Published in final edited form as:

Heart Fail Clin. 2010 January ; 6(1): 115–124. doi:10.1016/j.hfc.2009.08.002.

GENOMICS OF HEART FAILURE

Raghava S. Velagaleti, MD and Christopher J. O'Donnell, MD*

National Heart, Lung and Blood Institute (CJO) and the NHLBI's Framingham Heart Study (RSV, CJO), Framingham, MA; Boston University Medical Center (RSV), Boston, MA; and the Cardiovascular Division, Department of Medicine (CJO), Massachusetts General Hospital, Harvard Medical School Boston, MA

Introduction

Cardiovascular disease is the leading cause of death in men and women, and heart Failure (HF), a cardiovascular disease condition characterized by dyspnea, fluid retention and decreased functional capacity, is associated with particularly high rates of morbidity and mortality. Apart from the few known Mendelian diseases that lead to HF, most common forms of HF are non-Mendelian and the evidence for heritability is modest. The substrates for development of HF are structural and/or functional changes in the myocardium that precede the onset of the clinical syndrome. Thus, a diverse group of etiologies (e.g., major etiologies being hypertrophic, dilated, restrictive, and ischemic cardiomyopathies) lead to HF, making it very challenging to undertake studies to discern the genomic factors underpinning this syndrome. Study of the genetic susceptibility to HF has until recently been limited to candidate gene association studies in patients with distinct sub-types of HF. However, with the completion of the human genome project¹ and the development of the HapMap template², new large scale genome wide association studies (GWAS) are possible and underway. We will review the status of these ongoing efforts and other important new directions in genomics, in particular genome-wide sequencing, as well as other “omics” technologies that will likely advance our understanding of HF etiologies.

State of knowledge pertaining to the genetics and genomics of HF

Disorders with Mendelian inheritance that lead to HF

Our understanding of the genetics and genomics of HF to date has been grounded in research in rare families with strong evidence for a genetic predisposition for HF. In these families, rare mutations underlie the predisposition to HF. Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) are disorders associated with HF that demonstrate classical Mendelian inheritance pattern. HCM has an estimated prevalence of 1 in 500 in the general population³ and familial DCM (which accounts for 30% of all DCM) has an estimated prevalence of 1 in 20,000.⁴ People with these syndromes exhibit a diverse array of phenotypic manifestations thus complicating the effort to identify them on the basis of clinical characteristics alone. Over 400 hundred mutations in several sarcomeric proteins have been identified, including *MyHC*⁵, *MYH7*, *MYBP3*⁶, *TNNT2*⁷ and *TNNI*⁸, encoding beta myosin heavy chain, myosin heavy chain, myosin binding protein, cardiac troponin I

*Corresponding author: odonnellc@nhlbi.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and troponin T respectively. Approximately 70% of all HCM cases are accounted for by mutations in the aforementioned 4 genes.

DCM has heterogeneous manifestations and its cause is unknown in the majority of cases. In selected cases of DCM that appear to be familial, mutations in genes coding for dystrophin⁹, emerin¹⁰ and tafazin¹¹ lead to X-linked inheritance pattern whereas mutations in genes coding for actin¹², lamin A/C¹³ and desmin¹⁴ lead to an autosomal dominant pattern. In addition to these mutations, rare mutations in genes coding for laminin, troponin, titin and myosin have been reported in familial DCM cases. ARVC occurs approximately 1 in 5000 – 10000¹⁵. ARVC is a frequent cause of sudden cardiac death in the young, especially among athletes and is characterized by progressive degeneration, thinning and fibrosis of the right ventricle leading to left bundle branch block, arrhythmias and aneurysms. Mutations in the transforming growth factor- β ¹⁶, ryanodine receptor¹⁷, plakophilin-2¹⁸, desmoplakin¹⁹ and plakoglobin²⁰ genes have been implicated; the first three lead to an autosomal recessive inheritance and the latter two to a dominant inheritance.

Genomics of HF risk factors

In contrast to rare Mendelian conditions underlying HF, common forms of HF account for the vast majority of HF cases that lead to very high rates of morbidity and mortality from HF. A substantial proportion of the etiology of common forms of HF is explained by the prior occurrence of well characterized, common risk factors including hypertension, left ventricular hypertrophy, type II diabetes mellitus, and prior myocardial infarction. Common HF appears to have a heritable component. Investigators from the Framingham Heart study have previously reported that offspring of people with HF are more likely to have systolic dysfunction, ventricular dilatation and increased left ventricular mass.²¹ In cross-sectional analyses, the odds of increased left ventricular mass, left ventricular internal dimension of left ventricular systolic dysfunction were 1.35, 1.29 and 2.37 in people with at least one parent with HF, compared to people with no HF in either parent. Indeed HF in one parent portended a 70% increment in risk and HF in both parents a 90% increment in risk, of HF prospectively in the offspring, compared to people with HF in either parent. The heritability (H^2 ; percent of population variation attributable to genetic factors) of common HF is estimated to be 28%. While the minority of HF cases in the general population are explained by rare Mendelian causes, there is remarkably little reliable information on the actual proportion of risk for common HF that is conferred by rare mutations (eg, minor allele frequency [MAF] $\ll 0.1\%$) versus low frequency genetic variants (eg, MAF $< 0.1-1\%$) mutations versus high frequency variants (eg, MAF $\geq 1\%$).

Recently, investigators have conducted sequencing studies in general populations that lead to improved understanding about the role for of variants in genes known to underlie rare forms of HF. For example, in the Framingham Heart Study, genetic variation in exons of sarcomere protein genes and storage cardiomyopathy-causing genes was examined in association with increased left ventricular wall thickness in ~1800 persons. 7 mutations found in 5 sarcomere protein genes and 1 mutation in the alpha-galactosidase A (*GLA*) gene; one or more of these mutations was detected in only one percent of all persons in the community and in 18% of those with increased left ventricular wall thickness.²² In a separate sequencing study in the Framingham Heart Study, at least 1 out of 64 subjects was found to carry a functional mutation in one of three genes—*NCCT*, *NKCC2* and *ROMK*—previously known to cause rare recessive diseases featuring large reductions in blood pressure.²³ These two studies underscore the potential role of low frequency variants in common conditions—left ventricular hypertrophy and hypertension—that are well established “risk factors” for HF. However, our understanding of the full role of low frequency variants in HF awaits the availability of much lower cost sequencing.

