Review

Genome-Wide Association Studies of Hypertension and Several Other Cardiovascular Diseases

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Keywords

Genome-wide association study · Genetic risk score · Hypertension · Coronary artery disease

Abstract

Genome-wide association studies (GWAS) have greatly expanded our understanding of the genetic architecture of cardiovascular diseases in the past decade. They have revealed hundreds of suggestive genetic loci that replicate known biological candidate genes and indicate the existence of a previously unsuspected new biology relevant to cardiovascular disorders. These data have been used successfully to create genetic risk scores that may improve risk prediction and the identification of susceptible individuals. Furthermore, these GWAS-identified novel pathways may herald a new era of novel drug development and stratification of patients. In this review, we will briefly summarize the literature on the candidate genes and signals discovered by GWAS on hypertension and coronary artery disease and discuss their implications on clinical medicine.

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Introduction

A large majority of heart diseases are polygenetic, that is, the result of a combination of multiple common genetic variants and environmental factors. Unravelling the genetic basis of heart diseases has proceeded slowly through linkage studies, because of the much smaller effect size attributable to common modifying variants in complex disorders [1]. Chip-based

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Table 1. Genome-wide association studies of hypertension and several other cardiovascular diseases and abnormalities

Study [Ref.], year	Initial sample size, <i>n</i>	Replication sample size, <i>n</i>	Major ethnic group	Top locus
<i>Blood pressure</i>				
Levy et al. [8], 2009	29,136	34,433	European	SH2B3
Newton-Cheh et al. [7], 2009	34,433	113,236	European	CNNM2
Kato et al. [12], 2011	19,608	30,765	Asian	HECTD4
Wain et al. [10], 2011	74,064	48,607	European	ATXN2
Ehret et al. [9], 2011	69,395	133,361	European	CSK
Warren et al. [11], 2017	140,886	190,318	European	JAG1
<i>Coronary artery disease</i>				
Samani et al. [17], 2007	4,864	2,519	European	CDKN2B-AS1 – DMRTA1
Helgadottir et al. [42], 2007	8,335	9,289	European	CDKN2B-AS1 – DMRTA1
Trégouët et al. [43], 2009	4,864	14,398	European	LPA
Erdmann et al. [44], 2009	2,520	38,253	European	MRAS
Reilly et al. [45], 2011	2,723	17,053	European	ADAMTS7
C4D Genetics Consortium et al. [46], 2011	30,482	40,593	European, Asian	PHACTR1
Schunkert et al. [47], 2011	86,995	56,682	European	CDKN2B-AS1
Lu et al. [48], 2012	6,534	26,932	Asian	CDKN2B-AS1
Nikpay et al. [19], 2015	187,599	None	European, Asian	CDKN2B-AS1
Nelson et al. [20], 2017	63,731	276,868	European,	CDKN2B-AS1
<i>Congestive heart failure</i>				
Smith et al. [49], 2010	23,821	None	European, African	LRIG3
<i>Dilated cardiomyopathy</i>				
Villard et al. [50], 2011	2,287	2,467	European	TSPB7
<i>Atrial fibrillation</i>				
Gudbjartsson et al. [51], 2009	36,137	8,855	European	ZFHX3
Ellinor et al. [52], 2010	14,179	4,771	European	KCNN3
Ellinor et al. [53], 2012	59,133	5,381	European	PITX2 – MIR297
Low et al. [54], 2017	36,792	257,896	Asian, European	PITX2 – MIR297
<i>Electrocardiographic abnormalities in the PR interval</i>				
Pfeufer et al. [55], 2010	28,517	None	European	SCN10A
Chambers et al. [56], 2010	6,543	6,243	Asian	SCN10A
<i>QRS duration</i>				
Sotoodehnia et al. [57], 2010	40,407	7,170	European	SCN10A
<i>QT interval</i>				
Arking et al. [58], 2006	200	4,451	European	NOS1AP, LOC105371475
Newton-Cheh et al. [59], 2009	13,685	15,854	European	LOC107985450 – NOS1AP
Arking et al. [60], 2014	70,389	33,316	European	LOC107985450 – NOS1AP
<i>Heart rate</i>				
den Hoed et al. [61], 2013	92,355	88,823	European	MYH6
Nolte et al. [62], 2017	26,523	38,558	European, Hispanic, African American	NDUFA11
<i>Dyslipidemia</i>				
Saxena et al. [63], 2007	5,217	None	European	APOC1 – APOC1P1
Kooner et al. [64], 2008	2,011	10,536	European, Mexican, Asian	MLXIPL
Kathiresan et al. [35], 2008	19,840	20,623	European	HERPUD1 – CETP
Sandhu et al. [65], 2008	11,685	4,979	European	CELSR2 – PSRC1
Teslovich et al. [16], 2010	96,598	None	European	ZPR1
Kim et al. [66], 2011	12,545	30,395	Asian	ZPR1
Willer et al. [67], 2013	94,595	93,982	European	LDLR
Ko et al. [68], 2014	3,323	6,017	Mexican	ZPR1
Surakka et al. [69], 2015	62,166	None	European	APOE

microarray technology for assaying over 1 million interindividual genetic variants provides the foundation of genome-wide association studies (GWAS), which are defined as any studies of common genetic variation across the entire human genome designed to identify genetic associations with observable traits [2]. The common variants usually refer to those with a prevalence of at least 5% in a population. A stringent genome-wide significance threshold of $p < 5E-8$ is routinely used as a correction for multiple testing, which is based on the estimation of approximately 1 million independent SNPs in a population [3].

The past decade has witnessed substantial advances in understanding the genetic basis of heart diseases through GWAS. Furthermore, HapMap- and 1000 Genomes Project-based meta-analyses including hundreds of thousands of subjects have expanded our understanding of the genetic architecture of heart diseases to a great extent. In the GWAS catalog (www.ebi.ac.uk/gwas/), hundreds of loci have been reported that show an association with more than 10 heart diseases or traits; the major achievements are listed in Table 1.

In this review, we will give a brief summary of the achievements of GWAS regarding blood pressure (BP) and coronary artery disease (CAD), the progress in risk prediction at individual level, the novel pathophysiological pathways, and drug discoveries.

GWAS-Significant Loci

Blood Pressure

BP is a quantitative trait, normally distributed in the general population, whereas 30–50% of the variation in BP is determined by inherited genetic factors [4, 5]. Hypertension ranks as the leading cause of morbidity and mortality worldwide, contributing to CAD, atrial fibrillation, and heart failure, so that the knowledge about the genetics of hypertension or BP is an important factor in the diagnosis, control, and treatment of all of these heart diseases.

Until the middle of 2017, GWAS have identified and replicated genetic variants of modest or weak effect on BP over 200 loci; the strongest SNPs associated with different BP traits are summarized in Table 2a and b. However, the attempts to identify genetic variants associated with BP have been challenging and of relatively low yield in the early phase. In 2007, the first GWAS (by the Wellcome Trust Case Control Consortium [WTCCC]) [6] adopted a case-control study design using 3,000 shared controls and 14,000 cases (2,000 for hypertension) of European ancestry to study 7 complex diseases simultaneously. Hypertension was the only disease without any significant results. The first GWAS of quantitative BP phenotypes was conducted in the Framingham Heart Study, which included 1,400 family subjects and found no significant results either [5]. These two studies let researchers realize the complexity of the genetic mechanisms underlying BP regulation and the need for much larger sample sizes when looking for genes associated with BP/hypertension.

