

Gene-centric Meta-analysis in 87,736 Individuals of European Ancestry Identifies Multiple Blood-Pressure-Related Loci

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Table S1: Clinical Characteristics of the IBC-array genotyped cohorts present in this study

Discovery Cohorts	Age	Female/Male	SBP	DBP	MAP	PP	BMI	Taking anti-hypertensive medication
AIBILI	52.8 ± 9.2	249/209	119.9 ± 13.7	75.4 ± 7.6	90.2 ± 8.8	44.5 ± 10.3	25.7 ± 3.6	0.0%
AMC-PAS	42.9 ± 5.3	180/563	128.6 ± 17.9	79.9 ± 10.7	96.1 ± 12.1	48.8 ± 13.1	26.9 ± 4.1	33.2%
Amish	47.6 ± 15.0	713/691	121.9 ± 16.5	75.3 ± 9.4	90.8 ± 10.8	46.6 ± 12.2	27.3 ± 5.0	16.4%
ARIC	54.2 ± 5.7	5124/4453	118.3 ± 17	71.5 ± 10	87.1 ± 11.3	46.7 ± 12.7	26.9 ± 4.9	25.1%
ASCOT	63 ± 8.1	224/1015	161.4 ± 17.8	92.9 ± 9.9	115.7 ± 10.6	68.5 ± 16.1	29.1 ± 4.6	89.2%
BHS	22.5 ± 4.4	291/228	111.5 ± 10.2	71.8 ± 8.5	85 ± 8.3	39.7 ± 8	24.7 ± 6.1	2.7%
BRIGHT (controls)	58.7 ± 8.9	1088/647	123 ± 10.5	76.4 ± 7.2	91.9 ± 7.5	46.7 ± 8.3	25.3 ± 3.3	0.0%
BRIGHT (cases)	58 ± 10.3	1144/775	154.3 ± 21.1	93.9 ± 11.3	114 ± 13.3	60.4 ± 15.7	58 ± 10.3	92.5%
BWHHS	68.85 ± 5.51	337/30	146.53 ± 26.59	79.16 ± 12.85	102 ± 15	67.6 ± 19	27.25 ± 5.95	30.2%
CARDIA	40.6 ± 4.1	703/623	102.2 ± 30.5	71.9 ± 11.2	84.5 ± 11.4	37.7 ± 8.8	26.9 ± 6.4	3.7%
CCCS	64.2 ± 9.7	555/1402	136.94 ± 19.04	78.33 ± 10.61	156.48 ± 23.57	58.61 ± 15.69	29.2 ± 4.8/28.4 ± 6.5	88.7%
CFS	40.9 ± 19.9	302/252	121.1 ± 16.6	71.8 ± 11.7	88.2 ± 12.2	49.3 ± 12.4	30.1 ± 8.8	8.8%
CHS	72.6 ± 6.3	2208/1722	135.3 ± 21.5	69.9 ± 11.6	91.7 ± 12.9	65.4 ± 18.6	26.3 ± 4.8	39.7%
CLEAR	67.8 ± 9.6	0/1365	151.4 ± 22.4	82.2 ± 12.3	105.3 ± 13.8	69.2 ± 18.4	28.1 ± 5.0	67.0%
EHLRS-BOSS-BDES	58.1 ± 8.8	1965/1552	131.7 ± 20.9	78.8 ± 11.5	96.5 ± 13.6	52.9 ± 14.7	30.2 ± 5.9	32.98%
EPIC_NL	54.06 ± 10.11	4057/1137	133.13 ± 21.22	80.46 ± 10.93	97.98 ± 13.20	52.65 ± 15.68	26.77 ± 4.45	N/A
FHS	40.9 ± 9.1	3775/3134	118.6 ± 14.3	76.4 ± 9.8	90.5 ± 10.6	42.2 ± 9.4	26.1 ± 5	5.5%
