Title

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Journal

Hypertension, 63(4)

ISSN

0194-911X

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Publication Date

2014-04-01

DOI

10.1161/hypertensionaha.113.02077

Peer reviewed

Identifying Common Genetic Variants in Blood Pressure Due to Polygenic Pleiotropy With Associated Phenotypes

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Abstract—Blood pressure is a critical determinant of cardiovascular morbidity and mortality. It is affected by environmental factors, but has a strong heritable component. Despite recent large genome-wide association studies, few genetic risk factors for blood pressure have been identified. Epidemiological studies suggest associations between blood pressure and several diseases and traits, which may partly arise from a shared genetic basis (genetic pleiotropy). Using genome-wide association studies summary statistics and a genetic pleiotropy-informed conditional false discovery rate method, we systematically investigated genetic overlap between systolic blood pressure (SBP) and 12 comorbid traits and diseases. We found significant enrichment of single nucleotide polymorphisms associated with SBP as a function of their association with body mass index, low-density lipoprotein, waist/hip ratio, schizophrenia, bone mineral density, type 1 diabetes mellitus, and celiac disease. In contrast, the magnitude of enrichment due to shared polygenic effects was smaller with the other phenotypes (triglycerides, high-density lipoproteins, type 2 diabetes mellitus, rheumatoid arthritis, and height). Applying the conditional false discovery rate method to the enriched phenotypes, we identified 62 loci associated with SBP (false discovery rate <0.01), including 42 novel loci. The observed polygenic overlap between SBP and several related disorders indicates that the epidemiological associations are not mediated solely via lifestyle factors but also reflect an etiologic relation that warrants further investigation. The new gene loci identified implicate novel genetic mechanisms related to lipid biology and the immune system in SBP. **(*Hypertension*. 2014;63:819-826.)** ● **Online Data Supplement**

Key Words: arterial pressure ■ comorbidity ■ genetic pleiotropy ■ genome-wide association study

High blood pressure affects >1 billion individuals,[1] and even small increments increase morbidity and mortality. Though heritability estimates of systolic blood pressure (SBP) exceed 50%,[2,3] genes identified to date explain only a small proportion of heritability.[4] It has been argued that the genetic architecture of blood pressure regulation in the general population cannot be explained by commonly occurring genetic variation, suggesting that genome-wide association studies (GWAS) will continue to fail in hypertension.[5,6] However, recent results indicate that GWAS have the potential to explain a greater proportion of heritability of most common complex phenotypes.[7,8] This polygenic architecture suggests that a large number of single nucleotide polymorphisms (SNPs) will have associations too weak to be identified using traditionally used analytic methods and limited sample sizes.[9] This has led to recent National Institutes of Health and European Union calls for new cost-effective analytical methods to reliably identify a larger proportion of SNPs associated with complex diseases and traits using existing GWAS, because recruitment and genotyping of new participants are expensive. One such approach relies on genetic pleiotropy,[10] that is, the association of individual SNPs or genes with ≥2 phenotypes. Given the large number of traits in humans, and the relatively small number of genes, some genes are likely to affect multiple traits. Moreover, because there are often overlapping traits among behaviorally or clinically defined phenotypes, shared genetic influences between such phenotypes are likely.

Received July 21, 2013; first decision August 14, 2013; revision accepted December 6, 2013.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.02077/-/DC1.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.113.02077**

Epidemiological studies have identified several major risk factors for cardiovascular diseases (CVDs),[11,12] including hypertension, obesity, diabetes mellitus, and dyslipidemia.[1,13–15] Several other traits and disorders have also been associated with blood pressure, including height,[2,3,16] osteoporosis,[4,17] schizophrenia,[5,6,18] diabetes mellitus,[7,8,19] and autoimmune disorders.[9,20] However, observational and clinical studies cannot fully elucidate the etiologic relationship between these phenotypes. Methods for assessing genetic pleiotropy offer great promise for delineating the basis of shared phenotypic correlations and for cost-effective identification of new loci.[10,21,22] This could be particularly meaningful for essential hypertension, where multiple pathogenic processes are likely involved[11,12,23] and overlapping genetic associations with multiple phenotypes may be frequent. Here, we applied a recently developed genetic pleiotropy-informed analytical method for GWAS that captures more of the polygenic effects in complex disorders and traits (hereafter referred to as polygenic pleiotropy).[22] We used this approach to leverage the power of multiple large independent GWAS for identifying SNPs exhibiting pleiotropy between SBP and 12 associated traits and disorders where recent GWAS results are available, namely, bone mineral density (BMD),[24] low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides (TG),[25] type 2 diabetes mellitus (T2D),[26] body mass index (BMI),[27] waist/hip ratio (WHR),[28] height (HT),[29] schizophrenia (SCZ),[30] type 1 diabetes mellitus (T1D),[31] rheumatoid arthritis (RA),[32] and celiac disease (CeD).[33,34] By combining data from these different GWAS, we hypothesized that the genetic pleiotropy-informed approach can improve the discovery of SBP genes and inform the etiologic relationship between blood pressure and epidemiologically related phenotypes.

Methods

Participant Samples

We obtained complete GWAS results in the form of summary statistics *P* values from public access websites or through collaboration with investigators (Table 1). Details of inclusion criteria and phenotype characteristics of different GWAS are described elsewhere.[4,25–28] There was some overlap among several of the participants in the CVD risk factor GWAS and the SBP GWAS samples.[4] The relevant institutional review boards or ethics committees approved the research protocol of individual GWAS, and all participants gave written informed consent. All studies adhered to the principles of the Declaration of Helsinki.

Statistical Analyses

Genomic Control

We applied a control method using only intergenic SNPs to compute the inflation factor, λ_{GC}, and divided all test statistics by λ_{GC}, as detailed in previous publications.[21,22]

Conditional Quantile-Quantile Plots for Pleiotropic Enrichment

Enrichment of statistical association relative to that expected under the global null hypothesis can be visualized through quantile-quantile (Q-Q) plots of nominal *P* values obtained from GWAS summary statistics. Genetic enrichment results in a leftward shift in the Q-Q curve, corresponding to a larger fraction of SNPs with nominal $-\log_{10}$ *P* value greater than or equal to a given threshold. Conditional Q-Q plots are constructed by creating subsets of SNPs based on the significance of each SNP's association with a related phenotype and computing Q-Q plots separately for each level of association (for further details, see Andreassen et al[21,22]). We constructed conditional Q-Q plots of empirical quantiles of nominal $-\log_{10}(P)$ values for SNP association with SBP for all SNPs and for subsets of SNPs determined by nominal *P* values of their association with each of the 12 related phenotypes [$-\log_{10}(P)\geq 0$, $-\log_{10}(P)\geq 1$, $-\log_{10}(P)\geq 2$, and $-\log_{10}(P)\geq 3$ corresponding to $P\leq 1$, ≤ 0.1, ≤ 0.01, and ≤ 0.001, respectively]. The nominal *P* values [$-\log_{10}(P)$] are plotted on the *y* axis and the empirical quantiles [$-\log_{10}(q)$, where $q=1-\mathrm{CDF}(P)$] are plotted on the *x* axis. To assess polygenic effects, we focused the conditional Q-Q plots on SNPs with nominal $-\log_{10}(P)<7.3$ (corresponding to $P>5\times10^{-8}$).

Conditional False Discovery Rate

Enrichment seen in the conditional Q-Q plots can be directly interpreted in terms of false discovery rate (FDR)[21,22] (equivalent to [1–true discovery rate]).[35] We applied a conditional FDR method[22,36,37] and constructed true discovery rate plots, as described earlier[21,22] and detailed in the online-only Data Supplement.

Table 1. Genome-Wide Association Studies Data Used in the Current Study

Disease/Trait	N	Number of SNPs	Reference
Systolic blood pressure	203 056	2 382 073	International Consortium for Blood Pressure Genome-Wide Association Studies[4]
Low-density lipoprotein	99 900	2 508 375	Teslovich et al[25]
High-density lipoprotein	96 598	2 508 370	
Triglycerides	96 568	2 508 369	
Height	183 727	2 398 527	Lango Allen et al[29]
Body mass index	123 865	2 400 377	Speliotes et al[27]
Waist/hip ratio	77 167	2 376 820	Heid et al[28]
Type 2 diabetes mellitus	22 044	2 426 886	Voight et al[26]
Type 1 diabetes mellitus	16 559	841 622	Barrett et al[31]
Rheumatoid arthritis	25 708	2 560 000	Stahl et al[32]
Bone mineral density	32 961	2 500 000	Estrada et al[24]
Celiac disease	15 283	528 969	Dubois et al[34]
Schizophrenia	21 856	1 171 056	Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium[30]

For more details, see also http://www.genome.gov/gwastudies. SNP indicates single nucleotide polymorphism.

Conditional Statistics: Test of Association With SBP

To improve detection of SNPs associated with SBP, we conditioned SNPs based on *P* values in the related phenotype.[21,22] We then assigned a conditional FDR value (denoted as $FDR_{SBP \mid related\ phenotype}$) for SBP to each SNP, for each related phenotype by interpolation, using a 2-dimensional look-up table of conditional FDR values[21,22] computed for each of the specific data sets used in the current study (Figure S3 in the online-only Data Supplement). All SNPs with $FDR_{SBP \mid related\ phenotype}<0.01$ [$-\log_{10}(FDR_{SBP \mid related\text{-}phenotype})>2$] in SBP given association with any of the 12 related phenotypes are listed in Table 1 after pruning (ie, removing all SNPs with $r^2>0.2$ based on 1000 Genomes Project linkage disequilibrium [LD] structure). A significance threshold of FDR<0.01 corresponds to 1 false-positive per 100 reported associations.

Conditional FDR Manhattan Plots

To illustrate the localization of genetic markers associated with SBP given the related phenotype effect, we used a conditional FDR Manhattan plot, plotting all SNPs within an LD block in relation to their chromosomal locations. The strongest signal in each LD block was identified by ranking all SNPs in increasing order, based on the conditional FDR value for SBP and then removing SNPs in LD $r^2>0.2$ with any higher ranked SNP. Thus, the selected locus was most significantly associated with SBP in each LD block.

Results

Pleiotropic Enrichment–Polygenic Overlap

Conditional Q-Q plots for SBP conditioned on nominal *P* values of association with LDL, BMI, BMD, T1D, SCZ, and CeD showed enrichment across different levels of significance (Figure 1A–1F). For LDL, the proportion of SNPs in the $-\log_{10}(P_{LDL})\geq3$ category reaching a given significance level [eg, $-\log_{10}(P_{SBP})>6$] was ≈100 times greater than for $-\log_{10}(p_{LDL})\geq0$ category (all SNPs), indicating a high level of enrichment (Figure 1A). A similar level of enrichment was seen for BMI and SCZ (Figure 1B and 1C); CeD, T1D, and BMD also showed a high level of enrichment (Figure 1D–1F). Weaker pleiotropic enrichment was seen for WHR (Figure S1), with little or no evidence for enrichment in RA, HDL, TG, T2D, and HT (Figure S1). We also illustrated the high level of polygenic pleiotropic enrichment in LDL, BMI, BMD, T1D, SCZ, and CeD using enrichment plots (Figure S2).

