Published in final edited form as:
Hypertension. 2014 April ; 63(4): 819–826. doi:10.1161/HYPERTENSIONAHA.113.02077.

Identifying common genetic variants in blood pressure due to polygenic pleiotropy with associated phenotypes

Ole A. Andreassen[1,2,3,*], **Linda K. McEvoy**[4,5], **Wesley K. Thompson**[3], **Yunpeng Wang**[1,2,4,14], **Sjur Reppe**[7], **Andrew J. Schork**[4,6], **Verena Zuber**[1,2], **The International Consortium for Blood Pressure GWAS, The GEFOS Consortium**, **Elizabeth Barrett-Connor**[8], **Kaare Gautvik**[7,9,10], **Pål Aukrust**[11], **Tom H. Karlsen**[12,13], **Srdjan Djurovic**[1,2], **Rahul S. Desikan**[4,5], and **Anders M. Dale**[3,4,5,6,14,*]

[1]NORMENT - KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[2]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

[3]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

[4]Multimodal Imaging Laboratory, University of California at San Diego, La Jolla, CA, USA

[5]Department of Radiology, University of California, San Diego, La Jolla, CA, USA

[6]Cognitive Sciences Graduate Program, University of California, San Diego, La Jolla, CA, USA

[7]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway

[8]Family and Preventive Medicine, Division of Epidemiology, University of California, San Diego, La Jolla, CA, USA

[9]Department of Medical Biochemistry, Lovisenberg Deacon Hospital, Oslo, Norway

[10]Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

[11]Research Institute of Internal Medicine, and Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital Rikshospitalet and University of Oslo, Oslo, Norway

[12]Research Institute of Internal Medicine, Division of Cancer medicine, Surgery and Transplantation, Oslo University Hospital Rikshospitalet, Oslo, Norway

[13]Division of Gastroenterology, Institute of Medicine, University of Bergen, Bergen, Norway

[14]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA

Abstract

[*]Address correspondence to: Dr. Anders M. Dale Department of Radiology University of California, San Diego 8950 Villa La Jolla Drive, Suite C101 La Jolla, CA, USA 92037-0841 amdale@ucsd.edu Phone: (858)-822-6671 Fax: (858)-534-1078 Dr. Ole A. Andreassen: NORMENT; KG Jebsen Centre for Psychosis Research Building 49, Oslo University Hospital, Ullevål Kirkeveien 166, PO Box 4956 Nydalen 0424 Oslo, Norway o.a.andreassen@medisin.uio.no Ph: +47 23 02 73 50 (22 11 78 43 dir) Fax: +47 23 02 73 33.

Authors' contributions

Andreassen and Dale designed study; Djurovic, Schork, Reppe collected data, Schork prepared data; Dale performed the statistical analysis with assistance from Thompson, Wang, Zuber, Reppe; Andreassen and McEvoy drafted manuscript; Gautvik, Karlsen, Aukrust, Barrett-Connor, Desikan, McEvoy, Dale, Andreassen interpreted data; all authors critically revised manuscript and approved final version.

Disclosures

None reported.

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 and 12 co-morbid traits and diseases. We found significant 'enrichment' of single nucleotide polymorphisms associated with systolic blood pressure as a function of their association with body mass index, low density lipoprotein, waist hip ratio, schizophrenia, bone mineral density, type 1 diabetes 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, rheumatoid arthritis, and height). Applying the conditional False Discovery Rate method to the enriched phenotypes, we identified 62 loci associated with systolic blood pressure (False Discovery Rate < 0.01), including 42 novel loci. The observed polygenic overlap between systolic blood pressure and several related disorders indicates that the epidemiological associations are not mediated solely via lifestyle factors, but also reflect an etiological relation that warrants further investigation. The new gene loci identified implicate novel genetic mechanisms related to lipid biology and the immune system in systolic blood pressure.

Keywords

Genome-wide association study; genetic pleiotropy; systolic blood pressure; comorbid disorders

INTRODUCTION

High blood pressure affects over one 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 the 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 employed analytic methods and limited sample sizes[9]. This has led to recent National Institute 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 since recruitment and genotyping of new participants are expensive. One such approach relies on genetic pleiotropy[10], i.e. the association of individual SNPs or genes with two or more 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, since there are often overlapping traits among behaviorally or clinically defined phenotypes, shared genetic influences between such phenotypes are likely.

Epidemiological studies have identified several major risk factors for cardiovascular disease (CVD)[11,12] including hypertension, obesity, diabetes 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[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: bone mineral density (BMD)[24], low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG)[25], type 2 diabetes (T2D)[26], body mass index (BMI)[27], waist to hip ratio (WHR)[28], height (HT)[29], schizophrenia (SCZ)[30], type 1 diabetes (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 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 on the inclusion criteria and phenotype characteristics of the different GWAS are described in the original publications[4,25-28]. There was some overlap among several of the participants in the CVD risk factor GWAS and the SBP GWAS sample[4]. The relevant institutional review boards or ethics committees approved the research protocol of the 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 prior publications[21,22].

Conditional Quantile-Quantile (Q-Q) plots for pleiotropic enrichment— Enrichment of statistical association relative to that expected under the global null hypothesis can be visualized through 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 references 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 the 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 $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, and $p \leq 0.001$, respectively). The nominal p-values ($-\log_{10}(p)$) are plotted on the y-axis, and the empirical quantiles ($-\log_{10}(q)$, where q=1-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 (FDR)—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 (TDR)[35]). We applied a conditional FDR method[22,36,37], and constructed TDR plots, as described earlier[21,22], and detailed in Online Supplement (please see http://hyper.ahajournals.org).

Conditional statistics – test of association with Systolic Blood Pressure—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 $FDR_{SBP \mid related\text{-}phenotype}$) for SBP to each SNP, for each related phenotype by interpolation, using a two-dimensional look-up table of conditional FDR values[21,22] computed for each of the specific datasets used in the current study (Figure S3, please see http://hyper.ahajournals.org). All SNPs with $FDR_{SBP \mid related\text{-}phenotype} < 0.01$ ($-\log_{10}(FDR_{SBP \mid related\text{-}phenotype}) > 2$) in SBP given association with any of the 12 related phenotypes are listed in Table 1 after 'pruning' (i.e., 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 the 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 the 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-F). For LDL, the proportion of SNPs in the $-\log_{10}(p_{LDL}) \geq 3$ category reaching a given significance level (e.g., $-\log_{10}(p_{SBP}) > 6$) was roughly 100 times greater than for $-\log_{10}(p_{LDL}) \geq 0$ category (all SNPs), indicating a very high level of enrichment (Figure 1A). A similar level of enrichment was seen for BMI and SCZ (Figure 1B,C); CeD, T1D and BMD also showed a high level of enrichment (Figure 1D-F). Weaker pleiotropic enrichment was seen for WHR (Figure S1, please see http://hyper.ahajournals.org), with little or no evidence for enrichment in RA, HDL, TG, T2D, HT (Figure S1, please see http://hyper.ahajournals.org). We also illustrate the high level of polygenic pleiotropic enrichment in LDL, BMI, BMD, T1D, SCZ, and CeD using "Enrichment Plots" (Figure S2, please see http://hyper.ahajournals.org).