GIRAFH	44.5 ± 11.7	882/812	134.9 ± 19.2	82.0 ± 10.5	99.7 ± 12.3	52.9 ± 14.4	25.1 ± 3.5	9.3%
GRAPHIC	39.30 ± 14.50	1004/1020	127.09 ± 17.84	79.12 ± 10.96	95.1 ± 12.5	48 ± 11.9	26.11 ± 4.61	6.7%
GQ2	65.5 ± 10.5	385/93	130.51 ± 22.40	72.71 ± 12.89	149.78 ± 27.66	57.81 ± 18.47	29.7 ± 7.7/29.5 ± 6.3	76.2%
INVEST	69.4 ± 9.5	467/580	160.8 ± 17.4	90.6 ± 10.1	114.0 ± 10.6	70.1 ± 15.9	29.0 ± 4.7/28.4 ± 6.2	82.6%
LURIC	58.1 ± 8.6	558/1480	151.2 ± 24.4	89.8 ± 12.1	110.3 ± 15.0	61.4 ± 17.6	27.7 ± 4.2	85.6%
MDC	57.8 ± 5.9	1074/772	115.6 ± 5.8	73.6 ± 5.3	87.6 ± 4.7	42 ± 6	24.3 ± 3.3	100.0%
MEDAL	62.9 ± 9.0	1178/2820	136.8 ± 16.0	81.7 ± 9.6	94.9 ± 8.6	52.9 ± 11.5	30.5 ± 6.3	1.4%
MESA	62.7 ± 10.3	1199/1097	123.5 ± 20.8	70.1 ± 10.2	87.9 ± 12.3	53.4 ± 16.7	27.8 ± 5.1	33.3%
MONICA/KORA F3	57.6 ± 8.1	755/649	131.8 ± 19.4	83.3 ± 10.3	99.5 ± 12.6	48.5 ± 13.2	27.8 ± 4.5	30.1%
MONICA/KORA S12	51.8 ± 9.9	431/549	133.6 ± 19.1	81.5 ± 11.1	98.8 ± 12.5	52.1 ± 14.6	27.2 ± 4.0	16.6%
NBS	41.36 ± 12.37	1183/1169	N/A	N/A	N/A	N/A	N/A	N/A
NORDIL	56 ± 4	979/940	177.3 ± 14.6	105.9 ± 5.5	129.7 ± 7.1	71.5 ± 13.9	28.3 ± 4.6	0.0% a
NSHS95	49.4 ± 18.4	857/899	126.6 ± 17.7	76.7 ± 11.6	93.3 ± 11.8	49.9 ± 15.8	27.1 ± 5.5	N/A
PEAR	50.1 ± 9.4	194/244	151.8 ± 12.4	98.0 ± 5.7	115.9 ± 6.9	53.7 ± 10.8	[30.3 ± 4.4/30.4 ± 6.1]	0%
PennCAC	56.0 ± 8.0	631/1145	132 ± 23.2	72.4 ± 11.2	52.6 ± 12.6	59.5 ± 19.7	29.8 ± 5.9	N/A
PennCath	52.0 ± 9.0	739/1386	127 ± 15.1	76.7 ± 9.5	62.9 ± 10.5	51.9 ± 12.3	30.1 ± 5.9	32.8%
Procardis	59.34 ± 9.93	1634/1564	130.75 ± 17.11	79.63 ± 10.03	96.7 ± 11.2	51.1 ± 13.4	26.81 ± 4.37	19.3%
SMART	59.36 ± 12.25	206/299	158.64 ± 18.57	94.76 ± 11.80	116.06 ± 12.87	63.88 ± 13.78	27.35 ± 4.62	39.4%
WHI	68.0 ± 6.6	7606/0	133.0 ± 18.8	75.0 ± 9.7	94.3 ± 11.0	58.0 ± 16.2	28.3 ± 6.2	33.3%
WHII	60.83 ± 6.0	1845/3210	128.1 ± 16.7	74.6 ± 10.5	92.4 ± 11.8	53.5 ± 11.2	26.7 ± 4.3	22.8%
Total		49758/40496						