In the upcoming few years, the greatest opportunity for genomic discovery arises from the conduct of genome-wide association studies for HF and its risk factors. GWAS relate a large number of genomic sequence variants to a clinical disease or a continuous trait. To date, most GWAS have used a case-control study design. High-throughput genotyping technologies are used to assay hundreds of thousands of single-nucleotide polymorphisms (SNPs) in each subject, and agnostically compare genotype and allelic frequencies for each SNP between “cases” and “controls” to identify variants that are significantly associated with the disease or trait being studied. In the past three years, hundreds of new loci for many common diseases and traits have been identified and replicated in GWAS, leading to identification of many genes that have previously not been suspected to be related to the disease or trait under study. Of note, over a third of associated SNPs are not near protein coding regions of the genome. Although GWAS represent an important step in discovering new genome sequence variants associated with disease risk, they are also limited by their potential for false-positive and false-negative results and for biases related to selection and misclassification of participants, population substructure and genotyping errors. Therefore, replication studies in large, independent populations have become a mandatory part of the design of GWAS.²⁴

At present GWAS data for HF are very sparse, so we describe here the results of GWAS for the major risk factors that together explain a substantial proportion of HF risk—hypertension, type II diabetes mellitus, cardiac structural alterations, and prior myocardial infarction.

Hypertension

A substantial heritability of hypertension has long been observed and well characterized in the literature. In the St. Mary's study, familial aggregation of blood pressures in families with hypertensive (defined as diastolic pressure >100) and normal (defined as diastolic pressure < 85) probands was noted.²⁵ A much higher correlation for systolic and diastolic blood pressures was noted between biological siblings versus adopted siblings in the Montreal Adoption study.²⁶ The H^2 for hypertension is 30%.

hypertension with a Mendelian form of inheritance is very rare and mostly associated with disorders that affect renal handling of sodium. Glucocorticoid-remediable aldosteronism²⁷ and Liddle's syndrome²⁸ are two autosomal dominant disorders manifesting hypertension as part of their phenotype. The former is associated with increased aldosterone and sodium retention secondary to inappropriate control of aldosterone synthase by ACTH. The latter is associated with mutated sodium channel gene, leading to an increased number of sodium channels in the apical membrane and increased sodium reabsorption. Mineralocorticoid excess, secondary to 11-beta hydroxysteroid dehydrogenase mutations is an autosomal recessive condition with decreased turnover of cortisol to cortisone, thereby leading to salt retention.²⁹

The vast majority of people with hypertension have the common form, associated with polygenic influences. However, there has been little success in identifying putative genes. Candidates identified so have been poorly replicated, and most of the research has been focused on genes encoding renal sodium transport proteins (*SLC4A5*³⁰, *DRD1*³¹ etc) and elements of the renin angiotensin aldosterone system (*ACE*³², *AGTR1*³³, *REN*³⁴ etc). A major GWAS by the Wellcome Trust Case Control Consortium failed to identify any significant hypertension loci.³⁵ However, two recent GWAS have for the first time identified a total of 19 loci associated with hypertension^{36, 37} including *CYP17A1*, *CYP1A2*, *MTHFR*, *ATP2B1*, *PLEKHA7*, *CSK-ULK3*, *SH2B3* and *TBX3-TBX5*. Several loci have shown interesting pleiotropy with other phenotypes, which may potentially elevate the interest in these genes for HF. One example is *SH2B3*, which is associated with

hypertension³⁶ as well as myocardial infarction.³⁸ These findings for the first time describe the genetic architecture of hypertension and suggest some loci that may be candidates for the study of HF.

GWAS for type 2 diabetes mellitus

A number of GWAS investigating the genetic susceptibility to both type 1 and type 2 diabetes have been published recently. Loci within, or in close proximity to several genes have been consistently identified in various GWAS as conferring increased risk for type 2 diabetes, and have been replicated in various racial and ethnic groups. The genes include *KCNQ1*, *IGF2BP2*, *CDKAL1*, *CDKN2A*, *CDKN2B*, *TCF7L2*, *SLC30A8*, *HHEX*, *FTO*, *PPARG2*, and *KCNJ11*.^{39–49} The functional significance of the products of these genes and the mechanism by which altered gene products lead to diabetes has yet to be elucidated. It is worth noting that knowledge of these variants does not provide incremental information over clinical factors alone in identifying people at increased risk for type 2 diabetes; 2 studies that evaluated the incremental value of SNP information over conventional risk factors observed that the c-statistic of the models containing clinical factors improved very little by addition of genetic information.^{50, 51}

Cardiac structural alterations that predispose to heart failure

Limited data exist on the genome wide associations of cardiac structural traits (assessed by imaging). A previous report by Vasan et al⁵² from the Framingham Heart Study reported several associations with echocardiographically assessed cardiac structural traits. The top SNP associations were: for LV diastolic dimension, a SNP associated with *SLIT2* gene; for LV systolic dimension, a SNP associated with *KCNB2* gene; and for LV mass, and left atrial size, SNPs associated with *FAM5C* gene. Several other large GWAS have been combined in a consortium of multiple community based epidemiological studies, including the Framingham Heart Study, have assessed the genomic determinants of LV structure and function assessed by echocardiography and publication of the results are anticipated later in 2009.

Myocardial infarction (MI)

MI is a leading cause of HF. Common occurrence of MI does not demonstrate a Mendelian inheritance pattern. However, there are several lines of evidence confirming the existence of familial risk. Data from twin studies show an exceptionally strong association between identical twins (relative risk of 8.1 and 15 for men and women respectively if sibling experienced cardiovascular death before age 55), with less strong, but significant association between nonidentical twins (relative risk of 3.8 and 2.6 for men and women respectively).⁵³ Two previous reports from the Framingham Heart study established the increased risk for MI in people with affected parents⁵⁴ or siblings⁵⁵, with relative risks of the magnitude 1.7 to 2.0. Family history has proven to be a useful screening tool⁵⁶ to identify families at high risk for CVD.

A number of genome wide linkage and candidate gene studies reported both chromosomal loci and candidate genes with strong associations to MI and atherosclerotic CVD. Loci on chromosomes 1⁵⁷, 2^{58–60}, 3⁶¹, 5⁶², 13⁶³, 14⁶⁴, 16⁶⁵, 17⁶⁶ and X⁶⁰ have been implicated. However, loci identified through this approach have not been consistently replicated and its validity has been questioned.⁶⁷ A rare exception has been the study that identified the gene encoding the 5-lipoxygenase-activating protein (*ALOX5AP*)⁶³, which has been subsequently replicated in two other studies.^{68, 69}

A large number of candidate genes studies have been published that assessed the associations of individual genes to MI, CHD or subclinical measures of atherosclerosis.

Similar to linkage analyses, candidate gene studies have suffered from poor replication, likely secondary to genetic heterogeneity, inadequate sample size, differing patterns of expression in different population groups, false-positivity and confounding by environmental factors or population stratification. Some of the main gene variants identified by this approach are: *APOB*^{70, 71}, *APOE*^{72, 73}, *ACE* insertion/deletion^{74, 75}, *PAI-1*⁷⁶, *MTHFR*^{77–79}, *CETP*⁸⁰, *eNOS*⁸¹ and prothrombin.⁸² A comprehensive survey of candidate genes studies for MI is beyond the scope of this article.

