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REVIEW

Implications of discoveries from genome-wide association studies in current cardiovascular practice

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Abstract

Genome-wide association studies (GWAS) have identified several genetic variants associated with coronary heart disease (CHD), and variations in plasma lipoproteins and blood pressure (BP). Loci corresponding to *CDKN2A/CDKN2B/ANRIL*, *MTHFD1L*, *CELSR2*, *PSRC1* and *SORT1* genes have been associated with CHD, and *TMEM57*, *DOCK7*, *CELSR2*, *APOB*, *ABCG5*, *HMGCR*, *TRIB1*, *FADS2/S3*, *LDLR*, *NCAN* and *TOMM40-APOE* with total cholesterol. Similarly, *CELSR2-PSRC1-SORT1*, *PCSK9*, *APOB*, *HMGCR*, *NCAN-CILP2-PBX4*, *LDLR*, *TOMM40-APOE*, and *APOC1-APOE* are associated with variations in low-density lipoprotein cholesterol levels. Altogether, forty, forty three and twenty loci have been associated with high-density lipoprotein cholesterol, triglycerides and BP phenotypes, respectively. Some of these identified loci are common for all the traits, some do not map to functional genes, and some are located in genes that encode for proteins not previously known to be involved in the biological pathway of the trait. GWAS have been successful at identifying new and unexpected genetic loci common to diseases and traits, thus rapidly providing key novel insights into disease biology. Since genotype information is fixed, with minimum biological variability, it is useful in early life risk prediction. However, these variants explain only a small proportion of the observed variance of these traits. Therefore, the utility of genetic determinants in assessing risk at later stages of life has limited immediate clinical impact. The future application of genetic screening will be in identifying risk groups early in life to direct targeted preventive measures.

Key words: Genome-wide association studies; Cardiovascular disease; Lipids; Blood pressure

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mor-

bidity and mortality globally[1,2]. There is a concerted effort to reduce this disease burden, particularly that of coronary heart disease (CHD) and cerebrovascular disease in developed countries[3-5]. These range from primary preventive strategies targeted at risk factors through acute management and secondary prevention strategies[6-8]. Kahn *et al*[9] estimated that aggressive application of nationally recommended prevention activities for CVD would potentially add approximately 224 million quality adjusted life-years to the US adult population over the next 30 years and improve the average lifespan by at least 1.3 years.

CHD is the result of a combination of genetic and environmental factors. More than 200 risk factors have been associated with CHD and, among these low-density lipoprotein cholesterol (LDL-c) and blood pressure (BP) have been shown through randomized controlled trials to be causally related to CHD. A key factor in reducing the global burden of CVD is early prediction of disease to target preventive interventions. More personalised approaches to CVD prevention are attracting increasing interest. Whilst biomarkers and quantitative traits have been extremely useful in targeting primary prevention, the recent advances in genomics offer a smart option for predicting future risk of disease very early in life using the invariant nature of a genotype throughout an individual's life-span. For example, Cohen *et al*[10] demonstrated that a genetic variant resulting in a modest 28% reduction in LDL-c from birth results in an 88% reduction in the risk of CHD. Over the last 5 years, genome-wide association studies (GWAS) have revolutionised the discovery of common genetic variants associated with a range of diseases and traits.

There are three key characteristics of a genetic variant that determine its impact on the phenotype studied - (1) the frequency of the variant; (2) the effect size of the variant on the phenotype; and (3) the number of genetic variants acting on the phenotype. The "common disease common variant" hypothesis (CD:CV) is the model invoked to explain how genes influence common traits such as lipids, coronary artery disease (CAD) and BP[11]. This model proposes, using an evolutionary paradigm, that common disease is due to allelic variants with a frequency greater than 5% in the general population and small individual effect size[12]. The CD:CV framework requires population-wide genotyping of very large numbers of common genetic variants (Single Nucleotide Polymorphisms/SNPs) to determine which variants show significant association with the phenotype studied. Technological advances now allow reliable and high-throughput genotyping of hundreds of thousands of SNPs on a genome-wide scale[13]. Such studies employ large scale association mapping using SNPs, making no assumptions about the genomic location or function of the causal variant, and test the hypothesis that allele frequency differs between individuals with differences in phenotype. In most GWAS, emphasis is given to the "*P* value" for the association of genotype with disease risk, to reduce the potential for false positive association that arises when the association of hundreds of thousands to millions of markers are tested across the whole genome. The current popular method for multiple-test correction is the frequentist approach of adjusting for a number of independent tests - based on this, a significance level of 5×10^{-8} is commonly used, in populations of European ancestry for an overall genome-wide significance threshold of 0.05, adjusted for an estimated 1 million independent SNPs in the genome by the Bonferroni method[14]. It should be noted that the Bonferroni method is a fairly conservative correction method that may increase false negative rate. Other corrections like the False Discovery Rate or permutation testing can be used to set a different threshold. In this context, it is pertinent to recognise that the *P*-value is an index of a true positive signal and does not in any way reflect the predictive potential of the associated variant. The current gold standard of validity is multiple replication in independent samples. We review the implications of positive GWAS findings in current cardiovascular practice.

GWAS AND CHD

We summarise the GWAS results of CHD from nine case-control studies and three cohort studies[15-26] (Figure 1 and Table 1). The effect sizes (OR) of susceptibility alleles were modest and ranged from 1.05-2.0. Common variants in chromosome 9p21 were implicated in nine independent case-control studies[16-23,25] and in two cohort studies[15,25]. The most replicated SNPs at chromosome 9p21 were rs0757278 and rs13333049. The loci corresponding to *MTHFD1L*, initially identified in the Wellcome Trust Case Control Consortium (WTCCC) study[17], were later replicated in the German Family MI study[18] with genome-wide statistical significance. However, it did not reach genome-wide statistical significance in the combined analysis of ten different data sets in the study by Kathiresan *et al*[21]. Genetic loci corresponding to *CELSR2*, *PSRC1* and *SORT1* on chromosome 1p13.3 are identified in three independent studies[18,20,21].

GWAS AND LIPIDS

Aulchenko *et al*[27] studied total cholesterol (TC)-associated genetic markers and identified 11 loci significantly associated with the trait (Figure 2 and Table 2): these corresponded to *TMEM57*, *DOCK7*, *CELSR2*, *APOB*, *ABCG5*, *HMGCR*, *TRIB1*, *FADS2/S3*, *LDLR*, *NCAN* and *TOMM40-APOE*. Many of these genes are also implicated in other lipid traits. After screening the genome for common variants associated with plasma lipids in > 100 000 individuals of European ancestry, Teslovich *et al*[28] identified 39 novel loci associated with TC and replicated several other loci found to be associated with lipid traits in the previous GWAS.

Table 1 Single nucleotide polymorphisms associated with coronary heart disease in genome-wide association studies

Chromosome	SNP	Position	Sample size	MAF (%)	OR (95% CI)	*P* value	Proximal gene	Ref.
1	rs646776	109620053	9746/9746	81.0	1.17 (1.11-1.24)		*CELSR2*	[18,20,21]
	rs599839	109623689	2801/4582	-	1.29 (1.18-1.40)	4.05×10^{-9}	*PSRC1*	
	rs599839	109623689	1926/2938	80.8	1.20 (1.10-1.31)	1.30×10^{-5}	*SORT1*	
1	rs11206510	55268627	25538[1]	81.0	1.15 (1.10-1.21)		*PCSK9*	[21]
1	rs17465637	220890152	9746/9746	72.0	1.13 (1.08-1.18)		*MIA3*	[18,21]
			2801/4582	-	1.20 (1.12-1.30)	1.27×10^{-6}		
2	rs6725887	203454130	9746/9746	14.0	1.17 (1.11-1.23)		*WDR12*	[21]
2	rs2943634	226776324	2801/4582	37/32	1.21 (1.03-1.30)	1.60×10^{-7}	*Intergenic*	[18]
3	rs9818870	139604812	19407/21366	17.3/15.4	1.15 (1.11-1.19)	7.44×10^{-13}	*MRAS*	[23]
6	rs12526453	13035530	25538[1]	65.0	1.12 (1.08-1.17)		*PHACTR1*	[21]
6	rs6922269	151294678	2801/4582	30.0/26.0	1.23 (1.15-1.33)	2.90×10^{-8}	*MTHFD1L*	[18]
	rs6922269	151294678	1926/2938	29.4/25.3	1.17 (1.04-1.32)	1.50×10^{-5}		
6[2]	rs2048327	160783522	4976/4383	4.1/2.1	1.82 (1.57-2.12)	4.20×10^{-15}	*SLC22A3*	[22]
	rs3127599	160827124					*LPAL2*	
	rs7767084	160882493					*LPA*	
	rs10755578	160889728						
9	rs10757278	22114477	1607/6728	51.7/45.3	1.28 (1.22-1.35)	3.60×10^{-14}	*CDKN2A*	[15,16,18,19,21,22,23,25]
	rs10757274	22086055	-	25.3/20.4	1.33 (1.23-1.47)		*CDKN2B*	
	rs1333049	22115503	875/1644	54.0/48.0	1.33 (1.18-1.51)	3.40×10^{-6}		
	rs1333049	22115503	1926/2938	55.4/47.4	1.47 (1.27-1.70)	1.16×10^{-13}	*MTAP*	
	rs1333049	22115503	12004/28949	-	1.24 (1.20-1.28)			
	-		9746/9746	56.0	1.28 (1.23-1.33)			
	rs4977574	22088574	-	-	-			
	-		19407/21366	-	-			
	-		33282	-	1.20 (1.08-1.34)[3]			
	rs1333049	22115503						
10	rs1746048	44095830	9746/9746	84.0	1.14 (1.08-1.21)		*CXCL12*	[18,21]
	rs501120	44073873	2801/4582	-/-	1.33 (1.20-1.48)	9.46×10^{-8}		
12	rs2259816	119919970	19407/21366	37.4/35.8	1.08 (1.05-1.11)		*HNF1A-C12 or f43*	[23]
16	rs4329913	55462933	18245	-	1.29 (1.02-1.63)[3]		*CETP*	[26]
	rs7202364	55342891			0.76 (0.59-0.99)[3]			
19	rs1122608	11024601	25538[1]	75.0	1.15 (1.10-1.20)		*LDLR*	[20,21]
	rs6511720	11063306	1926/2938	90.2	1.29 (1.10-1.52)	6.70×10^{-4}		
19	rs4420638	50114786	1926/2938	20.9	1.17 (1.08-1.28)	1.00×10^{-4}	*APOE/C1/C4*	[20,21]
	rs4420638	50114786	14365/30576					
21	rs9982601	34520998	25538[1]	13.0	1.28 (1.23-1.33)		*MRPS6*	[21]
							SLC5A3	
							KCNE2	

[1]WTCC and GerMIFS I and GerMIFS II were added to the total sample; [2]Haplotype CCTC; [3]Hazard ratio per allele after adjustment for age and multiple risk factors. CELSR2: Cadherin EGF LAG seven-pass G-type receptor 2; PSRC1: Proline/serine-rich coiled-coil 1; SORT1: Sortilin 1; PCSK9: Proprotein convertase subtilisin/kexin type 9; MIA3: Melanoma inhibitory activity family member 3; WDR12: WD repeat protein 12; MRAS: Ras-related protein M-Ras; PHACTR1: Phosphatase and actin regulator 1; MTHFD1L: Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like; SLC22A3: Solute carrier family 22 (extraneuronal monoamine transporter), member 3; LPAL2: Lipoprotein; Lp(a)-like 2 pseudogene; LPA: Lipoprotein Lp(a); CDKN2A: Cyclin-dependent kinase inhibitor 2A; CDKN2B: Cyclin-dependent kinase inhibitor 2B; MTAP: Methylthioadenosine phosphorylase; CXCL12: Chemokine (C-X-C motif) ligand 12; HNF1A-C12: Hepatocyte nuclear factor-1 homeobox A; CETP: Cholesteryl ester transfer protein plasma; LDLR: Low density lipoprotein receptor; APOE/C1/C4: Apolipoprotein; MRPS6: Mitochondrial ribosomal protein S6; SLC5A3: Solute carrier family 5 (sodium/myo-inositol cotransporter) member 3; KCNE2: Potassium voltage-gated channel subfamily E member 2; SNP: Single nucleotide polymorphisms; MAF: Minor allele frequency; OR: Odds ratio.

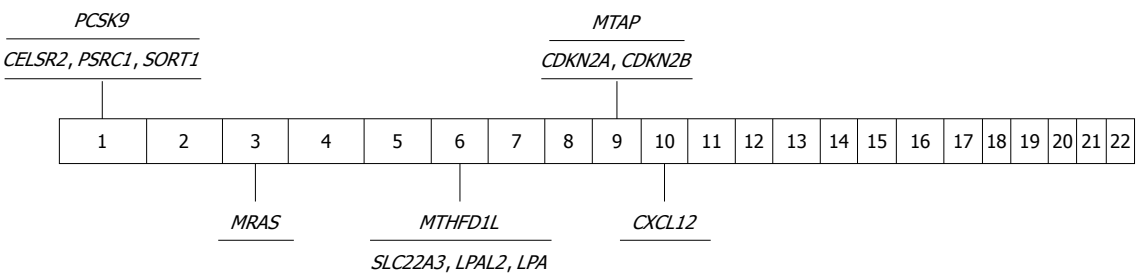

Figure 1 Significant genome-wide association study findings in coronary heart disease. CELSR2: Cadherin EGF LAG seven-pass G-type receptor 2; PSRC1: Proline/serine-rich coiled-coil 1; SORT1: Sortilin 1; PCSK9: Proprotein convertase subtilisin/kexin type 9; MRAS: Ras-related protein M-Ras; MTHFD1L: Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like; SLC22A3: Solute carrier family 22 (extraneuronal monoamine transporter), member 3; LPAL2: Lipoprotein, Lp(a)-like 2 pseudogene; LPA: Lipoprotein Lp(a); CDKN2A: Cyclin-dependent kinase inhibitor 2A; CDKN2B: Cyclin-dependent kinase inhibitor 2B; MTAP: Methylthioadenosine phosphorylase; CXCL12: Chemokine (C-X-C motif) ligand 12.