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 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 (IPA) are presented in Table S3 and S4 (please see http://hyper.ahajournals.org) identifying the traits in the categories “Cardiovascular disease” or “Cardiovascular System Development and Function”, respectively, that may be affected by the gene heterogeneities in the vicinity of the indicated SBP associated genes. Figure S4, made by the network function in IPA, demonstrates that a large proportion of SBP associated genes are functionally related (please see http://hyper.ahajournals.org).

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 identify 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, even though 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 while 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 that 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 suggests 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, 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 more than one 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 the overlap may be due to 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 two phenotypes, 24 loci were

identified. These phenotypes also showed strong polygenic pleiotropy, with clear enrichment in the Q-Q plots. While 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 and SBP. The immune-related mechanisms that are involved in SBP seem to be quite specific as we found little enrichment with RA, a prototypical auto-immune disorder. Moreover, while 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 that warrant further experimental investigation.

Due to the overlap in some of the GWAS samples examined, we cannot exclude contribution from environmental or behavioral factors, or other non-genetic 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 due to common genetic variation in potentially overlapping control groups. Further, the GWAS of blood lipids used the same sample to discover new genes for three different phenotypes[25]. Since we do not have access to additional samples or individual sub-studies, 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 employed here replicate at the same or higher rate than 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]. Due to the overlap in some of the GWAS samples examined, we cannot exclude contribution from environmental or behavioral factors, or other non-genetic 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, as 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] that may lead to personalized medicine approaches and potentially individual prediction of disease risk. We are currently working towards 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 etiological relationship between these phenotypes that could include lipid disturbances and certain immunological 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 etiological relation. Our findings also shed new light on the pathogenic mechanisms in SBP that 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank the DIAGRAM Consortium, The Psychiatric Genomics Consortium (PGC) Schizophrenia Working Group, the Celiac Disease GWAS Consortium, The Type 1 Diabetes Consortium for the summary statistics GWAS data.

Sources of Funding

OAA was supported by the Research Council of Norway, the South East Norway Health Authority and the Kristian Gerhard Jebsen Foundation. RSD was supported by a grant from the National Institutes of Health (T32 EB005970). AMD 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 manuscript.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 365:217–223. [PubMed: 15652604]
2. Kotchen TA, Kotchen JM, Grim CE, George V, Kaldunski ML, Cowley AW, Hamet P, Chelius TH. Genetic determinants of hypertension: identification of candidate phenotypes. Hypertension. 2000; 36:7–13. [PubMed: 10904005]
3. Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H, Cupples LA, Myers RH. Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham heart study. Hypertension. 2000; 36:477–483. [PubMed: 11040222]
4. International Consortium for Blood Pressure Genome-Wide Association Studies; Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC, Hwang S-J, Pihur V, Vollenweider P, O'Reilly PF, Amin N, Bragg-Gresham JL, Teumer A, Glazer NL, Launer L, Zhao JH, Aulchenko Y, Heath S, Sõber S, Parsa A, Luan J, Arora P, Dehghan A, Zhang F, Lucas G, Hicks AA, Jackson AU, Peden JF, Tanaka T, Wild SH, Rudan I, Igl W, Milaneschi Y, Parker AN, Fava C, Chambers JC, Fox ER, Kumari M, Go MJ, van der Harst P, Kao WHL, Sjögren M, Vinay DG, Alexander M, Tabara Y, Shaw-Hawkins S, Whincup PH, Liu Y, Shi G, Kuusisto J, Tayo B, Seielstad M, Sim X, Nguyen K-DH, Lehtimäki T, Matullo G, Wu Y, Gaunt TR, Onland-Moret NC, Cooper MN, Platou CGP, Org E, Hardy R, Dahgam S, Palmen J, Vitart V, Braund PS, Kuznetsova T, Uiterwaal CSPM, Adeyemo A, Palmas W, Campbell H, Ludwig B, Tomaszewski M, Tzoulaki I, Palmer ND, CARDIoGRAM consortium; CKDGen Consortium; KidneyGen Consortium; EchoGen consortium; CHARGE-HF consortium. Aspelund T, Garcia M, Chang Y-PC, O'Connell JR, Steinle NI, Grobbee DE, Arking DE, Kardia SL, Morrison AC, Hernandez D, Najjar S, McArdle WL, Hadley D, Brown MJ, Connell JM, Hingorani AD, Day INM, Lawlor DA, Beilby JP, Lawrence RW, Clarke R, Hopewell JC, Ongen H, Dreisbach AW, Li Y, Young JH, Bis JC, Kähönen M, Viikari J, Adair LS, Lee NR, Chen M-H, Olden M, Pattaro C, Bolton JAH, Köttgen A, Bergmann S, Mooser V, Chaturvedi N, Frayling TM, Islam M, Jafar TH, Erdmann J, Kulkarni SR, Bornstein SR, Grässler J, Groop L, Voight BF, Kettunen J, Howard P, Taylor A, Guarrera S, Ricceri F, Emilsson V, Plump A, Barroso I, Khaw K-T, Weder AB, Hunt SC, Sun YV, Bergman RN,