Gene Loci Associated With SBP

The conditional FDR Manhattan plot in Figure 2 shows the 62 independent gene loci significantly associated with SBP based on conditional FDR<0.01 obtained from associated phenotypes. The 30 complex loci and 32 single gene loci (after pruning) were located on 16 chromosomes (Table 2). Only 11 of these loci would have been discovered using standard statistical methods (Bonferroni correction; bold values in the SBP *P* value column; Table 2). Using the FDR method, 25 loci were identified (bold values in the SBP FDR column; Table 2). The remaining 37 loci would not have been identified

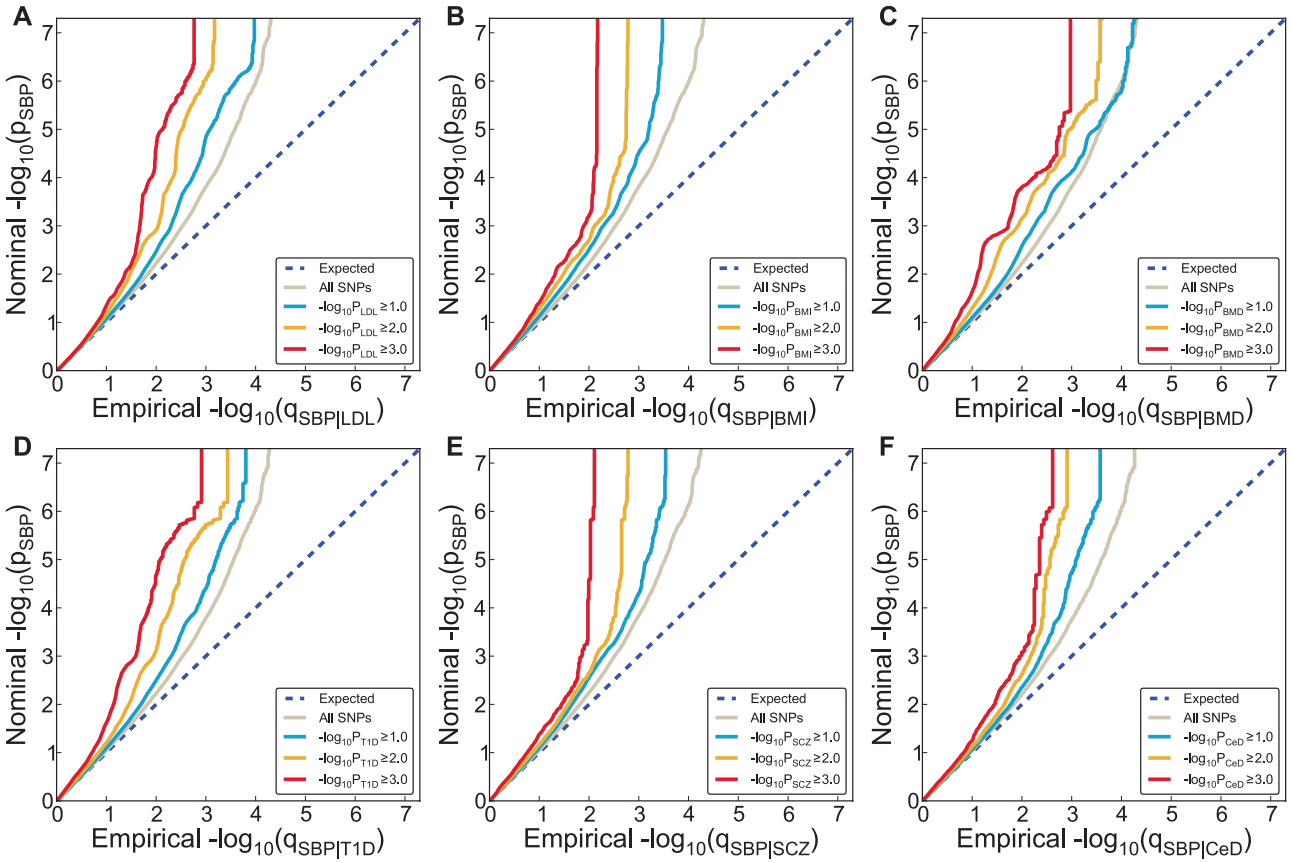

Figure 1. Quantile-quantile (Q-Q) plots of pleiotropic enrichment in systolic blood pressure (SBP) conditioned on associated phenotypes. Conditional Q-Q plot of nominal vs empirical $-\log_{10}$ *P* values (corrected for inflation) in SBP below the standard genome-wide association studies threshold of $P<5\times10^{-8}$ as a function of significance of association with (**A**) low-density lipoprotein cholesterol (LDL), (**B**) body mass index (BMI), (**C**) bone mineral density (BMD), (**D**) type 1 diabetes mellitus (T1D), (**E**) schizophrenia (SCZ), and (**F**) celiac disease (CeD) at the level of $-\log_{10}(P)>0$, $-\log_{10}(P)>1$, $-\log_{10}(P)>2$, $-\log_{10}(P)>3$ corresponding to $P<1$, <0.1, <0.01, <0.001, respectively. Dotted lines indicate the null hypothesis.

in the current sample without using the pleiotropy-informed conditional FDR method. Of the 62 loci identified, 42 were novel; 20 were reported in the primary analysis of the current sample.[4] Many of these new loci are located in regions with borderline significant association with SBP in previous studies.[4] Of interest, several loci had multiple pleiotropic SNPs from several associated phenotypes, indicating overlapping genetic factors among these phenotypes.

Follow-up ingenuity pathways analysis is presented in Tables S3 and S4, identifying the traits in the categories Cardiovascular Disease or Cardiovascular System Development and Function, respectively, that may be affected by gene heterogeneities in the vicinity of indicated SBP-associated genes. Figure S4, made by the network function in ingenuity pathways analysis, demonstrates that a large proportion of SBP-associated genes are functionally related.

Discussion

Our findings demonstrate polygenic pleiotropy between SBP and BMI, T1D, SCZ, CeD, and BMD, with strongest pleiotropy between SBP and LDL. Combining GWAS data from multiple different phenotypes, we identified 62 SBP susceptibility loci, including 42 novel loci.

In the original SBP GWAS sample, 29 loci were identified.[4] By combining the original SBP sample with GWAS of epidemiologically related phenotypes, we found significant pleiotropic signals in 62 loci. Thus, although the original SBP GWAS was quite large,[4] the increased power provided by additional GWAS of associated phenotypes together with the FDR method more than doubled gene discovery. These findings underline the cost-effectiveness of the current statistical methods and strongly suggest that SBP is a highly polygenic trait, in line with recent findings.[38]

Our findings also provide novel insights into the relationship between SBP and other major CVD risk factors, which frequently co-occur. The combination of dyslipidemia (primarily increased TG levels and decreased HDL levels), T2D, and high blood pressure forms the metabolic syndrome.[12–16] These results demonstrate an interesting genetic dissociation among cardiovascular risk factors. We found that LDL, a classic CVD risk factor, showed strongest pleiotropy with SBP, whereas factors associated with the metabolic syndrome (TG, HDL, and T2D) showed little genetic pleiotropy with SBP. Further research is needed to determine whether there is strong genetic pleiotropy among the metabolic risk factors, which would provide a genetic basis for the metabolic syndrome. The strong pleiotropy between LDL and SBP suggests that many genes related to lipid biology are pleiotropic with SBP and indicates common mechanisms related to atherosclerosis. This is further supported by the individual loci identified, of which the majority was based on conditional FDR with LDL, BMI, or WHR. Several of the genes in LD with these new SBP-associated loci are involved in lipid metabolism and regulation. Lipid metabolism regulation may also underlie the observed pleiotropy between SBP and BMD, as suggested by gene expression in bone tissue.[39] However,

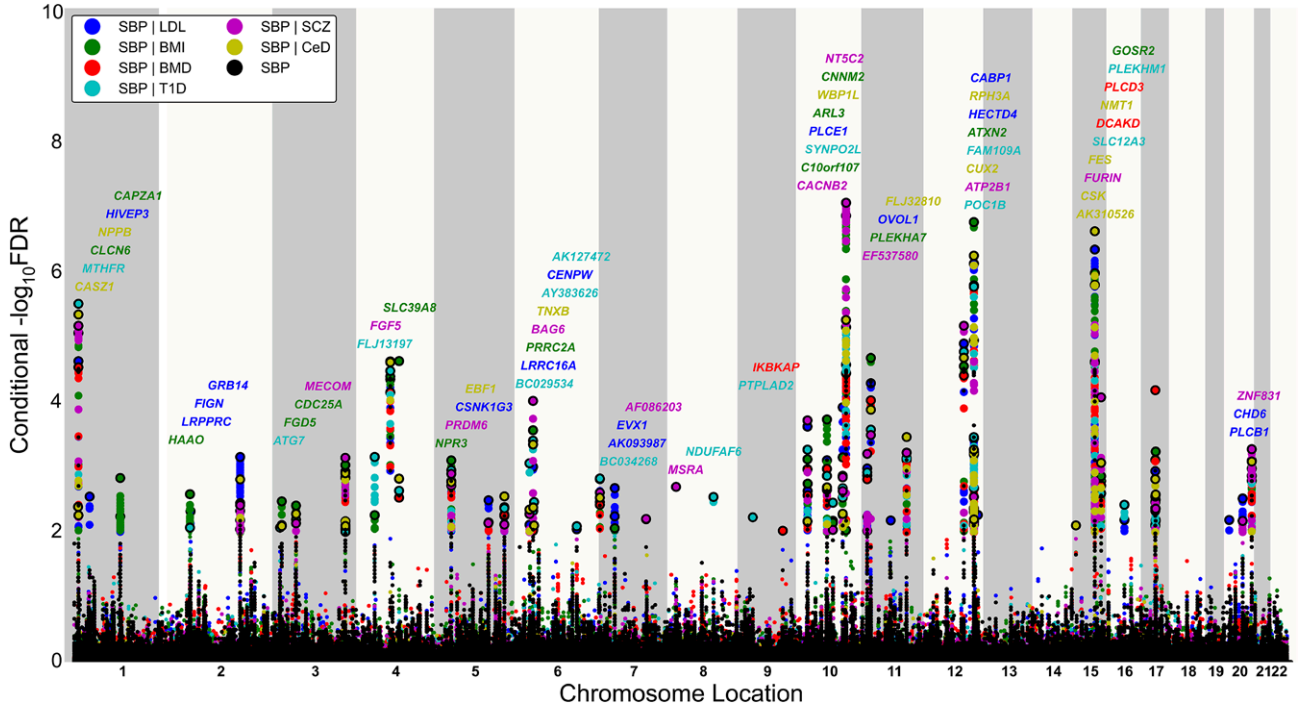

Figure 2. False discovery rate (FDR) Manhattan plot of conditional –log$_{10}$ (FDR) values for systolic blood pressure (SBP) alone (black) and SBP given the associated phenotypes low-density lipoprotein cholesterol (LDL; SBP|LDL, blue), body mass index (BMI; SBP|BMI, green), bone mineral density (BMD; SBP|BMD, red), type 1 diabetes mellitus (T1D; SBP|T1D, light blue), schizophrenia (SCZ; SBP|SCZ, purple), and celiac disease (CeD; SBP|CeD, chartreuse). Single nucleotide polymorphisms (SNPs) with conditional –log$_{10}$ FDR>2 (ie, FDR<0.01) are shown with large points. A black circle around the large points indicates the most significant SNP in each linkage disequilibrium block, and this SNP was annotated with the closest gene, which is listed above the symbols in each locus, except for the human leukocyte antigen (HLA) region on chromosome 6, and in Table S2 in the online-only Data Supplement. The figure shows the localization of 62 loci on 16 chromosomes (1–12, 15–17, and 20). Details for the loci with –log$_{10}$ FDR>2 (ie, FDR<0.01) are shown in Table 1.

