb can result in ischemia and impaired blood flow, manifest as leg pain with exertion or at rest. A non-invasive measure of lower limb disease is the ankle-brachial blood pressure index, the lower extremity blood pressure relative to the upper extremity, which when reduced identifies individuals with peripheral arterial disease. A large GWAS has been performed of this trait, and identified association with a locus on chromosome 9p21 that has also been associated with three other manifestations of atherosclerotic disease, coronary and carotid atherosclerotic disease and arterial aneurysms.[39, 40] A genetic variant in the *DAB2IP* gene associated with aortic aneurysms [41] has also shown suggestive evidence for association with lower limb ischemia and coronary artery disease.[41, 42] Furthermore, there is evidence that a missense variant in the nicotinic acetylcholine receptor gene cluster is associated with both nicotine dependence and lower limb ischemia, potentially corroborating the well-established role for smoking in this disease as for other atherosclerotic disease manifestations.[43] Recently, a polygenic score aggregating the effects of multiple individual genetic variants associated with CAD was also associated with both lower limb ischemia and ischemic stroke.[40]

Genetic loci linked to abdominal aortic aneurysms have also been identified, and include the aforementioned loci at chromosome 9p21, in the *SORT1* gene (discussed below)[44] and in the *DAB2IP* gene.[41, 45] Polygenic risk scores incorporating variants associated with LDL cholesterol and CAD have also been linked to abdominal aneurysms, confirming links between these disorders.[46] For thoracic aortic disease, the gene encoding fibrillin-1 has been associated with risk and is the same gene in which loss-of-function mutations cause Marfan's syndrome, characterized by thoracic aortic disease as well as other arteries. Fibrillin-1 is an extracellular matrix protein which anchors smooth muscle cells to the extracellular matrix, mutations in which are considered to disrupt mechanosensing and signaling in the aortic wall.[47] These different findings for abdominal and thoracic aneurysmal disease highlight some of the different mechanisms for aneurysmal disease in different aortic segments.

## 4. Coronary artery disease

Vascular degeneration in the coronary vasculature is the underlying pathophysiological process for the leading cause of death globally, myocardial infarction. Efforts to identify genetic regions associated with this disease have therefore been extensive.

To date, meta-analysis of GWASs of coronary disease including more than 60,000 cases and 130,000 controls have identified 46 genetic loci (Table 2).[18, 48] Of these, a total of 16 loci are also consistently associated with known risk factors in a consistent direction: 10 have also been associated with increased LDL, 5 have been associated with increased blood pressure (of which one also associated with lower LDL and HDL), 4 have been associated with increased triglycerides, and 7 associated with decreased HDL (Table 2). Other SNPs have not been associated with traditional risk factors. Interestingly, none of the SNPs

associated with type 2 diabetes or other glucometabolic traits such as fasting glucose and insulin, HOMA-B and HOMA-IR have been associated with coronary disease. Although the exact genes have not been identified in most cases, these observations suggest that the majority of SNPs act through novel pathways and thus have the potential to point to novel mechanisms in the pathophysiology of CAD.

Two notable examples of genetic loci where likely causal genes have been identified are on chromosomes 9p21 and 1p13. The locus on chromosome 9p21 was the first common variant CAD locus identified and shows the strongest evidence in most studies, owing both to a relatively large effect for a common variant and a high risk allele frequency in many populations, about 50%.[28, 29] The variant has been associated with increased burden of CAD and more severe disease, but not with infarction in patients with established CAD.[49–51] Genetic variants at this locus have been shown to be located in a cis-antisense transcript (*CDKN2B-AS1*) and are associated with altered expression of the most proximal downstream genes, *CDKN2B* and *CDKN2A*.[52–55] Knockdown of the orthologous region in mice results in reduced expression of *CDKN2A/CDKN2B*, suggestive of regulatory functions in the region.[56] Furthermore, aortic smooth muscle cells with this deletion exhibited excessive proliferation and diminished senescence. In a separate study, Harismendy et al cloned the CAD-associated risk variants into cell cultures and reported disruption of a STAT-1 binding enhancer, and increased *CDKN2B-AS1* expression of the risk allele. Long-range interaction of the enhancer region with *CDKN2A/CDKN2B* has also been reported, using a chromatin conformation capture assay, as well as altered chromatin structure in the region with differential STAT1-binding in response to interferon-gamma activation. [57] Taken together, these results implicate *CDKN2A/CDKN2B/CDKN2BAS1* as a novel link between inflammatory signaling and vascular proliferation. Additional studies are needed, however, as a recent study was unable to validate the results of Harismendy et al[58], and another study recently suggested widespread trans-effects of *CDKN2BAS1*.[59]