Table 2 Single nucleotide polymorphisms associated with total cholesterol identified through genome-wide association studies

Chromosome	Strongest SNP	Chromosome position	Sample size	MAF (average)	β	*P* value	Proximal gene	Ref.
1	rs10903129	25641524	22550	54	0.061	5.4×10^{-10}	*TMEM57*	[27]
1	rs1167998	62704220	17346	32	-0.073	6.4×10^{-10}	*DOCK7*	[27]
	rs108889353		19099	32	-0.079	3.7×10^{-12}		[27]
1	rs646776	109620053	17441	22	-0.128	8.5×10^{-22}	*CELSR2*	[27]
1	rs12027135	25648320	> 100000	45	-1.22	4.0×10^{-11}	*LDLRAP1*	[28]
1	rs7515577	92782026	> 100000	21	-1.18	3.0×10^{-8}	*EVI5*	[28]
1	rs2642442	219040186	> 100000	48	-1.36	5.0×10^{-14}	*IRF2BP2*	[28]
2	rs693	21085700	22500	52	-0.096	8.7×10^{-23}	*APOB*	[27]
2	rs6756629	43918594	17472	92	0.145	1.5×10^{-11}	*ABCG5*	[27]
2	rs7570971	135554376	> 100000	34	1.25	2.0×10^{-8}	*RAB3GAP1*	[28]
3	rs2290159	12603920	> 100000	22	-1.42	4.0×10^{-9}	*RAF1*	[28]
5	rs384662	35421429	20873	44	0.092	2.5×10^{-19}	*HMGCR*	[27]
	rs12916	74692295	> 100000	39	2.84	9.0×10^{-47}		[28]
5	rs6882076	156322875	> 100000	35	-1.98	7.0×10^{-28}	*TIMD4*	[28]
6	rs3177928	32520413	> 100000	16	2.31	4.0×10^{-19}	*HLA*	[28]
6	rs2814982	34654538	> 100000	11	-1.86	5.0×10^{-11}	*C6orf106*	[28]
6	rs9488822	116419586	> 100000	35	-1.18	2.0×10^{-10}	*FRK*	[28]
7	rs12670798	21573877	> 100000	23	1.43	9.0×10^{-10}	*DNAH11*	[28]
7	rs2072183	44545705	> 100000	25	2.01	3.0×10^{-11}	*NPC1L1*	[28]
8	rs6987702	126573908	17413	29	0.073	3.3×10^{-9}	*TRIB1*	[27]
8	rs2081687	59551119	> 100000	35	1.23	2.0×10^{-12}	*CYP7A1*	[28]
8	rs2737229	116717740	> 100000	30	-1.11	2.0×10^{-8}	*TRPS1*	[28]
10	rs2255141	113923876	> 100000	30	1.14	2.0×10^{-10}	*GPAM*	[28]
11	rs174570	61353788	20916	83	0.088	1.5×10^{-10}	*FADS2/3*	[27]
11	rs10128711	18589560	> 100000	28	-1.04	3.0×10^{-8}	*SPTY2D1*	[28]
11	rs7941030	122027585	> 100000	38	0.97	2.0×10^{-10}	*UBASH3B*	[28]
12	rs11065987	110556807	> 100000	42	-0.96	7.0×10^{-12}	*BRAP*	[28]
12	rs1169288	119901033	> 100000	33	1.42	1.0×10^{-14}	*HNF1A*	[28]
16	rs2000999	70665594	> 100000	20	2.34	3.0×10^{-24}	*HPR*	[28]
19	rs2228671	11071912	20910	88	0.158	9.3×10^{-24}	*LDLR*	[27]
19	rs2304130	19650528	20914	7	-0.153	2.0×10^{-15}	*NCAN*	[27]
19	rs2075650	50087459	17463	15	0.138	2.9×10^{-19}	*TOMM40-APOE*	[27]
	rs157580	50087106	20903	33	-0.09	5.1×10^{-17}		[27]
19	rs10401969	19268718	> 100000	7	-4.74	3.0×10^{-38}	*CILP2*	[28]
19	rs492602	53898229	> 100000	49	1.27	2.0×10^{-10}	*FLJ36070*	[28]
20	rs2277862		> 100000	15	-1.19	4.0×10^{-10}	*ERGIC3*	[28]
20	rs2902940	38524901	> 100000	29	-1.38	6.0×10^{-11}	*MAFB*	[28]

TMEM57: Transmembrane protein 57; DOCK7: Dedicator of cytokinesis 7; CELSR2: Cadherin, EGF LAG seven-pass G-type receptor 2; LDLRAP1: Low density lipoprotein receptor adaptor protein 1; EVI5: Ecotropic viral integration site 5; IRF2BP2: Interferon regulatory factor 2 binding protein 2; APOB: Apolipoprotein B; ABCG5: ATP-binding cassette sub-family G member 5; RAB3GAP1: RAB3 GTPase activating protein subunit 1 (catalytic); RAF1: v-raf-1 murine leukemia viral oncogene homolog 1; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; TIMD4: T-cell immunoglobulin and mucin domain containing 4; HLA: Human leukocyte antigen (HLA) complex; C6orf106: Chromosome 6 open reading frame 106; FRK: Fyn-related kinase; DNAH11: Dynein, axonemal, heavy chain 11; NPC1L1: NPC1 (Niemann-Pick disease, type C1, gene)-like 1; TRIB1: Tribbles Homolog-1 (*Trib1*); CYP7A1: Cytochrome P450, family 7, subfamily A, polypeptide 1; TRPS1: Trichorhinophalangeal syndrome 1; GPAM: Glycerol-3-phosphate acyltransferase; mitochondrial; FADS: Fatty acid desaturase; SPTY2D1: Suppressor of Ty, domain containing 1 (S. cerevisiae); UBASH3B: Ubiquitin associated and SH3 domain containing B; BRAP: BRCA1 associated protein; HNF1A: Hepatocyte nuclear factor-1 α; HPR: Haptoglobin-related protein; LDLR: Low density lipoprotein receptor; NCAN: Neurocan; TOMM40: Translocase of outer mitochondrial membrane 40 homolog; CILP2: Cartilage intermediate layer protein 2; ERGIC3: Endoplasmic reticulum-Golgi intermediate compartment protein 3; MAFB: V-maf musculoaponeurotic fibrosarcoma oncogene homolog B; SNP: Single nucleotide polymorphisms; MAF: Minor allele frequency.

Prior to the publication of the meta-analysis of blood lipids conducted by Teslovich *et al*[28], 29 loci had been found to be associated with variation in high-density lipoprotein cholesterol (HDL-c) levels[20,27-39]. Teslovich *et al*[28] identified 31 novel loci associated with HDL-c with genome-wide significance. The most commonly-replicated loci are *LPL*, *LIPC*, *CETP*, *ABCA1*, *LIPG*, *APOA1/C3/A4/A5* and *GALNT2* (Figure 3 and Table 3). The *LIPC* locus has a set of common variants nearly 50 kb upstream of the gene, strongly associated with HDL-c and appearing to be independent of previously described variants that overlap the transcribed sequence of the gene. SNPs close to the mevalonate kinase-methylmalonic aciduria cblB type (*MMAB*) locus were found to be associated with HDL-c initially by Willer *et al*[20] and later confirmed by Kathiresan *et al*[29].

GWAS have identified several genetic loci associated with LDL-c (Figure 4 and Table 4)[20,27-32,34,36,40], such as the study by Teslovich *et al*[28] which identified 22 novel and 25 previously implicated loci. *CELSR2-PSRC1-SORT1* and *PCSK9* loci on chromosome 1, *APOB*, *HMGCR*, *NCAN-CILP2-PBX4*, *LDLR*, *TOMM40-APOE*, and *APOC1-APOE* were the most commonly-replicated loci in LDL-c. Several of these loci were also associated with

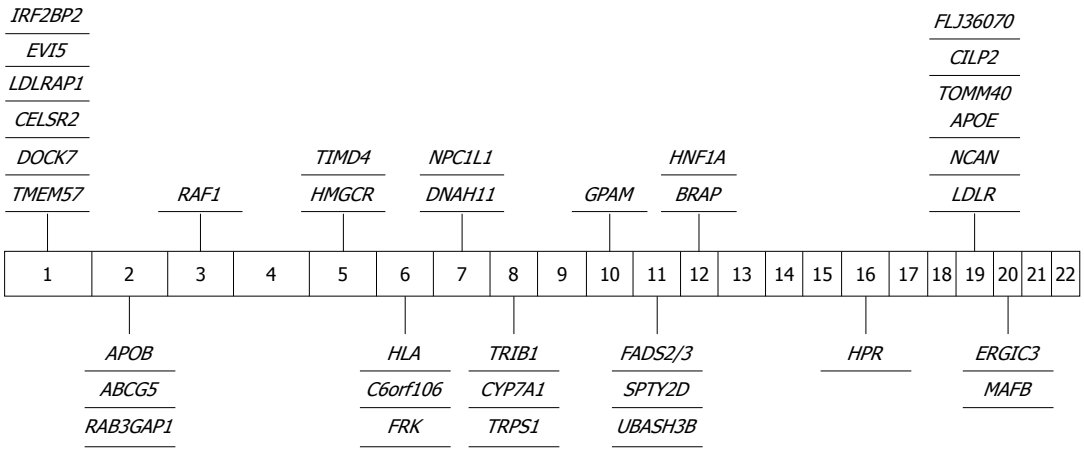

Figure 2 Significant genome-wide association study findings in total cholesterol. TMEM57: Transmembrane protein 57; DOCK7: Dedicator of cytokinesis 7; CELSR2: Cadherin, EGF LAG seven-pass G-type receptor 2; LDLRAP1: Low-density lipoprotein receptor adaptor protein 1; EVI5: Ecotropic viral integration site 5; IRF2BP2: Interferon regulatory factor 2 binding protein 2; APOB: Apolipoprotein B; ABCG5: ATP-binding cassette sub-family G member 5; RAB3GAP1: RAB3 GTPase activating protein subunit 1 (catalytic); RAF1: V-raf-1 murine leukemia viral oncogene homolog 1; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; TIMD4: T-cell immunoglobulin and mucin domain containing 4; HLA: Human leukocyte antigen (HLA) complex; C6orf106: Chromosome 6 open reading frame 106; FRK: Fyn-related kinase; DNAH11: Dynein, axonemal, heavy chain 11; NPC1L1: NPC1 (Niemann-Pick disease; type C1, gene)-like 1; TRIB1: Tribbles Homolog-1 (*Trib1*); CYP7A1: Cytochrome P450, family 7, subfamily A, polypeptide 1; TRPS1: Trichorhinophalangeal syndrome 1; GPAM: Glycerol-3-phosphate acyltransferase, mitochondrial; FADS: Fatty acid desaturase; SPTY2D1: Suppressor of Ty, domain containing 1 (S. cerevisiae); UBASH3B: Ubiquitin associated and SH3 domain containing B; BRAP: BRCA1 associated protein; HNF1A: Hepatocyte nuclear factor-1 α; HPR: Haptoglobin-related protein; LDLR: Low-density lipoprotein receptor; NCAN: Neurocan; TOMM40: Translocase of outer mitochondrial membrane 40 homolog; CILP2: Cartilage intermediate layer protein 2; ERGIC3: Endoplasmic reticulum-Golgi intermediate compartment protein 3; MAFB: V-maf musculoaponeurotic fibrosarcoma oncogene homolog B.

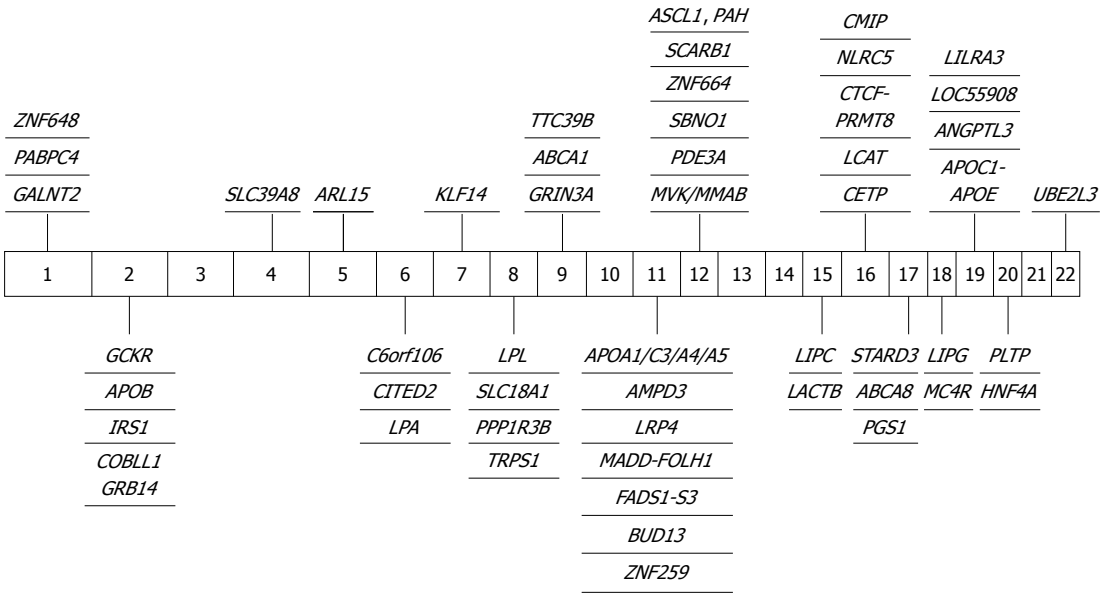

Figure 3 Significant genome-wide association study findings in high-density lipoprotein cholesterol. GALNT2: N-acetylgalactosaminyltransferase 2; PABPC4: Poly(A) binding protein; cytoplasmic 4 (inducible form); ZNF648: Zinc finger protein 648; GCKR: Glucokinase (hexokinase 4) regulator; APOB: Apolipoprotein B; IRS1: Insulin receptor substrate 1; COBLL1: COBL-like 1; GRB14: Growth factor receptor-bound protein 14; SLC39A8: Solute carrier family 39 (zinc transporter) member 8; ARL15: ADP-ribosylation factor-like 15; C6orf106: Chromosome 6 open reading frame 106; CITED2: Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain 2; LPA: Lipoprotein, Lp(a); KLF14: Kruppel-like factor 14; LPL: Lipoprotein lipase; SLC18A1: Solute carrier family 18 (vesicular monoamine) member 1; PPP1R3B: Protein phosphatase 1, regulatory (inhibitor) subunit 3B; TRPS1: Trichorhinophalangeal syndrome 1; GRIN3A: Glutamate receptor, ionotropic, N-methyl-D-aspartate 3A; ABCA1: ATP-binding cassette; sub-family A (ABC1) member 1; TTC39B: Tetratricopeptide repeat domain 39B; ABCA1: ATP-binding cassette, sub-family A (ABC1) member 1; APOA1: Apolipoprotein A-I; AMPD3: Adenosine monophosphate deaminase 3; LRP4: Low-density lipoprotein receptor-related protein 4; MADD-FOLH1: MAP-kinase activating death domain- folate hydrolase (prostate-specific membrane antigen) 1; FADS1-S3: Fatty acid desaturase 1; BUD13: BUD13 homolog; ZNF259: Zinc finger protein 259; MVK: Mevalonate kinase; MMAB: Methylmalonic aciduria (cobalamin deficiency) cblB type; PDE3A: Phosphodiesterase 3A; SBNO1: Strawberry notch homolog 1; ZNF664: Zinc finger protein 664; SCARB1: Scavenger receptor class B member 1; ASCL1: Achaete-scute complex homolog 1; PAH: Phenylalanine hydroxylase; LIPC: Hepatic lipase; LACTB: Lactamase β; CETP: Cholesteryl ester transfer protein plasma; LCAT: Lecithin-cholesterol acyltransferase; CTCF: CCCTC-binding factor (zinc finger protein); PRMT8: Protein arginine methyltransferase 8; NLRC5: NLR family CARD domain containing 5; STARD3: StAR-related lipid transfer (START) domain containing 3; ABCA8: ATP-binding cassette; sub-family A (ABC1) member 8; PGS1: Phosphatidylglycerophosphate synthase 1; LIPG: Lipase endothelial; MC4R: Melanocortin 4 receptor; APOC1: Apolipoprotein C-I; APOE: Apolipoprotein E; ANGPTL3: Angiopoietin-like 3; LILRA3: Leukocyte immunoglobulin-like receptor, subfamily A (without TM domain) member 3; PLTP: Phospholipid transfer protein; HNF4A: Hepatocyte nuclear factor 4 α; PLTP: Phospholipid transfer protein; UBE2L3: Ubiquitin-conjugating enzyme E2L 3.