To enhance the statistical power, international collaborations were established between studies and organized in consortia. Furthermore, detecting associations with BP as a continuous variable rather than in case-control studies also was successful. In 2009, two large-scale meta-analyses of GWAS from the Global Blood Pressure Genetics (Global BPgen) [7] and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) [8] consortia identified associations withstanding correction for multiple testing (genome-wide significance). Each of the study contained nearly 30,000 subjects at the discovery phase and found 8 genomic loci, among which 3 loci overlapped. In 2011, the International Consortium for Blood Pressure (ICBP) [9] used a multistage design with 200,000 individuals of European descent, replicated the previous 13 loci effectively and discovered 16 new loci significant at the genome-wide level. Then, the ICBP analyzed two derived BP phenotypes: mean arterial pressure and pulse pressure (PP) [10]. This study discovered 4 novel loci for PP and 2 novel

Table 2. Significant genetic loci for blood pressure and hypertension reported in genome-wide association studies in Europeans (a) and Asians and Africans (b)

Chr	Strongest SNP	Position	EA	EA F	OR or BETA	p value	N	Closest gene	Trait	Ref.
a Europeans										
1	rs1886773	1319056	A	0.03	-0.63	1.90E-10	233,789	NADK, CPSF3L	PP	[11]
1	rs14057	6623180	A	0.35	-0.3	2.50E-10	329,584	RNF207	SBP	[11]
1	rs9662255	9381890	A	0.43	-0.21	1.90E-10	310,618	chr1mb9	PP	[11]
1	rs880315	10736809	C	0.35	0.64	9.10E-16	133,125	CASZ1	SBP	[70]
1	rs17367504	11802721	G	0.15	-0.53	2.68E-18	149,714	MTHFR, NPPB	DBP	[70]
1	rs12744757	11846764	T	0.06	-0.7	7.54E-23	359,786	NPPA-AS1, NPPA	SBP	[70]
1	rs1042010	15467418	A	0.19	-0.41	3.03E-13	345,219	CELA2A	SBP	[70]
1	rs1048238	16015154	T	0.57	0.37	8.09E-07	140,299	HSPB7	SBP	[70]
1	rs6686889	24703979	T	0.25	0.19	3.60E-09	322,575	chr1mb25	DBP	[11]
1	rs871524	37945773	A	0.33	0.23	1.27E-11	304,987	INPP5B	PP	[70]
1	rs4360494	37990219	C	0.55	0.28	3.70E-16	282,851	SF3A3	PP	[11]
1	rs112557609	56111252	A	0.35	0.23	6.80E-12	325,952	RP4-710M16.1, PPAP2B	PP	[11]
1	rs3889199	59188070	A	0.71	0.35	1.80E-24	329,486	FGGY	PP	[11]
1	rs61767086	88600899	G	0.14	-0.41	1.90E-09	136,914	PKN2-AS1	PP	[70]
1	rs10922502	88894475	A	0.62	-0.38	2.20E-15	323,666	GTF2B	SBP	[11]
1	rs12129649	112688881	T	0.06	0.55	5.93E-19	343,172	MOV10	DBP	[70]
1	rs11466111	115286557	T	0.02	0.65	5.08E-10	319,490	chr1mb115	DBP	[11]
1	rs12405515	172388301	T	0.56	-0.17	1.40E-09	328,543	DNM3	DBP	[11]
1	rs12408022	217545447	T	0.26	0.2	2.40E-10	320,983	GPATCH2	DBP	[11]
1	rs10916082	227064925	A	0.73	-0.18	8.40E-09	327,636	CDC42BPA	DBP	[11]
1	rs2760061	228003374	A	0.47	0.23	2.10E-16	312,761	WNT3A	DBP	[11]
1	rs953492	243307890	A	0.46	0.22	7.40E-16	325,253	SDCCAG8	DBP	[11]
2	rs2289081	20682080	C	0.36	-0.22	5.50E-12	329,140	C2orf43	PP	[11]
2	rs55701159	24916727	T	0.89	0.29	7.20E-11	321,052	ADCY3	DBP	[11]
2	rs1275988	26691496	T	0.61	-0.58	2.35E-15	149,285	KCNK3	SBP	[70]
2	rs7562	28412873	T	0.52	0.26	1.90E-08	319,942	FOSL2	SBP	[11]
2	rs13420463	37290423	A	0.77	0.36	7.00E-11	330,307	PRKD3	SBP	[11]
2	rs4952611	40340603	T	0.58	-0.16	4.00E-08	309,395	SLC8A1	DBP	[11]
2	rs76326501	42940738	A	0.91	0.42	3.60E-18	318,127	AC016735.1	DBP	[11]
2	rs72876037	42967456	T	0.12	-0.53	1.65E-14	319,468	HAAO, ZFP36L2	SBP	[70]
2	rs11690961	46136197	A	0.88	0.34	3.90E-12	327,847	PRKCE	PP	[11]
2	rs74181299	65056838	T	0.62	0.23	9.60E-13	324,224	CEP68	PP	[11]
2	rs11689667	85264242	T	0.54	0.18	1.70E-08	330,634	TCF7L1	PP	[11]
2	rs2579519	96009418	T	0.63	-0.2	4.80E-12	311,557	GPAT2, FAHD2CP	DBP	[11]
2	rs62167177	145181135	T	0.14	-0.26	1.04E-09	289,338	TEX41	DBP	[11]
2	rs1446468	164106976	C	0.55	0.54	2.98E-13	141,331	FIGN, GRB14	SBP	[70]
2	rs79146658	178921341	T	0.91	-0.31	2.40E-10	321,318	CCDC141	DBP	[11]
2	rs13407401	179850979	A	0.29	-0.43	4.30E-08	145,919	ZNF385B	SBP	[70]
2	rs144073138	182410033	G	0.06	0.35	1.90E-08	295,411	PDE1A	DBP	[11]
2	rs7592578	190574865	T	0.19	-0.24	9.50E-12	304,672	TMEM194B	DBP	[11]
2	rs55780018	207661416	T	0.54	-0.39	5.90E-16	304,567	METTL21A, AC079767.3	SBP	[11]
2	rs1250259	215435759	A	0.74	-0.31	8.70E-19	325,485	FN1	PP	[11]
2	rs10932679	216787868	T	0.19	-0.23	1.70E-08	371,085	LOC101928278	PP	[70]
2	rs1063281	217804009	T	0.6	-0.2	1.30E-12	315,354	TNS1	DBP	[11]
3	rs142892876	1110752	T	0.001	10.69	5.00E-08	19,546	CNTN6	DBP	[71]
3	rs11716531	27415717	A	0.24	0.21	5.72E-14	373,386	SLC4A7	DBP	[70]
3	rs13082711	27496418	C	0.23	0.33	2.72E-10	146,340	SLC4A7	DBP	[70]
3	rs36022378	49876272	T	0.8	-0.2	4.70E-09	319,983	CAMKV, ACTBP13	DBP	[11]