Collins FS, Bonnycastle LL, Scott LJ, Stringham HM, Peltonen L, Perola M, Vartiainen E, Brand SM, Staessen JA, Wang TJ, Burton PR, Soler Artigas M, Dong Y, Snieder H, Wang X, Zhu H, Lohman KK, Rudock ME, Heckbert SR, Smith NL, Wiggins KL, Doumatey A, Shriner D, Veldre G, Viigimaa M, Kinra S, Prabhakaran D, Tripathy V, Langefeld CD, Rosengren A, Thelle DS, Corsi AM, Singleton A, Forrester T, Hilton G, McKenzie CA, Salako T, Iwai N, Kita Y, Ogihara T, Ohkubo T, Okamura T, Ueshima H, Umemura S, Eyheramendy S, Meitinger T, Wichmann HE, Cho YS, Kim HL, Lee JY, Scott J, Sehmi JS, Zhang W, Hedblad B, Nilsson P, Smith GD, Wong A, Narisu N, Stančáková A, Raffel LJ, Yao J, Kathiresan S, O'Donnell CJ, Schwartz SM, Ikram MA, Longstreth WT Jr, Mosley TH, Seshadri S, Shrine NR, Wain LV, Morken MA, Swift AJ, Laitinen J, Prokopenko I, Zitting P, Cooper JA, Humphries SE, Danesh J, Rasheed A, Goel A, Hamsten A, Watkins H, Bakker SJ, van Gilst WH, Janipalli CS, Mani KR, Yajnik CS, Hofman A, Mattace-Raso FU, Oostra BA, Demirkan A, Isaacs A, Rivadeneira F, Lakatta EG, Orru M, Scuteri A, Ala-Korpela M, Kangas AJ, Lyytikäinen LP, Soininen P, Tukiainen T, Würtz P, Ong RT, Dörr M, Kroemer HK, Völker U, Völzke H, Galan P, Hercberg S, Lathrop M, Zelenika D, Deloukas P, Mangino M, Spector TD, Zhai G, Meschia JF, Nalls MA, Sharma P, Terzic J, Kumar MV, Denniff M, Zukowska-Szczechowska E, Wagenknecht LE, Fowkes FG, Charchar FJ, Schwarz PE, Hayward C, Guo X, Rotimi C, Bots ML, Brand E, Samani NJ, Polasek O, Talmud PJ, Nyberg F, Kuh D, Laan M, Hveem K, Palmer LJ, van der Schouw YT, Casas JP, Mohlke KL, Vineis P, Raitakari O, Ganesh SK, Wong TY, Tai ES, Cooper RS, Laakso M, Rao DC, Harris TB, Morris RW, Dominiczak AF, Kivimaki M, Marmot MG, Miki T, Saleheen D, Chandak GR, Coresh J, Navis G, Salomaa V, Han BG, Zhu X, Kooner JS, Melander O, Ridker PM, Bandinelli S, Gyllensten UB, Wright AF, Wilson JF, Ferrucci L, Farrall M, Tuomilehto J, Pramstaller PP, Elosua R, Soranzo N, Sijbrands EJ, Altshuler D, Loos RJ, Shuldiner AR, Gieger C, Meneton P, Uitterlinden AG, Wareham NJ, Gudnason V, Rotter JI, Rettig R, Uda M, Strachan DP, Witteman JC, Hartikainen AL, Beckmann JS, Boerwinkle E, Vasan RS, Boehnke M, Larson MG, Järvelin MR, Psaty BM, Abecasis GR, Chakravarti A, Elliott P, van Duijn CM, Newton-Cheh C, Levy D, Caulfield MJ, Johnson T. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011; 478(7367):103–109. [PubMed: 21909115]

5. Kurtz TW. Genome-wide association studies will unlock the genetic basis of hypertension.: con side of the argument. Hypertension. 2010; 56:1021–1025. [PubMed: 21060005]
6. Doris PA. The genetics of blood pressure and hypertension: the role of rare variation. Cardiovasc Ther. 2011; 29:37–45. [PubMed: 21129164]
7. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large proportion of the heritability for human height. Nat Genet. 2010; 42:565–569. [PubMed: 20562875]
8. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, de Andrade M, Feenstra B, Feingold E, Hayes MG, Hill WG, Landi MT, Alonso A, Lettre G, Lin P, Ling H, Lowe W, Mathias RA, Melbye M, Pugh E, Cornelis MC, Weir BS, Goddard ME, Visscher PM. Genome partitioning of genetic variation for complex traits using common SNPs. Nat Genet. 2011; 43:519–525. [PubMed: 21552263]
9. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TFC, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. Nature. 2009; 461:747–753. [PubMed: 19812666]
10. Wagner GP, Zhang J. The pleiotropic structure of the genotype-phenotype map: the evolvability of complex organisms. Nat Rev Genet. 2011; 12:204–213. [PubMed: 21331091]
11. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008; 117:743–753. [PubMed: 18212285]
12. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003; 24:987–1003. [PubMed: 12788299]

13. Libby P. Pathophysiology of Coronary Artery Disease. Circulation. 2005; 111:3481–3488. [PubMed: 15983262]

14. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet. 2007; 370:591–603. [PubMed: 17707755]

15. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005; 365:1415–1428. [PubMed: 15836891]

16. Rosner B, Prineas RJ, Loggie JM, Daniels SR. Blood pressure nomograms for children and adolescents, by height, sex, and age, in the United States. J Pediatr. 1993; 123:871–886. [PubMed: 8229519]

17. Caudarella R, Vescini F, Rizzoli E, Francucci CM. Salt intake, hypertension, and osteoporosis. J Endocrinol Invest. 2009; 32:15–20. [PubMed: 19724161]

18. Birkenaes AB, Opjordsmoen S, Brunborg C, Engh JA, Jonsdottir H, Ringen PA, Simonsen C, Vaskinn A, Birkeland KI, Friis S, Sundet K, Andreassen OA. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 2007; 68:917–923. [PubMed: 17592917]

19. Group TAS. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med. 2010; 362:1575–1585. [PubMed: 20228401]

20. Panoulas VF, Metsios GS, Pace AV, John H, Treharne GJ, Banks MJ, Kitas GD. Hypertension in rheumatoid arthritis. Rheumatology. 2008; 47:1286–1298. [PubMed: 18467370]

21. Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR, Kendler KS, O'Donovan MC, Rujescu D, Werge T, Sklar P, Roddey JC, Chen C-H, McEvoy L, Desikan RS, Djurovic S, Dale AM. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. PLoS Genet. 2013; 9:e1003455. [PubMed: 23637625]

22. Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, Rujescu D, Werge T, van de Bunt M, Morris AP, McCarthy MI, Roddey JC, McEvoy LK, Desikan RS, Dale AM. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet. 2013; 92:197–209. [PubMed: 23375658]

23. Coffman TM. Under pressure: the search for the essential mechanisms of hypertension. Nat Med. 2011; 17:1402–1409. [PubMed: 22064430]