Table 3 Single nucleotide polymorphisms associated with high-density lipoprotein cholesterol identified through genome-wide association studies

Chromosome	Strongest SNP	Chromosome position	Sample size	MAF (average)	Change in HDLc/β	*P* value	Proximal gene	Ref.
1	rs2144300	228 361 539	8656	40	-	6.6×10^{-7}	*GALNT2*	[20]
	rs4846914	228 362 314	19 794	40	-0.05 SD	4.0×10^{-8}		[30]
1	rs4660293	39 800 767	> 100 000	23	-0.48	4.0×10^{-10}	*PABPC4*	[28]
1	rs1689800	180 435 508	> 100 000	35	-0.47	3.0×10^{-10}	*ZNF648*	[28]
2	rs1260326	27 584 444	16 682	41	0.93%	$< 5 \times 10^{-8}$	*GCKR*	[31]
2	rs6754295	21 059 688	17 915	25	2.63 (z-sc)[1]	4.4×10^{-8}	*APOB*	[27]
2	rs2972146	226 808 942	> 100 000	37	0.46	3.0×10^{-9}	*IRS1*	[28]
2	rs10490964	51 926 908	18 245	12	1.35 mg/dL	3.9×10^{-9}	*COBLL1, GRB14*	[26]
	rs12328675	165 249 046	> 100 000	13	0.68	3.0×10^{-10}	*COBLL1*	[28]
4	rs13107325	103 407 732	> 100 000	7	-0.84	7.0×10^{-11}	*SLC39A8*	[28]
5	rs6450176	53 333 782	> 100 000	26	-0.49	5.0×10^{-8}	*ARL15*	[28]
6	rs2814944	34 660 775	> 100 000	16	-0.49	4.0×10^{-9}	*C6orf106*	[28]
6	rs605066	139 871 359	> 100 000	42	-0.39	3.0×10^{-8}	*CITED2*	[28]
6	rs1084651	161 009 807	> 100 000	16	1.95	3.0×10^{-8}	*LPA*	[28]
7	rs4731702	130 083 924	> 100 000	48	0.59	1.0×10^{-15}	*KLF14*	[28]
8	rs2083637	19 909 455	17 922	26	4.14 (z-sc)[1]	5.5×10^{-18}	*LPL*	[27]
	rs10503669	19 891 970	8656	10		3.2×10^{-10}		[20]
	rs331	19 864 685	6382	28	1.5 mg/dL	9.1×10^{-7}		[32]
	rs17482753	19 876 926	8180	-		2.8×10^{-11}		[33]
	rs326	19 863 719	10 536	22-30		1.8×10^{-8}		[35]
	rs331	19 864 685	6382	28	1.5 mg/dL	9.1×10^{-7}		[32]
	rs12678919	19 888 502	19 794	10	0.23 SD	2.0×10^{-34}		[30]
	rs301	19 861 214	5592	25	0.04	9.3×10^{-11}		[36]
8	rs3916027	19 869 148	5592	27	0.04	5.4×10^{-10}	*SLC18A1*	[36]
8	rs331	19 864 685	16 809	27	0.43%	$< 5 \times 10^{-8}$	*Intergenic, PPP1R3B, LPL*	[31]
	rs9987289	9 220 768	> 100 000	9	-1.21	6.0×10^{-25}	*PPP1R3B*	[25]
8	rs2293889	116 668 374	> 100 000	0.41	-0.44	6.0×10^{-11}	*TRPS1*	[28]
9	r1323432	103 402 758	8656	12	1.93 mg/dL	2.5×10^{-8}	*GRIN3A*	[20]
9	rs3905000	106 696 891	17 913	14	-4.37 (z-sc)[1]	8.6×10^{-13}	*ABCA1*	[27]
	rs4149268	106 687 041	8656	36		3.3×10^{-7}		[20]
	rs3890182	106 687 476	21 312	-		3.0×10^{-10}		[29]
	rs9282541	106 660 656	10 536	0-9		4.8×10^{-8}		[35]
	rs2515614	106 724 139	16 798	34	0.20%	$< 5 \times 10^{-8}$		[31]
	rs1883025	106 704 122	19 371	26	-0.08 SD	1.0×10^{-9}		[30]
9	rs471364	15 279 578	40 414	12	-0.08 SD	3.0×10^{-10}	*TTC39B*	[29]
	rs581080	15 295 378	> 100 000	18	-0.65	3.0×10^{-12}		[28]
9	rs1883025	106 704 122	> 100 000	25	-0.94	2.0×10^{-33}	*ABCA1*	[28]
11	rs12225230	116 233 840	6382	18	1.5 mg/dL	5.3×10^{-5}	*APOA1/C3/A4/A5*	[32]
	rs618923	116 159 369	12 111	25	0.30%	$< 5 \times 10^{-8}$		[31]
	rs964184	116 154 127	19 794	14	-0.17 SD	1.0×10^{-12}		[30]
	rs7350481	116 091 493	8993	28	0.62%	8.8×10^{-10}		[36]
	rs7350481	116 091 493	18 245			2.8×10^{-12}		[26]
11	rs2923084	10 345 358	> 100 000	17	-0.41	5.0×10^{-8}	*AMPD3*	[28]
11	rs3136441	46 699 823	> 100 000	15	0.78	3.0×10^{-18}	*LRP4*	[28]
11	rs7395662		17 917	39	2.82 (z-sc)[1]	6.0×10^{-11}	*MADD-FOLH1*	[27]
11	rs174547	61 327 359	40 330	33	-0.09 SD	2.0×10^{-12}	*FADS1-S3*	[30]
11	rs6589565	116 145 447	5592	7	-0.05	4.4×10^{-7}	*BUD13*	[36]
11	rs2075290	116 158 506	5592	7	-0.05	4.2×10^{-7}	*ZNF259*	[36]
12	rs2338104	108 379 551	8656	45		1.9×10^{-6}	*MVK/MMAB*	[20]
	rs2338104	108 379 551	19 793	45	-0.07 SD	1.0×10^{-10}		[30]
	rs7134594	108 484 574	> 100 000	47	-0.44	7.0×10^{-15}		[28]
12	rs7134375	20 365 025	> 100 000	42	0.40	4.0×10^{-8}	*PDE3A*	[28]
12	rs4759375	122 362 191	> 100 000	6	0.86	7.0×10^{-9}	*SBNO1*	[28]
12	rs4765127	123 026 120	> 100 000	34	0.44	3.0×10^{-10}	*ZNF664*	[28]
12	rs838880	123 827 546	> 100 000	31	0.61	3.0×10^{-14}	*SCARB1*	[28]
12	rs1818702	102 047 685	16 844	29	0.22%	$< 5 \times 10^{-8}$	*Intergenic, ASCL1, PAH*	[31]
15	rs1532085	56 470 658	19 736	41	5.03 (z-sc)[1]	9.7×10^{-36}	*LIPC*	[27]
	rs4115041	121 186 681	8656	33		2.8×10^{-9}		[20]
	rs1532085	56 470 658	6382	37	1.8 mg/dL	1.3×10^{-10}		[32]
	rs1800588	56 510 967	21 312	-		2.0×10^{-32}		[29]
	rs11858164	56 530 023	10 536	27-55		7.0×10^{-8}		[35]
	rs1532085	56 470 658	6382	37	1.8 mg/dL	1.3×10^{-10}		[32]
	rs1800588	56 510 967	16 811	22	0.60%	$< 5 \times 10^{-8}$		[31]
	rs10468017	56 465 804	19 794	30	0.10 SD	8.0×10^{-23}		[30]
	rs1077834	56 510 771	5987	49	1.00%	1.3×10^{-14}		[36]

	rs1077834	56510771	18245			1.4×10^{-23}		[26]
	rs261342	56518445	5592	22	0.03	6.3×10^{-8}		[36]
	rs1532085	56470658	> 100000	39	1.45	3.0×10^{-96}		[28]
15	rs2652834	61183920	> 100000	20	-0.39	9.0×10^{-9}	*LACTB*	[28]
16	rs1800775	55552737	2623	47		2.5×10^{-13}	*CETP*	[28]
	rs1532624	55562980	19674	43	8.24 (z-sc)[1]	9.4×10^{-94}		[27]
	rs3764261	55550825	8656	31	2.42 mg/dL	2.8×10^{-19}		[20]
	rs3764261	55550825	6382	31	4.0 mg/dL	1.0×10^{-41}		[32]
	rs1800775	55552737	2758	49	2.6 mg/dL	3.0×10^{-13}		[29]
	rs1800775	55552737	1643	47	3.99 mg/dL	6.1×10^{-15}		[33]
	rs9989419	55542640	8216	-		8.5×10^{-27}		[33]
	rs7205804	55562390	10536	37-50		4.7×10^{-47}		[36]
	rs3764261	55550825	6382	31	4.0 mg/dL	1.0×10^{-41}		[32]
	rs1800775	55552737	16779	49	2.50%	$< 5 \times 10^{-8}$		[31]
	rs3764261	55550825	3228	-	6.2 mg/dL	3.4×10^{-12}		[39]
	rs3764261	55550825	18245			3.7×10^{-93}		[26]
	rs173539	55545545	19794	32	0.25 SD	4.0×10^{-75}		[30]
	rs3764261	55550825	5987	21	2.11%	4.8×10^{-29}		[37]
	rs3764261	55550825	18245	30-48		3.7×10^{-93}		[27]
	rs17231506	55552029	5592	32	0.07	2.3×10^{-36}		[36]
	rs3764261	55550825	> 100000	32	3.39	7.0×10^{-380}		[28]
16	rs255052	66582496	8656	17		1.5×10^{-6}	*LCAT*	[20]
	rs255052	66582496	8656 + 4534	-		1.2×10^{-7}		[20]
	rs2271293	66459571	31946	11	0.07 SD	9.0×10^{-13}		[30]
	rs16942887	66485543	> 100000	12	1.27	8.0×10^{-33}		[28]
16	rs2271293	66459571	17910	13	4.99 (z-sc)[1]	8.3×10^{-16}	*CTCF-PRMT8*	[27]
16	rs289743	55575297	5592	31	0.03	8.6×10^{-9}	*NLRC5*	[36]
16	rs2925979	80092291	> 100000	30	-0.45	2.0×10^{-11}	*CMIP*	[28]
17	rs11869286	35067382	> 100000	34	-0.48	1.0×10^{-13}	*STARD3*	[28]
17	rs4148008	64386889	> 100000	32	-0.42	2.0×10^{-10}	*ABCA8*	[28]
17	rs4129767	73915579	> 100000	49	-0.39	8.0×10^{-9}	*PGS1*	[28]
18	rs4939883	45421212	16258	17	-3.98 (z-sc)[1]	1.6×10^{-11}	*LIPG*	[27]
	rs2156552	45435666	8656	16		8.4×10^{-7}		[20]
	rs2156552	45435666	21312	-		2.0×10^{-7}		[29]
	rs4939883	45421212	16648	16	0.22%	$< 5 \times 10^{-8}$		[31]
	rs4939883	45421212	19785	17	-0.14 SD	7.0×10^{-15}		[30]
	rs4939883	45421212	18245			1.4×10^{-9}		[26]
	rs7241918	45414951	> 100000	17	-1.31	3.0×10^{-49}		[28]
18	rs12967135	56000003	> 100000	23	-0.42	7.0×10^{-9}	*MC4R*	[28]
19	rs769449	50101842	16728	12	0.30%	$< 5 \times 10^{-8}$	*APOC1-APOE*	[31]
			18245			2.6×10^{-11}		[26]
19	rs2967605	8375738	35151	16	-0.12 SD	1.0×10^{-8}	*ANGPTL3*	[30]
	rs7255436	8339196	> 100000	47	-0.45	3.0×10^{-8}		[28]
19	rs737337	11208493	> 100000	8	-0.64	3.0×10^{-9}	*LOC55908*	[28]
19	rs386000	59484573	> 100000	20	0.83	4.0×10^{-16}	*LILRA3*	[28]
20	rs6065906	43987422	16810	48	0.40%	$< 5 \times 10^{-8}$	*PLTP*	[31]
			18245			1.9×10^{-14}		[26]
20	rs1800961	42475778	30714	3	-0.19 SD	8.0×10^{-10}	*HNF4A*	[30]
	rs1800961	42475778	> 100000	3	-1.88	1.0×10^{-15}		[28]
20	rs7679	44009909	40248	19	-0.07 SD	4.0×10^{-9}	*PLTP*	[30]
	rs6065906	43987422	> 100000	18	-0.93	2.0×10^{-22}		[28]
22	rs181362	20262068	> 100000	20	-0.46	1.0×10^{-8}	*UBE2L3*	[28]