Table 2 (continued)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	N	Closest gene	Trait	Ref.
3	rs743757	50438947	C	0.14	0.25	2.40E-10	328,836	CACNA2D2	DBP	[11]
3	rs9827472	56692618	T	0.37	-0.18	4.30E-10	323,058	FAM208A	DBP	[11]
3	rs9834975	122398816	T	0.44	0.15	1.14E-08	330,670	chr3mb122	DBP	[11]
3	rs62270945	128483046	T	0.03	0.61	1.80E-09	279,925	GATA2	PP	[11]
3	rs9859176	134281183	T	0.4	0.32	1.30E-11	322,428	RYK	SBP	[11]
3	rs143112823	154990178	A	0.09	-0.4	1.40E-14	297,343	RP11-439C8.2	DBP	[11]
3	rs419076	169383098	T	0.47	0.41	1.78E-13	193,725	MECOM	SBP	[9]
3	rs12374077	185599886	C	0.35	0.16	9.20E-09	327,513	SENP2	DBP	[11]
3	rs528908640	193644588	C	0.0005	14.67	2.00E-08	19,546	OPA1	DBP	[71]
3	rs9815354	41912651	A	0.17	0.4	7.12E-11	135,381	ULK4	DBP	[70]
4	rs871606	53933078	C	0.1	-0.5	1.53E-10	144,494	CHIC2	PP	[70]
4	rs17004869	80283879	T	0.05	0.72	1.02E-09	278,498	FGF5	SBP	[11]
4	rs2014912	85794517	C	0.85	-0.42	3.86E-10	143,933	ARHGAP24	PP	[70]
4	rs13107325	102267552	T	0.05	-0.68	2.28E-17	150,920	SLC39A8	DBP	[9]
4	rs13112725	105990585	C	0.77	0.41	3.11E-16	357,230	NPNT, TBCK	SBP	[70]
4	rs33966350	110510288	A	0.01	1.66	2.10E-11	216,630	ENPEP	SBP	[11]
4	rs66887589	119588124	T	0.52	-0.22	3.40E-15	324,397	PDE5A	DBP	[11]
4	rs78049276	147506351	C	0.13	0.27	1.04E-08	321,315	chr4mb148	PP	[11]
4	rs13139571	155724361	C	0.76	0.26	2.17E-10	185,393	GUCY1A3, GUCY1B3	DBP	[9]
4	rs1566497	168795997	A	0.42	0.24	1.90E-13	320,948	PALLD	PP	[11]
4	rs17059668	173663512	C	0.92	-0.33	2.80E-08	313,277	chr4mb174	PP	[11]
5	rs1173771	32814922	G	0.6	0.5	1.79E-16	158,664	C5orf23, NPR3	SBP	[9]
5	rs10078021	75742606	T	0.63	-0.16	1.30E-08	314,172	POC5	DBP	[11]
5	rs10057188	78541966	A	0.46	-0.21	6.70E-11	325,985	LHFPL2	PP	[11]
5	rs10059921	88218698	T	0.08	-0.53	4.00E-09	298,543	TMEM161B	SBP	[11]
5	rs337100	123210816	A	0.41	-0.28	4.61E-09	149,200	PRDM6 – SUMO1P5	PP	[70]
5	rs6595838	128532506	A	0.3	0.34	7.60E-12	328,401	FBN2	SBP	[11]
5	rs31864	158793185	A	0.55	0.21	5.50E-11	326,557	EBF1	PP	[11]
5	rs72812846	173950633	A	0.28	-0.21	2.20E-11	312,601	CPEB4	DBP	[11]
6	rs6911827	22130372	T	0.45	0.3	2.00E-10	326,471	CASC15	SBP	[11]
6	rs1800562	26092913	A	0.06	0.39	8.69E-17	373,770	HFE	DBP	[70]
6	rs151168737	31638615	A	0.46	0.25	3.60E-20	315,660	PRRC2A – BAG6	DBP	[70]
6	rs805303	31648589	G	0.61	0.38	1.49E-11	201,745	BAT2, BAT5	SBP	[9]
6	rs185819	32082290	C	0.51	0.37	1.04E-17	364,144	TNXB	SBP	[70]
6	rs78648104	50715296	T	0.92	-0.48	1.30E-08	305,426	TFAP2D	SBP	[11]
6	rs13205180	51967696	T	0.49	0.17	7.00E-10	325,419	PKHD1	DBP	[11]
6	rs9372498	118251323	A	0.08	0.33	1.80E-11	330,625	SLC35F1	DBP	[11]
6	rs11154027	121460244	T	0.47	0.21	1.10E-10	316,708	GJA1	PP	[11]
6	rs13209747	126794309	T	0.45	0.27	1.12E-09	146,105	RSP03	DBP	[70]
6	rs17080102	150683634	C	0.07	-0.57	1.04E-10	147,869	PLEKHG1	DBP	[70]
6	rs36083386	152076778	I	0.11	0.44	1.50E-18	323,303	ESR1	PP	[11]
6	rs449789	159278093	C	0.14	0.36	2.40E-15	325,584	FNDC1	PP	[11]
6	rs147212971	165764963	T	0.06	-0.36	1.60E-09	296,010	PDE10A	DBP	[11]
6	rs1322639	169187008	A	0.78	0.32	4.80E-17	319,866	THBS2	PP	[11]
7	rs6461992	27181212	G	0.93	0.91	8.49E-24	311,598	HOXA3	SBP	[11]
7	rs1859168	27202740	C	0.92	0.44	1.85E-20	373,643	HOTTIP	DBP	[70]
7	rs76206723	40408372	A	0.1	-0.35	7.40E-12	328,162	SUGCT	PP	[11]
7	rs10260816	45970501	G	0.43	-0.3	5.31E-10	143,371	IGFBP3	PP	[70]
7	rs17477177	106771412	C	0.21	0.55	4.14E-22	149,296	PIK3CG	PP	[70]