The locus on chromosome 1p13 is associated with both coronary disease and LDL cholesterol. In a seminal paper, Musunuru and colleagues demonstrated that the risk allele of a SNP at the locus (rs12740374) creates a C/EBP transcription factor binding site and decreases hepatic expression in cis of the gene *SORT1*. [60] Using siRNAs in liver cells, it was further shown that SORT1 modulates hepatic VLDL secretion, resulting in lower blood levels of VLDL and LDL cholesterol, implicating the hepatic SORT1 pathway as a potential novel therapeutic target. More recently, the picture has become more complex in experimental studies with reports of other effects of *SORT1* on lipoprotein metabolism[61, 62] and on other processes with atherogenic potential such as cell survival.[63]

For most other loci discovered more recently, mechanistic studies are still in early stages. However, five of the other loci contain a missense SNP that is strongly correlated with the top SNP (r2>0.9). These loci include missense variants in the genes encoding plasminogen and gastric inhibitory peptide (GIP). Plasminogen is a fibrinolytic enzyme and the ultimate target of thrombolytics used in acute myocardial infarction to dissolve blood clots. GIP is an incretin hormone that has been shown to regulate insulin secretion and fatty acids. The other three genes containing missense variants (*SH2B3*, *ZC3HC1* and *WDR12*) have less obvious links to the CAD process, although it is interesting to note that the *SH2B3* variant is also

linked to blood pressure, cholesterol and several blood cell concentrations. The majority of remaining loci which lack coding variants are thus likely to act through effects on regulatory sequence. eQTL studies to elucidate the culprit genes at CAD loci could potentially be very valuable. However, sample sizes for relevant tissues are generally quite low and cell-type specific effects on expression are widespread. Large-scale efforts such as the GTEX project promise to expand the collections of tissues with expression and genome-wide genotyping.

In order to improve statistical power, most GWASs have combined both cases with coronary artery disease detected at coronary catheterization and myocardial infarction. It remains unclear to what extent genetic loci influence both the atherosclerotic process, clinically manifest as stable angina, and the plaque de-stabilization, rupture and thrombosis underlying many cases of acute myocardial infarction. One interesting study contrasted these two phenotypes, and suggested that many recently identified loci were primarily associated with CAD whereas only the ABO locus was associated with myocardial infarction among individuals with established CAD.[51]

Other studies have tested the association of genetic variants with angiographic coronary disease. Interestingly, the location of atherosclerotic plaque in the coronary tree has been shown to be heritable in a creative study of siblings with coronary disease.[64] However, the location of atherosclerotic plaques has not been studied in GWASs.

A GWAS has identified two loci associated with coronary calcium as identified on coronary computed tomography.[65] One is the locus on chromosome 9p21 associated with increased expression of *CDKN2A/CDKN2B*. The other is a locus on chromosome 6p24 associated with increased expression of the gene *PHACTR1* and CAD, migraine and cervical artery dissection although the possible mechanism remains unclear.[66, 67]

GWASs have also identified a large number of loci associated with metabolic risk factors for CAD, including cholesterol, diabetes, hypertension and obesity.[11] Genetic variants at such loci have been used in studies (termed Mendelian Randomization studies) with results supportive of the causal link between coronary disease and higher blood pressure[68, 69], higher plasma triglyceride level,[70] higher plasma LDL cholesterol level,[71] higher plasma lipoprotein(a) level[72], obesity[73], telomere length[74, 75] and plasma IL6 concentration.[76] However, such studies have overall not supported a causal association of lower plasma HDL level, a finding consistent with the recent negative clinical trials of HDL-raising therapies[77], as well as CRP[78], homocysteine[79], fibrinogen[80], Lp-PLA2[81], uric acid[82] or bilirubin[83]. For diabetes, genetic studies have supported an association, but the picture is likely to be complicated as the overall association of diabetes-associated genetic variants was substantially weaker than predicted suggesting the different diabetes mechanisms may play specific pathogenic roles.[84]

Studies have also examined the occurrence of ventricular fibrillation during the acute phase of myocardial infarction [85] as further discussed in section 8.