The advent of GWAS has generated much excitement about the potential for identifying loci associated with a risk for MI. Several recent large scale GWAS reported associations with MI.^{35, 83–86} The Wellcome Trust Case Control Consortium (WTCCC) demonstrated several loci associated with MI, the principal locus being 9p21. This finding was replicated by investigators of the German MI study and in several other studies including the Framingham 100k dataset. Subsequently, the MIGen Consortium has confirmed and extended the findings of association with 9p21 SNPs in a discovery GWAS of 2,967 cases and 3,075 controls and replication in 9,746 cases and 9,746 controls.⁸⁷ Genome wide associations were found in a total of nine gene loci, including *CELSR2*, *PSRC1*, *SORT1*, *MRPS6*, *KCNE2*, *MIA3*, *PHACTR1*, *LDLR*, *CXCL12*, *PCSK9*, and *WDR12*; in addition a separate consortium reported an association of *MRAS* SNPs with MI.⁸⁸ Taken together, these loci identify genes/SNPs that are strongly and consistently associated with MI and further study is warranted to understand the role if any of these genetic variants in the etiology of HF.

Candidate gene associations with heart failure

Several genes that either influence the risk for HF⁸⁹ or modify the clinical course⁹⁰ (modifier genes) have been reported recently. Most of the genes relate to specific phenotypes described above viz. dilated, hypertrophic and restrictive cardiomyopathies, or polymorphisms in the genes encoding proteins of the rennin-angiotensin system that influence treatment effect (described below). As noted above, HF is the culmination of several types of injury and few single candidate genes that strictly influences the occurrence of the common form of HF has been identified.

GWAS for HF

Large GWAS that exclusively address the genetic susceptibility to HF are underway but have not yet been reported. The Framingham Heart Study 100K project, addressing genome wide associations for cardiovascular disease outcomes, reported the results of a relatively small GWAS on HF outcomes.⁸³ In this report, no single SNP met genome-wide significance; in additive regression models, the lowest p-value was for a SNP associated with the gene *KIAA1598* on chromosome 10 ($p = 8.8 \times 10^{-4}$), and in family based association testing models, a SNP on chromosome 5 ($p = 4.72 \times 10^{-5}$). A thought-provoking result from this report was the association with HF risk of a SNP in the ryanodine receptor [*RYR2*] gene ($p = 3.6 \times 10^{-4}$); as noted above, *RYR2* is implicated in risk for ARVC.

Future Directions for HF Genomics

In the next few years, genomic studies of HF will likely include some or all of the following strategies: initial GWAS for HF; additional larger replication studies and larger GWAS using arrays in multiple ethnic groups; studies of copy number variations; targeted and whole-genome sequencing studies; and studies using other “omic” technologies to study HF. Ultimately, refinements in the HF phenotype due to advances in imaging and biomarker science will increase the quality and diagnostic accuracy of all future genomic studies of HF.

GWAS studies in larger sample sizes

A rising trend in GWAS studies is the formation of very large international consortia to allow study of ever larger numbers of disease cases and identify the totality of genetic variation underlying disease. For example, the GIANT Consortium has accumulated data on nearly 100,000 research participants for replicated GWAS studies of obesity.⁹¹ Similar consortia are under development for other HF risk factors including diabetes mellitus and myocardial infarction and will be valuable for pooling GWAS studies of HF as well. Due to increases in statistical power, large GWAS are able to detect significant associations with lower frequency alleles that may not be noted in smaller studies and the larger studies can more reliably exclude associations. An additional advantage of very large consortia is the possibility of studying gene by environment interactions and gene by gene interactions, for which smaller studies are statistically underpowered. Modifiers of HF that will be of interest in such large studies will include HF risk factors (HT, type II Diabetes, antecedent MI, LVH), as well as lifestyle and dietary factors such as physical activity and salt intake. Ultimately, dozens to hundreds of associated genetic variants may be detected for each clinically important phenotype as larger and larger studies are conducted.

Copy number variation

Copy number polymorphisms (CNPs), small insertions or deletions in various repeat patterns, are common in the human genome and have been hypothesized to underlie common diseases. To date, CNPs have not been shown to be associated with CVD in GWAS studies. For example, there was no evidence for association of CNPs with myocardial infarction in the MIGen Consortium.⁸⁷ However, available GWAS arrays only incompletely capture the total number and extent of CNPs in the human genome, so future more comprehensive studies will be needed to assess the role of CNPs in diseases including HF. Notably, a recent candidate gene study demonstrated the association of a deletion polymorphism in *MYBPC3* with HF phenotypes.⁹² Participants with a 25-basepair deletion in this gene had a seven-fold higher risk of developing HF, and this mutation was present in 4% of populations of Indian descent. This finding represents a rare example of a consistent, replicated association with HF, and it remains to be determined whether this gene influences restrictive or dilated CM.

Targeted and whole genome sequencing

One strategy that may become mandatory for identification of the functional genetic variation underlying associations from GWAS is sequencing targeted to the chromosomal region of association. A number of the SNPs that are strongly associated with MI or other phenotypes in GWAS are in or near protein coding genes. For these loci, sequencing is often conducted in persons selected from the extremes of a phenotype (eg, with versus without HF) targeted at exons, introns and nearby regulatory regions to identify differences in the prevalence of functional genetic variations in cases versus controls. As mentioned previously, this strategy has been successful in identification of gene variants underlying left ventricular hypertrophy and hypertension.^{22, 23} However, for the substantial proportion of GWAS associations far away from any known protein-coding gene, the conduct of sequencing studies will require more detailed and complex sequencing studies. Targeted sequencing studies have been successfully employed to identify rare variants underlying Mendelian HF conditions and may well be useful to identify the important genetic variation underlying GWAS associations with common forms of HF.

More generally, the emergence of “next generation” sequencing technology and decreases in the costs of sequencing have made possible for the first time the conduct of targeted sequencing in larger numbers of subjects as well as genomewide sequencing to characterize part or all of the personal genome sequence of thousands of persons at a time.⁹³

Technological advances have allowed the conduct of high throughput, genome-wide capture of exons and other parts of the human genome.⁹⁴ Such sequencing will allow characterization of the phenotype associations with the so-called “dark matter” of the genome, the large amount of currently unsequenced genome. While technological advances may enable the sequencing of the entire human genome sequence of over 3 billion base pairs in under \$1000 in upcoming years, a more imminent and tractable sequencing goal will be the sequencing of the entirety of human exons (ie, the “exome”). Multiple exon capture technology is now available and large-scale sequencing studies are now being envisioned to conduct exome sequencing in large sample sizes, including populations containing persons with HF.⁹³

The Role of “omics” in HF research

In parallel with largescale genomic studies of HF, a number of other “omic” technologies including transcriptomics and metabolomics are now feasible and increasingly cost effective in large populations of research participants.⁹⁵ Integration of transcription information with GWAS and HF phenotypes may allow more sophisticated understanding of the specific functional genetic variation underlying HF.⁹⁶ When possible, actual heart tissue obtained via biopsy or at time of surgery may provide helpful signals when tissue is available for such uses. An additional challenge for “omic” studies is the difficulty of conducting direct studies of human heart tissue. Because actual heart tissue is usually inaccessible in healthy persons and “omic” profiling studies in diseased heart tissue may be difficult to interpret in the setting of multiple treatments.