[1]z-sc: the ENGAGE consortium provided the effect size on the z-scale. GALNT2: N-acetylgalactosaminyltransferase 2; PABPC4: Poly(A) binding protein, cytoplasmic 4 (inducible form); ZNF648: Zinc finger protein 648; GCKR: Glucokinase (hexokinase 4) regulator; APOB: Apolipoprotein B; IRS1: Insulin receptor substrate 1; COBLL1: COBL-like 1; GRB14: Growth factor receptor-bound protein 14; SLC39A8: Solute carrier family 39 (zinc transporter) member 8; ARL15: ADP-ribosylation factor-like 15; C6orf106: Chromosome 6 open reading frame 106; CITED2: Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain 2; LPA: Lipoprotein, Lp(a); KLF14: Kruppel-like factor 14; LPL: Lipoprotein lipase; SLC18A1: Solute carrier family 18 (vesicular monoamine) member 1; PPP1R3B: Protein phosphatase 1, regulatory (inhibitor) subunit 3B; TRPS1: Trichorhinophalangeal syndrome 1; GRIN3A: Glutamate receptor, ionotropic, N-methyl-D-aspartate 3A; ABCA1: ATP-binding cassette, sub-family A (ABC1) member 1; TTC39B: Tetratricopeptide repeat domain 39B; ABCA1: ATP-binding cassette, sub-family A (ABC1) member 1; APOA1: Apolipoprotein A-I; AMPD3: Adenosine monophosphate deaminase 3; LRP4: Low density lipoprotein receptor-related protein 4; MADD-FOLH1: MAP-kinase activating death domain- folate hydrolase (prostate-specific membrane antigen) 1; FADS1-S3: Fatty acid desaturase 1; BUD13: BUD13 homolog; ZNF259: Zinc finger protein 259; MVK: Mevalonate kinase; MMAB: Methylmalonic aciduria (cobalamin deficiency) cblB type; PDE3A: Phosphodiesterase 3A; SBNO1: Strawberry notch homolog 1; ZNF664: Zinc finger protein 664; SCARB1: Scavenger receptor class B member 1; ASCL1: Achaete-scute complex homolog 1; PAH: Phenylalanine hydroxylase; LIPC: Hepatic lipase; LACTB: Lactamase β; CETP: Cholesteryl ester transfer protein plasma; LCAT: Lecithin-cholesterol acyltransferase; CTCF: CCCTC-binding factor (zinc finger protein); PRMT8: Protein arginine methyltransferase 8; NLRC5: NLR family CARD domain containing 5; STARD3: StAR-related lipid transfer (START) domain containing 3; ABCA8: ATP-binding cassette; sub-family A (ABC1) member 8; PGS1: Phosphatidylglycerophosphate synthase 1; LIPG: Lipase endothelial; MC4R: Melanocortin 4 receptor; APOC1: Apolipoprotein C-I; APOE: Apolipoprotein E; ANGPTL3: Angiopoietin-like 3; LILRA3: Leukocyte immunoglobulin-like receptor, subfamily A (without TM domain) member 3; PLTP: Phospholipid transfer protein; HNF4A: Hepatocyte nuclear factor 4 α; PLTP: Phospholipid transfer protein; UBE2L3: Ubiquitin-conjugating enzyme E2L 3; SNP: Single nucleotide polymorphisms; MAF: Minor allele frequency. HDLc: high-density lipoprotein cholesterol.

Table 4 Single nucleotide polymorphisms associated with low-density lipoprotein cholesterol identified through genome-wide association studies

Chromosome	Strongest SNP	Chromosome position	Sample size	MAF (average)	β	*P* value	Proximal gene	Ref.
1	rs1167998	62704220	12685	22	-0.155	7.8×10^{-23}	*PSRC1, CELSR2, SORT1*	[27]
	rs646776	109620053	6382	22	-	4.9×10^{-19}		[32]
	rs599839	109623689	1636	24	-	1.1×10^{-7}		[34]
	rs602633	109623034	8589	20	-	4.8×10^{-14}		[20]
	rs646776	109620053	16791	22	-0.04	$< 5 \times 10^{-8}$	*CELSR2*	[31]
	rs646776	109620053	21312	24	-0.16	5×10^{-42}	*PSRC1*	[29]
	rs12740374	109619113	19648	21	-0.23	2.0×10^{-42}		[30]
	rs599839	109623689	11685	21	-0.05	1.7×10^{-15}		[40]
	rs646776	109620053	4337	21	-0.16	4.3×10^{-9}		[40]
	rs12740374	109619113	5592	21	-0.15	1.8×10^{-9}	*SORT1*	[36]
	rs646776	109620053	5592	22	-0.14	3.8×10^{-8}		[36]
	rs629301	109619829	> 100000	22	-5.65	1.0×10^{-170}		[28]
1	rs11591147	55278235	16826	2	-0.12	$< 5 \times 10^{-8}$	*PCSK9*	[31]
	rs11591147	55278235	12167	2	-0.13	$< 5 \times 10^{-8}$		[31]
	rs11591147	55278235	21312	1	-0.26	2.0×10^{-24}		[30]
	rs11206510	55268627	19394			3.5×10^{-11}		[20]
	rs11206510	55268627	19629	19	-0.09	4.0×10^{-8}		[30]
	rs11591147	55278235	5592	2	-0.55	9.3×10^{-12}		[36]
	rs2479409	55277238	> 100000	30	2.01	2.0×10^{-28}		[28]
2	rs693	21085700	2601	22		7.1×10^{-7}	*APOB*	[38]
	rs562338	21141826	1636 + 2631	17		8.6×10^{-13}		[34]
	rs515135	21139562	8589	83		3.1×10^{-14}		[20]
	rs562338	21141826	8589 + 10849			5.6×10^{-22}		[20]
	rs693	21085700	16112	52	-0.098	3.6×10^{-17}		[28]
	rs506585	21250687	6382	20	-4.6	9.3×10^{-9}		[32]
	rs506585	21250687	16842	20	-0.04	$< 5 \times 10^{-8}$		[31]
	rs693	21085700	21312	48	0.12	1.0×10^{-21}		[29]
	rs515135	21139562	19648	20	-0.16	5.0×10^{-29}		[30]
	rs562338	21141826	11685	20	-0.04	1.4×10^{-9}		[40]
	rs1713222	21124828	4337	16	-0.17	1.0×10^{-8}		[40]
	rs562338	21141826	5592	18	-0.18	1.2×10^{-11}		[36]
	rs1367117	21117405	> 100000	30	4.05	4.0×10^{-114}		[28]
2	rs6756629	43918594	12706	92	0.157	2.6×10^{-10}	*ABCG5*	[27]
2	rs6544713	43927385	23456	32	0.15	2×10^{-20}	*ABCG8*	[30]
	rs4299376	43926080	> 100000	30	2.75	2.0×10^{-47}	*ABCG5/8*	[28]
2	rs780094	27594741	16841	40	0.03	$< 5 \times 10^{-8}$	*GCKR*	[31]
5	rs1501908	156330747	27280	37	-0.07	1×10^{-11}	*TIMD4-HAVCR1*	[30]
5	rs3846662	74686840	16135	44	0.079	1.5×10^{-11}	*HMGCR*	[27]
	rs12654264	74684359	2758 + 18554	39	0.1	1.0×10^{-20}		[29]
	rs3846663	74691482	19648	38	0.07	8.0×10^{-12}		[30]
	rs12654264	74684359	5592	38	0.11	5.8×10^{-8}		[36]
6	rs3757354	88570980	> 100000	22	-1.43	1.0×10^{-11}	*MYLIP*	[28]
6	rs1800562	26201120	> 100000	6	-2.22	6.0×10^{-10}	*HFE*	[28]
6	rs1564348	160498850	> 100000	17	-0.56	2.0×10^{-17}	*LPA*	[28]
7	rs12670798	21573877	12695	24	0.089	6.1×10^{-9}	*DNAH11*	[27]
7	rs4731702	130083924	16747	49	-0.02	$< 5 \times 10^{-8}$	*KLF14*	[31]
8	rs6982636	126548497	16798	47	-0.02	$< 5 \times 10^{-8}$	*TRIB1*	[31]
8	rs11136341	145115531	> 100000	40	1.4	4.0×10^{-13}	*PLEC1*	[28]
9	rs9411489	135144821	> 100000	20	2.24	6.0×10^{-13}	*ABO*	[28]
11	rs174570	61353788	16153	83	0.11	4.4×10^{-13}	*FADS2/3*	[31]
11	rs3135506	116167617	16837	6	-0.13	$< 5 \times 10^{-8}$	*APOA1-A5*	[31]
	rs2072560	116167036	5592	6	0.22	2.4×10^{-7}		[36]
11	rs11220462	125749162	> 100000	14	1.95	1.0×10^{-15}	*ST3GAL4*	[28]
12	rs7307277	123041109	16804	34	-0.02	$< 5 \times 10^{-8}$	*CCDC92/DNAH10/ZNF664*	[31]
12	rs2650000	119873345	39340	36	0.07	2.0×10^{-8}	*HNF1A*	[30]
14	rs8017377	51667587	> 100000	47	1.14	5.0×10^{-11}	*NYNRIN*	[28]
16	rs708272	55553789	16843	43	-0.04	$< 5 \times 10^{-8}$	*CETP*	[31]
	rs17231506	55552029	5592	32	-0.11	5.0×10^{-7}		[36]
17	rs7206971	42780114	> 100000	49	0.78	2.0×10^{-8}	*OSBPL7*	[28]
19	rs16996148	19519472	21312	10	-0.1	3×10^{-8}	*NCAN, CILP2, PBX4*	[29]
	rs2228603	19190924	8589	7		1.8×10^{-7}		[20]
	rs16996148	19519472	19394			2.7×10^{-9}		[20]
	rs10401969	19268718	19648	6	-0.05	2.0×10^{-8}		[30]
19	rs688	11088602	4267	45		7.3×10^{-7}	*LDLR*	[34]
	rs6511720	11063306	8589	9		6.8×10^{-10}		[20]

	rs6511720	11063306	19394			4.2×10^{-23}		[20]
	rs2228671	11071912	16148	82	0.136	4.2×10^{-14}		[27]
	rs6511720	11063306	6382	12	-7.7	5.2×10^{-15}		[32]
	rs6511720	11063306	16843	12	-0.04	$< 5 \times 10^{-8}$		[31]
	rs6511720	11063306	21312	10	-0.26	2×10^{-51}		[29]
	rs6511720	11063306	19648	10	-0.26	2.0×10^{-26}		[30]
	rs2228671	11071912	4337	12	-0.18	1.1×10^{-8}		[40]
	rs17248720	11059187	5592	13	-0.31	7.8×10^{-25}		[36]
	rs6511720	11063306	> 100000	11	6.99	4.0×10^{-117}		[28]
19	rs2075650	50087459	12697	15	0.16	9.3×10^{-19}	*TOMM40-APOE*	[27]
	rs157580	50087106	16160	68	-0.111	2.1×10^{-19}		[27]
	rs2075650	50087459	4337	13	0.23	7.1×10^{-14}		[40]
	rs2075650	50087459	5592	14	0.23	1.1×10^{-14}		[36]
19	rs4420638	50114786	2601	22		3.4×10^{-13}	*APOC1-APOE*	[38]
	rs4420638	50114786	4267	19		8.3×10^{-14}		[34]
	rs4420638	50114786	8589	12		1.5×10^{-21}		[20]
	rs4420638	50114786	19394			3.0×10^{-43}		[20]
	rs4803750	49939467	6382	7	-9.6	3.6×10^{-14}		[32]
	rs4803750	49939467	16616	7	-9.3	$< 5 \times 10^{-8}$		[32]
	rs4420638	50114786	21312	20	0.19	1.0×10^{-60}		[29]
	rs4420638	50114786	11881	16	0.29	4.0×10^{-27}		[30]
	rs4420638	50114786	11685	18	0.06	1.2×10^{-20}	*APOC2*	[40]
	rs12721046	50113094	5592	15	0.21	7.6×10^{-14}		[36]
	rs12721109	50139061	5592	2	-0.54	5.1×10^{-14}		[36]
	rs4420638	50114786	> 100000	17	7.14	9.0×10^{-147}	*APOE*	[28]
19	rs10402271	50021054	11685	33	0.03	4.1×10^{-8}	*BCAM*	[40]
	rs4605275	50030333	4337	31	-0.13	4.7×10^{-8}		[40]
19	rs4803750	49939467	4337	7	-0.28	2.4×10^{-11}	*BCL3*	[40]
	rs1531517	49934013	5592	7	-0.22	5.3×10^{-8}		[36]
19	rs10402271	50021054	5592	33	0.15	2.1×10^{-12}	*PVRL2*	[36]
20	rs6065906	43987422	16843	48	0.02	$< 5 \times 10^{-8}$	*PLPT*	[31]
20	rs6102059	38662198	28895	32	-0.06	4.0×10^{-9}	*MAFB*	[30]
20	rs6029526	39106032	> 100000	47	1.39	4.0×10^{-19}	*TOP1*	[28]

β: Estimated mean; CELSR2: Cadherin EGF LAG seven-pass G-type receptor 2; PSRC1: Proline/serine-rich coiled-coil 1; SORT1: Sortilin 1; PCSK9: Proprotein convertase subtilisin/kexin type 9; APOB: Apolipoprotein B; ABCG: ATP-binding cassette sub-family G; GCKR: Glucokinase (hexokinase 4) regulator; TIMD4: T-cell immunoglobulin and mucin domain containing 4; HAVCR1: Hepatitis A virus cellular receptor 1; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; MYLIP: Myosin regulatory light chain interacting protein; HFE: Human hemochromatosis; LPA: Lipoprotein, Lp(a); DNAH11: Dynein axonemal heavy chain 11; KLF14: Kruppel-like factor 14; TRIB1: Tribbles homolog 1; PLEC1: Plectin; ABO: ABO blood group (transferase A, α 1-3-N-acetylgalactosaminyltransferase, transferase B, α 1-3-galactosyltransferase); FADS: Fatty acid desaturase; APOA1: Apolipoprotein A1; ST3GAL4: ST3 β-galactoside α-2,3-sialyltransferase 4; CCDC92: Coiled-coil domain containing 92; DNAH10: Dynein axonemal heavy chain 10; ZNF664: Zinc finger protein 664; HNF1A: HNF1 homeobox A; NYNRIN: NYN domain and retroviral integrase containing; CETP: Cholesteryl ester transfer protein plasma; OSBPL7: Oxysterol binding protein-like 7; NCAN: Nucleoporin 214 kDa; CILP2: Cartilage intermediate layer protein 2; PBX4: Pre-B-cell leukemia homeobox 4; LDLR: Low density lipoprotein receptor; TOMM40: Translocase of outer mitochondrial membrane 40 homolog; APOE: Apolipoprotien E; APOC2: Apolipoprotein C-II; APOE: Apolipoprotein E; BCAM: Basal cell adhesion molecule; BCL3: B-cell CLL/lymphoma 3; PVRL2: Poliovirus receptor-related 2 (herpesvirus entry mediator B); PLPT: Proteolipid protein; MAFB: V-maf musculoaponeurotic fibrosarcoma oncogene homolog B; TOP1: Topoisomerase (DNA) 1; SNP: Single nucleotide polymorphisms; MAF: Minor allele frequency.