## 5. Ischemic stroke and carotid vascular disease

Ischemic stroke is a highly complex phenotype, with multiple contributing disease processes. The most successful GWASs for this disease have therefore focused on distinct etiologic subtypes, including stroke of presumed cardioembolic origin, stroke with carotid artery disease and intracranial small-vessel disease. (Table 3)

The most common identifiable cause of stroke is considered to be atrial fibrillation. It is therefore not surprising that genetic variants on chromosomes 4q25 and 16q22 that are associated with atrial fibrillation (see below) have also been associated with stroke of presumed cardioembolic origin.[86]

Ischemic stroke is also frequently seen in patients with CAD, particularly stroke of the subtype associated with carotid artery disease, which is considered to be related to similar atherosclerotic vascular processes as underlie most cases of coronary disease. Genetic variants on chromosomes 7p21, 9p21, 9q34, 12q24 associated with CAD have also been associated with ischemic stroke of presumed carotid origin whereas 12q24 is additionally associated with other forms of stroke.[86–90] Genetic variants on chromosome 7p21 are associated with increased expression in cis of *HDAC9* in human coronary arteries in the Genotype-Tissue Expression project (GTEx, http://www.gtexportal.org/) but not in aorta. Mechanisms underlying the association with 9p21 are described in section 5. CAD-associated alleles in *ABO* (9q34) and in *SH2B3* (12q24, a variant modestly correlated with the missense variant described for CAD) have also been associated with increased risk of stroke although the mechanisms remain unclear. Different variants in the genomic region of *MMP12* have also been associated with both stroke and CAD although they are uncorrelated and thus appear to reflect independent effects. Further evidence for shared underlying mechanisms for ischemic stroke and coronary disease comes from studies that have shown that polygenic risk scores of variants associated with CAD are also associated with stroke.[40, 91, 92] Interestingly, ischemic stroke of carotid origin has also been associated with a genetic locus on chromosome 6p21 that has not yet been associated with coronary disease.[93] However, this region is intergenic, located far from any known genes.

A GWAS recently identified two genetic regions associated with common carotid intima-media thickness and two additional regions associated with the presence of carotid plaque.[94] In contrast to stroke of cardioembolic and carotid origin, no loci have been convincingly associated with small-vessel disease or lacunar infarctions.

Finally, a genetic variant on chromosome 12p13 has also been associated with ischemic stroke in GWAS,[95] but did not replicate in subsequent, larger studies and may reflect a false-positive association.[96, 97]

## 6. Myocardial phenotypes related to the sarcomere

The myocardium also undergoes critical aging-related changes, including impaired cardiac conduction, prolonged repolarization and hypertrophy, leading to impaired relaxation during diastolic filling. These pathophysiologic processes lead respectively to bradycardia, arrhythmias, and heart failure. GWAS has also been performed for such traits as measured

by electrocardiography or echocardiography in the general population, and are summarized elsewhere.

The ultimate consequence of sarcomere dysfunction is the clinical condition known as heart failure. GWAS of heart failure have not identified any loci of genome-wide significance, likely reflecting the limited statistical power resulting from inadequate sample sizes and the etiological heterogeneity of this condition.[98] GWAS have however found genetic variants associated with specific etiological subsets of heart failure, mirroring results for ischemic stroke, in subsets typically presenting in younger patients, including a locus associated with peripartum cardiomyopathy (although with a very small sample size, awaiting replication),[99] three loci associated with dilated cardiomyopathy[100–102] and one locus associated with hypertrophic cardiomyopathy.[103] (Table 4) Of the five loci associated with cardiomyopathy, three contain missense variants ($r^2$>0.9): *HSPB7* and *BAG3* for dilated cardiomyopathy and *FHOD3* for HCM. Further support for a role of *BAG3* in dilated cardiomyopathy comes from findings of multiple rare variants in this gene in DCM families, and with a similar phenotype observed in a zebrafish knockdown.[104] Not much is currently known about mechanisms for these genes, however. A polymorphic deletion in the *MYBPC3* gene has been reported to be common in some groups in India and to confer increased risk of both dilated and hypertrophic cardiomyopathy and heart failure.[105]

GWAS have also been performed of echocardiographic traits reflecting cardiac structure and function, and identified one locus on chromosome 6q22 associated with left ventricular internal diameter, a characteristic of dilated cardiomyopathy. Importantly, the locus contains the *PLN* gene encoding phospholamban, a central regulator of calcium transport into the sarcoplasmic reticulum. Such studies are summarized in detail elsewhere. (Smith JG et al, submitted)

## 7. Cardiac phenotypes related to rhythm

The most common arrhythmias are atrial fibrillation (AF) and ventricular tachycardia and fibrillation, the latter two often manifesting as sudden cardiac arrest and death. AF can be easily identified from the EKG upon presentation to a hospital, whereas ventricular arrhythmia typically lead to sudden death if not successfully resuscitated and so are much more difficult to ascertain in genetic studies. GWAS has identified a total of 14 loci for AF [106–112] and two for ventricular arrhythmias.[85, 113] (Table 4)