Table 2 (continued)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	N	Closest gene	Trait	Ref.
7	rs13238550	131374297	A	0.4	0.33	1.90E-12	325,647	MKLN1	SBP	[11]
7	rs1011018	139763465	A	0.2	-0.33	1.50E-08	325,110	HIPK2	SBP	[11]
7	rs3918226	150993088	T	0.08	0.67	2.27E-13	118,604	NOS3	DBP	[70]
8	rs9693857	9409607	T	0.45	-0.34	2.40E-15	374,178	LOC105379231	SBP	[70]
8	rs1821002	10782555	G	0.6	-0.42	4.26E-19	323,712	BLK, GATA4	SBP	[11]
8	rs10107145	10900703	G	0.53	-0.36	1.44E-17	374,413	XKR6	SBP	[70]
8	rs6557876	26043159	T	0.25	-0.37	2.85E-14	369,457	EBF2	SBP	[70]
8	rs2978456	42467247	T	0.55	-0.19	1.20E-08	304,964	SLC20A2	PP	[11]
8	rs2978098	100664447	A	0.54	0.17	1.50E-09	324,424	SNX31	DBP	[11]
8	rs35783704	104954030	A	0.11	-0.41	7.08E-09	349,452	LRP12, ZFPM2	SBP	[70]
8	rs2071518	119423572	T	0.17	0.3	1.56E-08	149,046	NOV	PP	[10]
8	rs894344	134600502	A	0.6	-0.26	3.20E-08	329,834	ZFAT	SBP	[11]
8	rs4454254	140049929	A	0.63	-0.26	5.10E-16	330,022	TRAPPC9	PP	[11]
8	rs62524579	142979538	A	0.53	-0.18	3.80E-09	268,645	RP11-273G15.2	DBP	[11]
8	rs4076877	143820544	T	0.05	-0.42	3.57E-08	252,983	chr8mb144	DBP	[11]
9	rs872256	2496480	NA	NA	0.1	9.00E-09	8,423	SMARCA2, VLDLR	SBP	[72]
9	rs4364717	21801531	A	0.55	-0.18	1.30E-10	327,173	MTAP	DBP	[11]
9	rs568998724	107040156	A	0.0007	13.49	3.00E-08	19,546	LOC340512	DBP	[71]
9	rs72765298	125138717	T	0.87	-0.37	2.70E-14	316,271	SCAI	PP	[11]
10	rs9337951	30028144	A	0.34	0.28	2.50E-15	299,646	KIAA1462	PP	[11]
10	rs10826995	31793730	T	0.71	-0.21	1.10E-09	327,373	ARHGAP12, ZEB1	PP	[11]
10	rs4590817	61707795	G	0.83	-0.44	3.52E-13	146,522	C10orf107	MAP	[10]
10	rs932764	94136183	G	0.44	0.48	7.10E-16	160,885	PLCE1	SBP	[9]
10	rs112184198	100844757	A	0.1	-0.66	3.60E-18	323,791	PAX2	SBP	[11]
10	rs11191548	103086421	T	0.91	1.1	6.90E-26	161,709	NT5C2, CYP17A1	SBP	[9]
10	rs10787517	114055047	A	0.62	0.44	3.31E-18	272,852	ADRB1 – RNU6-709P	SBP	[70]
11	rs2649044	9742422	T	0.55	0.2	1.12E-14	343,652	SWAP70	DBP	[70]
11	rs7129220	10328991	G	0.89	-0.62	2.97E-12	182,871	ADM	SBP	[9]
11	rs177542	16901107	A	0.5	0.24	4.18E-08	143,257	PLEKHA7	DBP	[70]
11	rs11030119	27706555	A	0.31	-0.16	2.90E-08	330,002	BDNF	DBP	[11]
11	rs11442819	45186591	I	0.11	-0.28	7.10E-09	326,483	PRDM11	PP	[11]
11	rs751984	61510774	C	0.12	-0.41	1.98E-09	140,821	LRRC10B	DBP	[70]
11	rs4980532	63913247	T	0.56	0.3	1.53E-10	147,416	RCOR2	PP	[70]
11	rs67330701	69312240	T	0.09	-0.37	2.10E-12	276,760	MYEOV	DBP	[11]
11	rs2289125	89491285	A	0.21	-0.38	9.10E-22	307,682	NOX4	PP	[11]
11	rs633185	100722807	G	0.28	-0.56	1.21E-17	160,461	TMEM133, FLJ32810	SBP	[9]
11	rs8258	117412960	T	0.38	0.24	2.90E-13	327,038	CEP164	PP	[11]
11	rs11222084	130403335	T	0.35	0.35	2.26E-12	139,748	ADAMTS8	PP	[70]
12	rs10770612	20077705	A	0.8	0.31	6.90E-15	311,586	PDE3A	PP	[11]
12	rs73099903	53046995	T	0.07	0.51	1.95E-10	343,318	LOC283335	SBP	[70]
12	rs7312464	65980467	G	0.52	0.21	5.35E-10	289,978	chr12mb66	PP	[11]
12	rs17249754	89666809	A	0.16	-0.9	6.59E-20	146,304	ATP2B1	SBP	[70]
12	rs139236208	94486966	A	0.1	-0.36	1.60E-10	291,244	CCDC41	PP	[11]
12	rs3184504	111446804	T	0.47	0.45	3.59E-25	120,633	SH2B3	DBP	[9]
12	rs10850519	115490635	C	0.3	-0.21	5.10E-13	327,837	TBX5, TBX3	DBP	[11]
13	rs9549328	112981842	T	0.23	0.32	1.50E-08	313,787	MCF2L	SBP	[11]
14	rs12050260	23291885	T	0.35	0.19	2.60E-08	304,390	MYH6	PP	[11]
14	rs8904	35402011	A	0.38	0.31	1.31E-12	365,195	NFKBIA	SBP	[70]
14	rs9888615	52910822	T	0.29	-0.32	3.50E-10	326,235	FERMT2	SBP	[11]

Table 2 (continued)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	N	Closest gene	Trait	Ref.
14	rs8016306	63461828	A	0.8	0.34	3.70E-09	329,869	PPP2R5E	SBP	[11]
14	rs12434998	93989208	C	0.37	-0.19	1.64E-08	315,683	chr14mb94	PP	[11]
14	rs9323988	98121293	T	0.63	-0.21	4.10E-11	327,551	RP11-6101.1	PP	[11]
15	rs1036477	48622729	G	0.1	-0.42	3.81E-08	149,967	FBN1	PP	[70]
15	rs7178615	66576734	A	0.37	-0.18	2.60E-10	318,076	RP11-321F6.1	DBP	[11]
15	rs1563894	68343437	NA	NA	0.09	3.00E-08	10,090	ITGA11	SBP	[72]
15	rs117539635	69390577	G	0.03	-0.65	2.15E-08	196,789	chr15mb69	DBP	[11]
15	rs1378942	74785026	C	0.35	0.42	2.69E-26	163,115	CYP1A1, ULK3	DBP	[9]
15	rs6495122	74833304	A	0.42	0.4	1.84E-10	NA	CSK, ULK3	DBP	[8]
15	rs187680191	76002970	T	0.0006	18.58	3.00E-09	19,546	NRG4	DBP	[71]
15	rs62012628	78777658	T	0.29	-0.24	5.10E-12	244,143	ADAMTS7	DBP	[11]
15	rs11634851	80736624	G	0.46	0.32	5.38E-14	374,208	FAM108C1	SBP	[70]
15	rs2521501	90894158	T	0.31	0.65	5.20E-19	127,208	FURIN, FES	SBP	[9]
15	rs12906962	94768842	T	0.68	-0.22	5.60E-14	319,952	chr15mb95	DBP	[11]
15	rs4984496	96092669	G	0.67	-0.18	2.86E-09	307,660	chr15mb96	DBP	[11]
16	rs12921187	4893018	T	0.43	-0.17	2.50E-10	326,469	PPL	DBP	[11]
16	rs13333226	20354332	A	0.81	0.85	1.50E-13	39,706	UMOD	HT	[25]
16	rs72799341	30925422	A	0.24	0.19	5.80E-09	324,502	FBXL19	DBP	[11]
16	rs56249585	65231799	T	0.53	0.18	8.98E-09	318,082	chr16mb65	PP	[11]
16	rs141767645	69869262	T	0.02	1.3	1.90E-08	174,313	NFAT5	PP	[11]
16	rs200337503	70084312	I	0.03	1.31	6.88E-13	193,318	NFAT5	PP	[11]
16	rs117006983	70721707	A	0.01	0.99	4.10E-12	250,766	VAC14	PP	[11]
16	rs11643209	75297146	T	0.42	-0.34	1.80E-12	309,242	CFDP1	SBP	[11]
16	rs8059962	81540592	T	0.42	-0.17	1.30E-09	319,839	CMIP	DBP	[11]
16	rs7500448	83012185	A	0.75	0.33	1.10E-19	321,958	CDH13	PP	[11]
17	rs12941318	1430304	T	0.49	-0.27	2.50E-08	299,739	CRK	SBP	[11]
17	rs7226020	6570508	T	0.56	-0.26	2.30E-14	303,389	KIAA0753	PP	[11]
17	rs5417	7281743	A	0.57	0.21	1.10E-13	319,299	TP53, SLC2A4	DBP	[11]
17	rs138643143	42557849	A	0.07	0.5	3.30E-09	229,161	KCNH4, HSD17B1	PP	[11]
17	rs62080325	43983263	A	0.66	-0.19	4.00E-08	315,689	PYY	PP	[11]
17	rs12946454	45130754	T	0.28	0.57	1.00E-08	77,690	PLCD3	SBP	[7]
17	rs551011992	45851264	G	0.24	-0.33	3.32E-08	275,778	GOSR2	SBP	[11]
17	rs17608766	46935905	C	0.14	0.55	1.97E-15	137,066	GOSR2	PP	[70]
17	rs79917357	48747312	A	0.17	0.34	5.33E-09	336,863	LOC105371811 – LOC105371812	SBP	[70]
17	rs585736	48796910	A	0.03	0.61	2.50E-11	301,845	HOXB7	PP	[11]
17	rs12940887	49325445	T	0.37	0.26	1.18E-08	144,603	ZNF652	DBP	[70]
17	rs16948048	49363104	G	0.39	0.31	8.24E+04	82,441	PHB, ZNF652	DBP	[7]
17	rs740698	62689790	T	0.56	-0.23	3.10E-12	311,450	MRC2	PP	[11]
17	rs4459609	63471587	A	0.61	-0.2	2.03E-14	361,581	CYB561, ACE	DBP	[70]
17	rs4308	63482264	A	0.37	0.21	6.80E-14	319,394	ACE	DBP	[11]
17	rs2467099	75952964	T	0.22	-0.31	3.30E-08	326,401	ACOX1	SBP	[11]
17	rs57927100	77321218	G	0.26	-0.31	4.04E-10	347,188	SPET9	SBP	[70]
18	rs7236548	45517785	A	0.18	0.35	2.00E-18	330,075	SLC14A2	PP	[11]
18	rs745821	50616484	T	0.76	0.19	1.40E-09	330,954	MAPK4	DBP	[11]
19	rs36047283	7255690	G	0.11	-0.8	3.25E-26	281,588	INSR	SBP	[70]
19	rs2116941	10223767	C	0.81	-0.22	2.77E-08	321,960	chr19mb10	PP	[11]
19	rs77279095	11415506	A	0.04	0.86	7.26E-09	224,215	RGL3	SBP	[11]
19	rs62104477	29804084	T	0.33	0.18	1.20E-09	320,347	CCNE1	DBP	[11]
19	rs9710247	40254542	G	0.45	0.16	1.61E-09	308,028	AKT2	DBP	[70]

