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Genome-Wide Association Studies of Hypertension: Have They Been Fruitful?

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Abstract Over the last two decades candidate gene association studies and genome-wide linkage scans have met with little success in characterizing risk variants for hypertension. Several factors could be responsible for the relative lack of success, although our understanding of the genetics has evolved to support the belief that there are multiple common risk variants, which are associated with hypertension with modest effect sizes. Genome-wide association studies (GWAS) have successfully identified risk loci for several complex polygenic disease states. Until recently, the productivity of GWAS with respect to identifying risk loci for hypertension was limited. In this paper we describe the recent success of GWAS of hypertension in identifying over a dozen loci associated with essential hypertension. We will review these findings, and place these results in the context of the future potential of pharmocogenetics of hypertension.

Keywords Genome-Wide Association Study · Hypertension · Genetics · Blood Pressure

Genetics of Hypertension

Blood pressure is a quantitative trait, normally distributed in the general population, and is a significant determinant of ischemic heart disease, cerebrovascular disease, atrial fibrillation, and heart failure [1–3] The pressure exerted on arterial vasculature by the blood flow from the left ventricle in response to cardiac contraction follows a periodic elevation and decrease, described as systolic and diastolic blood pressures, respectively [4]. Hypertension is defined as a systolic blood pressure (SBP) measurement of ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or self-reported use of blood pressure lowering medication. Normal blood pressure is defined as a measured SBP≤140 mm Hg or DBP<90 mm Hg [5, 6]. Hypertension can be heterogeneous in nature. Patients can present with increased blood pressure at the time of the clinic visit despite a normal daytime ambulatory blood pressure, termed the white coat hypertension [7]. Patients suffering from this type of hypertension are at lower risk of complications [8]. On the contrary, patients may have normal blood pressure with a raised daytime ambulatory blood pressure [9]. Lack of standardization, dichotomization of blood pressure, and inappropriate selection of cases and controls produces substantial variation in the phenotype, which may have contributed to the slow progress in the identification of genetic variants associated with blood pressure [9]. We will review the evidence for familial hypertension and the results of the candidate and GWAS association studies and the future potential of improved treatment of blood pressure using pharmacogenetic profiles.

Blood Pressure Heritability Despite the lack of standardization of blood pressure measurements, there is reliable evidence to indicate a genetic component from familial and other sources with the studies in twins being most convincing. Familial studies of blood pressure demonstrate high concordance between parents and children and among siblings, with rates ranging from 20 to 66% in the general population [10–12]. Twin studies show a higher correlation

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in blood pressure measurements between monozygotic twins (r=0.56–0.62) then to dizygotic (r=0.21–28) twin pairs [13–15]. Results from twin studies are considered to be closest to actual heritability estimates given that these control for similar environmental effects. Heritability estimates for blood pressure in multiple twin studies exceed 50% indicating that more than half of the variation in blood pressure can be attributed to additive genetic effects [16–22]. While blood pressure is a heritable trait, there are other determinants of blood pressure that are important to consider especially when interpreting results from genetic studies of blood pressure. The burden of hypertension has risen in prevalence in multiple countries through the world in parallel with the rising prevalence of obesity and increased consumption of sodium in packaged and processed foods. The effect of these "environmental" influences on blood pressure cannot be underestimated as a 10-kg rise in body weight is associated with at least a 3-mm Hg rise in systolic BP and a 2.2-mm Hg rise in diastolic BP [23]. Further, a decrease in daily sodium intake equivalent to 100 mmol/day is equivalent to 1-mm Hg lower systolic BP and 0.1-mm Hg lower diastolic BP [24]. Similarly, variation in physical activity levels can dramatically affect blood pressure [25].