The first identified locus for AF lies in an intergenic region on chromosome 4q25. [106] The variant showed an unusually strong effect for a common genetic variant, although the effect has subsequently been shown to differ across different clinical contexts, consistent with etiological heterogeneity.[114] It has also been shown to be associated with increased recurrence of AF after pulmonary vein ablation,[115] cardioversion[116] and in patients on anti-arrhythmic drug therapy.[117] The polymorphisms have not been associated with atrial expression of proximal genes in adult hearts,[118] but have been proposed to be involved in regulating developmental expression of the most proximal gene *PITX2*. *PITX2* is a very strong candidate gene, as it has been shown to regulate left-right asymmetry in the developing heart and development of the pulmonary myocardium, both considered to be

central to AF pathogenesis.[119, 120] Murine deletion of *PITX2* has also been shown to predispose to pacing-induced AF.[119]

The second identified locus for AF was located on chromosome 16q22, intronic to another cardiac transcription factor (*ZFHX3*). Little is known about the function of *ZFHX3*, but it has been shown to regulate the function of *STAT3*, which in turn is a regulator of paracrine circuits in the heart essential for interstitial matrix deposition balance and capillary vasculature maintenance. Increased expression of STAT3 has been observed in animal models of AF and has been proposed to contribute to atrial matrix deposition.[121] Interestingly, interaction of this variant with presence of heart failure was shown to multiplicatively increase AF risk, which could be consistent with an important role of myocardial fibrosis in AF pathophysiology in such patients.[121]

Additional loci for AF include two other transcription factors expressed during cardiac development (*PRRX1* and *TBX5*) and two genes with well-established roles in atrial electrophysiology: the funny current channel (*HCN4*) and the gene encoding connexion-43 (*GJA1*).[110, 111] Variants at *TBX5* and *GJA1* loci were also shown to be associated with cardiac expression of these genes.[111]

A trait that is related to atrial fibrillation is sick sinus syndrome, in which the sinus node is dysfunctional, often resulting in a combination of bradycardia alternating with tachycardias such as atrial fibrillation, originating from other atrial foci. A genetic variant in the gene *MYH6*, encoding cardiac alpha-myosin, has also been associated with sick sinus syndrome.[122]

For ventricular arrhythmias, one locus on 2q24 has been identified in GWAS of sudden cardiac death,[113] and one locus on 21q21 has been linked to ventricular fibrillation in the setting of an acute myocardial infarction.[85] The variant on chromosome 21q21 has been shown to be associated with expression of the most proximal gene (*CXADR*), encoding a viral receptor implicated in myocarditis. Heterozygosity for this gene was associated with early onset of ventricular arrhythmia in a murine model of myocardial infarction. The underlying gene at the locus on 2q24 remains unclear, although the top variant is perfectly correlated with a missense variant in the gene *TANC1*, a gene involved in muscle development.

With regard to cardiac electrical function, GWAS have also identified >100 loci associated with EKG phenotypes in the general population, which are summarized elsewhere. (Smith JG et al, submitted)

## 8. Cardiac valvular phenotypes

With increasing age, cardiac valves can become increasingly dysfunctional and develop both stenosis and regurgitation. Calcification of the aortic valve cusps, a precursor to aortic stenosis, can be seen in nearly 30% of individuals at 70 years [123], more commonly than calcification of the mitral valve leaflets. In a recent GWAS of aortic and mitral calcification including 6942 individuals from the general population, a genetic variant in the *LPA* gene encoding lipoprotein(a) was found to be associated with increased risk of aortic sclerosis and

stenosis and with increased lipoprotein(a).[124] (Table 1) This finding has subsequently been confirmed in independent Canadian and Danish cohorts[125, 126] and reinforces the hypothesis that the process of valvular age-related degeneration shares key pathophysiologic features with that observed in atherosclerotic vessels.[127–129] In a second analysis of the same cohorts, it was further shown that a polygenic score comprised of alleles associated with increased LDL cholesterol also conferred increased risk of aortic valve calcium and stenosis, providing further support for a role of blood lipids beyond lipoprotein(a) in the development of calcific aortic valve disease.[130]

## 9. Functional annotation: from genetic locus to biological mechanism

Inherent to most methods of genetic mapping approaches such as GWAS is the limitation that they can identify genomic loci through correlation among neighboring variants, but resolution to identify the causal variant and gene can be limited. Although loci may inform risk prediction and explain heritability, novel biologic insights can only be obtained by identifying the causal variant, gene and underlying mechanism. How can this be achieved?

A set of expert recommendations for investigating causality of rare sequence variants has recently been compiled by a working group convened by the US National Human Genome Research Institute.[131] The recommendations presented largely apply to common variants as well.