Table 2. Independent Loci Associated With SBP Through Conditional False Discovery Rate (FDR; <0.01) With Associated Phenotypes

Locus	SNP	Position	Gene	Chr	SBP *P* Value	SBP FDR	Min condFDR	Associated Phenotype
1	rs2748975	1886519	*KIAA1751*	1	1.81E-06	0.01493	0.0095053	WHR
2	rs880315	10796866	*CASZ1*	1	1.44E-05	0.04983	0.0040514	CeD
3	rs17367504	11862778	*MTHFR**	1	**9.86E-11**	**0.00003**	0.0000013	WHR
	rs2050265	11879699	*CLCN6*	1	**2.38E-10**	**0.00003**	0.0000026	WHR
4	rs6676300	11925300	*NPPB*	1	1.47E-05	0.04983	0.0054695	CeD
5	rs783622	42366988	*HIVEP3*	1	1.04E-05	0.03839	0.0028136	LDL
6	rs12048528	113210534	*CAPZA1*	1	3.84E-06	0.02209	0.0014541	BMI
	rs2932538	113216543	*MOV10**	1	1.78E-06	0.01493	0.0014684	BMI
7	rs4332966	43083831	*HAAO*	2	1.58E-05	0.04983	0.0025790	BMI
8	rs9309112	44169889	*LRPPRC*	2	1.56E-05	0.04983	0.0047478	LDL
9	rs12619842	164945044	*FIGN*	2	1.01E-05	0.03839	0.0089999	LDL
	rs16849397	165108248	*GRB14*	2	4.76E-07	**0.00665**	0.0025354	WHR
10	rs2594992	11360997	*ATG7*	3	2.24E-06	0.01687	0.0076216	WHR
11	rs6806067	14948702	*FGD5*	3	2.23E-06	0.01493	0.0033240	BMI
12	rs6797587	48197614	*CDC25A*	3	1.32E-06	0.01180	0.0043919	BMI
13	rs223102	169100755	*MECOM**	3	**4.56E-08**	**0.00112**	0.0006796	WHR
14	rs9290369	169324783	*MECOM*	3	8.04E-07	**0.00909**	0.0066551	WHR
15	rs10006384	38385187	*FLJ13197*	4	2.71E-06	0.01687	0.0054382	BMI
16	rs1458038	81164723	*FGF5**	4	**1.08E-09**	**0.00004**	0.0000228	WHR
17	rs13107325	103188709	*SLC39A8**	4	1.55E-07	**0.00271**	0.0000229	BMI
18	rs1173743	32775047	*NPR3*	5	4.78E-07	**0.00665**	0.0007773	BMI
	rs1173771	32815028	*C5orf23**	5	8.44E-08	**0.00162**	0.0004338	WHR
19	rs458158	122482181	*PRDM6*	5	6.76E-06	0.02945	0.0071865	SCZ
20	rs11750782	122976743	*CSNK1G3*	5	6.75E-06	0.02945	0.0070289	BMD
21	rs11953630	157845402	*EBF1**	5	3.64E-07	**0.00558**	0.0029954	WHR
22	rs199205	7736417	*BMP6*	6	2.29E-06	0.01687	0.0076216	WHR
23	rs9467445	25234884	*BC029534*	6	2.20E-06	0.01493	0.0011956	T1D
24	rs11754013	25370200	*LRRC16A*	6	1.32E-05	0.04368	0.0076472	LDL
25	rs2736155	31605199	*PRRC2A (BAT2)**	6	1.41E-06	0.01180	0.0002670	BMI
	rs805303	31616366	*BAG6 (BAT3)**	6	8.17E-07	**0.00909**	0.0000941	SCZ
26	rs429150	32075563	*TNXB*	6	1.70E-05	0.04983	0.0090475	LDL
27	rs394199	33553580	*GGNBP1 (AY383626)*	6	3.96E-05	0.08570	0.0034152	T1D
28	rs581484	126665180	*CENPW (C6orf173)*	6	3.08E-06	0.01922	0.0089438	LDL
29	rs853964	127029267	*AK127472*	6	2.63E-06	0.01687	0.0076216	WHR
30	rs2969070	2512545	*BC034268*	7	2.64E-07	**0.00386**	0.0014814	T1D
31	rs3735533	27245893	*HOTTIP (AK093987)*	7	1.37E-05	0.04368	0.0056631	LDL
32	rs7777128	27337113	*EVX1*	7	6.04E-06	0.02945	0.0020776	LDL
33	rs7787898	106409897	*AF086203*	7	2.60E-06	0.01687	0.0062017	SCZ
34	rs3088186	10226355	*MSRA*	8	1.97E-05	0.05707	0.0019924	SCZ
35	rs4735337	95973465	*NDUFA6 (C8orf38)*	8	3.54E-05	0.07505	0.0028564	T1D
36	rs12006112	21042299	*PTPLAD2*	9	5.02E-05	0.09719	0.0058735	T1D
37	rs4978374	111646983	*IKBKAP*	9	9.87E-06	0.03839	0.0094345	BMD
38	rs12570727	18425519	*CACNB2**	10	**4.07E-08**	**0.00093**	0.0001882	SCZ
39	rs12258967	18727959	*CACNB2*	10	1.42E-07	**0.00271**	0.0015659	WHR

(*Continued*)

Table 2. Continued

Locus	SNP	Position	Gene	Chr	SBP *P* Value	SBP FDR	Min condFDR	Associated Phenotype
40	rs4590817	63467553	*C10orf107**	10	**3.40E-08**	**0.00077**	0.0001588	WHR
41	rs12247028	75410052	*SYNPO2L*	10	1.59E-06	0.01328	0.0067916	WHR
42	rs932764	95895940	*PLCE1**	10	1.47E-07	**0.00271**	0.0001182	LDL
43	rs10786156	96014622	*PLCE1*	10	2.51E-06	0.01687	0.0020927	BMI
44	rs10883766	104464763	*ARL3*	10	1.91E-05	0.05707	0.0071447	CeD
	rs284844	126665180	*WBP1L (C10orf26)*	10	**5.48E-09**	**0.00015**	0.0000039	BMI
	rs1926032	127029267	*CNNM2*	10	**2.77E-10**	**0.00003**	0.0000001	BMI
	rs11191548	2512545	*NT5C2**	10	**2.43E-10**	**0.00003**	0.0000001	SCZ
45	rs7129220	27245893	*EF537580**	11	6.92E-08	**0.00135**	0.0006154	SCZ
46	rs1580005	27337113	*EF537580*	11	2.80E-06	0.01687	0.0057696	LDL
47	rs381815	106409897	*PLEKHA7**	11	**1.25E-09**	**0.00005**	0.0000205	BMI
48	rs642803	10226355	*OVOL1*	11	1.14E-05	0.04368	0.0065527	LDL
49	rs633185	95973465	*FLJ32810**	11	**2.98E-08**	**0.00077**	0.0004474	WHR
50	rs11105328	21042299	*POC1B (WDR51B)*	12	**5.35E-10**	**0.00003**	0.0000080	SCZ
	rs2681472	111646983	*ATP2B1**	12	**5.14E-13**	**0.00003**	0.0000062	SCZ
51	rs7297186	18425519	*CUX2*	12	1.88E-06	0.01493	0.0005328	CeD
	rs3742004	18727959	*FAM109A*	12	6.39E-07	**0.00783**	0.0003417	WHR
	rs653178	63467553	*ATXN2*	12	**4.58E-10**	**0.00003**	0.0000002	BMI
	rs1005902	75410052	*HECTD4 (C12orf51)*	12	2.62E-06	0.01687	0.0005845	LDL
	rs12580178	95895940	*RPH3A*	12	4.21E-06	0.02209	0.0007345	LDL
52	rs7299238	96014622	*CABP1*	12	6.25E-05	0.10892	0.0053975	LDL
53	rs11070252	104464763	*GOLGA8T (AK310526)*	15	3.86E-06	0.02209	0.0078255	CeD
54	rs1378942	75077367	*CSK**	15	**1.63E-10**	**0.00003**	0.0000002	CeD
55	rs8032315	91418297	*FURIN*	15	1.83E-07	**0.00323**	0.0000828	SCZ
	rs2521501	91437388	*FES**	15	7.16E-08	**0.00162**	0.0011762	WHR
56	rs11643718	56933519	*SLC12A3*	16	3.30E-05	0.07505	0.0037698	T1D
57	rs4793172	43131480	*DCAKD*	17	7.05E-07	**0.00783**	0.0040625	SCZ
	rs2239923	43176804	*NMT1*	17	3.97E-07	**0.00558**	0.0008079	BMD
	rs12946454	43208121	*PLCD3*	17	5.17E-08	**0.00112**	0.0000647	BMD
58	rs11012		*PLEKHM1*	17	4.12E-05	0.08570	0.0034152	T1D
59	rs17608766		*GOSR2**	17	4.59E-07	**0.00665**	0.0005684	BMI
60	rs6055905		*PLCB1*	20	3.04E-05	0.07505	0.0064506	LDL
61	rs6072403		*CHD6*	20	5.59E-06	0.02552	0.0058812	LDL
62	rs6015450		*ZNF831**	20	5.63E-08	**0.00135**	0.0006154	SCZ

Independent complex or single-gene loci (r^2<0.2) of single nucleotide polymorphisms (SNPs) with a conditional FDR (condFDR)<0.01 in systolic blood pressure (SBP) given the significance level in the associated phenotype. We defined the most significant SBP SNP in each linkage disequilibrium (LD) block based on the minimum condFDR (min condFDR) for each associated phenotype. The most significant SNPs in each gene of the LD block are listed along with the associated phenotype that provided the signal. BMD indicates bone mineral density; BMI, body mass index; CeD, celiac disease; Chr, chromosome location; LDL, low-density lipoprotein cholesterol; SCZ, schizophrenia; T1D, type 1 diabetes mellitus; and WHR, waist/hip ratio. SBP FDR values <0.01 and *P* values <5×10^{-8} are in bold.