Table 2 (continued)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	N	Closest gene	Trait	Ref.
20	rs6108168	8645624	A	0.25	-0.21	1.10E-11	327,368	PLCB1	DBP	[11]
20	rs1327235	10988382	G	0.46	0.3	1.41E-15	158,454	JAG1	DBP	[9]
20	rs6081613	19485263	A	0.28	0.26	1.60E-13	315,546	SLC24A3	PP	[11]
20	rs80346118	48794612	A	0.15	-0.27	1.10E-12	327,614	PREX1	DBP	[11]
20	rs6015450	59176062	G	0.12	0.9	3.87E-23	159,190	EDN3, GNAS	SBP	[9]
21	rs12627651	43340723	A	0.29	0.32	2.40E-09	121,169	CRYAA, SIK1	DBP	[70]
22	rs4819852	20000644	A	0.29	0.26	1.43E-13	367,460	ARVCF	PP	[70]
22	rs73161324	41642782	T	0.05	0.5	2.80E-11	267,722	XRCC6	PP	[11]
b Asians and Africans										
<i>Asians</i>										
1	rs880315	10736809	C	0.65	0.56	3.05E-10	32,611	CASZ1	DBP	[12]
1	rs10745332	112646431	A	0.82	0.96	2.52E-09	46,269	MOV10	SBP	[13]
2	rs1344653	19531084	A	0.53	-0.27	7.79E-12	220,853	OSR1	PP	[73]
2	rs1275988	26691496	T	0.53	-0.37	4.95E-21	236,311	KCNK3	OH	[73]
2	rs7604423	43155602	C	0.66	-0.21	2.40E-08	217,072	NR	DBP	[73]
2	rs6736587	81628601	C	0.16	-1.38	5.3E-08	NA	CTNNA2	OH	[74]
2	rs16849225	164050310	C	0.61	0.75	3.45E-11	49,511	GRB14, FIGN	SBP	[12]
3	rs820430	27507409	A	0.32	0.76	1.36E-12	79,318	SLC4A7	SBP	[13]
3	rs9810888	53601568	G	0.39	0.39	4.0E-12	77,555	CACNA1D	DBP	[13]
4	rs1902859	80236549	C	0.41	1.34	1.76E-22	45,856	FGF5	SBP	[13]
4	rs2014912	85794517	T	0.16	0.62	5.37E-17	242,456	ARHGAP24	SBP	[73]
4	rs6825911	110460482	C	0.51	0.39	8.96E-09	49,511	ENPEP	DBP	[12]
4	rs13143871	155698052	T	0.80	0.96	5.16E-08	45,737	GUCY1A3	SBP	[13]
5	rs1173766	32804422	C	0.60	0.63	1.95E-08	49,970	NPR3	SBP	[12]
5	rs13359291	123140763	A	0.31	0.53	8.88E-16	229,584	PRDM6	SBP	[73]
5	rs9687065	149011577	A	0.78	0.26	7.36E-11	259,216	ABLIM3, SH3TC2	DBP	[73]
6	rs2021783	32077074	C	0.79	0.49	2.18E-12	78,911	CYP21A2	DBP	[13]
6	rs1563788	43340625	T	0.31	0.51	2.22E-16	220,757	ZNF318	SBP	[73]
6	rs1474698	56199399	T	0.62	-0.20	4.52E-09	274,981	NR	PP	[73]
7	rs2107595	19009765	A	0.23	0.31	3.91E-11	209,305	HDAC9	PP	[73]
7	rs10260816	45970501	C	0.61	0.31	1.51E-14	207,070	IGFBP3	PP	[73]
7	rs17477177	106771412	T	0.77	-0.53	3.69E-12	99,344	PIK3CG	PP	[73]
10	rs4919669	102712218	A	0.43	-0.65	2.63E-08	NA	ARL3	SBP	[74]
10	rs284844	102794772	A	0.49	-0.75	1.05E-11	NA	WBP1L	SBP	[74]
10	rs4409766	102856906	T	0.71	1.24	6.08E-17	46,030	CYP17A1	SBP	[13]
10	rs11191548	103086421	T	0.74	1.18	3.94E-17	41,315	CNNM2	SBP	[12]
10	rs11191580	103146454	T	0.74	0.97	4.44E-15	NA	NT5C2	SBP	[74]
11	rs4757391	16281393	C	0.28	0.88	5.20E-9	46,336	SOX6	SBP	[13]
11	rs751984	61510774	T	0.79	0.33	7.66E-12	233,082	LRRC10B, SYT7	MAP	[73]
12	rs12579720	20020830	C	0.32	-0.32	2.2E-16	218,606	PDE3A	DBP	[73]
12	rs17249754	89666809	G	0.64	1.17	7.72E-20	40,719	ATP2B1	SBP	[12]
12	rs3184504	111446804	T	0.46	0.54	2.20E-10	35,342	SH2B3	DBP	[73]
12	rs653178	111569952	T	0.50	-0.55	1.20E-08	35,342	ATXN2	DBP	[73]
12	rs11066280	112379979	T	0.75	1.01	1.32E-35	46,957	HECTD4	DBP	[12]
12	rs35444	115114632	A	0.75	0.52	9.62E-08	29,746	TBX3	DBP	[12]
12	rs11067763	115760536	A	0.62	0.51	2E-18	79,651	MED13L	DBP	[13]