Broadly, a modernized version of Koch's postulates can be applied.[132] Analogous to introducing microbial agents, a genotype suspected to confer risk of disease can be introduced into a cellular or animal model system using gene editing approaches. The consequences of that genotype can then be evaluated in terms of disease pathogenesis and perturbation of molecular pathways including effects on expression of mRNA, noncoding RNAs (microRNAs, antisense RNAs, lncRNAs), proteins as well as transcription factor binding and chromatin conformation, to determine the downstream effects of genotype. The major challenge of this approach is that a likely causal variant needs first to be found through genetic fine-mapping – high-density genotyping of neighboring variants to refine signals of genetic association – which can often lead to ambiguous results due to correlation among neighboring variants. Another major impediment is the unclear relevance of many animal and cellular models to human disease, which as previously noted is one of the major incentives for human genetic research. This is particularly a problem for regulatory regions, which are often poorly conserved across species.[133] The ability to dedifferentiate and reprogram human cells into virtually any cell type holds great promise in generating relevant human cells and potentially also tissues and organs.[134] In addition, mRNAs are frequently spliced to multiple potential transcripts in a tissue-specific manner, and proteins metabolized further to generate a large number of metabolites. Thus, although the 20,000 genes are limited in number, the number of transcripts, proteins and metabolites that can be altered are considerably higher. Wading through this veritable flood of data can pose substantial bioinformatics and statistical challenges.

In addition to fine-mapping, initial work can seek to determine whether coding variants that alter protein structure (missense, nonsense, splice-site altering, or frameshift variants) are

correlated with identified SNPs, and to annotate associated genomic regions with putative regulatory function, such as promoters, enhancers and 3′ untranslated regions. Notably, the majority of genetic variants identified in GWAS have been located outside of coding regions of known genes, and are therefore thought to reside in regions involved in regulation of gene expression, including enhancers, lncRNAs and miRNAs.[135] Indeed, of the 92 loci described here, only 11 harbor missense variants ($r^2$ of top SNP to missense SNP > 0.9). Much ongoing work is therefore focused on the comprehensive annotation of regulatory regions throughout the human genome in large-scale projects such as the ENCODE and FANTOM projects. Other large ongoing projects focus on characterizing the tissue-specificity of regulatory regions.[136–139] The ROADMAP Epigenomics project aims to provide an atlas of epigenetic modifications across hundreds of human tissues and cells, and recently published a global map of regulatory elements based on these epigenetic data.[139] The GTEx project aims to characterize effects of DNA variants on RNA and protein expressed by nearby genes (cis-QTL) or distant genes (trans-QTL) in human tissues, using next-generation sequencing to assay genome-wide mRNA and noncoding RNA expression in relation to genotypes across a large number of human tissues. The Human Protein Atlas (http://www.proteinatlas.org) provides information on both tissue-specific mRNA and protein expression. Identified variants with impact on gene expression and location in regulatory regions can further be characterized for their influence on transcription factor binding using multiplex assays[140], epigenomic characterization using chromatin immunoprecipitation,[141] and chromatin folding using chromatin conformation capture assays.[142]

As such work is rapidly evolving, we can expect additional mechanisms to be identified for cardiovascular pathogenesis in the coming years.

## 10. Clinical implications

Genetic studies can be a powerful tool to identify and prioritize potential drug targets. In addition, the robust identification of genetic sequence variants associated with human traits may set the stage for genetic disease prediction and individually tailored therapy by incorporating genetic information, often termed ‘precision medicine’. Large governmental investments have been announced to facilitate such developments in the United States and elsewhere through resequencing of whole genomes in thousands to millions of subjects.[143]

With regard to the findings from genome-wide association studies discussed here, a consistent observation has been that the allele frequency of identified variants typically scale with effect size, with small effects typically observed for common variants (as negative selection constrains the frequency of deleterious alleles of strong effect). Individually, such variants are therefore unlikely to be of clinical value, but in aggregate such variants may explain a substantial proportion of disease risk when combined into polygenic scores. For example, although individual SNPs explain less than 1% of CAD risk, the 46 identified loci for coronary artery disease in aggregate explain approximately 6% of CAD heritability,[18] whereas common genetic variation across the genome overall has been estimated to additively account for 48% of CAD risk.[144]

Polygenic scores incorporating multiple variants could thus be useful to guide clinical risk prediction and to individually tailor therapy. For example, in a recent study a polygenic score comprised of 27 CAD SNPs stratified 20% of the population into a high-risk group at 72% increased risk of CAD. In addition, this group derived both greater absolute and relative benefit with statin therapy as compared to patients at low genetic risk, with a roughly threefold decrease in the number needed to treat to prevent 1 event over 10 years in the high-risk group.[145] With incorporation of additional variants, taking gene-gene and gene-environment interactions into account, and validation in additional studies, this polygenic risk score may well become an important part in individual risk prediction and CAD prevention.