Clinical applications of genomic information

A number of potential “personalized medicine” clinical applications may be considered once there are significant, replicated findings of common and/or lower frequency SNPs underlying HF. First, genetic risk scores may be constructed to assess the additive and incremental predictive effect of risk prediction for each associated SNP. While such a score cannot yet be constructed for the HF phenotype, initial attempts have been made to construct and assess genetic risk scores for type II diabetes mellitus⁹⁷ and for myocardial infarction.^{87, 98} For myocardial infarction, a risk score was constructed comprising nine SNPs associated in prior GWAS with adverse lipid levels; the age- and sex-adjusted genetic risk score was associated with incident MI but there was no incremental prediction over and above traditional risk factors.⁹⁸ Thus, to date there is no evidence that genetic risk scores comprised of limited numbers of SNPs will predict CVD risk over and above known clinically measurable risk factors, and a similar assessment will need to take place. Other personalized medicine applications of HF genomic studies might include the development of new HF drug targets from novel HF genes and pharmacogenetic applications, which are covered elsewhere.

Conclusion

The field of genomics has advanced rapidly since completion of the human genome sequence. While a number of novel, strongly replicated genetic discoveries have been made in the past few years using GWAS for myocardial infarction and other HF risk factors, the genomic studies of HF and left ventricular dysfunction are now underway. In the near future, it is anticipated that initial GWAS studies of HF and next step investigations, including replication studies in larger consortia and targeted resequencing studies of top loci, will be conducted in a similar manner as for GWAS studies already completed for myocardial infarction and other HF risk factors.

Reference List

1. Finishing the euchromatic sequence of the human genome. *Nature* 2004 October 21;431(7011):931–45. [PubMed: 15496913]
2. The International HapMap Project. *Nature* 2003 December 18;426(6968):789–96. [PubMed: 14685227]
3. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation* 1995 August 15;92(4):785–9. [PubMed: 7641357]
4. Codd MB, Sugrue DD, Gersh BJ, Melton LJ III. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975–1984. *Circulation* 1989 September;80(3):564–72. [PubMed: 2766509]
5. Marian AJ, Roberts R. Recent advances in the molecular genetics of hypertrophic cardiomyopathy. *Circulation* 1995 September 1;92(5):1336–47. [PubMed: 7648684]
6. Bonne G, Carrier L, Bercovici J, Cruaud C, Richard P, Hainque B, Gautel M, Labeit S, James M, Beckmann J, Weissenbach J, Vosberg HP, Fiszman M, Komajda M, Schwartz K. Cardiac myosin binding protein-C gene splice acceptor site mutation is associated with familial hypertrophic cardiomyopathy. *Nat Genet* 1995 December;11(4):438–40. [PubMed: 7493026]
7. Thierfelder L, Watkins H, MacRae C, Lamas R, McKenna W, Vosberg HP, Seidman JG, Seidman CE. Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. *Cell* 1994 June 3;77(5):701–12. [PubMed: 8205619]
8. Kimura A, Harada H, Park JE, Nishi H, Satoh M, Takahashi M, Hiroi S, Sasaoka T, Ohbuchi N, Nakamura T, Koyanagi T, Hwang TH, Choo JA, Chung KS, Hasegawa A, Nagai R, Okazaki O, Nakamura H, Matsuzaki M, Sakamoto T, Toshima H, Koga Y, Imaizumi T, Sasazuki T. Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. *Nat Genet* 1997 August;16(4):379–82. [PubMed: 9241277]
9. Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics* 1988 January;2(1):90–5. [PubMed: 3384440]
10. Bione S, Maestrini E, Rivella S, Mancini M, Regis S, Romeo G, Toniolo D. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. *Nat Genet* 1994 December;8(4):323–7. [PubMed: 7894480]
11. Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D. A novel X-linked gene, G4.5, is responsible for Barth syndrome. *Nat Genet* 1996 April;12(4):385–9. [PubMed: 8630491]
12. Olson TM, Michels VV, Thibodeau SN, Tai YS, Keating MT. Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. *Science* 1998 May 1;280(5364):750–2. [PubMed: 9563954]
13. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Muehle G, Johnson W, McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999 December 2;341(23):1715–24. [PubMed: 10580070]
14. Li D, Tapscoft T, Gonzalez O, Burch PE, Quinones MA, Zoghbi WA, Hill R, Bachinski LL, Mann DL, Roberts R. Desmin mutation responsible for idiopathic dilated cardiomyopathy. *Circulation* 1999 August 3;100(5):461–4. [PubMed: 10430757]
15. Rampazzo A, Nava A, Danieli GA, Buja G, Daliento L, Fasoli G, Scognamiglio R, Corrado D, Thiene G. The gene for arrhythmogenic right ventricular cardiomyopathy maps to chromosome 14q23–q24. *Hum Mol Genet* 1994 June;3(6):959–62. [PubMed: 7951245]
16. Beffagna G, Occhi G, Nava A, Vitiello L, Ditadi A, Basso C, Baucé B, Carraro G, Thiene G, Towbin JA, Danieli GA, Rampazzo A. Regulatory mutations in transforming growth factor-beta3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. *Cardiovasc Res* 2005 February 1;65(2):366–73. [PubMed: 15639475]