CHD in the WTCCC study[17].

In total, 43 different loci have been found to be associated with triglycerides (TAG) in GWAS (Figure 5 and Table 5). SNPs in proximity to *ANGPTL3*, *APOB*, *GCKR*, *MLXIPL*, *LPL*, *TRIB1*, *APOA1/A4/A5/C3*, and *NCAN-CILP2-PBX4* have been associated with TAG in several GWAS.

GWAS AND BP

In 2007, the Framingham Heart Study[41] reported on 1327 individuals whose BP had been sampled longitudinally in the Framingham Community project. In the same year, the WTCCC[17] reported results from 2000 Northern European subjects with HTN. Although a few SNPs did reach a statistical significance of $P < 10^{-5}$, none of them achieved genome-wide significance ($P < 5 \times 10^{-8}$). The most significant GWAS findings in blood pressure are summarized in table 6 and figure 6[42-50].

The global BPgen consortium[42] studied 34433 subjects of European ancestry, subsequently followed up the findings with direct genotyping of 71225 individuals of European ancestry and 12889 individuals of Indian Asian ancestry and conducted a joint analysis. They identified an association between systolic or diastolic BP (SBP/DBP) and common variants in eight regions near the *CYP17A1* (intergenic *CNNM2/NT5C2*), *CYP1A2* (intron *CSK*), *FGF5*, *SH2B3* (intron *ATXN2*), *MTHFR*, c10orf107, *ZNF652* and intron *PLCD3*. Furthermore, three of these common variants (*MTHFR*, *CYP17A1* and *CYP17A2* or *CSK*) were associated with HTN ($P < 5 \times 10^{-8}$). The CHARGE consortium study ($n = 29136$)

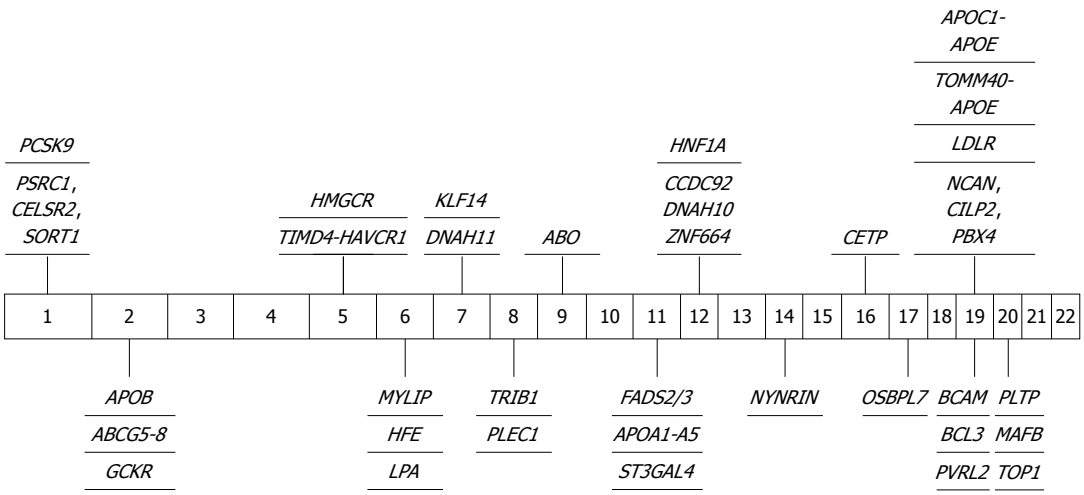

Figure 4 Significant genome-wide association study findings in low-density lipoprotein cholesterol. CELSR2: Cadherin EGF LAG seven-pass G-type receptor 2; PSRC1: Proline/serine-rich coiled-coil 1; SORT1: Sortilin 1; PCSK9: Proprotein convertase subtilisin/kexin type 9; APOB: Apolipoprotein B; ABCG: ATP-binding cassette sub-family G; GCKR: Glucokinase (hexokinase 4) regulator; TIMD4: T-cell immunoglobulin and mucin domain containing 4; HAVCR1: Hepatitis A virus cellular receptor 1; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; MYLIP: Myosin regulatory light chain interacting protein; HFE: Human hemochromatosis; LPA: Lipoprotein, Lp(a); DNAH11: Dynein axonemal heavy chain 11; KLF14: Kruppel-like factor 14; TRIB1: Tribbles homolog 1; PLEC1: Plectin; ABO: ABO blood group (transferase A, α 1-3-N-acetylgalactosaminyltransferase, transferase B, α 1-3-galactosyltransferase); FADS: Fatty acid desaturase; APOA1: Apolipoprotien A1; ST3GAL4: ST3 β-galactoside α-2;3-sialyltransferase 4; CCDC92: Coiled-coil domain containing 92; DNAH10: Dynein axonemal heavy chain 10; ZNF664: Zinc finger protein 664; HNF1A: HNF1 homeobox A; NYNRIN: NYN domain and retroviral integrase containing; CETP: Cholesteryl ester transfer protein plasma; OSBPL7: Oxysterol binding protein-like 7; NCAN: Nucleoporin 214kDa; CILP2: Cartilage intermediate layer protein 2; PBX4: Pre-B-cell leukemia homeobox 4; LDLR: Low-density lipoprotein receptor; TOMM40: Translocase of outer mitochondrial membrane 40 homolog; APOE: Apolipoprotein E; APOC2: Apolipoprotein C-II; BCAM: Basal cell adhesion molecule; BCL3: B-cell CLL/lymphoma 3; PVRL2: Poliovirus receptor-related 2 (herpesvirus entry mediator B); PLPT: Proteolipid protein; MAFB: V-maf musculoaponeurotic fibrosarcoma oncogene homolog B; TOP1: Topoisomerase (DNA) 1.

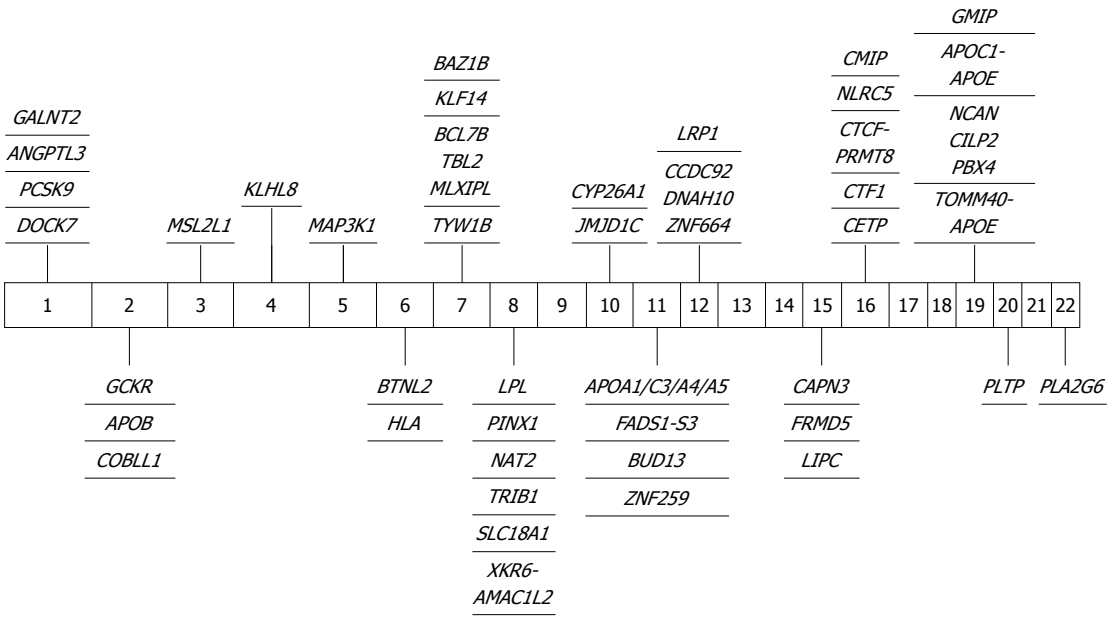

Figure 5 Significant genome-wide association study findings in triglycerides. DOCK7: Dedicator of cytokinesis 7; PCSK9: Proprotein convertase subtilisin/kexin type 9; GALNT2: N-acetylgalactosaminyltransferase 2; ANGPTL3: Angiopoietin-like 3; APOB: Apolipoprotien B; GCKR: Glucokinase (hexokinase 4) regulator; COBLL1: COBL-like 1; MSL2L1: Male-specific lethal 2 homolog; KLHL8: Kelch-like 8; MAP3K1: Mitogen-activated protein kinase kinase kinase 1; BTNL2: Butyrophilin-like 2 (MHC class II associated); HLA: Major histocompatibility complex; TYW1B: tRNA-yW synthesizing protein 1 homolog B; TBL2: Transducin (β)-like 2; BCL7B: B-cell CLL/lymphoma 7B; TBL2: Transducin (β)-like 2; MLXIPL: MLX interacting protein-like; KLF14: Kruppel-like factor 14; BAZ1B: Bromodomain adjacent to zinc finger domain 1B; PINX1: PIN2/TERF1 interacting, telomerase inhibitor 1; NAT2: N-acetyltransferase 2 (arylamine N-acetyltransferase); LPL: Lipoprotein lipase; PP1R3B: Protein phosphatase 1, regulatory (inhibitor) subunit 3B; TRIB1: Tribbles homolog 1; SLC18A1: Solute carrier family 18 (vesicular monoamine) member 1; XKR6: XK Kell blood group complex subunit-related family member 6; AMAC1L2: Acyl-malonyl condensing enzyme 1-like 2; JMJD1C: Jumonji domain containing 1C; CYP26A1: Cytochrome P450 family 26 subfamily A polypeptide 1; APOA1: Apolipoprotein A-I; FADS: Fatty acid desaturase; CCDC92: Coiled-coil domain containing 92; DNAH10: Dynein axonemal heavy chain 10; ZNF664: Zinc finger protein 664; LRP1: Low density lipoprotein receptor-related protein 1; CAPN3: Calpain 3, (p94); FRMD5: FERM domain containing 5; LIPC: Hepatic lipase; CTF1: Cardiotrophin 1; CETP: Cholesteryl ester transfer protein plasma; TOMM40: Translocase of outer mitochondrial membrane 40 homolog; APOE: Apolipoprotein E; NCAN: Nucleoporin 214kDa; CILP2: Cartilage intermediate layer protein 2; PBX4: Pre-B-cell leukemia homeobox 4; GMIP: GEM interacting protein; PLPT: Palmitoyl-protein thioesterase 1; PLA2G6: Phospholipase A2, group VI (cytosolic; calcium-independent).

Table 5 Single nucleotide polymorphisms associated with triglycerides identified through genome-wide association studies

Chromosome	Strongest SNP	Studies	Sample size	MAF (average)	β	*P* value	Proximal gene	Ref.
1	rs1167998	62704220	14268	32	-0.091	2.0×10^{-12}	*DOCK7*	[27]
	rs10889353	62890784	14337	32	-0.085	8.2×10^{-11}		[27]
1	rs11591147	55278235	16826	2	-0.09	$< 5 \times 10^{-8}$	*PCSK9*	[31]
1	rs12042319	62822407	4267	34		3.2×10^{-7}	*ANGPTL3*	[34]
	rs10889353	62890784	16831	33	-0.03	$< 5 \times 10^{-8}$		[31]
	rs10889353	62890784	8993	14	-0.13	2.0×10^{-9}		[37]
	rs12130333	62964365	21312	22	-0.11	2.0×10^{-8}		[29]
	rs10889353	62890784	19834	33	-0.05	3.0×10^{-7}		[30]
	rs1748195	62822181	18243			1.7×10^{-10}		[20]
	rs2131925	62798530	> 100000	32	-4.94	9.0×10^{-43}		[28]
1	rs4846914	228362314	21312	40	0.08	7.0×10^{-15}	*GALNT2*	[28]
2	rs6754295	21059688	14338	25	-0.077	2.5×10^{-8}	*APOB*	[27]
	rs673548	21091049	12694	76	0.086	1.1×10^{-8}		[27]
	rs673548	21091049	16797	21	-0.04	$< 5 \times 10^{-8}$		[31]
	rs693	21085700	21312	48	0.12	1.0×10^{-21}		[29]
	rs7557067	21061717	19840	22	-0.08	9.0×10^{-12}		[30]
	rs1042034	21078786	> 100000	22	-5.99	1.0×10^{-45}		[28]
2	rs780094	27594741	2659	35		3.7×10^{-8}	*GCKR*	[38]
	rs780094	27594741	4267	39		8.1×10^{-14}		[34]
	rs1260326	27584444	8684	40		1.5×10^{-15}		[20]
	rs780094	27594741	18243			6.1×10^{-32}		[20]
	rs780094	27594741	17790	63	-0.103	3.1×10^{-20}		[27]
	rs1260326	27584444	6382	41	0.07	1.3×10^{-16}		[32]
	rs1260326	27584444	16650	41	0.07	$< 5 \times 10^{-8}$		[31]
	rs1260326	27584444	8993	45	-0.101	1.1×10^{-11}		[37]
	rs780094	27594741	21312	34	0.13	3.0×10^{-14}		[29]
	rs1260326	27584444	19840	45	0.12	2.0×10^{-31}		[30]
	rs1260326	27584444	5592	40	0.06	1.8×10^{-7}		[36]
	rs1260326	27584444	> 100000	41	8.76	6.0×10^{-133}		[28]
2	rs10195252	165221337	> 100000	40	-2.01	2.0×10^{-10}	*COBLL1*	[28]
3	rs645040	137409312	> 100000	22	-2.22	3.0×10^{-8}	*MSL2L1*	[28]
4	rs442177	88249285	> 100000	41	-2.25	9.0×10^{-12}	*KLHL8*	[28]
5	rs9686661	55897543	> 100000	20	2.57	1.0×10^{-10}	*MAP3K1*	[28]
6	rs2076530	32471794	16829	43	0.03	$< 5 \times 10^{-8}$	*BTNL2*	[31]
6	rs2247056	31373469	> 100000	25	-2.99	2.0×10^{-15}	*HLA*	[28]
7	rs13238203	71767603	> 100000	4	-7.91	1.0×10^{-9}	*TYW1B*	[28]
7	rs17145738	72620810	2758 + 18554	13	-0.14	7.0×10^{-22}	*BCL7B, TBL2, MLXIPL TBL2*	[29]
	rs11974409	72627326	5592	20	-0.08	5.7×10^{-9}	*MLXIPL*	[36]
	rs10551921	107998852	5592	20	-0.08	1.3×10^{-8}		[36]
7	rs2240466	72494205	12680	87	0.137	1.1×10^{-12}	*MLXIPL*	[27]
	rs11974409	72627326	16839	19	-0.04	$< 5 \times 10^{-8}$		[31]
	rs714052	72502805	19840	12	-0.16	3.0×10^{-15}		[30]
	rs17145738	72620810	18243			2.0×10^{-12}		[20]
	rs17145738	72620810	> 100000	12	-9.32	6.0×10^{-58}		[28]
7	rs4731702	130083924	16714	49	-0.03	$< 5 \times 10^{-8}$	*KLF14*	[31]
7	rs17145713	72542746	5592	20	-0.09	5.3×10^{-10}	*BAZ1B*	[36]
8	rs11776767	10721339	> 100000	37	2.01	1.0×10^{-8}	*PINX1*	[28]
8	rs1495741	18317161	> 100000	22	2.85	5.0×10^{-14}	*NAT2*	[28]
8	rs2083637	19909455	14344	26	-0.107	1.0×10^{-14}	*LPL*	[27]
	rs10096633	19875201	12708	88	0.174	1.9×10^{-18}		[27]
	rs12678919	19888502	19840	10	-0.25	2.0×10^{-41}		[30]
	rs10096633	19875201	8993	12	-0.169	9.3×10^{-14}		[37]
	rs331	19864685	5592	25	-0.08	1.7×10^{-11}		[36]
	rs12678919	19888502	> 100000	12	-13.64	2.0×10^{-115}		[28]
8	rs17482753	19876926	2652	11		4.9×10^{-7}	*LPL*	[38]
	rs17482753	19876926	1636	10		1.2×10^{-9}		[34]
	rs17482753	19876926	1636 + 2631			5.2×10^{-15}		[34]
	rs6993414	19947198	8684	46		1.4×10^{-13}		[20]
	rs10503669	19891970	4267			3.9×10^{-22}		[20]
	rs328	19864004	6382	11	-0.09	4.7×10^{-11}	*Intergenic, PPP1R3B, LPL*	[32]
	rs331	19864685	6382	28	-0.06	1.7×10^{-9}		[32]
	rs328	19864685	16812	11	-0.09	$< 5 \times 10^{-8}$	*LPL*	[31]
	rs328	19864004	21242	9	-0.19	2.0×10^{-28}		[29]
8	rs6982636	126548497	16765	47	-0.03	$< 5 \times 10^{-8}$	*TRIB1*	[31]
	rs17321515	12655591	21242	49	-0.08	4.0×10^{-17}		[29]
	rs2954029	126560154	8684	56		2.8×10^{-8}		[20]