## 11. Conclusions

Over the past 10 years, GWASs have been highly successful in identifying genetic regions associated with many common diseases, including aging-related cardiovascular diseases. However, much additional work is required to understand the mechanisms linking these loci to disease. Major obstacles for mechanistic studies include both experimental, bioinformatic and statistical issues. This work is therefore likely to require collaboration across traditional scientific boundaries, but offers great opportunities to improve our understanding of the cardiovascular aging process and to identify novel therapeutic targets that may facilitate longevity and healthy aging. In the longer term, individual tailoring of therapy in clinical medicine may be possible but the road there is long and winding, much like the human genome.

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## Highlight

- A genetic component to late-onset cardiovascular diseases has been established
- GWAS have identified many loci contributing to risk of late-onset CVD
- We summarize loci identified with a stringent statistical significance threshold
- Only for a few loci have mechanisms explaining CVD association been described
- Mechanistic insights hold promise for novel therapeutic and preventive strategies

**Table 1**

Vascular and valvular phenotypes: genetic loci with genome-wide significant association.

| Phenotype | Chromosome | Candidate gene | SNP | P-value | Study |
|---|---|---|---|---|---|
| ***Aortic valve*** | | | | | |
| Aortic valve calcium and stenosis | 6q25 | *LPA* | rs10455872 | $9\times10^{-10}$ | [124] |
| ***Aorta*** | | | | | |
| Abdominal aneurysm | 1p13 | *SORT1* | rs599839 | $7\times10^{-14}$ | [44] |
| Abdominal aneurysm | 1q21 | *IL6R* | rs2228145 | $3\times10^{-11}$ | [146] |
| Abdominal aneurysm | 9p21 | *CDKN2A/CDKN2B* | rs10757278 | $1\times10^{-12}$ | [45] |
| Abdominal aneurysm | 9q33 | *DAB2IP* | rs7025486 | $5\times10^{-10}$ | [41] |
| Abdominal aneurysm | 12q13 | *LRP1* | rs1466535 | $5\times10^{-10}$ | [147] |
| Abdominal aneurysm | 19p13 | *LDLR* | rs6511720 | $2\times10^{-10}$ | [148] |
| Thoracic aneurysm and dissection | 15q21 | *FBN1* | rs2118181 | $6\times10^{-12}$ | [149] |
| ***Peripheral arterial disease*** | | | | | |
| Ankle-brachial index | 9p21 | *CDKN2A/CDKN2B* | rs10757269 | $3\times10^{-9}$ | [39] |
| **Vascular stiffness** | | | | | |
| Pulse wave velocity | 13q34 | *COL4A1* | rs3742207* | $5\times10^{-8}$ | [36] |
| Pulse wave velocity | 14q32 | *BCL11B* | rs7152623 | $3\times10^{-15}$ | [35] |

Because genetic associations implicate genetic variation in a region, the causal variant and the gene which it influences are often unknown. We indicate throughout this review the chromosomal region, the nearest candidate gene and the SNP in the reported studies demonstrating the strongest evidence of association (lowest p-value). P-values and references refer to the initial discovery study.

* coding variant with $r^2 > 0.9$ to index SNP in 1000 Genomes CEU.

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**Table 2**

Coronary artery disease: genetic loci with genome-wide significant association.