Table 2 (continued)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	N	Closest gene	Trait	Ref.
17	rs2240736	61408032	T	0.66	0.35	2.20E-16	217,197	C17orf82, TBX2	MAP	[73]
18	rs403814	6282594	A	NA	1.15	6.13E-09	NA	L3MBTL4	HT	[75]
19	rs740406	2232222	A	0.87	-0.55	3.10E-15	193,219	PLEKHJ1, DOT1L	PP	[73]
20	rs1887320	10985350	A	0.53	0.78	1.48E-08	46,123	JAG1	SBP	[13]
<i>Africans</i>										
3	rs1717027	41946428	T	0.64	0.49	4.90E-13	29,322	ULK4	HT	[76]
6	rs13209747	126794309	T	0.19	0.56	2.40E-11	28,708	RSPO3	DBP	[76]
6	rs76987554	133759717	C	0.09	-1.69	2.28E-10	62,297	TARID, TCF21	SBP	[15]
6	rs17080102	150683634	C	0.1	-0.74	1.90E-11	29,323	PLEKHG1	DBP	[76]
7	rs6969780	27119517	C	0.3	0.46	3.27E-10	85,397	HOXA	DBP	[15]
7	rs17428471	27298248	T	0.14	1.20	2.00E-12	29,326	HOXA, EVX1	SBP	[76]
7	rs11563582	27312031	A	0.13	0.67	1.71E-11	84,816	EVX1, HOXA	DBP	[15]
7	rs7801190	100860471	C	0.72	1.31	3.40E-08	10,771	SLC12A9	HT	[77]
8	rs7006531	94098516	G	0.85	-1.02	5.96E-12	72,887	CDH17	PP	[15]
8	rs78192203	141364973	T	0.2	0.84	4.00E-11	62,681	GPR20	DBP	[15]
9	rs115795127	83378986	T	0.89	0.17	1.13E-08	32,149	FRMD3	HT	[15]

Chr, chromosome; EA, effect allele; EAF, effect allele frequency; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; HT, hypertension; OH, orthostatic hypotension; NA, not available.

loci for mean arterial pressure. The latest GWAS among UK Biobank participants of European ancestry included ~140,000 subjects from a single source at the discovery phase. With dense 1000 Genomes Project and UK10K imputation, they yielded a data set with ~9.8 million variants for the meta-analysis. With the help of major international consortia for parallel replication, they included GWAS data from 330,956 individuals in total and reported 107 significant loci, among which 24 were associated with systolic BP (SBP), 41 with diastolic BP (DBP), and 42 with PP [11].

The first large meta-analysis of GWAS on BP traits among East Asians was conducted by the Asian Genetic Epidemiology Network (AGEN) consortium [12]. Our group was one of the 8 groups participating in stage 1 meta-analysis, which included 19,608 individuals totally. After de novo genotyping in two stages of replication involving 10,518 and 20,247 East Asian samples, we confirmed 7 loci previously identified in the European population reported by Global BPgen and CHARGE, and additionally identified 6 novel loci: ST7L-CAPZA1, FIGN-GRB14, ENPEP, NPR3, TBX3, and ALDH2. In another meta-analysis of a Han Chinese population, which involved 11,816 subjects in the discovery stage and 69,146 subjects for replication [13], the authors replicated 8 previously reported loci and 4 novel loci: CASZ1, MOV10, FGF5, CYP17A1, SOX6, ATP2B1, ALDH2, JAG1, CACNA1D, CYP21A2, MED13L, and SLC4A7. These findings suggest a possible presence of allelic heterogeneity in BP regulation between Europeans and Asians and provide new mechanistic insight into hypertension.

African-descent populations are the most ancestral and have smaller regions of linkage disequilibrium due to the accumulation of more recombination events in that group, so that GWAS performed on Africans need more SNPs with better overall genomic coverage [14].

Table 3. Significant loci for coronary artery disease reported by genome-wide association studies in Europeans (a) and Asians (b)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	n	Closest gene	Ref.
a Europeans									
1	rs11206510	55030366	T	0.85	1.08	2.34E-08	188,372	PCSK9	[19]
1	rs17114036	56497149	A	0.91	1.17	3.81E-19	133,226	PPAP2B	[47]
1	rs629301	109275684	NA	NA	NA	1.00E-49	NA	CELSR2	[78]
1	rs11810571	151789832	G	0.79	1.06	4.34E-08	345,035	TDRKH	[20]
1	rs6689306	154423470	A	0.44	1.05	1.50E-09	NA	IL6R	[20]
2	rs16986953	19742712	A	0.07	1.11	4.80E-10	NA	AKO97927	[20]
2	rs7568458	85561052	A	0.45	1.06	2.40E-13	NA	VAMP5, VAMP8, GGCX	[20]
2	rs17678683	144528992	G	0.09	1.10	3.00E-09	179,585	ZEB2, ACO74093.1	[19]
2	rs1250229	215439661	T	0.26	1.07	2.88E-13	270,189	FN1	[20]
3	rs7623687	49411133	A	0.86	1.08	3.54E-10	333,836	RHOA	[20]
3	rs142695226	124756354	G	0.14	1.07	1.58E-09	345,188	UMPS, ITGB5	[20]
3	rs9818870	138403280	T	0.15	1.15	7.44E-13	40,773	MRAS	[44]
3	rs12493885	154122077	C	0.87	1.07	3.23E-08	251,805	ARHGEF26	[20]
4	rs17087335	56972417	T	0.21	1.06	4.60E-08	NA	NOA1, REST	[19]
4	rs10857147	80259918	T	0.27	1.05	5.81E-09	345,133	PRDM8, FGF5	[20]
4	rs7678555	119988346	C	0.28	1.05	1.35E-08	345,126	PDE5A, MAD2L1	[20]
4	rs6841581	147480038	A	0.15	1.07	4.60E-10	NA	EDNAA	[20]
6	rs6909752	22612400	A	0.33	1.05	2.26E-09	343,171	HDGFL1	[20]
6	rs17609940	35067023	G	0.75	1.07	1.36E-08	137,412	ANKS1A	[47]
6	rs56336142	39166323	T	0.81	1.07	1.85E-08	188,349	KCNK5	[19]
6	rs12190287	133893387	C	0.62	1.08	1.70E-12	130,888	TCF21	[47]
6	rs10455872	160589086	G	0.07	1.31	1.70E-49	NA	LPA	[20]
6	rs4252185	160702419	C	0.06	1.34	1.64E-32	NA	PLG	[19]
7	rs2107595	19009765	A	0.18	1.08	3.40E-13	NA	HDAC9	[20]
7	rs11556924	130023656	C	0.62	1.09	9.18E-18	134,200	ZC3HC1	[47]
7	rs3918226	150993088	T	0.07	1.13	1.60E-12	NA	NOS3	[20]
8	rs2954029	125478730	A	0.54	1.06	5.20E-13	NA	TRIB1	[20]
9	rs579459	133278724	C	0.21	1.10	4.08E-14	123,978	ABO	[47]
10	rs2505083	30046193	C	0.39	1.06	6.85E-09	169,421	KIAA1462	[19]
10	rs501120	44258419	T	0.87	1.33	9.46E-08	7,181	CXCL12	[17]
10	rs2246942	89245129	G	0.35	1.08	3.50E-16	NA	LIPA	[20]
10	rs12413409	102959339	G	0.89	1.12	1.03E-09	129,741	NT5C2, CNNM2, CYP17A1	[47]
11	rs10840293	9729649	A	0.55	1.05		NA	SWAP70	[20]
11	rs3993105	13281524	T	0.68	1.05	4.88E-08	340,699	ARNTL	[20]
11	rs974819	103789839	T	0.32	1.07	2.41E-09	64,881	PDGFD	[46]
11	rs964184	116778201	NA	NA	NA	2.00E-108	NA	ZPR1	[78]
12	rs3184504	111446804	T	0.42	1.07	1.03E-09	NA	SH2B3	[19]
12	rs11830157	117827636	G	0.36	1.12	2.12E-09	NA	KSR2	[19]
12	rs2244608	120979185	G	0.35	1.05	7.90E-10	345,106	HFN1A	[20]
13	rs1924981	28448508	T	0.33	1.05	1.90E-07	NA	FLT1	[20]
14	rs2895811	99667605	C	0.43	1.07	1.14E-09	114,238	HHIPL1	[47]
15	rs56062135	67163292	C	0.79	1.07	4.52E-09	184,037	SMAD3	[19]
15	rs7164479	78830712	T	0.58	1.07	6.40E-18	NA	ADAMTS7	[20]
15	rs8042271	89030987	G	0.90	1.10	3.68E-08	162,206	MFG8, ABHD2	[19]