a No medication for two weeks prior to when BP was measured.

Replication Cohorts	Age	Female/Male	SBP	DBP	MAP	PP	BMI	Taking anti-hypertensive medication
GBPG cohorts (Nature Genetics 2009) b								
BLSA	42.4 ± 13.2	311/397	119.5 ± 15.0	77.3 ± 10.2	N/A	N/A	24.5 ± 3.6	5.2%
B58C – T1DGC	44.3 ± 0.3	1315/1265	121.7 ± 15.3	79.4 ± 10.5	N/A	N/A	27.4 ± 4.9	4.7%
B58C – WTCCC	44.9 ± 0.4	736/737	126.7 ± 15.2	79.1 ± 10.2	N/A	N/A	27.4 ± 4.7	4.2%
CoLaus	51.7 ± 9.5	2634/2335	127.3 ± 17.4	79.4 ± 10.8	N/A	N/A	25.8 ± 4.6	16.0%
EPIC- Norfolk - GWAS	57.2 ± 7.8	1134/966	136.7 ± 19.1	83.9 ± 11.9	N/A	N/A	26.3 ± 3.9	16.0%
Finland	45.0 ± 7.3	785/616	122.8 ± 16.3	75.5 ± 10.7	N/A	N/A	27.1 ± 4.9	5.5%
InCHIANTI	56.9 ± 14.5	309/253	138.4 ± 20.1	81.4 ± 10.1	N/A	N/A	27.1 ± 4.2	23.7%
KORA	52.5 ± 10.1	838/806	133.4 ± 18.5	81.8 ± 10.9	N/A	N/A	27.3 ± 4.1	17.0%
NFBC1966		31 2476/2285	125.2 ± 13.8	77.5 ± 11.7	N/A	N/A	24.6 ± 4.2	2.0%
SardINIA	40.8 ± 15.3	2279/1719	128.7 ± 28.4	79.7 ± 17.3	N/A	N/A	25.1 ± 4.6	10.0%
SHIP	45.0 ± 13.9	1754/1556	133.1 ± 20.2	83.5 ± 11.3	N/A	N/A	26.9 ± 4.7	16.3%
SUVIMAX	50.5 ± 6.2	1094/729	120.9 ± 12.3	78.0 ± 8.1	N/A	N/A	23.5 ± 3.3	0.0%
TwinsUK	45.8 ± 11.9	873/0	122.9 ± 15.4	78.2 ± 10.3	N/A	N/A	24.8 ± 4.6	22.0%
DGI controls	56.1 ± 8.7	651/626	133.3 ± 18.4	80.1 ± 10.0	N/A	N/A	26.7 ± 3.8	18.0%
FUSION NGT controls	58.2 ± 10.7	509/529	139.4 ± 19.3	81.5 ± 10.3	N/A	N/A	27.1 ± 4.0	21.0%
MiGen controls	48.9 ± 8.3	426/695	127.1 ± 17.8	80.2 ± 11.6	N/A	N/A	27.1 ± 5.2	13.4%
LIFELINES	47.3 ± 11.2	4640/3483	127.9 ± 15.7	75.1 ± 9.1	52.7 ± 11.8	92.7 ± 10.3	26.3 ± 4.3	15.5%
PREVEND	49.6 ± 12.5	1752/1869	129.1 ± 19.9	74.1 ± 9.9	54.9 ± 13.9	92.4 ± 12.5	26.1 ± 4.3	14.2%
WGHS	54.2 ± 7.1	22625/0	125.5 ± 16.4	78.0 ± 10.7	93.8 ± 11.9	47.6 ± 10.4	25.9 ± 5.0	12.9%
Total		47141/20866						

DBP = diastolic blood pressure

SBP = systolic blood pressure

MAP = median arterial pressure

PP = pulse pressure

BMI = body mass index

Means±Standard deviation is given for each phenotype, except % where indicated.

MAP and PP demographics were not available for the GBPG cohorts.