Genetic Linkage Studies for Hypertension

Family-based genetic linkage studies have been widely used to study the molecular genetics of hypertension. Rarer forms of monogenic hypertension, which contribute to less than 1% of the overall cases of hypertension, have benefited the most from these studies. Several genome-wide [26, 27] and candidate gene-based linkage scans [27, 28] have been performed. While linkage peaks have been identified, the majority have not reached genome-wide significance levels. Secondly, there has been the lack of replication of quantitative traits loci (QTL) in independent populations. Further the relatively large QTL intervals identified in linkage scans containing multiple genes have made it difficult to pinpoint risk variants.

Candidate Gene Association Studies for Hypertension

Candidate gene association studies of blood pressure have been widely employed. Despite the large number of reported associations, findings have not been replicated to establish risk variants. Apart from the selection of candidate genes based on physiological systems, systematic analysis of genes harboring mutations leading to rare diseases with large variations in blood pressure has been reported [29, 30]. Ji et al. [29] studied individuals heterozygous for rare deleterious mutations in three renal salt handling genes (SLC12A3, SLC12A1, and KCNJ1) in 1,985 unrelated subjects and 1,140 relatives from the Framingham Heart Study. Studying rare variations (minor allele frequency <1%) Ji et al. described significant deviations in blood pressure values from the mean (6.3 and 3.4 mm Hg, respectively for systolic and diastolic blood pressure) in individuals carrying 30 different mutations in 49 subjects (p<0.001). Similarly Tobin et al. described their results from 2,037 adults assigned to 520 nuclear families [30]. Following genotyping of 298 tag SNPs across 11 candidate genes, Tobin et al. described multiple associations of tag SNPs in the *KCNJ1* gene, with minor alleles of the rs2846679 and rs2186832 variants. Both of these variants were associated with reductions equivalent to 1.58 and 0.95 mm Hg in 24-h systolic and diastolic BP. A recent genome-wide study failed to confirm these associations [31]. Recent genome-wide association studies are inputting SNPs to provide denser coverage of the genome; thus, lack of genetic coverage in the future is unlikely to be the reason for not confirming these associations.

Candidate gene association studies have often focused on variation in genes encoding proteins involved in renal sodium transport and renin–angiotensin–aldosterone system [32]. Recently Sober at al. [33] assessed 160 candidate genes for association with essential hypertension based on genotyping results available from the Affymetrix 500-k chip. Sober et al. discuss the lack of complete genetic coverage in the selected candidate genes based on the Affymetrix 500-k chip. Further, they show that the genome-wide SNP array available from Affymetrix only captures half of the common variation in the studied candidate genes. None of the associations in this study reached nominal significance levels after Bonferroni correcting for multiple hypotheses testing. The candidate gene approach has also failed to identify genetic variants associated with other cardiovascular diseases. Pare et al. [34] and Morgan et al. [35] undertook a candidate gene association analysis of 103 and 70 genes for coronary artery disease based on literature review. Neither of these studies identified any genetic variants associated with disease risk following Bonferroni corrections.

Lack of Evidence for Hypertension Genes from Initial GWAS Studies

Attempts by researchers to identify genetic variants associated with blood pressure have been challenging and of relatively low yield. The Wellcome Trust Case Control Consortium (WTCCC) reported the first genome-wide association results for hypertension. This study identified several risk variants, but none reached the statistical significance required in this study (5×10^{-7}) for hypertension despite capturing approximately 65 [36, 37] common

genetic variations in the HapMap (CEU) European population. The WTCCC study however, did identify SNPs associated with heart disease including 9p21 with odds ratios ranging from 1.1 to 1.40. These results led investigators to suggest that genetic variants for hypertension are likely to have smaller effect sizes than those observed for genetic variants associated with heart disease. It was advocated that larger sample sizes through meta-analysis be applied along with denser coverage of the genome. However, a major concern for the WTCCC study is the inappropriate selection of cases and controls. The study was not designed for any specific disease. The mean age of the controls is 48 years, which would indicate that a significant percentage of these controls will develop coronary artery disease and hypertension within the next two decades. This would significantly decrease the sensitivity of WTCCC to detect risk variants contributing to coronary artery disease or hypertension. The more appropriate controls for hypertension or CAD would be elderly healthy individuals without evidence of the disease. Similarly, the average age of the cases in WTCCC was 68 years, and a younger cohort would have been more appropriate to enrich the study for identifying genetic risk.