*Same locus identified in previous SBP genome-wide association studies. The most significant phenotype associations per gene are shown. All genes are shown in Table S1 in the online-only Data Supplement. All data were first corrected for genomic inflation. Gene titles and gene ontology functional terms are displayed in Table S2. Ingenuity pathway analysis was used to generate a network displaying direct interactions among proteins encoded by these SBP-related genes (shown in Figure S3). The molecules associated with some of the top functional clusters of these genes are shown in Tables S3 and S4.

age-related mechanisms may also underlie the overlap seen between SBP and BMD.[40]

Pleiotropy is defined as a single gene or variant being associated with >1 distinct phenotype.[41] Rather than representing genetic pleiotropy, it is also possible that some of the loci identified in the current study may underlie common aspects of the SBP and CVD phenotypes. Moreover, the shared genetic loci may also represent mediated pleiotropy. For example, for LDL and SBP overlap may be because of the fact that lipid deposition leads to stiff arteries and thus higher blood pressure.

Another novel finding is the overlap between SBP and immune-related disorders, including CeD and T1D. Based on conditional analysis of these 2 phenotypes, 24 loci were identified. These phenotypes also showed strong polygenic pleiotropy, with clear enrichment in the Q-Q plots. Although previous studies have suggested a link between T2D and SBP, the present study found an overlap between T1D, but not T2D, and SBP, suggesting immune-mediated rather than metabolic links between diabetes mellitus and SBP. The immune-related mechanisms involved in SBP seem to be quite specific because we found little enrichment with RA, a prototypical autoimmune disorder. Moreover, although we found no or weak association with other inflammatory bowel disorders (data not shown), CeD, a T-cell–mediated disease,[42] showed much stronger enrichment. SCZ also showed strong enrichment with 12 independent SBP loci identified based on enrichment from the SCZ GWAS. In a previous study,[21] we successfully used the polygenic pleiotropy approach to increase gene discovery in SCZ by enriching on CVD risk factors, identifying a shared genetic basis for the increased CVD mortality and higher incidence of hypertension in SCZ patients.[18] Our findings of several shared loci between SBP and SCZ point to common underlying mechanisms, which warrant further experimental investigation.

Because of the overlap in some of the GWAS samples examined, we cannot exclude contribution from environmental or behavioral factors or other nongenetic correlations. Still, our genetic pleiotropy results strongly imply the existence of shared pathophysiological processes across SBP and associated phenotypes, because we controlled for pleiotropic inflation using genomic control correction of each primary single-phenotype GWAS. Moreover, the overlapping loci are located on 16 chromosomes, suggesting that the findings are not because of common genetic variation in potentially overlapping control groups. Furthermore, the GWAS of blood lipids used the same sample to discover new genes for 3 different phenotypes.[25] Because we do not have access to additional samples or individual substudies, we cannot provide evidence of replication, which is a limitation of the current study. However, we have previously shown that the genetic findings obtained using the conditional FDR approach used here replicate at the same or higher rate compared with findings obtained with traditional GWAS methods. Importantly, we have also demonstrated that these FDR-based methods increase sensitivity for a given specificity, thus improving statistical power for SNP detection.[22] Because of the overlap in some of the GWAS samples examined, we cannot exclude the contribution from environmental or behavioral factors or other nongenetic correlations.

Another limitation of the current study is our inability to relate the genetic findings to clinical outcomes, such as stroke and congestive heart failure, because we do not have access to clinical outcome measures. However, the current findings suggest that leveraging more powerful statistical techniques, building on empirical Bayesian mixture models, may be a fruitful approach to better select plausible candidate SNPs for improved polygenic risk scores,[43] which may lead to personalized medicine approaches and potentially individual prediction of disease risk. We are currently working toward developing prediction and stratification algorithms that incorporate multiple small effects to increase prediction and classification power.

In conclusion, we found substantial genetic overlap between SBP and several related conditions, including BMI, WHR, T1D, SCZ, CeD, BMD, and in particular LDL. This suggests an etiologic relationship between these phenotypes, which could include lipid disturbances and certain immunologic pathways.

Perspectives

The current results demonstrate the feasibility of using a genetic epidemiology framework that leverages overlap in genetic signal from independent GWAS of associated phenotypes, both for cost-effective gene discovery and for elucidating the shared genetic basis between related phenotypes. This approach identified 42 novel gene loci in SBP, arguing that GWAS have the potential to uncover more of the genetic basis of hypertension when new statistical methods are used. The observed polygenic overlap between SBP and several comorbid disorders indicates that the epidemiological associations are not mediated solely via lifestyle factors but also reflect an etiologic relation. Our findings also shed new light on the pathogenic mechanisms in SBP, which warrants further investigation. The novel genetic loci identified here implicate genetic mechanisms related to lipid biology and the immune system in SBP. These findings may have implications for early diagnosis, prevention strategies, and therapeutic regimens for hypertension.

Acknowledgments

We thank the DIAGRAM Consortium, Psychiatric Genomics Consortium Schizophrenia Working Group, Celiac Disease GWAS Consortium, and Type 1 Diabetes Consortium for the summary statistics of genome-wide association studies data.

Sources of Funding

O.A.A. was supported by the Research Council of Norway (213837), the South East Norway Health Authority (2010-074), and the Kristian Gerhard Jebsen Foundation. R.S.D. was supported by a grant from the National Institutes of Health (NIH; T32 EB005970). A.M.D. was supported by NIH grants R01AG031224, R01EB000790, and RC2DA29475. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures

None.

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Novelty and Significance

What Is New?

- We used new statistical methods to improve gene discovery.
- We identified 42 novel gene loci associated with blood pressure.
- We demonstrated shared genes between blood pressure and several associated diseases/traits.

What Is Relevant?

- The new gene loci may inform the underlying genetic mechanisms of hypertension.
- The genetic overlap with immune-mediated diseases and blood lipids suggests common mechanisms with hypertension.
- The findings may have implications for early diagnosis, prevention strategies, and therapeutic regimens in hypertension.

Summary

We identified 42 new gene loci for blood pressure and found genetic overlap between blood pressure and several associated diseases and traits, particularly immune-mediated diseases and blood lipids. This suggests an etiologic relationship between hypertension and lipid disturbances and immunologic abnormalities.

Hypertension
Journal of the American Heart Association

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International Consortium for Blood Pressure Genome-Wide Association Studies, Genetic Factors for Osteoporosis Consortium

Hypertension. 2014;63:819-826; originally published online January 6, 2014;
doi: 10.1161/HYPERTENSIONAHA.113.02077
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

ONLINE SUPPLEMENT

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Statistical Analysis

Conditional False Discovery Rate (FDR)

As we have previously described[1-3], the FDR for a given p-value cut-off value is defined as

$$FDR(p) = \pi_0 F_0(p) / F(p), \qquad [1]$$

where π_0 is the proportion of null SNPs, F_0 is the null cdf, and F is the cdf of all SNPs, both null and non-null; see below for details on this simple mixture model formulation[4]. Under the null hypothesis, F_0 is the cdf of the uniform distribution on the interval [0,1], so that Eq. [1] reduces to

$$FDR(p) = \pi_0 p / F(p), \qquad [2]$$

The cdf F can be estimated by the empirical cdf $q = N_p / N$, where N_p is the number of SNPs with p-values less than or equal to p, and N is the total number of SNPs. Replacing F by q in Eq. [2], we get

$$\text{Estimated } FDR(p) = \pi_0 p / q, \qquad [3]$$

which is biased upwards as an estimate of the FDR[4]. Replacing π_0 in Eq. [3] with unity gives an estimated FDR that is further biased upward;

$$q^* = p/q \qquad [4]$$

If π_0 is close to one, as is likely true for most GWAS, the increase in bias from Eq. [3] is minimal. The quantity 1 – p/q, is therefore biased downward, and hence is a conservative estimate of the TDR. Referring to the formulation of the Q-Q plots, we see that q* is equivalent to the nominal p-value divided by the empirical quantile, as defined earlier. Given the $-\log_{10}$ of the Q-Q plots we can easily obtain

$$-\log_{10}(q^*) = \log_{10}(q) - \log_{10}(p) \qquad [5]$$

demonstrating that the (conservatively) estimated FDR is directly related to the horizontal shift of the curves in the conditional Q-Q plots from the expected line x = y, with a larger shift corresponding to a smaller FDR[1-3]. For each subset of p-values in an associated trait, we calculated the TDR as a function of p-value in SBP using each observed p-value as a threshold, according to Eq. [5].

Pathway Analysis

The 74 different genes associated with the 62 loci are listed with complete name and gene ontology in Table S2, and were analyzed by Ingenuity Pathway Analysis (IPA) to identify clusters among these genes known to be related to SBP. In the category "Top Bio Functions", Cardiovascular Disease was among the top 5 with p-values: $2.07x10^{-3}$ – $3.68\ x10^{-2}$. These genes are associated with 19 Functional Annotations as shown in Table S3. In the category "Physiological System Development and Function", Cardiovascular System Development and Function were among the top 5 with 12 molecules as shown in Table S4.

Using the network function in IPA, we demonstrate that many of the genes have functional interactions as illustrated in Figure S2. This suggests that the genes in the vicinity of the identified SNPs are associated with the trait SBP.