24. Estrada K, Styrkarsdottir U, Evangelou E, Hsu Y-H, Duncan EL, Ntzani EE, Oei L, Albagha OME, Amin N, Kemp JP, Koller DL, Li G, Liu C-T, Minster RL, Moayyeri A, Vandenput L, Willner D, Xiao S-M, Yerges-Armstrong LM, Zheng H-F, Alonso N, Eriksson J, Kammerer CM, Kaptoge SK, Leo PJ, Thorleifsson G, Wilson SG, Wilson JF, Aalto V, Alen M, Aragaki AK, Aspelund T, Center JR, Dailiana Z, Duggan DJ, Garcia M, Garcia-Giralt N, Giroux S, Hallmans G, Hocking LJ, Husted LB, Jameson KA, Khusainova R, Kim GS, Kooperberg C, Koromila T, Kruk M, Laaksonen M, Lacroix AZ, Lee SH, Leung PC, Lewis JR, Masi L, Mencej-Bedrac S, Nguyen TV, Nogues X, Patel MS, Prezelj J, Rose LM, Scollen S, Siggeirsdottir K, Smith AV, Svensson O, Trompet S, Trummer O, van Schoor NM, Woo J, Zhu K, Balcells S, Brandi ML, Buckley BM, Cheng S, Christiansen C, Cooper C, Dedoussis G, Ford I, Frost M, Goltzman D, González-Macías J, Kähönen M, Karlsson M, Khusnutdinova E, Koh J-M, Kollia P, Langdahl BL, Leslie WD, Lips P, Ljunggren Ö , Lorenc RS, Marc J, Mellström D, Obermayer-Pietsch B, Olmos JM, Pettersson-Kymmer U, Reid DM, Riancho JA, Ridker PM, Rousseau F, Slagboom PE, Tang NLS, Urreizti R, Van Hul W, Viikari J, Zarrabeitia MT, Aulchenko YS, Castano-Betancourt M, Grundberg E, Herrera L, Ingvarsson T, Johannsdottir H, Kwan T, Li R, Luben R, Medina-Gomez C, Palsson ST, Reppe S, Rotter JI, Sigurdsson G, van Meurs JBJ, Verlaan D, Williams FMK, Wood AR, Zhou Y, Gautvik KM, Pastinen T, Raychaudhuri S, Cauley JA, Chasman DI, Clark GR, Cummings SR, Danoy P, Dennison EM, Eastell R, Eisman JA, Gudnason V, Hofman A, Jackson RD, Jones G, Jukema JW, Khaw K-T, Lehtimäki T, Liu Y, Lorentzon M, McCloskey E, Mitchell BD, Nandakumar K, Nicholson GC, Oostra BA, Peacock M, Pols HA, Prince RL, Raitakari O, Reid IR, Robbins J, Sambrook PN, Sham PC, Shuldiner AR, Tylavsky FA, van Duijn CM, Wareham NJ, Cupples LA, Econs MJ, Evans DM, Harris TB, Kung AW, Psaty BM, Reeve J, Spector TD, Streeten EA, Zillikens MC, Thorsteinsdottir U, Ohlsson C, Karasik D, Richards JB, Brown MA, Stefansson K, Uitterlinden AG, Ralston SH, Ioannidis JP, Kiel DP, Rivadeneira F.

Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet. 2012; 44:491–501. [PubMed: 22504420]

25. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee J-Y, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RYL, Wright AF, Witteman JCM, Wilson JF, Willemsen G, Wichmann H-E, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJG, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BWJH, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PKE, Lucas G, Luben R, Loos RJF, Lokki M-L, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw K-T, Kaprio J, Kaplan LM, Johansson A, Jarvelin M-R, Janssens ACJW, Ingelsson E, Igl W, Kees Hovingh G, Hottenga J-J, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Faire U, Crawford G, Chen YD, Caulfield MJ, Boekholdt SM, Assimes TL, Quertermous T, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Taylor HA Jr, Gabriel SB, Holm H, Gudnason V, Krauss RM, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Strachan DP, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010; 466:707–713. [PubMed: 20686565]

26. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Langenberg C, Hofmann OM, Dupuis J, Qi L, Segrè AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bengtsson Boström K, Bravenboer B, Bumpstead S, Burtt NP, Charpentier G, Chines PS, Cornelis M, Couper DJ, Crawford G, Doney ASF, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves CJ, Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PRV, Jørgensen T, Kao WHL, Klopp N, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Perry JRB, Petersen A-K, Platou C, Proença C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shrader P, Sigurdsson G, Sparsø T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haeften TW, van Herpt T, Van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllensten U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Mohlke KL, Morris AD, Palmer CNA, Pramstaller PP, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Wareham NJ, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Hu FB, Meigs JB, Pankow JS, Pedersen O, Wichmann H-E, Barroso I, Florez JC, Frayling TM, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI, MAGIC investigators; GIANT Consortium. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet. 2010; 42:579–589. [PubMed: 20581827]

27. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, Lindgren CM, Luan J, Magi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segre AV, Estrada K, Liang L, Nemesh J, Park J-H, Gustafsson S, Kilpelainen TO, Yang J, Bouatia-Naji N, Esko TON, Feitosa MF, Kutalik ZAN, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E,

Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga J-J, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JRB, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ, Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson J-O, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MTS, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AIF, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proencca C, Chen Y-DI, Chen C-M, Chines PS, Clarke R, Coin L, Connell J, Day INM, Heijer den M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJC, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grassler JUR, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen A-L, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jørgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, König IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaløy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimäki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B, MAGIC; Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ, O'Rahilly S, Ong KK, Oostra B, Paré G, Parker AN, Perola M, Pichler I, Pietiläinen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstråle M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tönjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kähönen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Grönberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H, Procardis Consortium. Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42:937–948. [PubMed: 20935630]

28. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, Thorleifsson G, Zillikens MC, Speliotes EK, Mägi R, Workalemahu T, White CC, Bouatia-Naji N, Harris TB, Berndt SI, Ingelsson E, Willer CJ, Weedon MN, Luan J, Vedantam S, Esko T, Kilpeläinen TO, Kutalik Z, Li S, Monda KL, Dixon AL, Holmes CC, Kaplan LM, Liang L, Min JL, Moffatt MF, Molony C, Nicholson G, Schadt EE, Zondervan KT, Feitosa MF, Ferreira T, Allen HL, Weyant RJ, Wheeler E, Wood AR, Estrada K, Goddard ME, Lettre G, Mangino M, Nyholt DR, Purcell S, Vernon Smith A, Visscher PM, Yang J, McCarroll SA, Nemesh J, Voight BF, Absher D, Amin N, Aspelund T, Coin L, Glazer NL, Hayward C, Heard-Costa NL, Hottenga J-J, Johansson A, Johnson T, Kaakinen M, Kapur K, Ketkar S, Knowles JW, Kraft P, Kraja AT, Lamina C, Leitzmann MF, McKnight B, Morris AP, Ong KK, Perry JRB, Peters MJ, Polasek O, Prokopenko I, Rayner NW, Ripatti S, Rivadeneira F, Robertson NR, Sanna S, Sovio U, Surakka I, Teumer A, van Wingerden S, Vitart V, Zhao JH, Cavalcanti-Proença C, Chines PS, Fisher E, Kulzer JR,

Lecoeur C, Narisu N, Sandholt C, Scott LJ, Silander K, Stark K, Tammesoo M-L, Teslovich TM, Timpson NJ, Watanabe RM, Welch R, Chasman DI, Cooper MN, Jansson J-O, Kettunen J, Lawrence RW, Pellikka N, Perola M, Vandenput L, Alavere H, Almgren P, Atwood LD, Bennett AJ, Biffar R, Bonnycastle LL, Bornstein SR, Buchanan TA, Campbell H, Day INM, Dei M, Dörr M, Elliott P, Erdos MR, Eriksson JG, Freimer NB, Fu M, Gaget S, Geus EJC, Gjesing AP, Grallert H, Grässler J, Groves CJ, Guiducci C, Hartikainen A-L, Hassanali N, Havulinna AS, Herzig K-H, Hicks AA, Hui J, Igl W, Jousilahti P, Jula A, Kajantie E, Kinnunen L, Kolcic I, Koskinen S, Kovacs P, Kroemer HK, Krzelj V, Kuusisto J, Kvaloy K, Laitinen J, Lantieri O, Lathrop GM, Lokki ML, Luben RN, Ludwig B, McArdle WL, McCarthy A, Morken MA, Nelis M, Neville MJ, Paré G, Parker AN, Peden JF, Pichler I, Pietiläinen KH, Platou CG, Pouta A, Ridderstråle M, Samani NJ, Saramies J, Sinisalo J, Smit JH, Strawbridge RJ, Stringham HM, Swift AJ, Teder-Laving M, Thomson B, Usala G, van Meurs JB, van Ommen GJ, Vatin V, Volpato CB, Wallaschofski H, Walters GB, Widen E, Wild SH, Willemsen G, Witte DR, Zgaga L, Zitting P, Beilby JP, James AL, Kähönen M, Lehtimäki T, Nieminen MS, Ohlsson C, Palmer LJ, Raitakari O, Ridker PM, Stumvoll M, Tönjes A, Viikari J, Balkau B, Ben-Shlomo Y, Bergman RN, Boeing H, Smith GD, Ebrahim S, Froguel P, Hansen T, Hengstenberg C, Hveem K, Isomaa B, Jørgensen T, Karpe F, Khaw KT, Laakso M, Lawlor DA, Marre M, Meitinger T, Metspalu A, Midthjell K, Pedersen O, Salomaa V, Schwarz PE, Tuomi T, Tuomilehto J, Valle TT, Wareham NJ, Arnold AM, Beckmann JS, Bergmann S, Boerwinkle E, Boomsma DI, Caulfield MJ, Collins FS, Eiriksdottir G, Gudnason V, Gyllensten U, Hamsten A, Hattersley AT, Hofman A, Hu FB, Illig T, Iribarren C, Jarvelin MR, Kao WH, Kaprio J, Launer LJ, Munroe PB, Oostra B, Penninx BW, Pramstaller PP, Psaty BM, Quertermous T, Rissanen A, Rudan I, Shuldiner AR, Soranzo N, Spector TD, Syvanen AC, Uda M, Uitterlinden A, Völzke H, Vollenweider P, Wilson JF, Witteman JC, Wright AF, Abecasis GR, Boehnke M, Borecki IB, Deloukas P, Frayling TM, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, North KE, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, Hirschhorn JN, Assimes TL, Wichmann HE, Thorsteinsdottir U, van Duijn CM, Stefansson K, Cupples LA, Loos RJ, Barroso I, McCarthy MI, Fox CS, Mohlke KL, Lindgren CM. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2011; 43:1164–1164.

29. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, Willer CJ, Jackson AU, Vedantam S, Raychaudhuri S, Ferreira T, Wood AR, Weyant RJ, Segre AV, Speliotes EK, Wheeler E, Soranzo N, Park J-H, Yang J, Gudbjartsson D, Heard-Costa NL, Randall JC, Qi L, Vernon Smith A, Magi R, Pastinen T, Liang L, Heid IM, Luan J, Thorleifsson G, Winkler TW, Goddard ME, Sin Lo K, Palmer C, Workalemahu T, Aulchenko YS, Johansson A, Zillikens MC, Feitosa MF, Esko TON, Johnson T, Ketkar S, Kraft P, Mangino M, Prokopenko I, Absher D, Albrecht E, Ernst F, Glazer NL, Hayward C, Hottenga J-J, Jacobs KB, Knowles JW, Kutalik ZAN, Monda KL, Polasek O, Preuss M, Rayner NW, Robertson NR, Steinthorsdottir V, Tyrer JP, Voight BF, Wiklund F, Xu J, Zhao JH, Nyholt DR, Pellikka N, Perola M, Perry JRB, Surakka I, Tammesoo M-L, Altmaier EL, Amin N, Aspelund T, Bhangale T, Boucher G, Chasman DI, Chen C, Coin L, Cooper MN, Dixon AL, Gibson Q, Grundberg E, Hao K, Juhani Junttila M, Kaplan LM, Kettunen J, Konig IR, Kwan T, Lawrence RW, Levinson DF, Lorentzon M, McKnight B, Morris AP, Muller M, Suh Ngwa J, Purcell S, Rafelt S, Salem RM, Salvi E, Sanna S, Shi J, Sovio U, Thompson JR, Turchin MC, Vandenput L, Verlaan DJ, Vitart V, White CC, Ziegler A, Almgren P, Balmforth AJ, Campbell H, Citterio L, De Grandi A, Dominiczak A, Duan J, Elliott P, Elosua R, Eriksson JG, Freimer NB, Geus EJC, Glorioso N, Haiqing S, Hartikainen A-L, Havulinna AS, Hicks AA, Hui J, Igl W, Illig T, Jula A, Kajantie E, Kilpeläinen TO, Koiranen M, Kolcic I, Koskinen S, Kovacs P, Laitinen J, Liu J, Lokki M-L, Marusic A, Maschio A, Meitinger T, Mulas A, Pare G, Parker AN, Peden JF, Petersmann A, Pichler I, Pietiläinen KH, Pouta A, Ridderstråle M, Rotter JI, Sambrook JG, Sanders AR, Schmidt CO, Sinisalo J, Smit JH, Stringham HM, Bragi Walters G, Widen E, Wild SH, Willemsen G, Zagato L, Zgaga L, Zitting P, Alavere H, Farrall M, McArdle WL, Nelis M, Peters MJ, Ripatti S, van Meurs JB, Aben KK, Ardlie KG, Beckmann JS, Beilby JP, Bergman RN, Bergmann S, Collins FS, Cusi D, den Heijer M, Eiriksdottir G, Gejman PV, Hall AS, Hamsten A, Huikuri HV, Iribarren C, Kähönen M, Kaprio J, Kathiresan S, Kiemeney L, Kocher T, Launer LJ, Lehtimäki T, Melander O, Mosley TH Jr, Musk AW, Nieminen MS, O'Donnell CJ, Ohlsson C, Oostra B, Palmer LJ, Raitakari O, Ridker PM, Rioux JD, Rissanen A, Rivolta C, Schunkert H, Shuldiner AR, Siscovick DS, Stumvoll M, Tönjes A, Tuomilehto J, van Ommen GJ, Viikari J, Heath AC, Martin NG, Montgomery GW, Province