| **Clinical coronary artery disease** | | | | |
|---|---|---|---|---|
| 1p13 (*SORT1*) rs602633[*,#] p=1×10$^{-25}$ | 3q22 (*MRAS*) rs9818870 p=3×10$^{-9}$ | 6q26 (*PLG*) rs4252120[£] p=5×10$^{-10}$ | 10q23 (*LIPA*) rs2246833 p=9×10$^{-6}$ | 17p11 (*PEMT*) rs12936587 p=1×10$^{-9}$ |
| 1p32 (*PPAP2B*) rs17114036 p=6×10$^{-12}$ | 4q31 (*EDNRA*) rs1878406 p=3×10$^{-8}$ | 7p21 (*HDAC9*) rs2023938 p=5×10$^{-8}$ | 10q24 (*CYP17A1*) rs12413409[¤] p=6×10$^{-8}$ | 17p13 (*SMG6*) rs2281727 p=8×10$^{-9}$ |
| 1p32 (*PCSK9*) rs11206510[*] p=2×10$^{-5}$ | 4q32 (*GUCY1A3*) rs7692387[¤] p=3×10$^{-11}$ | 7q22 (*COG5*) rs12539895 p=5×10$^{-4}$ | 11q22 (*PGFD*) rs974819 p=4×10$^{-11}$ | 17q21 (*GIP*) rs15563[£] p=9×10$^{-6}$ |
| 1q21 (*IL6R*) rs4845625 p=4×10$^{-10}$ | 5q31 (*SLC22A4*) rs273909 p=1×10$^{-9}$ | 7q32 (*ZC3HC1*) rs11556924[¤,£] p=7×10$^{-17}$ | 11q23 (*APOA1*) rs9326246[*,§,#] p=2×10$^{-7}$ | 19p13 (*LDLR*) rs1122608[*] p=6×10$^{-14}$ |
| 1q41 (*MIA3*) rs17464857 p=6×10$^{-5}$ | 6p21 (*ANKS1A*) rs12205331[#] p=4×10$^{-5}$ | 8p21 (*LPL*) rs264[§,#] p=3×10$^{-9}$ | 12q24 (*SH2B3*) rs3184504[¤,#,&,£] p=5×10$^{-11}$ | 19q13 (*APOE*) rs2075650[*,§,#] p=6×10$^{-11}$ |
| 2p11 (*VAMP8*) rs1561198 p=1×10$^{-10}$ | 6p21 (*KCNK5*) rs10947789 p=1×10$^{-8}$ | 8q24 (*TRIB1*) rs2954029[*,§,#] p=5×10$^{-9}$ | 13q12 (*FLT1*) rs9319428 p=7×10$^{-11}$ | 21q22 (*KCNE2*) rs9982601 p=8×10$^{-17}$ |
| 2p21 (*ABCG5*) rs6544713[*] p=2×10$^{-9}$ | 6p24 (*ADTRP*) rs6903956 p=5×10$^{-12}$ | 9p21 (*CDKN2A/CDKN2B*) rs1333049 p=1×10$^{-52}$ | 13q34 (*COL4A1-COL4A2*) rs4773144 p=1×10$^{-11}$ | |
| 2p24 (*APOB*) rs515135[*] p=3×10$^{-10}$ | 6p24 (*PHACTR1*) rs9369640 p=8×10$^{-22}$ | 9q34 (*ABO*) rs579459[*] p=3×10$^{-8}$ | 14q32 (*HHIPL1*) rs2895811 p=4×10$^{-10}$ | |
| 2q22 (*ZEB2*) rs2252641 p=5×10$^{-8}$ | 6q23 (*TCF21*) rs12190287 p=5×10$^{-13}$ | 10p11 (*KIAA1462*) rs2505083 p=1×10$^{-11}$ | 15q25 (*ADAMTS7*) rs7173743 p=7×10$^{-13}$ | |
| 2q33 (*WDR12*) rs6725887[£] p=1×10$^{-15}$ | 6q25 (*LPA*) rs3798220[*] p=5×10$^{-5}$ | 10q11 (*CXCL12*) rs501120 p=2×10$^{-9}$ | 15q26 (*FURIN*) rs17514846[¤] p=9×10$^{-11}$ | |
| **Coronary artery calcium** | | | | |
| **Chromosome** | **Candidate gene** | **SNP** | **P-value** | |
| 6p24 | *PHACTR1* | rs9349379 | p=3×10$^{-11}$ | |
| 9p21 | *CDKN2A/CDKN2B* | rs1333049 | p=8×10$^{-19}$ | |

Chromosomal loci, candidate genes, SNP and p-value at the 46 genetic loci associated with coronary artery disease in genome-wide association studies (p<5×10$^{-8}$). Adapted from the CARDIoGRAMplusC4D study [18] (up to >60,000 cases and >130,000 controls) and a study of coronary artery calcium on computed tomography (nearly 16,000 subjects). [65] One locus (6p24 in ADTRP) was reported separately in a Chinese study. [48]

[*] 10 loci associated with higher LDL for CAD risk alleles,

[&] 1 locus with lower LDL,

[§] 4 loci with higher TG,

[#] 7 loci with lower HDL,

[¤] 5 loci with higher blood pressure.,

[£] 5 coding variants with $r^2 > 0.9$ to index SNP in 1000 Genomes CEU.