Table 3 (continued)

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	n	Closest gene	Ref.
15	rs17514846	90873320	A	0.44	1.05	3.10E-07	NA	FURIN, FES	[19]
16	rs7500448	83012185	A	0.77	1.06	4.90E-10	337,399	CDH13	[20]
17	rs216172	2223210	C	0.37	1.07	1.15E-09	111,538	SMG6, SRR	[47]
17	rs46522	48911235	T	0.53	1.06	1.81E-08	137,633	UBE2Z	[47]
17	rs7212798	60936127	C	0.15	1.08	1.88E-08	188,377	BCAS3	[19]
18	rs8082812	8522684	NA	NA	NA	5.00E-67	NA	THEMIS3P – AKR1B1P6	[78]
18	rs663129	60171168	A	0.26	1.06	3.20E-08	NA	PMAIP1, MC4R	[19]
19	rs6511720	11091630	G	0.88	1.14	7.90E-22	NA	LDLR	[20]
19	rs12976411	32391114	A	0.09	1.49	1.18E-14	NA	ZNF507, LOC400684	[19]
19	rs8108632	41348629	T	0.48	1.05	4.13E-08	345,058	TGFB1	[20]
19	rs4420638	44919689	NA	NA	NA	1.00E-22	NA	APOC1 – APOC1P1	[78]
19	rs1964272	45687010	G	0.52	1.05	2.52E-08	343,548	SNAPD2	[20]
21	rs28451064	34221526	A	0.12	1.14	2.60E-23	NA	KCNE2	[20]
21	rs460976	41463567	NA	NA	NA	1.00E-08	NA	MX1 – TMPRSS2	[78]
22	rs180803	24262890	G	0.97	1.20	1.64E-10	174,076	POM121L9P, ADORA2A	[19]
b Asians									
2	rs2123536	19745816	T	0.39	1.12	6.83E-11	33,466	TTC32, WDR35	[48]
4	rs1842896	155590307	T	0.76	1.14	1.26E-11	33,466	GUCY1A3	[48]
6	rs9349379	12903725	G	0.349	1.34	8.02E-10	4,496	PHACTR1	[79]
6	rs9268402	32373576	G	0.59	1.16	2.77E-15	33,466	BTNL2, C6orf10	[48]
6	rs12524865	133875536	C	0.61	1.11	1.87E-07	24,724	TCF21	[48]
9	rs10738607	22088095	G	0.64	0.78	2.37E-08	1,237	CDKN2A, CDKN2B	[80]
12	rs7136259	89687411	T	0.39	1.11	5.68E-10	33,466	ATP2B1	[48]
12	rs3782889	110912851	C	0.21	1.26	3.95E-14	13,742	MYL2	[81]
12	rs671	111803962	A	0.23	1.43	1.6E-34	12,041	ALDH2	[82]
12	rs11066280	112379979	A	0.17	1.19	1.69E-11	24,741	C12orf51	[48]

Chr, chromosome; EA, effect allele; EAF, effect allele frequency; NA, not available.

There are fewer loci reaching GWAS significance in African populations than in Europeans or Asians. The largest GWAS performed in an African-origin population analyzed 21 GWAS comprising 31,968 individuals of African ancestry and validated their results with an additional 54,395 individuals from multiethnic studies [15]. The authors found 9 loci with 11 independent variants for either SBP, DBP, hypertension, or combined traits.

Coronary Artery Disease

Heritability of CAD has been estimated between 40 and 60% based on family and twin studies [16]. The first robust locus associated with CAD identified by GWAS was reported in 2007 [6, 17, 18], when three independent groups reported common variants at the 9p21 locus. It was associated with a ~30% increased risk of CAD per copy of the risk allele. Since then, progressively larger-sample-size meta-analyses of additional GWAS, mainly on subjects of European descent, have identified additional loci of smaller effect size. In 2015, the CARDIoGRAMplusC4D Consortium published a GWAS meta-analysis of 185,000 CAD cases and

controls, interrogating 6.7 million common variants as well as 2.7 million low-frequency variants [19]. In this study, the authors confirmed most CAD loci known at that time and identified 10 novel loci. The majority of the significant loci had a frequency of more than 5%, which indicated that the genetics of CAD was largely determined by the cumulative effect of multiple common risks of small effect size and strongly supported the common disease/common variant hypothesis. In 2017, Nelson et al. [20] further meta-analyzed the results from 10,801 cases in the UK Biobank against 137,914 controls in combination with the CARDIoGRAMplusC4D 1000 Genomes and the MIGen/CARDIoGRAM Exome chip studies. They found 12 new signals reaching genome-wide significance. They also reported that 304 independent variants meeting the 5% false discovery rate threshold explained 21.2% of CAD heritability. This finding highlighted the importance of the false discovery rate approach in the expansion of associated variants. The strongest SNPs associated with CAD which had reached genome-wide significance are listed in Table 3a and b.

Although the majority of GWAS for CAD has been carried out on European populations, there were still important studies performed on Asian and Black populations with smaller sample sizes [19]. Unlike the similar effect sizes of CAD risk alleles in East Asian and European populations, the effect size was apparently attenuated in South Asian and Black populations. The lower level of linkage disequilibrium in the African genome might lead to failure to tag potentially shared causal variants [21].

Clinical Implications

It is undeniable that GWAS have achieved considerable success in exploring the genetic architecture of heart diseases. However, it is important to point out that the significant variant is often merely tagged. The gene indicated by the GWAS signal would not be considered as the causal variant until the functional mechanism can be found. The ultimate goals of the study of the genetics of CAD or hypertension are to understand the pathophysiological mechanism and subsequently to establish risk prediction methods and develop effective therapeutic strategies (Fig. 1).

The effect of the susceptibility variants identified by GWAS is small individually, but their effects are independent and additive, which can be calculated as a genetic risk score (GRS) in an unweighted manner by adding risk allele numbers or with a weighted mean [22]. As DNA is stable over the course of the lifetime, a genetic risk can be ascertained from birth; therefore, GRS may be particularly useful in risk prediction among younger patients in whom the cumulative impact of lifestyle factors is less pronounced.