17. Baucé B, Nava A, Rampazzo A, Daliento L, Muriago M, Basso C, Thiene G, Danieli GA. Familial effort polymorphic ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy map to chromosome 1q42–43. *Am J Cardiol* 2000 March 1;85(5):573–9. [PubMed: 11078270]
18. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, Lerman BB, Markowitz SM, Ellinor PT, MacRae CA, Peters S, Grossmann KS, Drenckhahn J, Michely B, Sasse-Klaassen S, Birchmeier W, Dietz R, Breithardt G, Schulze-Bahr E, Thierfelder L. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat Genet* 2004 November;36(11):1162–4. [PubMed: 15489853]
19. Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, Nadvoretzkiy VV, DeFreitas G, Carabello B, Brandon LI, Godsel LM, Green KJ, Saffitz JE, Li H, Danieli GA, Calkins H, Marcus F, Towbin JA. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Res* 2006 September 15;99(6):646–55. [PubMed: 16917092]
20. Asimaki A, Syrris P, Wichter T, Matthias P, Saffitz JE, McKenna WJ. A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2007 November;81(5):964–73. [PubMed: 17924338]
21. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med* 2006 July 13;355(2):138–47. [PubMed: 16837677]
22. Morita H, Larson MG, Barr SC, Vasan RS, O'Donnell CJ, Hirschhorn JN, Levy D, Corey D, Seidman CE, Seidman JG, Benjamin EJ. Single-gene mutations and increased left ventricular wall thickness in the community: the Framingham Heart Study. *Circulation* 2006 June 13;113(23):2697–705. [PubMed: 16754800]
23. Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW, Levy D, Lifton RP. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008 May;40(5):592–9. [PubMed: 18391953]
24. Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF Jr, Freimer NB, Gerhard DS, Gunter C, Guttacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, Roberts J, Rotimi C, Tucker MA, Vogan KJ, Wacholder S, Wijsman EM, Winn DM, Collins FS. Replicating genotype-phenotype associations. *Nature* 2007 June 7;447(7145):655–60. [PubMed: 17554299]
25. HAMILTON M, PICKERING GW, ROBERTS JA, SOWRY GS. The aetiology of essential hypertension. 4. The role of inheritance. *Clin Sci (Lond)* 1954 May;13(2):273–304. [PubMed: 13161192]
26. Annett JL, Sing CF, Biron P, Mongeau JG. Familial aggregation of blood pressure and weight in adoptive families. II. Estimation of the relative contributions of genetic and common environmental factors to blood pressure correlations between family members. *Am J Epidemiol* 1979 October;110(4):492–503. [PubMed: 507040]
27. Lifton RP, Dluhy RG, Powers M, Rich GM, Cook S, Ulick S, Lalouel JM. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. *Nature* 1992 January 16;355(6357):262–5. [PubMed: 1731223]
28. Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, Schambelan M, Gill JR Jr, Ulick S, Milora RV, Findling JW. Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* 1994 November 4;79(3):407–14. [PubMed: 7954808]
29. White PC, Dupont J, New MI, Leiberman E, Hochberg Z, Rosler A. A mutation in CYP11B1 (Arg-448----His) associated with steroid 11 beta-hydroxylase deficiency in Jews of Moroccan origin. *J Clin Invest* 1991 May;87(5):1664–7. [PubMed: 2022736]
30. Barkley RA, Chakravarti A, Cooper RS, Ellison RC, Hunt SC, Province MA, Turner ST, Weder AB, Boerwinkle E. Positional identification of hypertension susceptibility genes on chromosome 2. *Hypertension* 2004 February;43(2):477–82. [PubMed: 14732741]
31. Sato M, Soma M, Nakayama T, Kanmatsuse K. Dopamine D1 receptor gene polymorphism is associated with essential hypertension. *Hypertension* 2000 August;36(2):183–6. [PubMed: 10948075]

32. O'Donnell CJ, Lindpaintner K, Larson MG, Rao VS, Ordovas JM, Schaefer EJ, Myers RH, Levy D. Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. *Circulation* 1998 May 12;97(18):1766–72. [PubMed: 9603529]
33. Bonnardeaux A, Davies E, Jeunemaitre X, Fery I, Charru A, Clauser E, Tiret L, Cambien F, Corvol P, Soubrier F. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. *Hypertension* 1994 July;24(1):63–9. [PubMed: 8021009]
34. Frossard PM, Lestrinant GG, Elshahat YI, John A, Obineche EN. An MboI two-allele polymorphism may implicate the human renin gene in primary hypertension. *Hypertens Res* 1998 September;21(3):221–5. [PubMed: 9786608]
35. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007 June 7;447(7145):661–78. [PubMed: 17554300]
36. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasani RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet.* 2009 May 10;
37. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der HP, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeuffer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet.* 2009 May 10;
38. Gudbjartsson DF, Bjornsdottir US, Halapi E, Helgadottir A, Sulem P, Jonsdottir GM, Thorleifsson G, Helgadottir H, Steinthorsdottir V, Stefansson H, Williams C, Hui J, Beilby J, Warrington NM, James A, Palmer LJ, Koppelman GH, Heinzmann A, Krueger M, Boezen HM, Wheatley A, Altmuller J, Shin HD, Uh ST, Cheong HS, Jonsdottir B, Gislason D, Park CS, Rasmussen LM, Porsbjerg C, Hansen JW, Backer V, Werge T, Janson C, Jonsson UB, Ng MC, Chan J, So WY, Ma R, Shah SH, Granger CB, Quyyumi AA, Levey AI, Vaccarino V, Reilly MP, Rader DJ, Williams MJ, van Rij AM, Jones GT, Trabetti E, Malerba G, Pignatti PF, Boner A, Pescollidung L, Girelli D, Olivieri O, Martinelli N, Ludviksson BR, Ludviksdottir D, Eyjolfsson GI, Arnar D, Thorgeirsson G, Deichmann K, Thompson PJ, Wjst M, Hall IP, Postma DS, Gislason T, Gulcher J, Kong A, Jonsdottir I, Thorsteinsdottir U, Stefansson K. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nat Genet* 2009 March;41(3):342–7. [PubMed: 19198610]
39. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho

- YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadowaki T, Kasuga M. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet.* 2008 August 17;
40. Sanghera DK, Ortega L, Han S, Singh J, Ralhan SK, Wander GS, Mehra NK, Mulvihill JJ, Ferrell RE, Nath SK, Kamboh MI. Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF2BP2, TCF7L2 and FTO variants confer a significant risk. *BMC Med Genet* 2008;9:59. [PubMed: 18598350]
 41. Cauchi S, Meyre D, Durand E, Proenca C, Marre M, Hadjadj S, Choquet H, De Graeve F, Gaget S, Allegaert F, Delplanque J, Permutt MA, Wasson J, Blech I, Charpentier G, Balkau B, Vergnaud AC, Czernichow S, Patsch W, Chikri M, Glaser B, Sladek R, Froguel P. Post genome-wide association studies of novel genes associated with type 2 diabetes show gene-gene interaction and high predictive value. *PLoS ONE* 2008;3(5):e2031. [PubMed: 18461161]
 42. Palmer ND, Goodarzi MO, Langefeld CD, Ziegler J, Norris JM, Haffner SM, Bryer-Ash M, Bergman RN, Wagenknecht LE, Taylor KD, Rotter JI, Bowden DW. Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. *Diabetes* 2008 April;57(4):1093–100. [PubMed: 18252897]
 43. Meigs JB, Manning AK, Fox CS, Florez JC, Liu C, Cupples LA, Dupuis J. Genome-wide association with diabetes-related traits in the Framingham Heart Study. *BMC Med Genet* 2007;8 (Suppl 1):S16. [PubMed: 17903298]
 44. Pascoe L, Tura A, Patel SK, Ibrahim IM, Ferrannini E, Zeggini E, Weedon MN, Mari A, Hattersley AT, McCarthy MI, Frayling TM, Walker M. Common variants of the novel type 2 diabetes genes CDKAL1 and HHEX/IDE are associated with decreased pancreatic beta-cell function. *Diabetes* 2007 December;56(12):3101–4. [PubMed: 17804762]
 45. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 2007 June 1;316(5829):1341–5. [PubMed: 17463248]
 46. Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson BK, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjogren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007 June 1;316(5829):1331–6. [PubMed: 17463246]
 47. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir S, Emilsson V, Ghosh S, Baker A, Snorraddottir S, Bjarnason H, Ng MC, Hansen T, Bagger Y, Wilensky RL, Reilly MP, Adeyemo A, Chen Y, Zhou J, Gudnason V, Chen G, Huang H, Lashley K, Doumatey A, So WY, Ma RC, Andersen G, Borch-Johnsen K, Jorgensen T, Vliet-Ostapchouk JV, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Rotimi C, Gurney M, Chan JC, Pedersen O, Sigurdsson G, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet* 2007 June;39(6):770–5. [PubMed: 17460697]
 48. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007 February 22;445(7130):881–5. [PubMed: 17293876]