MA, Kayser M, Arnold AM, Atwood LD, Boerwinkle E, Chanock SJ, Deloukas P, Gieger C, Grönberg H, Hall P, Hattersley AT, Hengstenberg C, Hoffman W, Lathrop GM, Salomaa V, Schreiber S, Uda M, Waterworth D, Wright AF, Assimes TL, Barroso I, Hofman A, Mohlke KL, Boomsma DI, Caulfield MJ, Cupples LA, Erdmann J, Fox CS, Gudnason V, Gyllensten U, Harris TB, Hayes RB, Jarvelin MR, Mooser V, Munroe PB, Ouwehand WH, Penninx BW, Pramstaller PP, Quertermous T, Rudan I, Samani NJ, Spector TD, Völzke H, Watkins H, Wilson JF, Groop LC, Haritunians T, Hu FB, Kaplan RC, Metspalu A, North KE, Schlessinger D, Wareham NJ, Hunter DJ, O'Connell JR, Strachan DP, Wichmann HE, Borecki IB, van Duijn CM, Schadt EE, Thorsteinsdottir U, Peltonen L, Uitterlinden AG, Visscher PM, Chatterjee N, Loos RJ, Boehnke M, McCarthy MI, Ingelsson E, Lindgren CM, Abecasis GR, Stefansson K, Frayling TM, Hirschhorn JN. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010; 467:832–838. [PubMed: 20881960]

30. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011; 43:969–976. [PubMed: 21926974]
31. Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, Plagnol V, Pociot F, Schuilenburg H, Smyth DJ, Stevens H, Todd JA, Walker NM, Rich SS, Type 1 Diabetes Genetics Consortium. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet. 2009; 41:703–707. [PubMed: 19430480]
32. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, Li Y, Kurreeman FAS, Zhernakova A, Hinks A, Guiducci C, Chen R, Alfredsson L, Amos CI, Ardlie KG, BIRAC Consortium; Barton A, Bowes J, Brouwer E, Burtt NP, Catanese JJ, Coblyn J, Coenen MJH, Costenbader KH, Criswell LA, Crusius JBA, Cui J, de Bakker PIW, de Jager PL, Ding B, Emery P, Flynn E, Harrison P, Hocking LJ, Huizinga TWJ, Kastner DL, Ke X, Lee AT, Liu X, Martin P, Morgan AW, Padyukov L, Posthumus MD, Radstake TRDJ, Reid DM, Seielstad M, Seldin MF, Shadick NA, Steer S, Tak PP, Thomson W, van der Helm-van Mil AHM, van der Horst-Bruinsma IE, van der Schoot CE, van Riel PLCM, Weinblatt ME, Wilson AG, Wolbink GJ, Wordsworth BP, YEAR Consortium. Wijmenga C, Karlson EW, Toes REM, de Vries N, Begovich AB, Worthington J, Siminovitch KA, Gregersen PK, Klareskog L, Plenge RM. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet. 2010; 42:508–514. [PubMed: 20453842]
33. Franke A, McGovern DPB, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel J-F, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Gearry R, Glas J, Van Gossum A, Guthery SL, Halfvarson J, Verspaget HW, Hugot J-P, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhart AH, Stokkers PCF, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annese V, Hakonarson H, Daly MJ, Parkes M. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010; 42:1118–1125. [PubMed: 21102463]
34. Dubois PCA, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, Zhernakova A, Heap GAR, Adány R, Aromaa A, Bardella MT, van den Berg LH, Bockett NA, la Concha de EG, Dema B, Fehrmann RSN, Fernández-Arquero M, Fiatal S, Grandone E, Green PM, Groen HJM, Gwilliam R, Houwen RHJ, Hunt SE, Kaukinen K, Kelleher D, Korponay-Szabo I, Kurppa K, MacMathuna P, Mäki M, Mazzilli MC, McCann OT, Mearin ML, Mein CA, Mirza MM, Mistry V, Mora B, Morley KI, Mulder CJ, Murray JA, Núñez C, Oosterom E, Ophoff RA, Polanco I, Peltonen L, Platteel M, Rybak A, Salomaa V, Schweizer JJ, Sperandeo MP, Tack GJ, Turner G, Veldink JH, Verbeek WHM, Weersma RK, Wolters VM, Urcelay E, Cukrowska B, Greco L, Neuhausen SL, McManus R, Barisani D, Deloukas P, Barrett JC, Saavalainen P, Wijmenga C, van Heel DA.