The interpretation of GWAS often is complicated by the nature of significant loci, which are mostly located in the intergenic region. Bioinformatic approaches could narrow down the list, prioritizing a gene for subsequent functional study according to expression quantitative trait locus [23], genome-wide chromatin profiles of histone modifications, data on transcription factor-binding sites, chromatin immunoprecipitation sequencing [24], etc. Below, we describe some examples of clinical implications of GWAS results for risk prediction and mechanism interpretation.

Hypertension

With the expansion of significant BP loci by GWAS, robust associations with some biological candidate genes previously suspected to influence BP were detected. The latest GWAS by Warren et al. [11] identified multiple loci involved in BP regulation, including angiotensin-converting enzyme, voltage-dependent calcium channel auxiliary subunit, metallo-endopeptidase/neutral endopeptidase, adrenergic β 2B receptor, and phosphodiesterase 5a.

Fig. 1. Clinical implications from genome-wide association studies (GWAS).

Moreover, in the pathway analysis, they also showed an enrichment of pathways associated with cardiovascular disease, including the α -adrenergic pathway, CXCR4 chemokine signaling pathway, endothelin system, and angiotensin-receptor pathways.

In the ICBP GWAS [10], the difference in SBP and DBP between the top and the bottom quintile of the GRS was 4.6 and 3.0 mm Hg, respectively. Furthermore, the GRS generated by combination of 107 loci by Warren et al. [11] showed that the group with GRS in the lowest quintile had an SBP approximately 9–10 mm Hg lower than those with GRS in the highest quintile. Reductions in BP of such a magnitude might lead to significantly lower cardiovascular morbidity and mortality among hypertensive patients. The GRS could therefore be useful in early life to assess the risk of hypertension and direct dietary or lifestyle modifications.

The GWAS findings had also provided clues for personalized prevention and treatment of hypertension. One good example is the uromodulin gene (UMOD), which was identified in an extreme case-control design [25]: rs1333226-G in UMOD showed an association with lower risk of hypertension and reduced urinary UMOD excretion. Uromodulin is mainly expressed in the thick portion of the ascending limb of the loop of Henle, which indicates that it may participate in BP regulation through an effect on sodium hemostasis. Trudu et al. [26] modeled the effect of UMOD in transgenic mice and demonstrated that uromodulin influenced BP through activation of the renal sodium cotransporter NKCC2. The subjects with the UMOD risk variant had increased UMOD excretion, greater salt sensitivity, hypertension, and a greater BP response to loop diuretics. This finding presents an opportunity for hypertension precision medicine and new drug development.

The AGEN study [12] found an ethnicity-specific locus on 12q24.13, where the acetaldehyde dehydrogenase (ALDH2) gene is located. ALDH2 is a key enzyme in the major pathway of alcohol metabolism, and glutamate-lysine substitution (rs671, E504K) produces an inactive subunit of ALDH2, resulting in an inability to metabolize acetaldehyde and subsequent accumulation of acetaldehyde after alcohol intake [27]. The SNP rs671 is not polymorphic in Europeans, but it is close to rs3184504 at the SH2B3 locus, which is significantly associated with BP in Europeans and has no polymorphism in East Asians. This phenomenon indicates the natural selection that has occurred. Furthermore, rs671 displays pleiotropic effects both on risk factors for cardiovascular disease and on CAD susceptibility. Interestingly, the locus exhibits a deleterious effect on BP but has protective effects on HDL cholesterol and LDL

cholesterol, which results in a net reduction in CAD risk. Moreover, most of the associations between rs671 and each of the cardiovascular risk factors are influenced by alcohol intake.

Coronary Artery Disease

Since 2007, nearly 70 distinct genetic loci for CAD have been found due to the progressively larger sample sizes. A minority of all these risk variants appears to modulate CAD risk by influencing classic risk factors such as plasma lipids, diabetes, and hypertension, reinforcing the key role for these pathways in the development of CAD. The rest of the risk variants identified by GWAS are located in regulatory regions of unclear function.

In a large prospective cohort study with a median of 10.7 years of follow-up, Ripatti et al. [28] found that individuals with a GRS in the top quintile derived from 13 multilocus SNPs of CAD exhibited a 1.66-fold increased risk adjusting for traditional risk factors. However, the GRS did not improve the C-index over the traditional risk factors and family history or the net reclassification of risk categories. A recent survey on 55,685 subjects from three prospective studies and one cross-sectional study confirmed the association between GRS and incidence of CAD [29], with subjects in the top GRS quintiles having a 91% higher relative risk than those in the bottom quintiles. They also reported that a favorable lifestyle was associated with a relative risk of CAD nearly 50% lower than with an unfavorable lifestyle.

The 9p21.3 locus was the first one identified by GWAS, consisting of a cluster of 59 linked SNPs in a 53,000-bp region [30]. Among the CAD risk alleles, rs10811656 and rs10757278 are located in an enhancer element and disrupt a binding site for ATAT1 [31]. This enhancer locus interacts with CDKN2A/B and IFNA21, which encodes interferon- γ in human vascular endothelial cells and participates in the inflammatory process. It is also suggested that this region probably encodes for a long noncoding RNA designated as ANRIL (antisense noncoding RNA in the INK4 locus). ANRIL influences the expression of CDKN2A/B, which is involved in regulating the cell cycle and cellular proliferation [32]. A meta-analysis also confirmed that the 9p21.3 locus increases the burden of atherosclerosis but not the risk of myocardial infarction, which indicated the stimulatory effect of this locus in atherosclerosis [33].

The 1p13 locus has been independently associated with CAD in several GWAS. Among a number of genes located in this region, SORT1 was found as the target one by expression quantitative trait locus and expression studies. SORT1 encodes sortilin, which is a multiligand type 1 receptor and is expressed in many cell and tissue types [34]. Overexpression of Sort1 might decrease the very-low-density lipoprotein secretion rate and increase plasma low-density lipoprotein turnover [35]. However, the knockout or knockdown of Sort1 in different studies resulted in either increased or decreased very-low-density lipoprotein secretion [36, 37]. Whether Sort1 was the gene causing CAD or just a signal found in the GWAS still needs to be clarified. The concrete molecular mechanism by which sortilin influences lipid metabolism and CAD risk has not yet been elucidated.

Perspectives

The GWAS findings have identified novel biological signals involved in human heart diseases. However, there are still certain challenges. The heritability of BP as derived from family studies varies from 30 to 50%, but the collective effect of all BP loci identified through GWAS only explains ~3.5% of BP heritability. The missing heritability is not unique to BP genetics but is universally observed in almost all common heart diseases. Heritability reflects the degree of phenotypic resemblance between relatives, which not only depends on the genetic architecture contributing to the trait but also is the result of environmental factors and interactions within the genome. In GWAS on hypertension-related phenotypes, signif-

icant gene-environment interaction has been identified for alcohol consumption [38], body mass index, smoking [39], educational level, and other modifiable lifestyle factors. These findings may help identify the causal genetic loci that contribute to missing heritability. In addition, gene-gene interaction [40], rare variants [41], and epigenetic mechanisms likely explain a certain fraction of complex heart diseases. Future research will focus on the application of variants identified in GWAS for the identification of individuals at risk of disease, guidance of clinical management decisions, and prediction of prognosis.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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