Discovery cohorts : Allied Irish Bank Workers Study III (AIBILI); Academic Medical Center Amsterdam Premature Atherosclerosis Study (AMC-PAS); Atherosclerosis Risk in Communities (ARIC); Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT); Bogalusa Heart Study (BHS); British Genetics of Hypertension (BRIGHT); British Women's Heart and Health Study (BWHHS); Coronary Artery Risk Development in Young Adults (CARDIA); Cleveland Clinic CHARISMA Study (CCCS); Cleveland Family Study (CFS); Cardiovascular Health Study (CHS); Carotid Lesion Epidemiology And Risk (CLEAR); European Prospective Investigation into Cancer and Nutrition in the Netherlands (EPIC-NL); Framingham Heart Study (FHS); Genetic Identification of Risk factors in Familial Hypercholesterolemia (GIRAFH); Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC); Heredity and Phenotype Intervention (HAPI) in the Amish; International Verapamil SR Trandolapril Study (INVEST); Ludwigshafen Risk and Cardiovascular Health Study (LURIC); Malmo Diet and Cancer (MDC) Study; Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program; Multi-Ethnic Study of Atherosclerosis (MESA); MONICA Cooperative Health Research in the Region of Augsburg Study (KORA (F3 and S12 subst)); Nordic Dilatation (NORDIL) Study; Pharmacogenomics Evaluation of Antihypertensive Responses (PEAR); University of Pennsylvania Coronary Artery Calcification Study (PennCAC); University of Pennsylvania Catheterization study program (PennCATH); Second Manifestations of ARterial disease SMART) and Women's Health Initiative (WHI); Whitehall II study (WHII). †Members of the NHLBI Candidate gene Association Resource (CARE).

b The Global BPgen (GBPG) consortium comprises 17 GWAS studies: the Baltimore Longitudinal Study of Aging (BLSA), British 1958 Birth Cohort (B58C-T1DGC and B58C-WTCCC), Cohorte Lausannoise (CoLaus), Diabetes Genetics Initiative (DGI), European Prospective Investigation of Cancer-Norfolk-Genome Wide Association Study (EPIC-Norfolk-GWAS), Finland Study, Finland-United States Investigation of NIDDM Genetics (FUSION) study, Invecchiare in Chianti (InCHIANTI), Kooperative Gesundheitsforschung in der Region Augsburg (KORA), the Myocardial Infarction Genetics Consortium (MiGen), Northern Finland Birth Cohort of 1966 (NFBC1966), SardINIA, Study of Health in Pomerania (SHIP), Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) and TwinsUK. The PROCARDIS data submitted to GBPG was excluded as this study contributed to the discovery analyses.