Supplemental references

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Table S1. Independent loci associated with SBP through Conditional FDR with associated phenotypes.

locus	SNP	Gene	chr	SBP p-value	SBP FDR	Min cond FDR	Associated Phenotype
1	rs2748975	*KIAA1751*	1	1.81E-06	0.01493	0.0095053	WHR
2	rs880315	*CASZ1*	1	1.44E-05	0.04983	0.0040514	CeD
3	rs17367504	*MTHFR*†	1	**9.86E-11**	**0.00003**	0.0000013	WHR
	rs2050265	*CLCN6*	1	**2.38E-10**	**0.00003**	0.0000026	WHR
	rs12567136	*CLCN6*	1	**1.62E-10**	**0.00003**	0.0000023	WHR
4	rs6676300	*NPPB*	1	1.47E-05	0.04983	0.0054695	CeD
5	rs783622	*HIVEP3*	1	1.04E-05	0.03839	0.0028136	LDL
6	rs6690292	*CAPZA1*	1	6.37E-06	0.02945	0.0043802	BMI
	rs12048528	*CAPZA1*	1	3.84E-06	0.02209	0.0014541	BMI
	rs2932538	*MOV10*†	1	1.78E-06	0.01493	0.0014684	BMI
7	rs1347930	*HAAO*	2	1.68E-05	0.04983	0.0037835	BMI
	rs4332966	*HAAO*	2	1.58E-05	0.04983	0.0025790	BMI
8	rs9309112	*LRPPRC*	2	1.56E-05	0.04983	0.0047478	LDL
9	rs12619842	*FIGN*	2	1.01E-05	0.03839	0.0089999	LDL
	rs2218101	*GRB14*	2	6.66E-07	**0.00783**	0.0006895	LDL
	rs1371182	*GRB14*	2	5.20E-07	**0.00665**	0.0006913	LDL
	rs16849397	*GRB14*	2	4.76E-07	**0.00665**	0.0025354	WHR
	rs16849404	*GRB14*	2	5.80E-07	**0.00783**	0.0015277	CeD
10	rs2594992	*ATG7*	3	2.24E-06	0.01687	0.0076216	WHR
	rs2606738	*ATG7*	3	1.67E-05	0.04983	0.0084614	T1D
11	rs6806067	*FGD5*	3	2.23E-06	0.01493	0.0033240	BMI
12	rs12495221	*CDC25A*	3	2.04E-06	0.01493	0.0045240	BMI
	rs6766754	*CDC25A*	3	2.06E-06	0.01493	0.0038713	BMI
	rs6797587	*CDC25A*	3	1.32E-06	0.01180	0.0043919	BMI
13	rs223102	*MECOM*†	3	**4.56E-08**	**0.00112**	0.0006796	WHR
	rs448378	*MECOM*	3	5.21E-08	**0.00112**	0.0006796	WHR
	rs6779380	*MECOM*	3	1.31E-07	**0.00229**	0.0012231	CeD
14	rs9290369	*MECOM*	3	8.04E-07	**0.00909**	0.0066551	WHR
	rs9290370	*MECOM*	3	9.90E-07	0.01041	0.0069713	BMI
	rs7619166	*MECOM*	3	2.15E-06	0.01493	0.0080103	CeD
15	rs10006384	*FLJ13197*	4	2.71E-06	0.01687	0.0054382	BMI
	rs12509057	*FLJ13197*	4	2.85E-06	0.01922	0.0006895	T1D
16	rs1458038	*FGF5*†	4	**1.08E-09**	**0.00004**	0.0000228	WHR
17	rs13107325	*SLC39A8*†	4	1.55E-07	**0.00271**	0.0000229	BMI
18	rs1173743	*NPR3*	5	4.78E-07	**0.00665**	0.0007773	BMI
	rs1173771	*C5orf23*†	5	8.44E-08	**0.00162**	0.0004338	WHR
	rs7733331	*C5orf23*	5	1.24E-07	**0.00229**	0.0006654	WHR
	rs13154066	*C5orf23*	5	1.27E-07	**0.00229**	0.0006026	WHR
19	rs458158	*PRDM6*	5	6.76E-06	0.02945	0.0071865	SCZ

20	rs10477646	*CSNK1G3*	5	8.58E-06	0.03370	0.0031951	LDL
	rs11750782	*CSNK1G3*	5	6.75E-06	0.02945	0.0070289	BMD
21	rs4704775	*EBF1*	5	1.65E-06	0.01328	0.0075865	SCZ
	rs11953630	*EBF1*†	5	3.64E-07	**0.00558**	0.0029954	WHR
	rs12187017	*EBF1*	5	3.78E-07	**0.00558**	0.0026225	WHR
	rs12332652	*EBF1*	5	7.93E-06	0.03370	0.0040996	LDL
22	rs199205	*BMP6*	6	2.29E-06	0.01687	0.0076216	WHR
23	rs9467445	*BC029534*	6	2.20E-06	0.01493	0.0011956	T1D
	rs11755567	*BC029534*	6	3.09E-06	0.01922	0.0008619	T1D
24	rs11754013	*LRRC16A*	6	1.32E-05	0.04368	0.0076472	LDL
25	rs2736155	*PRRC2A (BAT2)*†	6	1.41E-06	0.01180	0.0002670	BMI
	rs1077393	*BAG6(BAT3)*	6	1.45E-06	0.01328	0.0003843	BMI
	rs805303	*BAG6(BAT3)*†	6	8.17E-07	**0.00909**	0.0000941	SCZ
26	rs429150	*TNXB*	6	1.70E-05	0.04983	0.0090475	LDL
	rs2269426	*TNXB*	6	2.02E-05	0.05707	0.0041353	CeD
27	rs394199	*GGNBP1 (AY383626)*	6	3.96E-05	0.08570	0.0034152	T1D
28	rs581484	*CENPW (C6orf173)*	6	3.08E-06	0.01922	0.0089438	LDL
29	rs853964	*AK127472*	6	2.63E-06	0.01687	0.0076216	WHR
30	rs2969070	*BC034268*	7	2.64E-07	**0.00386**	0.0014814	T1D
31	rs3735533	*HOTTIP (AK093987)*	7	1.37E-05	0.04368	0.0056631	LDL
32	rs7777128	*EVX1*	7	6.04E-06	0.02945	0.0020776	LDL
33	rs7787898	*AF086203*	7	2.60E-06	0.01687	0.0062017	SCZ
34	rs3088186	*MSRA*	8	1.97E-05	0.05707	0.0019924	SCZ
35	rs4735337	*NDUFA6 (C8orf38)*	8	3.54E-05	0.07505	0.0028564	T1D
36	rs12006112	*PTPLAD2*	9	5.02E-05	0.09719	0.0058735	T1D
37	rs4978374	*IKBKAP*	9	9.87E-06	0.03839	0.0094345	BMD
38	rs2357790	*CACNB2*	10	7.05E-07	**0.00783**	0.0032139	SCZ
	rs12570727	*CACNB2*†	10	**4.07E-08**	**0.00093**	0.0001882	SCZ
39	rs11014166	*CACNB2*	10	3.66E-06	0.02209	0.0023029	LDL
	rs12258967	*CACNB2*	10	1.42E-07	**0.00271**	0.0015659	WHR
40	rs2393833	*C10orf107*	10	1.52E-07	**0.00271**	0.0002575	BMI
	rs4590817	*C10orf107*†	10	**3.40E-08**	**0.00077**	0.0001588	WHR
41	rs9664184	*SYNPO2L*	10	1.76E-06	0.01328	0.0034926	T1D
	rs12247028	*SYNPO2L*	10	1.59E-06	0.01328	0.0067916	WHR
42	rs2901761	*PLCE1*	10	1.76E-07	**0.00271**	0.0001993	LDL
	rs932764	*PLCE1*†	10	1.47E-07	**0.00271**	0.0001182	LDL
	rs11187808	*PLCE1*	10	2.72E-06	0.01687	0.0035477	BMI
43	rs10786156	*PLCE1*	10	2.51E-06	0.01687	0.0020927	BMI
44	rs10883766	*ARL3*	10	1.91E-05	0.05707	0.0071447	CeD
	rs284844	*WBP1L*	10	**5.48E-09**	**0.00015**	0.0000039	BMI

		(C10orf26)					
	rs1926032	*CNNM2*	10	**2.77E-10**	**0.00003**	0.0000001	BMI
	rs943037	*CNNM2*	10	**3.17E-10**	**0.00003**	0.0000001	BMI
	rs11191548	*NT5C2*†	10	**2.43E-10**	**0.00003**	0.0000001	SCZ
	rs12220743	*NT5C2*	10	**2.89E-10**	**0.00003**	0.0000001	BMI
45	rs7129220	*EF537580*†	11	6.92E-08	**0.00135**	0.0006154	SCZ
46	rs1580005	*EF537580*	11	2.80E-06	0.01687	0.0057696	LDL
47	rs381815	*PLEKHA7*†	11	**1.25E-09**	**0.00005**	0.0000205	BMI
	rs11024074	*PLEKHA7*	11	**1.75E-08**	**0.00042**	0.0001290	CeD
48	rs642803	*OVOL1*	11	1.14E-05	0.04368	0.0065527	LDL
49	rs633185	*FLJ32810*†	11	**2.98E-08**	**0.00077**	0.0004474	WHR
	rs604723	*FLJ32810*	11	**4.49E-08**	**0.00112**	0.0003394	CeD
50	rs11105328	*POC1B (WDR51B)*	12	**5.35E-10**	**0.00003**	0.0000080	SCZ
	rs2681472	*ATP2B1*†	12	**5.14E-13**	**0.00003**	0.0000062	SCZ
51	rs7297186	*CUX2*	12	1.88E-06	0.01493	0.0005328	CeD
	rs3742004	*FAM109A*	12	6.39E-07	**0.00783**	0.0003417	WHR
	rs10774625	*ATXN2*	12	**5.61E-10**	**0.00003**	0.0000002	BMI
	rs653178	*ATXN2*	12	**4.58E-10**	**0.00003**	0.0000002	BMI
	rs1005902	*HECTD4 (C12orf51)*	12	2.62E-06	0.01687	0.0005845	LDL
	rs741334	*RPH3A*	12	5.15E-06	0.02552	0.0008286	LDL
	rs12580178	*RPH3A*	12	4.21E-06	0.02209	0.0007345	LDL
52	rs7299238	*CABP1*	12	6.25E-05	0.10892	0.0053975	LDL
53	rs11070252	*GOLGA8T (AK310526)*	15	3.86E-06	0.02209	0.0078255	CeD
54	rs4886629	*CSK*	15	**6.38E-10**	**0.00004**	0.0000008	LDL
	rs1378942	*CSK*†	15	**1.63E-10**	**0.00003**	0.0000002	CeD
	rs3784789	*CSK*	15	**5.10E-10**	**0.00003**	0.0000007	LDL
	rs12442901	*CSK*	15	**7.06E-10**	**0.00004**	0.0000008	LDL
55	rs8032315	*FURIN*	15	1.83E-07	**0.00323**	0.0000828	SCZ
	rs2521501	*FES*†	15	7.16E-08	**0.00162**	0.0011762	WHR
	rs1029420	*FES*	15	1.61E-07	**0.00271**	0.0008476	CeD
56	rs11643718	*SLC12A3*	16	3.30E-05	0.07505	0.0037698	T1D
57	rs4793172	*DCAKD*	17	7.05E-07	**0.00783**	0.0040625	SCZ
	rs2239923	*NMT1*	17	3.97E-07	**0.00558**	0.0008079	BMD
	rs12946454	*PLCD3*	17	5.17E-08	**0.00112**	0.0000647	BMD
58	rs11012	*PLEKHM1*	17	4.12E-05	0.08570	0.0034152	T1D
59	rs17608766	*GOSR2*†	17	4.59E-07	**0.00665**	0.0005684	BMI
60	rs6055905	*PLCB1*	20	3.04E-05	0.07505	0.0064506	LDL
61	rs6072403	*CHD6*	20	5.59E-06	0.02552	0.0058812	LDL
	rs4810332	*CHD6*	20	1.36E-05	0.04368	0.0030113	LDL
62	rs6026728	*ZNF831*	20	1.63E-07	**0.00271**	0.0012300	SCZ
	rs6026742	*ZNF831*	20	2.15E-07	**0.00323**	0.0008109	CeD

rs6026747	*ZNF831*	20	7.04E-08	**0.00135**	0.0005233	SCZ
rs6015450	*ZNF831*†	20	5.63E-08	**0.00135**	0.0006154	SCZ

Independent complex or single gene loci ($r^2 < 0.2$) of SNP(s) with a conditional FDR (condFDR) < 0.01 in Systolic Blood Pressure (SBP) given the significance level in the associated phenotype. We defined the most significant SBP SNP in each LD block based on the minimum condFDR (min condFDR) for each associated phenotype. The most significant SNPs in each gene of the LD block are listed along with the associated phenotype that provided the signal. Low density lipoprotein (LDL) cholesterol, body mass index (BMI), waist hip ratio (WHR), bone mineral density (BMD), type 1 diabetes (T1D), celiac disease (CeD), schizophrenia (SCZ), chromosome location (Chr). SBP FDR values < 0.01 and p-values < 5×10^{-8} are in bold. †Same locus identified in previous SBP genome-wide association studies. Gene titles and gene ontology functional terms are displayed in Table S2. All data were first corrected for genomic inflation.