	rs17321515	12655591	14176			7.0×10^{-13}		[20]
	rs2954029	126560154	19840	44	-0.11	3.0×10^{-19}		[30]
	rs2954029	126560154	> 100000	47	-5.64	3.0×10^{-55}		[28]
8	rs3916027	19869148	5592	27	-0.08	1.0×10^{-10}	*SLC18A1*	[36]
8	rs7819412	11082571	33336	48	-0.04	3.0×10^{-8}	*XKR6-AMAC1L2*	[30]
10	rs10761731	64697616	> 100000	43	-2.38	3.0×10^{-12}	*JMJD1C*	[28]
10	rs2068888	94829632	> 100000	46	-2.28	2.0×10^{-8}	*CYP26A1*	[28]
11	rs12272004	116108934	12622	7	-0.181	5.4×10^{-13}	*APO (A1/A4/A5/C3)*	[27]
	rs6589566	116157633	1636	6		1.5×10^{-11}		[34]
	rs6589566	116157633	1636 + 2631			3.7×10^{-12}		[34]
	rs964184	116154127	8684	12		1.5×10^{-16}		[20]
	rs12286037	116157417	18422			1.0×10^{-26}		[20]
	rs3135506	116167617	6382	6	0.13	5.5×10^{-12}		[32]
	rs662799	116168917	6382	6	0.14	2.9×10^{-15}		[32]
	rs3135506	116167617	16804	6	0.14	$< 5 \times 10^{-8}$		[31]
	rs7350481	116091493	8993	43	0.24	1.4×10^{-49}		[37]
	rs28927680	116124283	21312	7	0.26	2.0×10^{-17}		[29]
	rs964184	116154127	19840	14	0.3	4.0×10^{-62}		[30]
	rs651821	116167789	5592	6	0.21	8.8×10^{-21}	*APOA1*	[36]
	rs964184	116154127	> 100000	13	16.95	7.0×10^{-240}		[28]
11	rs174547	61327359	38846	33	0.06	2.0×10^{-14}	*FADS1-S3*	[30]
	rs174546	61326406	> 100000	34	3.82	5.0×10^{-24}		[28]
11	rs6589565	116145447	5592	7	0.19	4.5×10^{-20}	*BUD13*	[36]
11	rs2075290	116158506	5592	7	0.19	6.6×10^{-20}	*ZNF259*	[36]
12	rs7307277	123041109	16771	34	-0.04	$< 5 \times 10^{-8}$	*CCDC92/DNAH10/ ZNF664*	[31]
12	rs11613352	-	> 100000	23	-2.7	4.0×10^{-10}	*LRP1*	[28]
15	rs2412710	40471079	> 100000	2	7	2.0×10^{-8}	*CAPN3*	[28]
15	rs2929282	42033223	> 100000	5	5.13	2.0×10^{-11}	*FRMD5*	[28]
15	rs4775041	56461987	8684	67		7.3×10^{-5}	*LIPC*	[20]
	rs4775041	56461987	17104			1.6×10^{-8}		[20]
16	Rs11649653	30825988	> 100000	40	-2.13	3.0×10^{-8}	*CTF1*	[28]
16	rs1800775	55552737	16779	49	-0.03	$< 5 \times 10^{-8}$	*CETP*	[31]
19	rs157580	50087106	16160	33	-0.069	1.2×10^{-8}	*TOMM40-APOE*	[27]
	rs439401	50106291	11885	68	0.086	1.8×10^{-9}		[27]
19	rs16996148	19519472	21312	10	-0.1	4.0×10^{-9}	*NCAN, CILP2, PBX4*	[29]
	rs10401969	19268718	8684	8		2.3×10^{-7}		[20]
	rs16996148	19519472	18391			2.5×10^{-9}		[20]
	rs17216525	46471516	19840	7	-0.11	4.0×10^{-11}		[30]
	rs12610185	19582722	5592	9	-0.1	5.6×10^{-7}		[36]
19	rs439401	50106291	16638	35	-0.04	$< 5 \times 10^{-8}$	*APOC1-APOE*	[31]
	rs439401	50106291	> 100000	36	-5.5	1.0×10^{-30}	*APOE*	[28]
19	rs2304128	19607151	5592	9	-0.1	3.2×10^{-7}	*GMIP*	[36]
20	rs6065906	43987422	16810	48	0.04	$< 5 \times 10^{-8}$	*PLPT*	[31]
	rs7679	44009909	38561	19	0.07	7.0×10^{-11}		[30]
22	rs5756931	36875979	> 100000	40	-1.54	4.0×10^{-8}	*PLA2G6*	[28]

β: Estimated mean; DOCK7: Dedicator of cytokinesis 7; PCSK9: Proprotein convertase subtilisin/kexin type 9; GALNT2: N-acetylgalactosaminyltransferase 2; ANGPTL3: Angiopoietin-like 3; APOB: Apolipoprotein B; GCKR: Glucokinase (hexokinase 4) regulator; COBLL1: COBL-like 1; MSL2L1: Male-specific lethal 2 homolog; KLHL8: Kelch-like 8; MAP3K1: Mitogen-activated protein kinase kinase kinase 1; BTNL2: Butyrophilin-like 2 (MHC class II associated); HLA: Major histocompatibility complex; TYW1B: tRNA-yW synthesizing protein 1 homolog B; TBL2: Transducin (β)-like 2; BCL7B: B-cell CLL/lymphoma 7B; TBL2: Transducin (β)-like 2; MLXIPL: MLX interacting protein-like; KLF14: Kruppel-like factor 14; BAZ1B: Bromodomain adjacent to zinc finger domain 1B; PINX1: PIN2/TERF1 interacting, telomerase inhibitor 1; NAT2: N-acetyltransferase 2 (arylamine N-acetyltransferase); LPL: Lipoprotein lipase; PP1R3B: Protein phosphatase 1, regulatory (inhibitor) subunit 3B; TRIB1: Tribbles homolog 1; SLC18A1: Solute carrier family 18 (vesicular monoamine) member 1; XKR6: XK Kell blood group complex subunit-related family member 6; AMAC1L2: Acyl-malonyl condensing enzyme 1-like 2; JMJD1C: Jumonji domain containing 1C; CYP26A1: Cytochrome P450 family 26 subfamily A polypeptide 1; APOA1: Apolipoprotein A-I; FADS: Fatty acid desaturase; CCDC92: Coiled-coil domain containing 92; DNAH10: Dynein axonemal heavy chain 10; ZNF664: Zinc finger protein 664; LRP1: Low density lipoprotein receptor-related protein 1; CAPN3: Calpain 3, (p94); FRMD5: FERM domain containing 5; LIPC: Hepatic lipase; CTF1: Cardiotrophin 1; CETP: Cholesteryl ester transfer protein plasma; TOMM40: Translocase of outer mitochondrial membrane 40 homolog; APOE: Apolipoprotein E; NCAN: Nucleoporin 214 kDa; CILP2: Cartilage intermediate layer protein 2; PBX4: Pre-B-cell leukemia homeobox 4; GMIP: GEM interacting protein; PLPT: Palmitoyl-protein thioesterase 1; PLA2G6: Phospholipase A2, group VI (cytosolic, calcium-independent); SNP: Single nucleotide polymorphisms; MAF: Minor allele frequency.

identified 13, 20 and 10 SNPs for SBP, DBP and HTN respectively[43].

In a joint meta-analysis of CHARGE consortium data with BPgen consortium data (n = 34433)[43], four CHARGE loci attained genome-wide significance for SBP (*ATP2B1*, *CYP17A1*, *PLEKHA7*, *SH2B3*), six for DBP (*ATP2B1*, *CACNB2*, *CSK-ULK3*, *SH2B3*, *TBX3-TBX5*, *ULK4*) and one for HTN (*ATP2B1*). The KORA study by Org *et al*[48] in a South German Cohort identified a SNP upstream of T-cadherin adhesion molecule (*CDH13*) gene on chromosome 16 (rs11646213) as significantly associated with HTN at a genome-wide level. Finally, in a

Table 6 Single nucleotide polymorphisms associated with hypertension and blood pressure in genome-wide association studies

Chr	SNP	Position	Ancestry	N (discovery)	Phenotype	Risk allele	Risk allele frequency	OR/β	*P*	Nearest gene	Ref.
1	rs17367504	11785365	E	34433	SBP	G	0.14	-0.85	2×10^{-13}	*MTHFR, CLCN6, NPPA, NPPB, AGTRAP*	[42,43]
2	rs6749447	168749632	E	542	SBP	G	0.28	1.90	8×10^{-5}	*STK39*	[47]
3	rs9815354	41887655	E	29136	DBP	A	0.17	0.49	3×10^{-9}	*ULK4*	[42,43]
4	rs16998073	81403365	E	34433	DBP	T	0.21	0.50	1×10^{-21}	*FGF5, PRDM8, C4orf22*	[42,43]
4	rs991316	100541468	AA	1017	SBP	T	0.45	1.62	5×10^{-6}	*ADH7*	[44]
10	rs11014166	18748804	E	29136	DBP	A	0.66	0.37	1×10^{-8}	*CACNB2*	[42,43]
10	rs1530440	63194597	E	34433	DBP	T	0.19	-0.39	1×10^{-9}	*C10orf107, TMEM26, RTKN2, RHOBTB1, ARID5B, CYP17A1*	[42,43]
10	rs1004467	104584497	E	29136	SBP	A	0.90	1.05	1×10^{-10}	*TMEM26, RTKN2, RHOBTB1, ARID5B, CYP17A1*	[42,43]
10	rs11191548	104836168	E	34433	SBP	T	0.91	1.16	3×10^{-7}	*CYP17A1, AS3MT, CNNM2, NT5C2*	[42,43]
11	rs381815	16858844	E	29136	SBP	T	0.26	0.65	2×10^{-9}	*PLEKHA7*	[42,43]
12	rs17249754	88584	EA	8842	SBP, DBP	A	0.37	1.06	9×10^{-7}	*ATP2B1*	[49]
12	rs2681472	88533090	E	29136	SBP, DBP, HTN	A	0.83	0.50	2×10^{-9}	*ATP2B1*	[42,43]
12	rs2681492,	88537220	E	29136	SBP, DBP, HTN	T	0.80	0.85	4×10^{-11}	*ATP2B1*	[42,43]
12	rs3184504	110368991	E	29136	SBP, DBP	T	0.49	0.48	3×10^{-14}	*ATXN2, SH2B3*	[42,43]
12	rs653178	110492139	E	34433	DBP	T	0.53	-0.46	3×10^{-18}	*ATXN2, SH2B3*	[42,43]
12	rs2384550	113837114	E	29136	DBP	A	0.35	0.43	4×10^{-8}	*TBX3, TBX5*	[42,43]
15	rs1550576	56000706	AA	1017	SBP	C	0.86	1.92	3×10^{-6}	*ALDH1A2*	[44]
15	rs1378942	72865396	E	34433	DBP	C	0.36	0.43	1×10^{-23}	*CSK, CYP1A1, CYP1A2, LMAN1L, CPLX3, ARID3B, ULK3*	[42,43]
15	rs6495122	72912698	E	29136	DBP	A	0.42	0.40	2×10^{-10}	*CSK, CYP1A1, CYP1A2, LMAN1L, CPLX3, ARID3B, ULK3*	[42,43]
16	rs13333226	20273155	E	3320	HTN	A	0.81	1.15	4×10^{-11}	*UMOD*	[50]
16	rs11646213	81200152	E	1977	HTN	T	0.60	1.28	8×10^{-6}	*CDH13*	[48]
17	rs12946454	40563647	E	34433	SBP	T	0.28	0.57	1×10^{-8}	*PLCD3, ACBD4, HEXIM1, HEXIM2*	[42,43]
17	rs16948048	44795465	E	34433	DBP	G	0.39	0.31	5×10^{-9}	*ZNF652, PHB*	[42,43]

E: European; AA: African American; EA: East Asians; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HTN: Hypertension; ACBD4: Acyl-CoA binding domain containing 4; ADH7: Alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide; AGTRAP: Angiotensin II receptor-associated protein; ALDH1A2: Aldehyde dehydrogenase 1 family, member A2; ARID5B: AT rich interactive domain 5B (MRF1-like); AS3MT: Arsenic (+3 oxidation state) methyltransferase; ATP2B1: ATPase; Ca^{++} transporting; plasma membrane 1; ATXN2: Ataxin 2; C10orf107: Chromosome 10 open reading frame 107; C4orf22: Chromosome 4 open reading frame 22; CACNB2: Calcium channel, voltage-dependent, β 2 subunit; CDH13: Cadherin 13, H-cadherin (heart); CLCN6: Chloride channel 6; CNNM2: Cyclin M2; CPLX3: Complexin 3; CSK: C-src tyrosine kinase; CYP17A1: Cytochrome P450, family 17, subfamily A, polypeptide 1; CYP1A1: Cytochrome P450; family 1, subfamily A, polypeptide 1; CYP1A2: Cytochrome P450, family 1, subfamily A, polypeptide 2; FGF5: Fibroblast growth factor 5; HEXIM1: Hexamethylene bis-acetamide inducible 1; HEXIM2: Hexamthylene bis-acetamide inducible 2; LMAN1L: Lectin, mannose-binding, 1 like; MTHFR: Methylenetetrahydrofolate reductase (NAD(P)H); NPPA: Natriuretic peptide A; NPPB: Natriuretic peptide B; NT5C2: 5'-nucleotidase, cytosolic II; PHB: Prohibitin; PLCD3: Phospholipase C, Δ 3; PLEKHA7: Pleckstrin homology domain containing, family A member 7; PRDM8: PR domain containing 8; RHOBTB1: Rho-related BTB domain containing 1; RTKN2: Rhotekin 2; SH2B3: SH2B adaptor protein 3; STK39: Serine threonine kinase 39; TBX3: T-box 3; TBX5: T-box 5; TMEM26: Transmembrane protein 26; ULK3: Unc-51-like kinase 3 (C. elegans); ULK4: Unc-51-like kinase 4 (C. elegans); UMOD: Uromodulin, ZNF652: Zinc finger protein 652; SNP: Single nucleotide polymorphisms; OR: Odds ratio.

population of African origin, Adeyemo *et al*[44] identified four common variants (*MYLIP*, chr 6; *YWHAZ*, chr 8; *IPO7*, chr 11 and *SLC24A4*, chr 14) associated with SBP with genome-wide significance.