49. Groves CJ, Zeggini E, Minton J, Frayling TM, Weedon MN, Rayner NW, Hitman GA, Walker M, Wiltshire S, Hattersley AT, McCarthy MI. Association analysis of 6,736 U.K. subjects provides replication and confirms TCF7L2 as a type 2 diabetes susceptibility gene with a substantial effect on individual risk. *Diabetes* 2006 September;55(9):2640–4. [PubMed: 16936215]
50. Lango H, Palmer CN, Morris AD, Zeggini E, Hattersley AT, McCarthy MI, Frayling TM, Weedon MN. Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. *Diabetes*. 2008 June 30;
51. van Hoek M, Dehgan A, Witteman JC, van Duijn CM, Uitterlinden AG, Oostra BA, Hofman A, Sijbrands EJ, Janssens AC. Predicting type 2 diabetes based on polymorphisms from genome wide association studies: a population-based study. *Diabetes*. 2008 August 11;
52. Vasan RS, Larson MG, Aragam J, Wang TJ, Mitchell GF, Kathiresan S, Newton-Cheh C, Vita JA, Keyes MJ, O'Donnell CJ, Levy D, Benjamin EJ. Genome-wide association of echocardiographic dimensions, brachial artery endothelial function and treadmill exercise responses in the Framingham Heart Study. *BMC Med Genet* 2007;8 (Suppl 1):S2. [PubMed: 17903301]
53. Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. *N Engl J Med* 1994 April 14;330(15):1041–6. [PubMed: 8127331]
54. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, Wilson PW, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004 May 12;291(18):2204–11. [PubMed: 15138242]
55. Murabito JM, Pencina MJ, Nam BH, D'Agostino RB Sr, Wang TJ, Lloyd-Jones D, Wilson PW, O'Donnell CJ. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *JAMA* 2005 December 28;294(24):3117–23. [PubMed: 16380592]
56. Williams RR, Hunt SC, Heiss G, Province MA, Bensen JT, Higgins M, Chamberlain RM, Ware J, Hopkins PN. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). *Am J Cardiol* 2001 January 15;87(2):129–35. [PubMed: 11152826]
57. Wang Q, Rao S, Shen GQ, Li L, Moliterno DJ, Newby LK, Rogers WJ, Cannata R, Zirzow E, Elston RC, Topol EJ. Premature myocardial infarction novel susceptibility locus on chromosome 1P34–36 identified by genomewide linkage analysis. *Am J Hum Genet* 2004 February;74(2):262–71. [PubMed: 14732905]
58. Samani NJ, Burton P, Mangino M, Ball SG, Balmforth AJ, Barrett J, Bishop T, Hall A. A genomewide linkage study of 1,933 families affected by premature coronary artery disease: The British Heart Foundation (BHF) Family Heart Study. *Am J Hum Genet* 2005 December;77(6):1011–20. [PubMed: 16380912]
59. Harrap SB, Zammit KS, Wong ZY, Williams FM, Bahlo M, Tonkin AM, Anderson ST. Genome-wide linkage analysis of the acute coronary syndrome suggests a locus on chromosome 2. *Arterioscler Thromb Vasc Biol* 2002 May 1;22(5):874–8. [PubMed: 12006406]
60. Pajukanta P, Cargill M, Viitanen L, Nuotio I, Kareinen A, Perola M, Terwilliger JD, Kempas E, Daly M, Lilja H, Rioux JD, Brettin T, Viikari JS, Ronnemaa T, Laakso M, Lander ES, Peltonen L. Two loci on chromosomes 2 and X for premature coronary heart disease identified in early- and late-settlement populations of Finland. *Am J Hum Genet* 2000 December;67(6):1481–93. [PubMed: 11078477]
61. Chiodini BD, Lewis CM. Meta-analysis of 4 coronary heart disease genome-wide linkage studies confirms a susceptibility locus on chromosome 3q. *Arterioscler Thromb Vasc Biol* 2003 October 1;23(10):1863–8. [PubMed: 12947017]
62. Hauser ER, Crossman DC, Granger CB, Haines JL, Jones CJ, Mooser V, McAdam B, Winkelmann BR, Wiseman AH, Muhlestein JB, Bartel AG, Dennis CA, Dowdy E, Estabrooks S, Eggleston K, Francis S, Roche K, Clevenger PW, Huang L, Pedersen B, Shah S, Schmidt S, Haynes C, West S, Asper D, Booze M, Sharma S, Sundseth S, Middleton L, Roses AD, Hauser MA, Vance JM, Pericak-Vance MA, Kraus WE. A genomewide scan for early-onset coronary artery disease in 438 families: the GENECARD Study. *Am J Hum Genet* 2004 September;75(3):436–47. [PubMed: 15272420]