Multiple common variants for celiac disease influencing immune gene expression. Nat Genet. 2010; 42:295–302. [PubMed: 20190752]

35. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Ser B Stat Methodol. 1995; 57:289–300.
36. Sun L, Craiu RV, Paterson AD, Bull SB. Stratified false discovery control for large-scale hypothesis testing with application to genome-wide association studies. Genet Epidemiol. 2006; 30:519–530. [PubMed: 16800000]
37. Yoo YJ, Pinnaduwage D, Waggott D, Bull SB, Sun L. Genome-wide association analyses of North American Rheumatoid Arthritis Consortium and Framingham Heart Study data utilizing genome-wide linkage results. BMC Proceedings. 2009; 3(Suppl 7):S103. [PubMed: 20017967]
38. Schork AJ, Thompson WK, Pham P, Torkamani A, Roddey JC, Sullivan PF, Kelsoe JR, O'Donovan MC, Furberg H, Schork NJ, Andreassen OA, Dale AM. All SNPs Are Not Created Equal: Genome-Wide Association Studies Reveal a Consistent Pattern of Enrichment among Functionally Annotated SNPs. PLoS Genet. 2013; 9:e1003449. [PubMed: 23637621]
39. Reppe S, Refvem H, Gautvik VT, Olstad OK, Høvring PI, Reinholt FP, Holden M, Frigessi A, Jemtland R, Gautvik KM. Eight genes are highly associated with BMD variation in postmenopausal Caucasian women. Bone. 2010; 46:604–612. [PubMed: 19922823]
40. Dokos C, Savopoulos C, Hatzitolios A. Reconsider hypertension phenotypes and osteoporosis. J J Clin Hypertens (Greenwich). 2011; 13:E1–2.
41. Sivakumaran S, Agakov F, Theodoratou E, Prendergast JG, Zgaga L, Manolio T, Rudan I, McKeigue P, Wilson JF, Campbell H. Abundant pleiotropy in human complex diseases and traits. Am J Hum Genet. 2011; 89:607–618. [PubMed: 22077970]
42. Qiao S-W, Sollid LM, Blumberg RS. Antigen presentation in celiac disease. Curr Opin Immunol. 2009; 21:111–117. [PubMed: 19342211]
43. Andreassen OA, Thompson WK, Dale AM. Boosting the power of schizophrenia genetics by leveraging new statistical tools. Schizophr Bull. 2014 In Press.

Novelty and Significance

1. 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

2. 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

3. 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 etiological relationship between hypertension and lipid disturbances and immunological abnormalities.

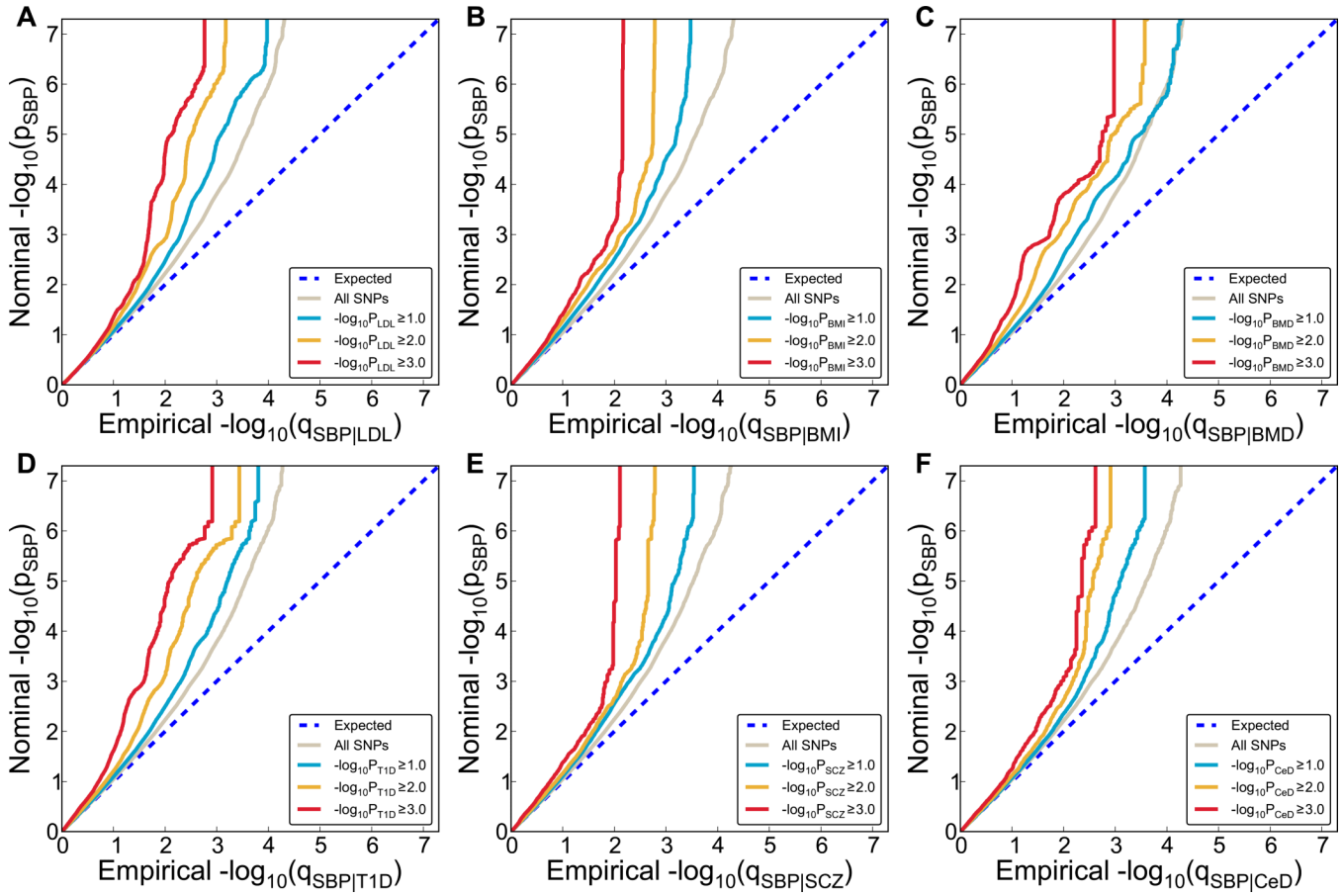

Figure 1. Q-Q plots of pleiotropic enrichment in SBP conditioned on associated phenotypes

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 $p < 5\times10^{-8}$ 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 (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 $p < 1$, $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. Dotted lines indicate the null-hypothesis.