Table S2 Gene titles and gene ontology function terms

Gene Symbol	Gene Title	go molecular function term
AF086203		
AK127472		
ARL3	ADP-ribosylation factor-like 3	GTPase activity /// protein binding /// GTP binding /// microtubule binding /// GDP binding /// metal ion binding
ATG7	autophagy related 7	nucleotide binding /// catalytic activity /// ubiquitin activating enzyme activity /// protein binding /// APG12 activating enzyme activity /// protein homodimerization activity
ATP2B1	ATPase, Ca++ transporting, plasma membrane 1	nucleotide binding /// catalytic activity /// calcium-transporting ATPase activity /// protein binding /// calmodulin binding /// ATP binding /// ATPase activity, coupled to transmembrane movement of ions, phosphorylative mechanism /// hydrolase activity, acting on acid anhydrides, catalyzing transmembrane movement of substances /// metal ion binding
ATXN2	ataxin 2	RNA binding /// epidermal growth factor receptor binding /// protein binding /// protein C-terminus binding
BAG6 (BAT3)	BCL2-associated athanogene 6	protein binding /// polyubiquitin binding /// ribosome binding /// proteasome binding
BC029534		
BC034268		
BMP6	bone morphogenetic protein 6	cytokine activity /// growth factor activity /// protein heterodimerization activity /// BMP receptor binding
C10orf107	chromosome 10 open reading frame 107	
C5orf23	chromosome 5 open reading frame 23	
CABP1	calcium binding protein 1	enzyme inhibitor activity /// calcium ion binding /// metal ion binding /// calcium-dependent protein binding
CACNB2	calcium channel, voltage-dependent, beta 2 subunit	ion channel activity /// voltage-gated ion channel activity /// voltage-gated calcium channel activity /// calcium channel regulator activity /// calcium channel activity /// protein binding
CAPZA1	capping protein (actin filament) muscle Z-line, alpha 1	actin binding
CASZ1	castor zinc finger 1	DNA binding /// zinc ion binding /// metal ion binding
CDC25A	cell division cycle 25 homolog A (S. pombe)	phosphoprotein phosphatase activity /// protein tyrosine phosphatase activity /// protein binding /// hydrolase activity /// protein kinase binding
CENPW (C6orf173)	centromere protein W	DNA binding /// protein binding
CHD6	chromodomain helicase DNA binding protein 6	nucleotide binding /// nucleic acid binding /// DNA binding /// chromatin binding /// helicase activity /// ATP binding /// ATP-dependent helicase activity /// hydrolase activity, acting on acid anhydrides
CLCN6	chloride channel, voltage-sensitive 6	nucleotide binding /// ion channel activity /// voltage-gated chloride channel activity /// ATP binding /// antiporter activity
CNNM2	cyclin M2	
CSK	c-src tyrosine kinase	nucleotide binding /// protein kinase activity /// protein tyrosine kinase activity /// non-membrane spanning protein tyrosine kinase activity /// protein binding /// ATP binding /// protein C-terminus binding /// kinase activity /// transferase activity /// transferase activity, transferring phosphorus-containing groups /// protein phosphatase binding /// proline-rich region binding

CSNK1G3	casein kinase 1, gamma 3	nucleotide binding /// protein serine/threonine kinase activity /// ATP binding /// transferase activity, transferring phosphorus-containing groups
CUX2	cut-like homeobox 2	sequence-specific DNA binding transcription factor activity /// sequence-specific DNA binding
DCAKD	dephospho-CoA kinase domain containing	nucleotide binding /// dephospho-CoA kinase activity /// ATP binding
EBF1	early B-cell factor 1	DNA binding /// sequence-specific DNA binding transcription factor activity /// metal ion binding /// C2H2 zinc finger domain binding
EF537580		
EVX1	even-skipped homeobox 1	sequence-specific DNA binding transcription factor activity
FAM109A	family with sequence similarity 109, member A	protein binding /// phospholipid binding /// protein homodimerization activity
FES	feline sarcoma oncogene	nucleotide binding /// protein tyrosine kinase activity /// non-membrane spanning protein tyrosine kinase activity /// ATP binding /// lipid binding /// kinase activity /// transferase activity, transferring phosphorus-containing groups /// immunoglobulin receptor binding /// phosphatidylinositol binding
FGD5	FYVE, RhoGEF and PH domain containing 5	guanyl-nucleotide exchange factor activity /// Rho guanyl-nucleotide exchange factor activity /// phospholipid binding /// small GTPase binding /// metal ion binding
FGF5	fibroblast growth factor 5	fibroblast growth factor receptor binding /// growth factor activity
FIGN	fidgetin	nucleotide binding /// ATP binding /// protein C-terminus binding /// nucleoside-triphosphatase activity
FLJ13197	uncharacterized FLJ13197	
FLJ32810		
FURIN	furin (paired basic amino acid cleaving enzyme)	protease binding /// serine-type endopeptidase activity /// serine-type endopeptidase inhibitor activity /// peptidase activity /// serine-type peptidase activity /// hydrolase activity /// peptide binding /// metal ion binding /// nerve growth factor binding
GGNBP1 (AY383626)	gametogenetin binding protein 1 (pseudogene)	
GOLGA8T (AK310526)	golgin A8 family, member T	
GOSR2	golgi SNAP receptor complex member 2	receptor activity /// transporter activity
GRB14	growth factor receptor-bound protein 14	receptor activity /// SH3/SH2 adaptor activity /// phospholipid binding /// phosphoprotein binding
HAAO	3-hydroxyanthranilate 3,4-dioxygenase	3-hydroxyanthranilate 3,4-dioxygenase activity /// iron ion binding /// electron carrier activity /// oxidoreductase activity, acting on single donors with incorporation of molecular oxygen, incorporation of two atoms of oxygen /// oxygen binding /// metal ion binding
HECTD4 (C12orf51)	HECT domain containing E3 ubiquitin protein ligase 4	ubiquitin-protein ligase activity /// ligase activity /// acid-amino acid ligase activity
HIVEP3	human immunodeficiency virus type I enhancer binding protein 3	nucleic acid binding /// DNA binding /// zinc ion binding /// metal ion binding
HOTTIP (AK093987)	HOXA distal transcript antisense RNA	
IKBKAP	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	DNA binding /// protein kinase activity /// signal transducer activity /// protein binding /// ATP binding /// phosphorylase kinase regulator activity /// kinase activity
KIAA1751	KIAA1751	
LRPPRC	leucine-rich pentatricopeptide repeat containing	DNA binding /// single-stranded DNA binding /// RNA binding /// protein binding /// microtubule binding /// beta-tubulin binding /// actin filament binding

LRRC16A	leucine rich repeat containing 16A	
MECOM	MDS1 and EVI1 complex locus	nucleic acid binding /// DNA binding /// sequence-specific DNA binding transcription factor activity /// protein binding /// zinc ion binding /// protein homodimerization activity /// metal ion binding
MOV10	Mov10, Moloney leukemia virus 10, homolog (mouse)	nucleotide binding /// RNA binding /// helicase activity /// protein binding /// ATP binding /// hydrolase activity
MSRA	methionine sulfoxide reductase A	peptide-methionine-(S)-S-oxide reductase activity /// oxidoreductase activity, acting on a sulfur group of donors, disulfide as acceptor
MTHFR	methylenetetrahydrofolate reductase (NAD(P)H)	methylenetetrahydrofolate reductase (NADPH) activity /// oxidoreductase activity /// modified amino acid binding
NDUFA6 (C8orf38)	NADH dehydrogenase (ubiquinone) complex I, assembly factor 6	NADH dehydrogenase (ubiquinone) activity
NMT1	N-myristoyltransferase 1	glycylpeptide N-tetradecanoyltransferase activity /// transferase activity, transferring acyl groups /// myristoyltransferase activity
NPPB	natriuretic peptide B	receptor binding /// hormone activity /// diuretic hormone activity /// peptide hormone receptor binding
NPR3	natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C)	receptor activity /// G-protein coupled peptide receptor activity /// natriuretic peptide receptor activity /// peptide hormone binding /// hormone binding /// protein homodimerization activity
NT5C2	5'-nucleotidase, cytosolic II	nucleotide binding /// catalytic activity /// protein binding /// 5'-nucleotidase activity /// hydrolase activity /// metal ion binding
OVOL1	ovo-like 1(Drosophila)	RNA polymerase II core promoter proximal region sequence-specific DNA binding transcription factor activity involved in negative regulation of transcription /// DNA binding /// zinc ion binding /// metal ion binding
PLCB1	phospholipase C, beta 1 (phosphoinositide-specific)	phosphatidylinositol phospholipase C activity /// phospholipase C activity /// signal transducer activity /// GTPase activator activity /// calcium ion binding /// protein binding /// calmodulin binding /// lamin binding /// phosphatidylinositol-4,5-bisphosphate binding /// phosphoric diester hydrolase activity /// hydrolase activity /// enzyme binding /// protein homodimerization activity
PLCD3	phospholipase C, delta 3	phosphatidylinositol phospholipase C activity /// phospholipase C activity /// signal transducer activity /// calcium ion binding /// phospholipid binding /// phosphoric diester hydrolase activity /// metal ion binding
PLCE1	Phospholipase C, epsilon 1	phosphatidylinositol phospholipase C activity /// phospholipase C activity /// signal transducer activity /// receptor signaling protein activity /// guanyl-nucleotide exchange factor activity /// calcium ion binding /// protein binding /// phosphoric diester hydrolase activity /// hydrolase activity /// Ras GTPase binding /// enzyme binding
PLEKHA7	pleckstrin homology domain containing, family A member 7	phospholipid binding /// delta-catenin binding
PLEKHM1	pleckstrin homology domain containing, family M (with RUN domain) member 1	phospholipid binding
POC1B (WDR51B)		polypeptide N-acetylgalactosaminyltransferase activity /// transferase activity, transferring glycosyl groups /// carbohydrate binding
PRDM6	PR domain containing 6	nucleic acid binding /// methyltransferase activity /// zinc ion binding /// transferase activity /// histone-lysine N-methyltransferase activity /// protein homodimerization activity /// metal ion binding
PRRC2A (BAT2)	proline-rich coiled-coil 2A	protein binding
PTPLAD2	protein tyrosine phosphatase-like A domain containing 2	lyase activity
RPH3A	rabphilin 3A homolog (mouse)	transporter activity /// calcium ion binding /// protein binding /// phosphatidylinositol-4,5-bisphosphate binding /// zinc ion binding ///

		selenium binding /// Rab GTPase binding /// phosphate ion binding /// metal ion binding /// inositol 1,4,5 trisphosphate binding
SLC12A3	solute carrier family 12 (sodium/chloride transporters), member 3	transporter activity /// protein binding /// symporter activity /// cation:chloride symporter activity /// sodium:chloride symporter activity
SLC39A8	solute carrier family 39 (zinc transporter), member 8	metal ion transmembrane transporter activity
SYNPO2L	synaptopodin 2-like	actin binding
TNXB	tenascin XB	receptor binding /// integrin binding /// extracellular matrix structural constituent /// collagen binding /// heparin binding
WBP1L (C10orf26)	WW domain binding protein 1-like	
ZNF831	zinc finger protein 831	nucleic acid binding /// zinc ion binding /// metal ion binding