Wang *et al*[47] identified *STK39*, *SPAK* (STE20/SPS1-related proline and alanine rich kinase; a serine/threonine kinase) with a *P* value of 1.6×10^{-7} in an Amish cohort. Several other studies also identified potentially important genetic loci associated with BP traits with borderline genome-wide significance. These include *ATP2B1*[43,51] (ATPase, Ca^{++} transporting, plasma membrane 1) on chromosome 12, *FOXD3*[41] (fork head box D3) on chromosome 1, *CCNG1* (cyclin G1)[48] on chromosome 5, *BCAT1* (branched chain aminotransferase 1, cytosolic)[17] on chromosome 12, *ATXN2* (ataxin 2)[42,43] on chromosome 12 and *TBX3* (T-box3)[43] on chromosome 12 (Figure 6

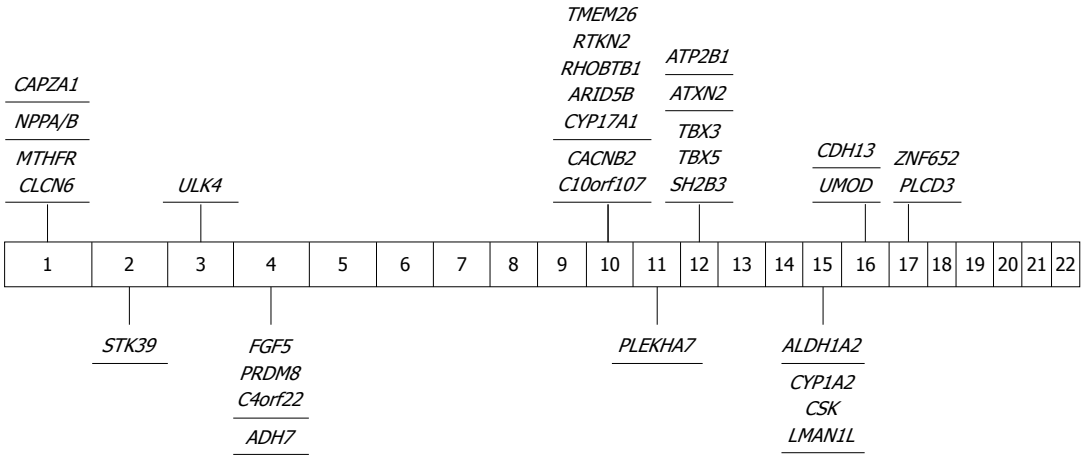

Figure 6 Significant genome-wide association study findings in blood pressure. ACBD4: Acyl-CoA binding domain containing 4; ADH7: Alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide; AGTRAP: Angiotensin II receptor-associated protein; ALDH1A2: Aldehyde dehydrogenase 1 family, member A2; ARID5B: AT rich interactive domain 5B (MRF1-like); AS3MT: Arsenic (+3 oxidation state) methyltransferase; ATP2B1: ATPase, Ca^{++} transporting; plasma membrane 1; ATXN2: Ataxin 2; C10orf107: Chromosome 10 open reading frame 107; C4orf22: Chromosome 4 open reading frame 22; CACNB2: Calcium channel, voltage-dependent, β 2 subunit; CDH13: Cadherin 13, H-cadherin (heart); CLCN6: Chloride channel 6; CNNM2: Cyclin M2; CPLX3: Complexin 3; CSK: C-src tyrosine kinase; CYP17A1: Cytochrome P450, family 17, subfamily A; polypeptide 1; CYP1A1: Cytochrome P450, family 1, subfamily A, polypeptide 1; CYP1A2: Cytochrome P450, family 1, subfamily A, polypeptide 2; FGF5: Fibroblast growth factor 5; HEXIM1: Hexamethylene bis-acetamide inducible 1; HEXIM2: Hexamthylene bis-acetamide inducible 2; LMAN1L: Lectin, mannose-binding, 1 like; MTHFR: Methylenetetrahydrofolate reductase (NAD(P)H); NPPA: Natriuretic peptide A; NPPB: Natriuretic peptide B; NT5C2: 5'-nucleotidase, cytosolic II; PHB: Prohibitin; PLCD3: Phospholipase C, Δ 3; PLEKHA7: Pleckstrin homology domain containing, family A member 7; PRDM8: PR domain containing 8; RHOBTB1: Rho-related BTB domain containing 1; RTKN2: Rhotekin 2; SH2B3: SH2B adaptor protein 3; STK39: Serine threonine kinase 39; TBX3: T-box 3; TBX5: T-box 5; TMEM26: Transmembrane protein 26; ULK3: Unc-51-like kinase 3 (C. elegans); ULK4: Unc-51-like kinase 4 (C. elegans); UMOD: Uromodulin; ZNF652: Zinc finger protein 652.

and Table 6). However, none of these loci were replicated in other studies. Using an extreme case-control design, Padmanabhan *et al*[50] identified a novel HTN locus on chromosome 16 in the promoter region of uromodulin (UMOD; rs13333226, combined P value 3.6×10^{-11}). The minor G allele of this SNP is associated with a lower risk of HTN [OR (95% CI): 0.87 (0.84-0.91)], reduced urinary UMOD excretion and increased estimated glomerular filtration rate (3.6 mL/min per minor-allele, $P = 0.012$), and borderline association with renal sodium balance.

CLINICAL IMPLICATIONS

GWAS are a useful tool in the identification of new and unexpected genetic loci of common diseases and traits, thus providing key novel insights into disease biology. But the clinical utility of these discoveries is negligible at this stage. The comparatively small numbers of variants which have been successfully replicated in several independent studies explain only a small proportion of the observed variation of these traits and explain in aggregate less than 20% of disease heritability. For example, the loci underpinning LDL-C levels[28] and BP account for < 20% of the variance of these quantitative traits. The variants associated with CHD increase disease risk by up to 20% per allele[51,52]. Next generation sequencing is now used to study low-frequency and rare variants that may potentially explain some of the missing heritabilities; however it is likely that studies designed to test for gene-environment interactions and gene-gene interactions may hold the answer. There were attempts to develop genetic profiles using the results from GWAS studies, but these have very limited value in personalised risk prediction as the genotype-phenotype effect sizes are very small. In the few studies that have evaluated the ability of a panel of genetic markers to discriminate CHD cases, the area under the receiver operating characteristic curve has been small indicating that conventional risk factors and family history are better at predicting risk and the incremental advantage of adding genetic markers is negligible. A few studies have attempted reclassification based on incorporation of SNPs from GWAS of CAD, lipids, *etc*.[52-58], and while they showed some improvement in net reclassification, the interpretation of these are still controversial and not translatable into general use[59]. Many companies are providing direct-to-consumer genetic tests that provide a "genetic risk profile" for an individual using risk alleles of small-to-moderate effects despite the clinical utility of genetic screening not being established. None of the major healthcare providers in Europe and USA have adopted these tests for CHD risk prediction, and the FDA has advised that direct-to-consumer genetic tests should be considered to be medical devices requiring FDA approval for commercial use. The future application of genetic screening will be in identifying risk groups early in life to direct targeted preventive measures and potentially pharmacogenetic tests to identify those at higher risk for adverse events. While technology is not a barrier to achieving this, the discovery, evaluation and deployment of these tests will require the same standards as non-genetic tests[60].

REFERENCES

1 **World Health Organization.** The World Health Report,

2002: reducing risks, promoting healthy life. Geneva, 2002.
2 **Ezzati M**, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; **360**: 1347-1360
3 **Unal B**, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; **109**: 1101-1107
4 **Ford ES**, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol* 2007; **50**: 2128-2132
5 **Peeters A**, Nusselder WJ, Stevenson C, Boyko EJ, Moon L, Tonkin A. Age-specific trends in cardiovascular mortality rates in the Netherlands between 1980 and 2009. *Eur J Epidemiol* 2011; **26**: 369-373
6 **Ford ES**, Capewell S. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. *Annu Rev Public Health* 2011; **32**: 5-22
7 **Unal B**, Critchley JA, Fidan D, Capewell S. Life-years gained from modern cardiological treatments and population risk factor changes in England and Wales, 1981-2000. *Am J Public Health* 2005; **95**: 103-108
8 **Kabir Z**, Bennett K, Shelley E, Unal B, Critchley J, Feely J, Capewell S. Life-years-gained from population risk factor changes and modern cardiology treatments in Ireland. *Eur J Public Health* 2007; **17**: 193-198
9 **Kahn R**, Robertson RM, Smith R, Eddy D. The impact of prevention on reducing the burden of cardiovascular disease. *Circulation* 2008; **118**: 576-585
10 **Cohen JC**, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006; **354**: 1264-1272
11 **Lander ES**. The new genomics: global views of biology. *Science* 1996; **274**: 536-539
12 **McCarthy MI**, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP, Hirschhorn JN. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 2008; **9**: 356-369
13 **Ku CS**, Loy EY, Pawitan Y, Chia KS. The pursuit of genome-wide association studies: where are we now? *J Hum Genet* 2010; **55**: 195-206
14 **Pe'er I**, Yelensky R, Altshuler D, Daly MJ. Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. *Genet Epidemiol* 2008; **32**: 381-385
15 **McPherson R**, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. *Science* 2007; **316**: 1488-1491
16 **Helgadottir A**, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 2007; **316**: 1491-1493
17 **Wellcome Trust Case Control Consortium**. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661-678
18 **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; **357**: 443-453
19 **Schunkert H**, Götz A, Braund P, McGinnis R, Tregouet DA, Mangino M, Linsel-Nitschke P, Cambien F, Hengstenberg C, Stark K, Blankenberg S, Tiret L, Ducimetiere P, Keniry A, Ghori MJ, Schreiber S, El Mokhtari NE, Hall AS, Dixon RJ, Goodall AH, Liptau H, Pollard H, Schwarz DF, Hothorn LA, Wichmann HE, König IR, Fischer M, Meisinger C, Ouwehand W, Deloukas P, Thompson JR, Erdmann J, Ziegler A, Samani NJ. Repeated replication and a prospective meta-analysis of the association between chromosome 9p21.3 and coronary artery disease. *Circulation* 2008; **117**: 1675-1684
20 **Willer CJ**, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Heath SC, Timpson NJ, Najjar SS, Stringham HM, Strait J, Duren WL, Maschio A, Busonero F, Mulas A, Albai G, Swift AJ, Morken MA, Narisu N, Bennett D, Parish S, Shen H, Galan P, Meneton P, Hercberg S, Zelenika D, Chen WM, Li Y, Scott LJ, Scheet PA, Sundvall J, Watanabe RM, Nagaraja R, Ebrahim S, Lawlor DA, Ben-Shlomo Y, Davey-Smith G, Shuldiner AR, Collins R, Bergman RN, Uda M, Tuomilehto J, Cao A, Collins FS, Lakatta E, Lathrop GM, Boehnke M, Schlessinger D, Mohlke KL, Abecasis GR. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet* 2008; **40**: 161-169
21 **Kathiresan S**, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, Stoll M, Girelli D, McKeown PP, Patterson CC, Siscovick DS, O'Donnell CJ, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Melander O, Altshuler D, Ardissino D, Merlini PA, Berzuini C, Bernardinelli L, Peyvandi F, Tubaro M, Celli P, Ferrario M, Fetiveau R, Marziliano N, Casari G, Galli M, Ribichini F, Rossi M, Bernardi F, Zonzin P, Piazza A, 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, Spreafico 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, Burtt 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, Knouff CW, Waterworth DM, Walker MC, Mooser V, Epstein SE, Rader DJ, Scheffold T, Berger K, Stoll M, Huge 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, Hólm H, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Engert JC, Do R, Xie C, Anand S, Kathiresan S, Ardissino 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; **41**: 334-341
22 **Trégouët DA**, König IR, Erdmann J, Munteanu A, Braund PS, Hall AS, Grosshennig A, Linsel-Nitschke P, Perret C, DeSuremain M, Meitinger T, Wright BJ, Preuss M, Balmforth AJ, Ball SG, Meisinger C, Germain C, Evans A, Arveiler D,

Luc G, Ruidavets JB, Morrison C, van der Harst P, Schreiber S, Neureuther K, Schäfer A, Bugert P, El Mokhtari NE, Schrezenmeir J, Stark K, Rubin D, Wichmann HE, Hengstenberg C, Ouwehand W, Ziegler A, Tiret L, Thompson JR, Cambien F, Schunkert H, Samani NJ. Genome-wide haplotype association study identifies the SLC22A3-LPAL2-LPA gene cluster as a risk locus for coronary artery disease. *Nat Genet* 2009; **41**: 283-285