**Table 3**

Ischemic stroke and carotid artery disease: genetic loci with genome-wide significant association.

| Phenotype | Chromosome | Candidate gene | SNP | P-value | Study |
|---|---|---|---|---|---|
| ***Carotid artery disease*** | | | | | |
| Common carotid IMT | 8q24 | *ZHX2* | rs11781551 | $2\times10^{-11}$ | [94] |
| Common carotid IMT | 8p23 | *PINX1* | rs6601530 | $2\times10^{-8}$ | [94] |
| Common carotid IMT | 19q13 | *APOC1* | rs445925 | $2\times10^{-8}$ | [94] |
| Carotid plaque | 4q31** | *EDNRA* | rs1878406 | $7\times10^{-12}$ | [94] |
| Carotid plaque | 7q22 | *PIK3CG* | rs17398575 | $2\times10^{-12}$ | [94] |
| ***Ischemic stroke*** | | | | | |
| Cardioembolic stroke | 4q25* | *PITX2* | rs6843082 | $3\times10^{-16}$ | [86] |
| Cardioembolic stroke | 16q22* | *ZFHX3* | rs879324 | $3\times10^{-8}$ | [86, 107] |
| Carotid-artery stroke | 6p21 | *CDC5L/VEGFA* | rs556621 | | [93] |
| Carotid-artery stroke | 7p21** | *HDAC9* | rs2107595 | $2\times10^{-12}$ | [86, 88] |
| Carotid-artery stroke | 9p21** | *CDKN2A/CDKN2B* | rs2383207 | $3\times10^{-5}$ | [86, 87] |
| Carotid-artery stroke | 11q22 | *MMP12* | rs660599 | $3\times10^{-8}$ | [150] |
| Ischemic stroke | 12q24 | *SH2B3/ALDH2* | rs10744777 | $7\times10^{-11}$ | [90] |

P-values and references refer to the initial discovery study.

* Also associated with atrial fibrillation.

** Also associated with coronary artery disease.

**Table 4**

Cardiac arrhythmia and cardiomyopathy: genetic loci with genome-wide significant association.

| Phenotype | Chromosome | Candidate gene | SNP | P-value | Reference |
|---|---|---|---|---|---|
| ***Ventricular arrhythmia*** | | | | | |
| Sudden cardiac death | 2q24 | *TANC1** | rs4665058 | $2\times10^{-10}$ | [113] |
| Ventricular fibrillation | 21q21 | *CXADR* | rs2824292 | $3\times10^{-10}$ | [85] |
| ***Atrial arrhythmia*** | | | | | |
| Atrial fibrillation | 1q21 | *KCNN3* | rs13376333 | $2\times10^{-21}$ | [109] |
| Atrial fibrillation | 1q24 | *PRRX1* | rs3903230 | $8\times10^{-14}$ | [110] |
| Atrial fibrillation | 3p25 | *CAND2* | rs4642101 | $1\times10^{-8}$ | [111] |
| Atrial fibrillation | 4q25 | *PITX2* | rs2200733 | $2\times10^{-30}$ | [106] |
| Atrial fibrillation | 6q22 | *GJA1* | rs13216675 | $2\times10^{-8}$ | [111] |
| Atrial fibrillation | 7q31 | *CAV1* | rs3807989 | $4\times10^{-12}$ | [110] |
| Atrial fibrillation | 9q22 | *C9orf3* | rs10821415 | $4\times10^{-11}$ | [110] |
| Atrial fibrillation | 10q22 | *SYNPO2L* | rs10824026 | $4\times10^{-9}$ | [110] |
| Atrial fibrillation | 10q24 | *NEURL* | rs12415501 | $7\times10^{-16}$ | [111] |
| Atrial fibrillation | 12q24 | *TBX5* | rs10507248 | $6\times10^{-11}$ | [111] |
| Atrial fibrillation | 12q24 | *CUX2* | rs6490029 | $4\times10^{-9}$ | [111] |
| Atrial fibrillation | 14q23 | *SYNE2* | rs1152591 | $6\times10^{-13}$ | [110] |
| Atrial fibrillation | 15q24 | *HCN4* | rs7164883 | $3\times10^{-17}$ | [110] |
| Atrial fibrillation | 16q22 | *ZFHX3* | rs2106261 | $2\times10^{-15}$ | [107, 108] |
| Sick sinus syndrome | 14q11 | *MYH6* | rs2231801 | $1\times10^{-13}$ | [122] |
| ***Cardiomyopathy*** | | | | | |
| Dilated cardiomyopathy | 1p36 | *HSPB7** | rs1739843 | $5\times10^{-13}$ | [100, 101] |
| Dilated cardiomyopathy | 6p21 | *HCG22* | rs9262636 | $5\times10^{-9}$ | [102] |
| Dilated cardiomyopathy | 10q26 | *BAG3** | rs2234962 | $6\times10^{-13}$ | [100] |
| Hypertrophic cardiomyopathy | 18q12 | *FHOD3** | rs2303510 | $2\times10^{-9}$ | [103] |
| Peripartum cardiomyopathy | 12p11 | *PTHLH* | rs258415 | $2\times10^{-8}$ | [99] |

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P-values and references refer to the initial discovery study.

* coding variant with $r^2 > 0.9$ to index SNP in 1000 Genomes CEU.