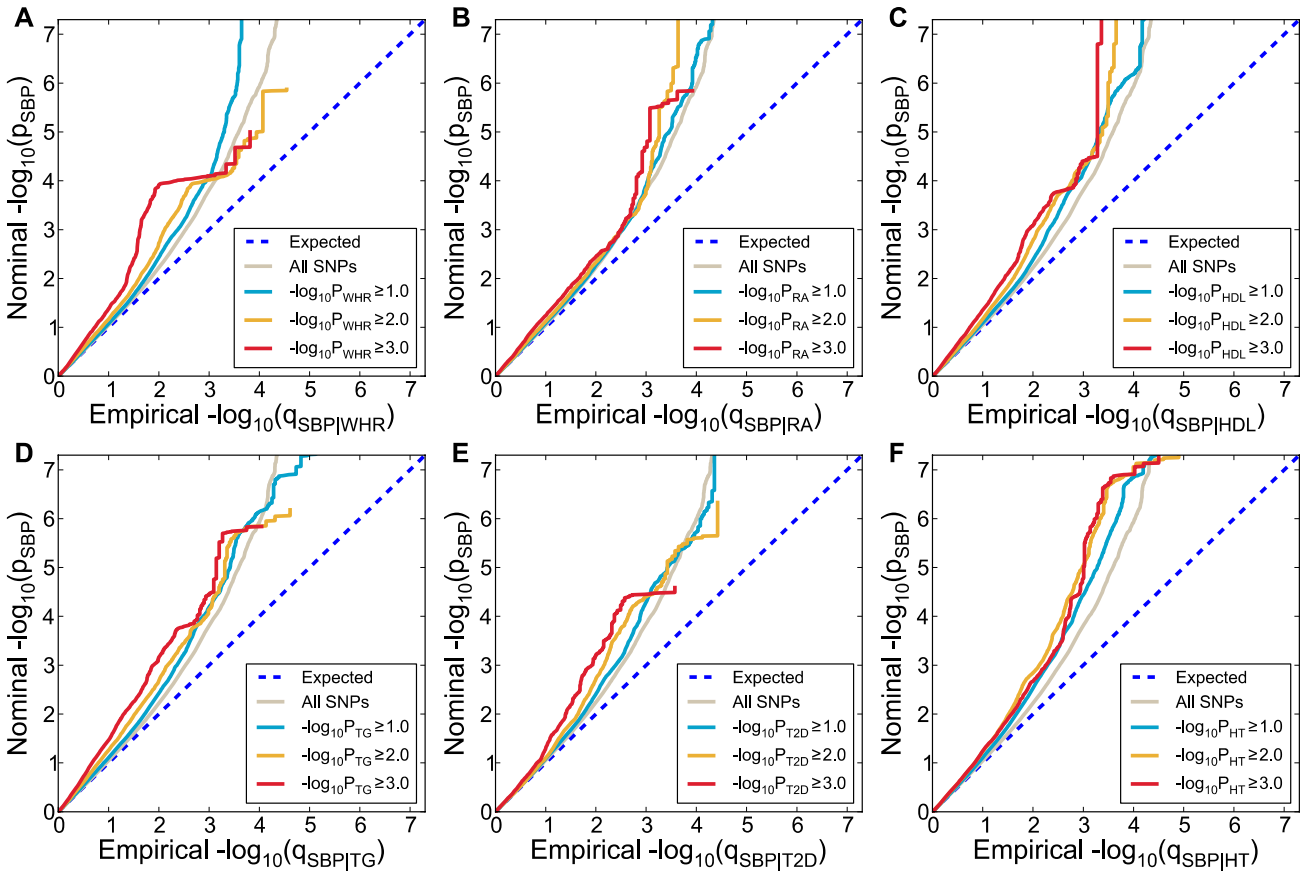
Table S3 Diseases and disorders – Cardiovascular disease

Functions Annotation	p-Value	Molecules
Cardiomyopathy	2,07E-03	CACNB2, FURIN, LRPPRC, NPPB, NPR3
hypertrophy of ventricular myocytes	3,30E-03	PLCB1, PLCE1
Leigh syndrome	3,74E-03	LRPPRC
French-Canadian type Leigh syndrome	3,74E-03	LRPPRC
chronic right ventricular overload	3,74E-03	NPPB
pulmonary valve regurgitation	3,74E-03	PLCE1
Danish type familial amyloid cardiomyopathy	7,46E-03	FURIN
dysfunction of heart	1,07E-02	CACNB2, GRB14
non-ST elevation myocardial infarction	1,12E-02	NPPB
valvular regurgitation of aortic valve	1,12E-02	PLCE1
stenosis of aortic valve	1,28E-02	FURIN, PLCE1
Pulmonary Hypertension	1,33E-02	NPPB,NPR3
Heart Disease	1,53E-02	CACNB2 ,FES, FURIN, LRPPRC, MECOM, MSRA, NPPB, NPR3, PLCE1
acute pulmonary embolism	2,22E-02	NPPB
diastolic heart failure	2,59E-02	NPR3
Hypotension	2,60E-02	NPPB, NPR3
Hypertension	2,76E-02	MECOM, NPPB, NPR3, SLC12A3
Brugada syndrome	2,95E-02	CACNB2
cardia bifida	3,68E-02	FURIN

Table S4 Diseases and disorders – Cardiovascular System Development and Function

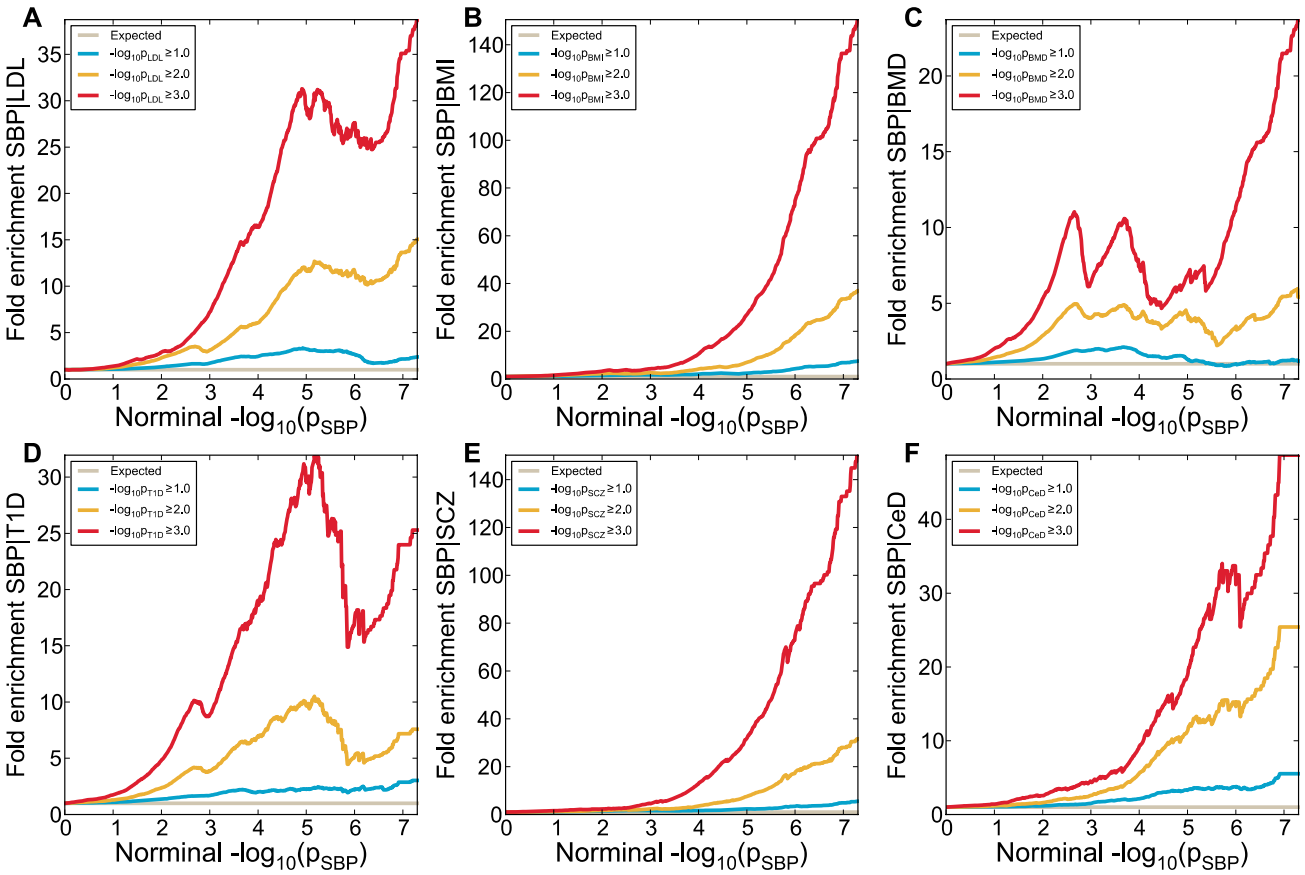
Functions Annotation	p-Value	Molecules
looping morphogenesis of heart	1,60E-03	FURIN, IKBKAP, MECOM
formation of endothelial progenitor cells	3,74E-03	MTHFR
migration of cardiomyocytes	3,74E-03	FURIN
diameter of carotid artery	7,46E-03	MTHFR
development of cardiovascular system	1,17E-02	BMP6, CSK, FES,FGF5, FURIN, IKBKAP, MECOM, NPPB, PLCD3, PLCE1
morphogenesis of blood vessel	1,73E-02	FES, FURIN
development of blood vessel	1,82E-02	BMP6, CSK, FES, FGF5, FURIN, IKBKAP, NPPB, PLCD3
outgrowth of microvessel	2,22E-02	BMP6
vasculogenesis of yolk sac	2,22E-02	FURIN
abnormal morphology of dilated heart ventricle	2,39E-02	FES,PLCE1
proliferation of ventricular myocytes	2,95E-02	PLCE1
abnormal morphology of blood platelets	3,31E-02	MECOM
development of vascular tissue	3,31E-02	FURIN
proliferation of cardiac fibroblasts	3,31E-02	NPPB
morphogenesis of capillary vessel	3,68E-02	FES
abnormal morphology of enlarged heart	3,68E-02	FES, PLCE1
proliferation of heart cells	4,02E-02	NPPB, PLCE1
size of ventricular myocytes	4,04E-02	PLCB1
morphology of pulmonary valve	4,75E-02	PLCE1