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

24 **Elliott P**, Chambers JC, Zhang W, Clarke R, Hopewell JC, Peden JF, Erdmann J, Braund P, Engert JC, Bennett D, Coin L, Ashby D, Tzoulaki I, Brown IJ, Mt-Isa S, McCarthy MI, Peltonen L, Freimer NB, Farrall M, Ruokonen A, Hamsten A, Lim N, Froguel P, Waterworth DM, Vollenweider P, Waeber G, Jarvelin MR, Mooser V, Scott J, Hall AS, Schunkert H, Anand SS, Collins R, Samani NJ, Watkins H, Kooner JS. Genetic Loci associated with C-reactive protein levels and risk of coronary heart disease. *JAMA* 2009; **302**: 37-48

25 **Karvanen J**, Silander K, Kee F, Tiret L, Salomaa V, Kuulasmaa K, Wiklund PG, Virtamo J, Saarela O, Perret C, Perola M, Peltonen L, Cambien F, Erdmann J, Samani NJ, Schunkert H, Evans A. The impact of newly identified loci on coronary heart disease, stroke and total mortality in the MORGAM prospective cohorts. *Genet Epidemiol* 2009; **33**: 237-246

26 **Ridker PM**, Paré G, Parker AN, Zee RY, Miletich JP, Chasman DI. Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: Genome-wide analysis among 18 245 initially healthy women from the Women's Genome Health Study. *Circ Cardiovasc Genet* 2009; **2**: 26-33

27 **Aulchenko YS**, Ripatti S, Lindqvist I, Boomsma D, Heid IM, Pramstaller PP, Penninx BW, Janssens AC, Wilson JF, Spector T, Martin NG, Pedersen NL, Kyvik KO, Kaprio J, Hofman A, Freimer NB, Jarvelin MR, Gyllensten U, Campbell H, Rudan I, Johansson A, Marroni F, Hayward C, Vitart V, Jonasson I, Pattaro C, Wright A, Hastie N, Pichler I, Hicks AA, Falchi M, Willemsen G, Hottenga JJ, de Geus EJ, Montgomery GW, Whitfield J, Magnusson P, Saharinen J, Perola M, Silander K, Isaacs A, Sijbrands EJ, Uitterlinden AG, Witteman JC, Oostra BA, Elliott P, Ruokonen A, Sabatti C, Gieger C, Meitinger T, Kronenberg F, Döring A, Wichmann HE, Smit JH, McCarthy MI, van Duijn CM, Peltonen L. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. *Nat Genet* 2009; **41**: 47-55

28 **Teslovich TM**, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010; **466**: 707-713

29 **Kathiresan S**, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen MR, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet* 2008; **40**: 189-197

30 **Kathiresan S**, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, Kaplan L, Bennett D, Li Y, Tanaka T, Voight BF, Bonnycastle LL, Jackson AU, Crawford G, Surti A, Guiducci C, Burtt NP, Parish S, Clarke R, Zelenika D, Kubalanza KA, Morken MA, Scott LJ, Stringham HM, Galan P, Swift AJ, Kuusisto J, Bergman RN, Sundvall J, Laakso M, Ferrucci L, Scheet P, Sanna S, Uda M, Yang Q, Lunetta KL, Dupuis J, de Bakker PI, O'Donnell CJ, Chambers JC, Kooner JS, Hercberg S, Meneton P, Lakatta EG, Scuteri A, Schlessinger D, Tuomilehto J, Collins FS, Groop L, Altshuler D, Collins R, Lathrop GM, Melander O, Salomaa V, Peltonen L, Orho-Melander M, Ordovas JM, Boehnke M, Abecasis GR, Mohlke KL, Cupples LA. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet* 2009; **41**: 56-65

31 **Chasman DI**, Paré G, Mora S, Hopewell JC, Peloso G, Clarke R, Cupples LA, Hamsten A, Kathiresan S, Mälarstig A, Ordovas JM, Ripatti S, Parker AN, Miletich JP, Ridker PM. Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. *PLoS Genet* 2009; **5**: e1000730

32 **Chasman DI**, Paré G, Zee RY, Parker AN, Cook NR, Buring JE, Kwiatkowski DJ, Rose LM, Smith JD, Williams PT, Rieder MJ, Rotter JI, Nickerson DA, Krauss RM, Miletich JP, Ridker PM. Genetic loci associated with plasma concentration of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein A1, and Apolipoprotein B among 6382 white women in genome-wide analysis with replication. *Circ Cardiovasc Genet* 2008; **1**: 21-30

33 **Heid IM**, Boes E, Müller M, Kollerits B, Lamina C, Coassin

S, Gieger C, Döring A, Klopp N, Frikke-Schmidt R, Tybjaerg-Hansen A, Brandstätter A, Luchner A, Meitinger T, Wichmann HE, Kronenberg F. Genome-wide association analysis of high-density lipoprotein cholesterol in the population-based KORA study sheds new light on intergenic regions. *Circ Cardiovasc Genet* 2008; **1**: 10-20

34 **Wallace C**, Newhouse SJ, Braund P, Zhang F, Tobin M, Falchi M, Ahmadi K, Dobson RJ, Marçano AC, Hajat C, Burton P, Deloukas P, Brown M, Connell JM, Dominiczak A, Lathrop GM, Webster J, Farrall M, Spector T, Samani NJ, Caulfield MJ, Munroe PB. Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. *Am J Hum Genet* 2008; **82**: 139-149

35 **Kooner JS**, Chambers JC, Aguilar-Salinas CA, Hinds DA, Hyde CL, Warnes GR, Gómez Pérez FJ, Frazer KA, Elliott P, Scott J, Milos PM, Cox DR, Thompson JF. Genome-wide scan identifies variation in MLXIPL associated with plasma triglycerides. *Nat Genet* 2008; **40**: 149-151

36 **Talmud PJ**, Drenos F, Shah S, Shah T, Palmen J, Verzilli C, Gaunt TR, Pallas J, Lovering R, Li K, Casas JP, Sofat R, Kumari M, Rodriguez S, Johnson T, Newhouse SJ, Dominiczak A, Samani NJ, Caulfield M, Sever P, Stanton A, Shields DC, Padmanabhan S, Melander O, Hastie C, Delles C, Ebrahim S, Marmot MG, Smith GD, Lawlor DA, Munroe PB, Day IN, Kivimaki M, Whittaker J, Humphries SE, Hingorani AD. Gene-centric association signals for lipids and apolipoproteins identified via the HumanCVD BeadChip. *Am J Hum Genet* 2009; **85**: 628-642

37 **Kamatani Y**, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y, Nakamura Y, Kamatani N. Genome-wide association study of hematological and biochemical traits in a Japanese population. *Nat Genet* 2010; **42**: 210-215

38 **Saxena R**, Voight BF, Lyssenko V, Burtt 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 Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren 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; **316**: 1331-1336

39 **Hiura Y**, Shen CS, Kokubo Y, Okamura T, Morisaki T, Tomoike H, Yoshida T, Sakamoto H, Goto Y, Nonogi H, Iwai N. Identification of genetic markers associated with high-density lipoprotein-cholesterol by genome-wide screening in a Japanese population: the Suita study. *Circ J* 2009; **73**: 1119-1126

40 **Sandhu MS**, Waterworth DM, Debenham SL, Wheeler E, Papadakis K, Zhao JH, Song K, Yuan X, Johnson T, Ashford S, Inouye M, Luben R, Sims M, Hadley D, McArdle W, Barter P, Kesäniemi YA, Mahley RW, McPherson R, Grundy SM, Bingham SA, Khaw KT, Loos RJ, Waeber G, Barroso I, Strachan DP, Deloukas P, Vollenweider P, Wareham NJ, Mooser V. LDL-cholesterol concentrations: a genome-wide association study. *Lancet* 2008; **371**: 483-491

41 **Levy D**, Larson MG, Benjamin EJ, Newton-Cheh C, Wang TJ, Hwang SJ, Vasan RS, Mitchell GF. Framingham Heart Study 100K Project: genome-wide associations for blood pressure and arterial stiffness. *BMC Med Genet* 2007; **8 Suppl 1**: S3

42 **Newton-Cheh C**, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Döring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvänen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dörr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Völker 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, Völzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009; **41**: 666-676

43 **Levy D**, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Köttgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet* 2009; **41**: 677-687

44 **Adeyemo A**, Gerry N, Chen G, Herbert A, Doumatey A, Huang H, Zhou J, Lashley K, Chen Y, Christman M, Rotimi C. A genome-wide association study of hypertension and blood pressure in African Americans. *PLoS Genet* 2009; **5**: e1000564

45 **Kato N**, Miyata T, Tabara Y, Katsuya T, Yanai K, Hanada H, Kamide K, Nakura J, Kohara K, Takeuchi F, Mano H, Yasunami M, Kimura A, Kita Y, Ueshima H, Nakayama T, Soma M, Hata A, Fujioka A, Kawano Y, Nakao K, Sekine A, Yoshida T, Nakamura Y, Saruta T, Ogihara T, Sugano S, Miki T, Tomoike H. High-density association study and nomination of susceptibility genes for hypertension in the Japanese National Project. *Hum Mol Genet* 2008; **17**: 617-627

46 **Yang HC**, Liang YJ, Wu YL, Chung CM, Chiang KM, Ho HY, Ting CT, Lin TH, Sheu SH, Tsai WC, Chen JH, Leu HB, Yin WH, Chiu TY, Chen CI, Fann CS, Wu JY, Lin TN, Lin SJ, Chen YT, Chen JW, Pan WH. Genome-wide association study of young-onset hypertension in the Han Chinese population of Taiwan. *PLoS One* 2009; **4**: e5459

47 **Wang Y**, O'Connell JR, McArdle PF, Wade JB, Dorff SE, Shah SJ, Shi X, Pan L, Rampersaud E, Shen H, Kim JD, Subramanya AR, Steinle NI, Parsa A, Ober CC, Welling PA, Chakravarti A, Weder AB, Cooper RS, Mitchell BD, Shuldiner AR, Chang YP. From the Cover: Whole-genome association study identifies STK39 as a hypertension susceptibility gene. *Proc Natl Acad Sci USA* 2009; **106**: 226-231

48 **Org E**, Eyheramendy S, Juhanson P, Gieger C, Lichtner P, Klopp N, Veldre G, Döring A, Viigimaa M, Sõber S, Tomberg K, Eckstein G, Kelgo P, Rebane T, Shaw-Hawkins S, Howard P, Onipinla A, Dobson RJ, Newhouse SJ, Brown M, Dominiczak A, Connell J, Samani N, Farrall M, Caulfield MJ,

Munroe PB, Illig T, Wichmann HE, Meitinger T, Laan M. Genome-wide scan identifies CDH13 as a novel susceptibility locus contributing to blood pressure determination in two European populations. *Hum Mol Genet* 2009; **18**: 2288-2296

49 **Cho YS**, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, Cha SH, Kim JW, Han BG, Min H, Ahn Y, Park MS, Han HR, Jang HY, Cho EY, Lee JE, Cho NH, Shin C, Park T, Park JW, Lee JK, Cardon L, Clarke G, McCarthy MI, Lee JY, Lee JK, Oh B, Kim HL. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet* 2009; **41**: 527-534

50 **Padmanabhan S**, Melander O, Johnson T, Di Blasio AM, Lee WK, Gentilini D, Hastie CE, Menni C, Monti MC, Delles C, Laing S, Corso B, Navis G, Kwakernaak AJ, van der Harst P, Bochud M, Maillard M, Burnier M, Hedner T, Kjeldsen S, Wahlstrand B, Sjögren M, Fava C, Montagnana M, Danese E, Torffvit O, Hedblad B, Snieder H, Connell JM, Brown M, Samani NJ, Farrall M, Cesana G, Mancia G, Signorini S, Grassi G, Eyheramendy S, Wichmann HE, Laan M, Strachan DP, Sever P, Shields DC, Stanton A, Vollenweider P, Teumer A, Völzke H, Rettig R, Newton-Cheh C, Arora P, Zhang F, Soranzo N, Spector TD, Lucas G, Kathiresan S, Siscovick DS, Luan J, Loos RJ, Wareham NJ, Penninx BW, Nolte IM, McBride M, Miller WH, Nicklin SA, Baker AH, Graham D, McDonald RA, Pell JP, Sattar N, Welsh P, Munroe P, Caulfield MJ, Zanchetti A, Dominiczak AF. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. *PLoS Genet* 2010; **6**: e1001177

51 **Ioannidis JP**. Prediction of cardiovascular disease outcomes and established cardiovascular risk factors by genome-wide association markers. *Circ Cardiovasc Genet* 2009; **2**: 7-15

52 **Morrison AC**, Bare LA, Chambless LE, Ellis SG, Malloy M, Kane JP, Pankow JS, Devlin JJ, Willerson JT, Boerwinkle E. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2007; **166**: 28-35

53 **Paynter NP**, Chasman DI, Buring JE, Shiffman D, Cook NR, Ridker PM. Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. *Ann Intern Med* 2009; **150**: 65-72

54 **Kathiresan S**, Melander O, Anevski D, Guiducci C, Burtt 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; **358**: 1240-1249

55 **Talmud PJ**, Cooper JA, Palmen J, Lovering R, Drenos F, Hingorani AD, Humphries SE. Chromosome 9p21.3 coronary heart disease locus genotype and prospective risk of CHD in healthy middle-aged men. *Clin Chem* 2008; **54**: 467-474

56 **Paynter NP**, Chasman DI, Paré G, Buring JE, Cook NR, Miletich JP, Ridker PM. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA* 2010; **303**: 631-637

57 **Rosenberg S**, Elashoff MR, Beineke P, Daniels SE, Wingrove JA, Tingley WG, Sager PT, Sehnert AJ, Yau M, Kraus WE, Newby LK, Schwartz RS, Voros S, Ellis SG, Tahirkheli N, Waksman R, McPherson J, Lansky A, Winn ME, Schork NJ, Topol EJ. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. *Ann Intern Med* 2010; **153**: 425-434

58 **Ripatti S**, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, Guiducci C, Perola M, Jula A, Sinisalo J, Lokki ML, Nieminen MS, Melander O, Salomaa V, Peltonen L, Kathiresan S. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* 2010; **376**: 1393-1400

59 **Pepe MS**, Feng Z, Gu JW. Comments on 'Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond' by M. J. Pencina et al., Statistics in Medicine (DOI: 10.1002/sim.2929). *Stat Med* 2008; **27**: 173-181

60 **Hlatky MA**, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, Go AS, Harrell FE, Hong Y, Howard BV, Howard VJ, Hsue PY, Kramer CM, McConnell JP, Normand SL, O'Donnell CJ, Smith SC, Wilson PW. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation* 2009; **119**: 2408-2416

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