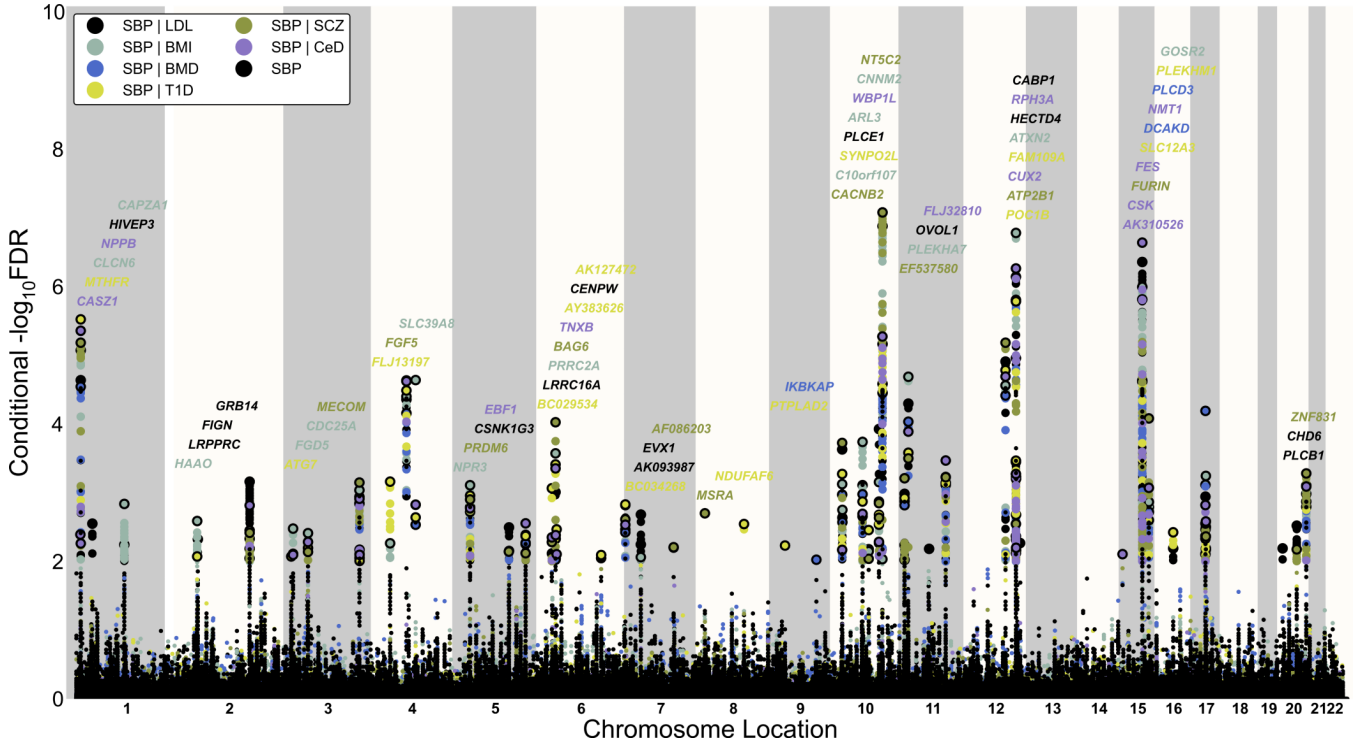

Figure 2. 'Conditional FDR Manhattan plot'

'Conditional 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, red), body mass index (BMI; SBP|BMI, orange), bone mineral density (BMD; SBP|BMD, green), type 1 diabetes (T1D; SBP|T1D, purple), schizophrenia (SCZ; SBP|SCZ; turquois) and celiac disease (CeD; SBP|CeD, blue). SNPs with conditional $-\log_{10}$ FDR > 2 (i.e. FDR < 0.01) are shown with large points. A black circle around the large points indicates the most significant SNP in each LD block and this SNP was annotated with the closest gene which is listed above the symbols in each locus, except for the HLA region on chromosome 6, and in Table S2 (please see http://hyper.ahajournals.org). 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 (i.e. FDR < 0.01) are shown in Table 1.

Table 1

The GWAS data used in the current study

Disease/Trait	N	# SNPs	Reference
Systolic Blood Pressure (SBP)	203,056	2,382,073	Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature 2011;478:103-9.
Low Density Lipoprotein (LDL)	99,900	2,508,375	Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010;466:707-13.
High Density Lipoprotein (HDL)	96,598	2,508,370	
Triglycerides (TG)	96,568	2,508,369	
Height (HT)	183,727	2,398,527	Lango Allen et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature 2010, 467: 832-8
Body Mass Index (BMI)	123,865	2,400,377	Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010;42:937-48.
Waist to hip ratio (WHR)	77,167	2,376,820	Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet 2010;42:949-60.
Type 2 Diabetes (T2D)	22,044	2,426,886	Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 2010;42:579-89.
Type 1 Diabetes (T1D)	16,559	841,622	Barrett, J.C. et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. NatGen 2009, 41, 703-7.
Rheumatoid arthritis (RA)	25,708	2,560,000	Stahl, E.A. et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet 2010 42, 508-14.
Bone Mineral Density (BMD)	32,961	2,500,000	Estrada, K. et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet 2012;44:491-501.
Celiac Disease (CeD)	15,283	528,969	Dubois, P.C. et al Multiple common variants for celiac disease influencing immune gene expression. Nat Genet 2010, 42, 295-302
Schizophrenia	21,856	1,171,056	Schizophrenia Psychiatric Genome-Wide Associatino Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. Nat Genet 2011;43:969-76.

For more details, see also http://www.genome.gov/gwastudies

Table 2

Independent loci associated with SBP through Conditional FDR (<0.01) with associated phenotypes.

Locus	SNP	Pos	Gene	chr	SBP p-value	SBP FDR	Min cond FDR	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

Locus	SNP	Pos	Gene	chr	SBP p-value	SBP FDR	Min cond FDR	Associated Phenotype
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
40	rs4590817	63467553	*C10orf107* †	10	**3.40E-08**	**0.00077**	0.0001588	WHR
41	rs12247028	75410052	*SYNPO2L*	10	1.59E-06	0.0132B	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	1425519	*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 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. The most significant phenotype associations per gene are shown. All genes are shown in Table S1. All data were first corrected for genomic inflation. Gene titles and gene ontology functional terms are displayed in Table S2 (please see http://hyper.ahajournals.org). Ingenuity pathway analysis was used to generate a network displaying direct interactions among proteins encoded by these SBP-related genes (shown in Figure S3, please see http://hyper.ahajournals.org). The molecules associated with some of the top functional clusters of these genes are show in Tables S3 and S4 (please see http://hyper.ahajournals.org).