Figure S1 Conditional Q-Q Plots



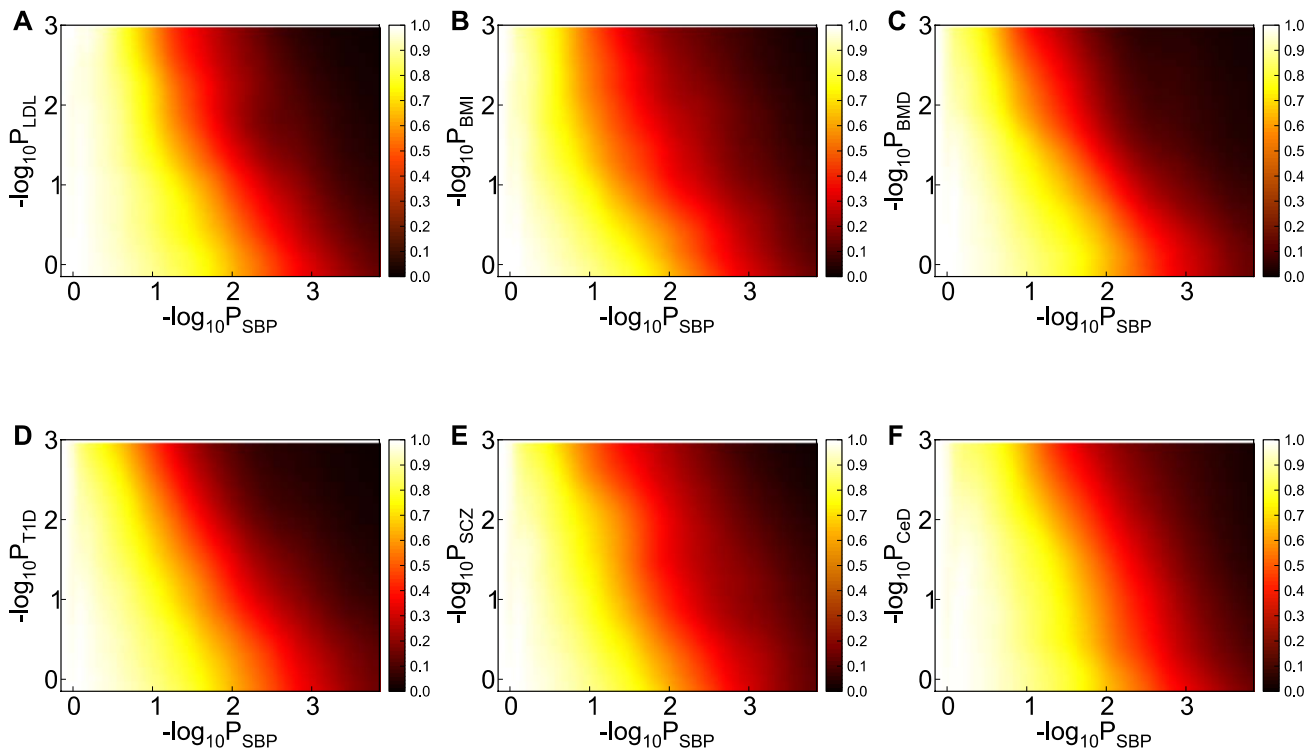
Pleiotropic Enrichment. Conditional Q-Q plot of nominal versus empirical -$\log_{10}$ p-values (corrected for inflation) in systolic blood pressure (SBP) below the standard GWAS threshold of $p < 5x10\text{-}8$ as a function of significance of association with A) Waist to Hip Ratio (WHR), B) Rheumatoid Arthritis (RA), C) High Density Lipoprotein (HDL), D) Triglycerides (TG), E) Type 2 Diabetes (T2D) and F) Height (HT) at the level of $-\log_{10}(p) > 0$, $-\log_{10}(p) > 1$, $-\log_{10}(p) > 2$, $-\log_{10}(p) > 3$ corresponding to $p < 1$, $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. Dotted lines indicate the null-hypothesis.

Figure S2 Enrichment Plots



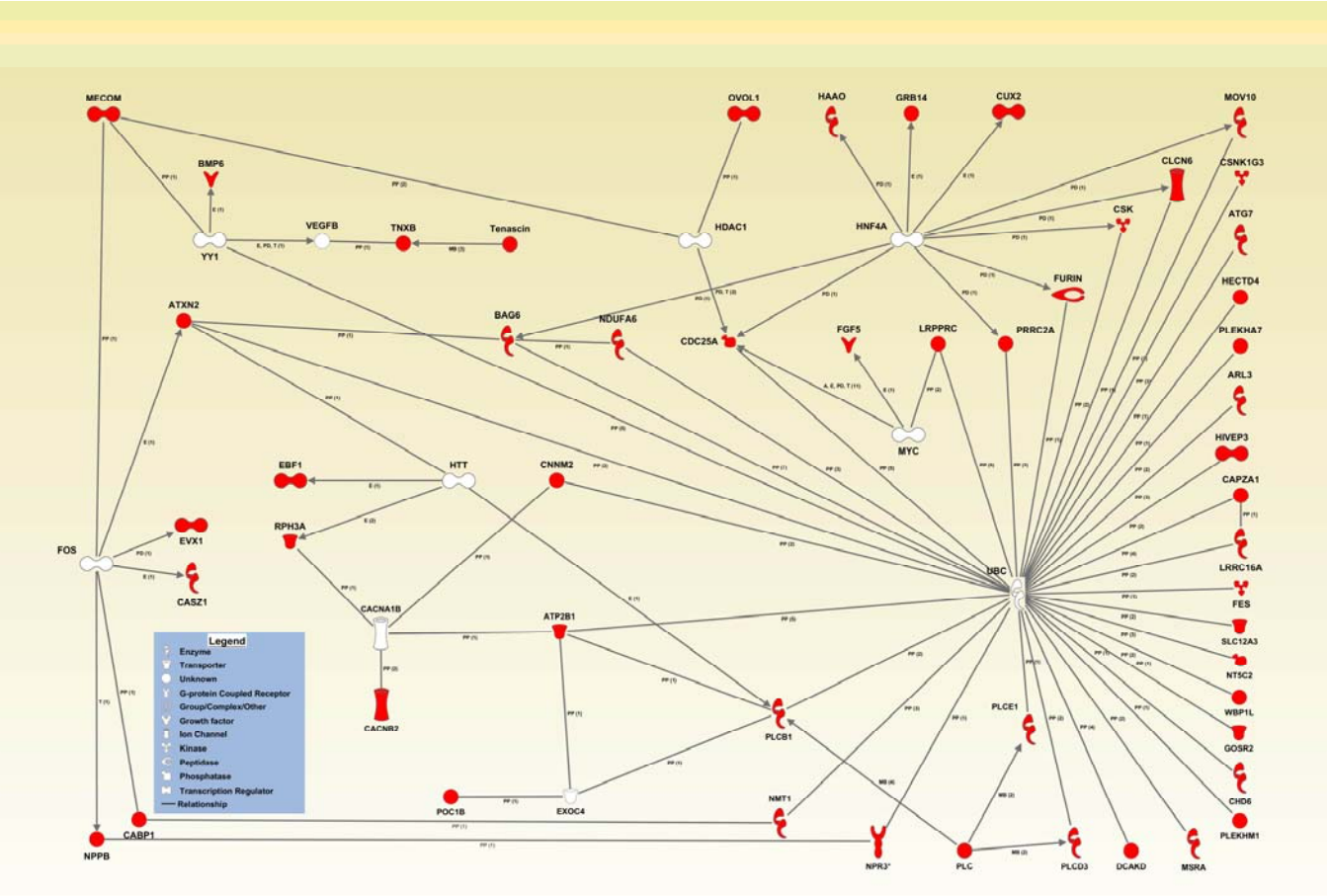
Pleiotropic Enrichment. Enrichment plot of x-fold enrichment vs. empirical -$\log_{10}$ p-values (corrected for inflation) in systolic blood pressure (SBP) below the standard GWAS threshold of $p < 5x10\text{-}8$ as a function of significance of association with **A**) Low density Lipoprotein cholesterol (LDL), **B**) Body Mass Index (BMI), **C**) Bone Mineral Density (BMD), **D**) Type 1 Diabetes (T1D), **E**) Schizophrenia (SCZ) and **F**) Celiac Disease (CeD) at the level of -log10(p) > 0, –log10(p) > 1, –log10(p) > 2, –log10(p) > 3 corresponding to $p < 1$, $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively.

Figure S3 Conditional look-up tables



Based on the combination of p-value for the SNPs in Systolic Blood Pressure (SBP) (P_{SBP}) and that of the pleiotropic trait: A. low density lipoprotein (LDL) cholesterol (P_{LDL}), B. body mass index (BMI) (P_{BMI}), C. bone mineral density (BMD) (P_{BMD}), D. type 1 diabetes (T1D) (P_{T1D}), E. schizophrenia (SCZ) (P_{SCZ}), F. celiac disease (CeD) (P_{CeD}), we assigned a conditional FDR value to each SNP associated with SBP, by interpolation into a 2-D look-up table. Color scale refers to the conditional FDR values.

Figure S4



Ingenuity pathway analysis was used to generate a network displaying direct interactions among proteins encoded by the 74 SBP related genes (red symbols) based on the manually curated IPA database. Red symbols are identified in Table S1. White symbols represent the following genes: HNF4A: hepatocyte nuclear factor 4, alpha; MYC: myelocytomatosis viral oncogene homolog; YY1: YY1 transcription factor; HTT: huntingtin; FOS: FBJ murine osteosarcoma viral oncogene homolog; CACNA1B: calcium channel, voltage-dependent, N type, alpha 1B subunit; EXOC4: exocyst complex component 4; UBC: ubiquitin C