Table S4. eQTL supporting information on BP associated SNPs

Locus	IndexSNP	eSNP	r ² (index to eSNP)	Tissue	Reference	eSNP.p	Chr	Pos (B36)	ArrayID	Transcript	isCis?	Best eSNP/transcript	Best eSNP.p	Tissue	‡ Best to BP eSNP	D'
2	rs2854275	rs2187668	1	Monocytes		4.82E-95	6	32713862		HLA-DRB4	Y	rs2187668	4.82E-95	Monocytes	Same	Same
2	rs2854275	rs2187668	1	Blood	Fehrmann et al 20	3.20E-59	6	32713862	780403	HLA-DRB1	Y	rs2187668	3.20E-59	Blood(Fehrmann et al)	Same	Same
2	rs2854275	rs2187668	1	Liver	Schröder et al 201	1.31E-10	6	32713862		HLA-DRB4	Y	rs2187668	1.31E-10	Liver(Schroder)	Same	Same
3	rs2282978	rs2282978	IndexSNP	CR:Norm		0.00002616	7	92102346	10023821866	CDK6	Y	Index SNP	0.00002616	CR:Norm	Index SNP	Index SNP
4	rs4746172	rs10824069	1	Lung		<2E-16	10	75532802	100300544_TGI_at	ADK	Y	rs10824069	<2E-16	Lung	Same	Same
5	rs217727	rs217727	IndexSNP	LCL (MuTHER)	Grundberg et al 2f	2.40E-06	11	1973484	ILMN_1830423	AK126915	Y	Index SNP	2.40E-06	LCL (MuTHER)	Same	Same
5	rs217727	rs217727	IndexSNP	Skin (MuTHER)	Grundberg et al 2f	6.59E-06	11	1973484	ILMN_1830423	AK126915	Y	Index SNP	6.59E-06	Skin (MuTHER)	Same	Same
6	rs757081	rs757081	IndexSNP	LCL in asthmatics (Liang 1kg)	Liang et 2013	1.56E-16	11	17308259	229838_at	NUCB2	Y	rs214083	3.28E-45	LCL in asthmatics (Liang 1kg)	0.415	1
6	rs757081	rs757081	IndexSNP	LCL (MuTHER)	Grundberg et al 2f	3.10E-05	11	17308259	ILMN_1799381	SNORD14A	Y	rs1541533	6.17E-44	LCL (MuTHER)	0.034	1
7	rs3741378	rs2306365	0.898	Lymph		2.54E-15	11	65183922	hmm1261-5	PCNXL3	Y	rs2306365	2.54E-15	Lymph	Same	Same
7	rs3741378	rs11227247	0.92	VC:All		7.60E-11	11	65179429	10023850638	MALAT1	Y	rs11227247	7.60E-11	VC:All	Same	Same
7	rs3741378	rs11227247	0.92	Omental Adipose	Dobrin et al 2011	2.16E-08	11	65179429	10023850638	MALAT1	Y	rs11227247	2.16E-08	omental	Same	Same
7	rs3741378	rs7101916	0.879	SubCutAdipose(Greenawalt)	Greenawalt et al 2	4.70E-07	11	65187936	10023850638	MALAT1	Y	rs7101916	4.70E-07	SubCutAdipose(Greenawalt)	Same	Same
7	rs3741378	rs7101916	0.879	CR:All		7.47E-06	11	65187936	10023850638	MALAT1	Y	rs7101916	7.47E-06	CR:All	Same	Same
7	rs3741378	rs11227247	0.92	Liver(UChicago)		0.005228942	11	65179429	A_23_P161624	FOSL1	Y	rs11227247	0.00522894	Liver(UChicago)	Same	Same
7	rs3741378	rs11227247	0.92	Lymph		1.61E-14	11	65179429	hmm1261-5	PCNXL3	Y	rs2306365	2.54E-15	Lymph	0.915	1
9	rs33063	rs33063	IndexSNP	BcellsTransformed_HapMapJPT		9.55E-08	16	68197718	GI_40217627-5	LOC283970	Y	rs9939092	4.74E-21	BcellsTransformed_HapMapJPT	Unknown	Unknown

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Table S6. ENCODE supporting data on BP associated SNPs