63. Helgadottir A, Manolescu A, Thorleifsson G, Gretarsdottir S, Jonsdottir H, Thorsteinsdottir U, Samani NJ, Gudmundsson G, Grant SF, Thorgeirsson G, Sveinbjornsdottir S, Valdimarsson EM, Matthiasson SE, Johannsson H, Gudmundsdottir O, Gurney ME, Sainz J, Thorhallsdottir M, Andresdottir M, Frigge ML, Topol EJ, Kong A, Gudnason V, Hakonarson H, Gulcher JR, Stefansson K. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. *Nat Genet* 2004 March;36(3):233–9. [PubMed: 14770184]
64. Broeckel U, Hengstenberg C, Mayer B, Holmer S, Martin LJ, Comuzzie AG, Blangero J, Nurnberg P, Reis A, Riegger GA, Jacob HJ, Schunkert H. A comprehensive linkage analysis for myocardial infarction and its related risk factors. *Nat Genet* 2002 February;30(2):210–4. [PubMed: 11818963]
65. Francke S, Manraj M, Lacquemant C, Lecoecur C, Lepretre F, Passa P, Hebe A, Corset L, Yan SL, Lahmidi S, Jankee S, Gunness TK, Ramjuttun US, Balgobin V, Dina C, Froguel P. A genome-wide scan for coronary heart disease suggests in Indo-Mauritians a susceptibility locus on chromosome 16p13 and replicates linkage with the metabolic syndrome on 3q27. *Hum Mol Genet* 2001 November 15;10(24):2751–65. [PubMed: 11734540]
66. Farrall M, Green FR, Peden JF, Olsson PG, Clarke R, Hellenius ML, Rust S, Lagercrantz J, Franzosi MG, Schulte H, Carey A, Olsson G, Assmann G, Tognoni G, Collins R, Hamsten A, Watkins H. Genome-wide mapping of susceptibility to coronary artery disease identifies a novel replicated locus on chromosome 17. *PLoS Genet* 2006 May;2(5):e72. [PubMed: 16710446]
67. Altmuller J, Palmer LJ, Fischer G, Scherb H, Wjst M. Genomewide scans of complex human diseases: true linkage is hard to find. *Am J Hum Genet* 2001 November;69(5):936–50. [PubMed: 11565063]
68. Zee RY, Cheng S, Hegener HH, Erlich HA, Ridker PM. Genetic variants of arachidonate 5-lipoxygenase-activating protein, and risk of incident myocardial infarction and ischemic stroke: a nested case-control approach. *Stroke* 2006 August;37(8):2007–11. [PubMed: 16778124]
69. Kajimoto K, Shioji K, Ishida C, Iwanaga Y, Kokubo Y, Tomoike H, Miyazaki S, Nonogi H, Goto Y, Iwai N. Validation of the association between the gene encoding 5-lipoxygenase-activating protein and myocardial infarction in a Japanese population. *Circ J* 2005 September;69(9):1029–34. [PubMed: 16127181]
70. Boekholdt SM, Peters RJ, Fountoulaki K, Kastelein JJ, Sijbrands EJ. Molecular variation at the apolipoprotein B gene locus in relation to lipids and cardiovascular disease: a systematic meta-analysis. *Hum Genet* 2003 October;113(5):417–25. [PubMed: 12942366]
71. Chiodini BD, Barlera S, Franzosi MG, Beceiro VL, Intronati M, Tognoni G. APO B gene polymorphisms and coronary artery disease: a meta-analysis. *Atherosclerosis* 2003 April;167(2):355–66. [PubMed: 12818419]
72. Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med* 2004 July 20;141(2):137–47. [PubMed: 15262670]
73. Wilson PW, Schaefer EJ, Larson MG, Ordovas JM. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. *Arterioscler Thromb Vasc Biol* 1996 October;16(10):1250–5. [PubMed: 8857921]
74. Keavney B, McKenzie C, Parish S, Palmer A, Clark S, Youngman L, Delepine M, Lathrop M, Peto R, Collins R. Large-scale test of hypothesised associations between the angiotensin-converting-enzyme insertion/deletion polymorphism and myocardial infarction in about 5000 cases and 6000 controls. International Studies of Infarct Survival (ISIS) Collaborators. *Lancet* 2000 February 5;355(9202):434–42. [PubMed: 10841123]
75. Agerholm-Larsen B, Nordestgaard BG, Tybjaerg-Hansen A. ACE gene polymorphism in cardiovascular disease: meta-analyses of small and large studies in whites. *Arterioscler Thromb Vasc Biol* 2000 February;20(2):484–92. [PubMed: 10669647]
76. Boekholdt SM, Bijsterveld NR, Moons AH, Levi M, Buller HR, Peters RJ. Genetic variation in coagulation and fibrinolytic proteins and their relation with acute myocardial infarction: a systematic review. *Circulation* 2001 December 18;104(25):3063–8. [PubMed: 11748101]
77. Lewis SJ, Ebrahim S, Davey SG. Meta-analysis of MTHFR 677C->T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? *BMJ* 2005 November 5;331(7524):1053. [PubMed: 16216822]
78. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002 November 23;325(7374):1202. [PubMed: 12446535]

79. Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, Schouten EG. MTHFR 677C-->T polymorphism and risk of coronary heart disease: a meta-analysis. *JAMA* 2002 October 23;288(16):2023–31. [PubMed: 12387655]
80. Boekholdt SM, Sacks FM, Jukema JW, Shepherd J, Freeman DJ, McMahon AD, Cambien F, Nicaud V, de Grooth GJ, Talmud PJ, Humphries SE, Miller GJ, Eiriksdottir G, Gudnason V, Kauma H, Kakko S, Savolainen MJ, Arca M, Montali A, Liu S, Lanz HJ, Zwinderman AH, Kuivenhoven JA, Kastelein JJ. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: individual patient meta-analysis of 13,677 subjects. *Circulation* 2005 January 25;111(3):278–87. [PubMed: 15655129]
81. Casas JP, Bautista LE, Humphries SE, Hingorani AD. Endothelial nitric oxide synthase genotype and ischemic heart disease: meta-analysis of 26 studies involving 23028 subjects. *Circulation* 2004 March 23;109(11):1359–65. [PubMed: 15007011]
82. Burzotta F, Paciaroni K, De S, Crea VF, Maseri A, Leone G, Andreotti F. G20210A prothrombin gene polymorphism and coronary ischaemic syndromes: a phenotype-specific meta-analysis of 12 034 subjects. *Heart* 2004 January;90(1):82–6. [PubMed: 14676252]
83. Larson MG, Atwood LD, Benjamin EJ, Cupples LA, D'Agostino RB Sr, Fox CS, Govindaraju DR, Guo CY, Heard-Costa NL, Hwang SJ, Murabito JM, Newton-Cheh C, O'Donnell CJ, Seshadri S, Vasan RS, Wang TJ, Wolf PA, Levy D. Framingham Heart Study 100K project: genome-wide associations for cardiovascular disease outcomes. *BMC Med Genet* 2007;8 (Suppl 1):S5. [PubMed: 17903304]
84. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. *Science* 2007 June 8;316(5830):1488–91. [PubMed: 17478681]
85. Ozaki K, Ohnishi Y, Iida A, Sekine A, Yamada R, Tsunoda T, Sato H, Sato H, Hori M, Nakamura Y, Tanaka T. Functional SNPs in the lymphotoxin-alpha gene that are associated with susceptibility to myocardial infarction. *Nat Genet* 2002 December;32(4):650–4. [PubMed: 12426569]
86. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, König IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007 August 2;357(5):443–53. [PubMed: 17634449]
87. Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardisino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, Stoll M, Girelli D, McKeown PP, Patterson CC, Siscovick DS, O'Donnell CJ, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Melander O, Altshuler D, Ardisino D, Merlini PA, Berzuini C, Bernardinelli L, Peyvandi F, Tubaro M, Celli P, Ferrario M, Fève R, Marziliano N, Casari G, Galli M, Ribichini F, Rossi M, Bernardi F, Zonzi P, Piazza A, Mannucci PM, Schwartz SM, Siscovick DS, Yee J, Friedlander Y, Elosua R, Marrugat J, Lucas G, Subirana I, Sala J, Ramos R, Kathiresan S, Meigs JB, Williams G, Nathan DM, MacRae CA, O'Donnell CJ, Salomaa V, Havulinna AS, Peltonen L, Melander O, Berglund G, Voight BF, Kathiresan S, Hirschhorn JN, Asselta R, Duga S, Sreafico M, Musunuru K, Daly MJ, Purcell S, Voight BF, Purcell S, Nemesh J, Korn JM, McCarroll SA, Schwartz SM, Yee J, Kathiresan S, Lucas G, Subirana I, Elosua R, Surti A, Guiducci C, Gianniny L, Mirel D, Parkin M, Burt N, Gabriel SB, Samani NJ, Thompson JR, Braund PS, Wright BJ, Balmforth AJ, Ball SG, Hall AS, Schunkert H, Erdmann J, Linsel-Nitschke P, Lieb W, Ziegler A, König I, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Schunkert H, Samani NJ, Erdmann J, Ouwehand W, Hengstenberg C, Deloukas P, Scholz M, Cambien F, Reilly MP, Li M, Chen Z, Wilensky R, Matthai W, Qasim A, Hakonarson HH, Devaney J, Burnett MS, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Epstein SE, Rader DJ, Scheffold T, Berger K, Stoll M, Häge A, Girelli D, Martinelli N, Olivieri O, Corrocher R, Morgan T, Spertus JA, McKeown P, Patterson CC, Schunkert H, Erdmann E, Linsel-Nitschke P, Lieb W, Ziegler A, König IR, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Holm H, Thorleifsson

- G, Thorsteinsdottir U, Stefansson K, Engert JC, Do R, Xie C, Anand S, Kathiresan S, Ardisino D, Mannucci PM, Siscovick D, O'Donnell CJ, Samani NJ, Melander O, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Altshuler D. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet* 2009 March;41(3):334–41. [PubMed: 19198609]
88. Erdmann J, Grosshennig A, Braund PS, König IR, Hengstenberg C, Hall AS, Linsel-Nitschke P, Kathiresan S, Wright B, Tregouet DA, Cambien F, Bruse P, Aherrahrou Z, Wagner AK, Stark K, Schwartz SM, Salomaa V, Elosua R, Melander O, Voight BF, O'Donnell CJ, Peltonen L, Siscovick DS, Altshuler D, Merlini PA, Peyvandi F, Bernardinelli L, Ardisino D, Schillert A, Blankenberg S, Zeller T, Wild P, Schwarz DF, Tiret L, Perret C, Schreiber S, El Mokhtari NE, Schafer A, Marz W, Renner W, Bugert P, Kluter H, Schrezenmeier J, Rubin D, Ball SG, Balmforth AJ, Wichmann HE, Meitinger T, Fischer M, Meisinger C, Baumert J, Peters A, Ouwehand WH, Deloukas P, Thompson JR, Ziegler A, Samani NJ, Schunkert H. New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nat Genet* 2009 March;41(3):280–2. [PubMed: 19198612]
89. Severino A, Campioni M, Straino S, Salloum FN, Schmidt N, Herbrand U, Frede S, Toietta G, Di Rocco G, Bussani R, Silvestri F, Piro M, Liuzzo G, Biasucci LM, Mellone P, Feroce F, Capogrossi M, Baldi F, Fandrey J, Ehrmann M, Crea F, Abbate A, Baldi A. Identification of protein disulfide isomerase as a cardiomyocyte survival factor in ischemic cardiomyopathy. *J Am Coll Cardiol* 2007 September 11;50(11):1029–37. [PubMed: 17825711]
90. Le Corvoisier P, Park HY, Rockman HA. Modifier genes and heart failure. *Minerva Cardioangiol* 2003 April;51(2):107–20. [PubMed: 12783067]
91. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccascaccia RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P, Kuokkanen M, Kuusisto J, Laitinen J, Lakatta EG, Luan J, Luben RN, Mangino M, McArdle WL, Meitinger T, Mulas A, Munroe PB, Narisu N, Ness AR, Northstone K, O'Rahilly S, Purmann C, Rees MG, Ridderstrale M, Ring SM, Rivadeneira F, Ruukonen A, Sandhu MS, Saramies J, Scott LJ, Scuteri A, Silander K, Sims MA, Song K, Stephens J, Stevens S, Stringham HM, Tung YC, Valle TT, van Duijn CM, Vimalaswaran KS, Vollenweider P, Waeber G, Wallace C, Watanabe RM, Waterworth DM, Watkins N, Witterman JC, Zeggini E, Zhai G, Zillikens MC, Altshuler D, Caulfield MJ, Chanock SJ, Farooqi IS, Ferrucci L, Guralnik JM, Hattersley AT, Hu FB, Jarvelin MR, Laakso M, Mooser V, Ong KK, Ouwehand WH, Salomaa V, Samani NJ, Spector TD, Tuomi T, Tuomilehto J, Uda M, Uitterlinden AG, Wareham NJ, Deloukas P, Frayling TM, Groop LC, Hayes RB, Hunter DJ, Mohlke KL, Peltonen L, Schlessinger D, Strachan DP, Wichmann HE, McCarthy MI, Boehnke M, Barroso I, Abecasis GR, Hirschhorn JN. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009 January;41(1):25–34. [PubMed: 19079261]
92. Dhandapany PS, Sadayappan S, Xue Y, Powell GT, Rani DS, Nallari P, Rai TS, Khullar M, Soares P, Bahl A, Tharkan JM, Vaideeswar P, Rathinavel A, Narasimhan C, Ayapati DR, Ayub Q, Mehdi SQ, Oppenheimer S, Richards MB, Price AL, Patterson N, Reich D, Singh L, Tyler-Smith C, Thangaraj K. A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. *Nat Genet* 2009 February;41(2):187–91. [PubMed: 19151713]
93. Shendure J, Ji H. Next-generation DNA sequencing. *Nat Biotechnol* 2008 October;26(10):1135–45. [PubMed: 18846087]
94. Turner EH, Lee C, Ng SB, Nickerson DA, Shendure J. Massively parallel exon capture and library-free resequencing across 16 genomes. *Nat Methods* 2009 May;6(5):315–6. [PubMed: 19349981]
95. Samuel JL, Schaub MC, Zaugg M, Mamas M, Dunn WB, Swynghedauw B. Genomics in cardiac metabolism. *Cardiovasc Res* 2008 July 15;79(2):218–27. [PubMed: 18326557]

96. Schadt EE, Zhang B, Zhu J. Advances in systems biology are enhancing our understanding of disease and moving us closer to novel disease treatments. *Genetica* 2009 June;136(2):259–69. [PubMed: 19363597]
97. Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008 November 20;359(21):2208–19. [PubMed: 19020323]
98. Kathiresan S, Melander O, Anevski D, Guiducci C, Burt NP, Roos C, Hirschhorn JN, Berglund G, Hedblad B, Groop L, Altshuler DM, Newton-Cheh C, Orho-Melander M. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med* 2008 March 20;358(12):1240–9. [PubMed: 18354102]