Sentinel SNP	Chr	Genome position (hg19)	Highest scoring Proxy SNP	Combined functional score	r2 LD	D' LD	RegulomeDB ζ	Gene ID	Entrez_ID	Cardiovascular Disease (MESH)	Vascular Disease (MESH)	Hypertension (MESH)	Regulation of Blood Pressure (GO)	direct interactor with Hypertension MESH gene	MESH candidate	Functional Candidate (<4 score)	Literature Candidate	Druggable annotation
rs1682312	2	183210447	rs864417		5	0.77	0.93	Chromatin_Str	PDE1A	5136	No	No	Yes	Class 2: tools available
rs2854275	6	32623223	rs9273327		1	0.59	0.77	Single_Nucleo	HLA-DQB1	3119	No	Yes	Yes	Non-druggable
rs2854275	6	32713862	rs2854275	eQTL					HLA-DRB4	3126	No	Yes	No	Non-druggable
rs2282978	7	92264410	rs2282978		2	1	1	Motifs PWM L	CDK6	1021	.	y	.	Y	Yes	Yes	Yes	Class 2:tools available
rs1022400	7	151403260	rs57807319		2	0.77	0.91	Motifs Footprir	PRKAG2	51422	.	.	.	Y	Yes	Yes	Yes	Non-druggable
rs4746172	10	75853796	rs10824069		5	0.98	1	Motifs PWM P	VCL	7414	.	.	.	Y	Yes	No	Yes	Class 4 :predicted dru
rs4746172	10	75883129	rs201890718		3	0.92	0.96	Motifs PWM R	AP3M1	26985	.	.	.	Y	Yes	Yes	No	Non-druggable
rs4746172	10	75911680	rs3812639		2	0.5	0.96	Motifs PWM F	ADK	132	.	.	.	Y	Yes	Yes	No	Class 2:tools available
rs217727	11	1973484	rs217727	eQTL					AK126915		No	Yes	No	Non-druggable
rs217727	11	2002472	rs10840140		4	0.7	0.93	Motifs Footprir	MRPL23	6150	No	No	No	Non-druggable
rs217727	11	2011205	rs11564745		2	0.52	0.83	Motifs PWM Z	MRPL23-AS1	1E+08	No	Yes	No	Non-druggable
rs217727	11	2021980	rs2525883		2	0.79	0.91	Motifs Footprir	H19	283120	.	.	.	Y	Yes	Yes	Yes	Non-druggable
rs757081	11	17230850	rs140613036		2	0.5	0.74	Motifs PWM C	PIK3C2A	5286	No	Yes	No	Class 3:Gene Related
rs757081	11	17260918	rs10832750		1	0.52	0.83	Single_Nucleo	NUCB2	4925	.	.	.	Y	Yes	Yes	Yes	Class 4 :predicted dru
rs757081	11	17308259	rs757081	eQTL					SNORD14A	26822	No	Yes	No	Non-druggable
rs757081	11	17375260	rs10535629		2	0.57	-0.87	Motifs Footprir	NCR3LG1	374383	No	Yes	No	Class 4 :predicted dru
rs757081	11	17405617	rs1002226		4	0.52	-0.81	Chromatin_Str	KCNJ11	3767	Y	.	Y	.	Yes	No	Yes	Class 1:Drug on Mark
rs3741378	11	65380124	rs1078457		4	0.52	0.93	Chromatin_Str	MAP3K11	4296	.	.	.	Y	Yes	No	No	Class 2:tools available
rs3741378	11	65384727	rs12790427		2	0.56	0.99	Motifs PWM L	PCNXL3	399909	No	Yes	No	Class 4 :predicted dru
rs3741378	11	65408937	rs3741378		1	1	1	Chromatin_Str	SIPA1	6494	No	Yes	No	Non-druggable
rs3741378	11	65422591	rs7119750		4	0.9	0.97	Chromatin_Str	RELA	5970	.	.	.	Y	No	No	Yes	Class 2:tools available
rs3741378	11	65484719	rs2236683		4	0.79	0.93	Chromatin_Str	KAT5	10524	.	.	.	Y	Yes	No	No	Class 2:tools available
rs3741378	11	65499692	rs12361032		6	0.61	0.81	Motifs PWM P	RNASEH2C	84153	No	No	No	Non-druggable
rs3741378	11	65549506	rs61895678		5	0.51	0.73	Motifs PWM A	AP5B1	91056	No	No	No	Non-druggable
rs7297416	12	54417576	rs736825		3	0.6	0.91	Motifs PWM K	HOXC5	3222	.	.	.	Y	Yes	Yes	No	Non-druggable
rs7297416	12	54424123	rs7308105		2	0.52	0.82	Motifs PWM Z	HOXC6	3223	.	.	.	Y	Yes	Yes	No	Non-druggable
rs7297416	12	54445215	rs199718335		2	0.79	0.95	Motifs PWM R	HOXC4	3221	.	.	.	Y	Yes	Yes	No	Non-druggable
rs1036477	15	48793615	rs77360718		2	0.77	0.94	Motifs Footprir	FBN1	2200	Y	Y	.	Y	Yes	Yes	Yes	Non-druggable
rs33063	16	68197718	rs33063	eQTL					LOC283970		No	Yes	No	Non-druggable
rs33063	16	69548788	rs7200764		7	0.7	0.86	No data	CYB5B	80777	No	No	No	Non-druggable
rs33063	16	69590366	rs1549287		1	0.87	0.94	Single_Nucleo	NFAT5	10725	.	.	.	Y	Yes	Yes	Yes	Non-druggable
rs33063	16	69742387	rs56125990		6	0.82	-0.9	Motifs PWM N	NQO1	1728	.	.	.	Y	Yes	No	Yes	Class 1:Drug on Mark
rs33063	16	69775500	rs17299478		1	0.71	-0.86	Single_Nucleo	NOB1	28987	No	Yes	No	Non-druggable
rs33063	16	69795323	rs56140069		6	0.59	-0.82	Motifs PWM M	WWP2	11060	No	No	Yes	Non-druggable