Genome-Wide Association Studies in Founder Populations

Sabatti et al. reported a genome-wide association study of blood pressure in 4,763 participants from the Northern Finland Birth Cohort study of 1966, which failed to identify any genetic variants associated with blood pressure [38]. Wang et al. reported the first novel genetic variant, associated with essential hypertension in a study of 542 subjects from the Amish Family Diabetes Study (AFDS) [39]. A cluster of common variants across the *STK39* (serine threonine kinase 39) were found to be associated with systolic blood pressure with p values ranging from $p=8.9\times10^{-6}$ to 9.1×10^{-5}. However, these p values with Bonferroni correction are not significant. Combining data from three Amish population studies, Wang et al. reported a 3-mm Hg higher SBP and a 1-mm Hg higher DBP for carrying each minor allele copy of the rs6749447 variant. In a combined meta-analysis of Amish and non-Amish cohorts (Diabetes Genetics Initiative and Framingham Heart Study) an effect size of 1.9 [1.2–2.6] mm Hg increase in systolic blood pressure was observed ($p=1.6\times10^{-7}$, $n=7{,}125$, SNP=rs6749447).

Novel Variants Identified from Recent Genome-Wide Association Studies

Org et al. [40] reported a genome-wide scan employing 395,912 single nucleotide polymorphisms (SNPs) in 1,644 individuals representing the general population in the KORA (Kooperative Gesundheitsforschung in der Region Augsburg) S3 cohort study. No SNPs were found to be associated with blood pressure or hypertension at genome-wide levels of significance ($p\leq10^{-8}$). While attempting to replicate the 80 strongest associations with blood pressure and hypertension in two further population-based European cohorts (Kora S4, $n=1{,}830$ and HYPEST=1,823), Org et al. identified a single variant at the *CDH13* (cadherin 13 preprotein) locus (rs11646213), which was associated with blood pressure and hypertension (hypertension, $p=5.30\times10^{-8}$, SBP, $p<0.008$, SBP, $p=5.55\times10^{-5}$).

To date, GWAS for hypertension, pursuing an association with blood pressure as a continuous variable rather than as a case control study, have had significant success. Two recent large GWA studies became available that were performed in large consortiums, CHARGE [6] and GBP-gen [5]. The approach adopted by both of these GWAS was blood pressure as a continuous variable. The continuous trait approach offers greater power than a binary approach using hypertension as a phenotype to identify genetic predisposition for blood pressure. These studies identified multiple loci associated with either systolic or diastolic blood pressure.

Newton-Cheh et al. [5] in the GBP-gen consortium performed the largest genome-wide association study using blood pressure as a continuous trait. The study design involved combining the 500-K SNP array plus the imputation of 2.5 million SNPs in a stage-1 meta-analysis of 34,433 European individuals from 13 prospective and 4 case-control type studies. Stage 2 was subdivided into stages 2a and 2b. Stage 2a focused on replication in 71,225 individuals of European ancestry and stage 2b in 12,889 individuals of Indian Asian ancestry. In a meta-analysis study of stage-1 and stage-2 data Newton-Cheh at al identified three loci associated with SBP at genome-wide significance levels ($p<5\times10^{-8}$). These included variants at the *MTHFR*, *CYP17A1*, and *PLCD3* loci. A further five loci were associated with diastolic BP at genome-wide levels of significance. These included *FGF5, C10orf107, SH2B3, CYP1A2*, and *ZNF652* (Table 1). Newton-Cheh et al. studied the associations of eight blood pressure genes with hypertension. All eight variants were found to be associated with hypertension in the same direction as expected from associations with blood pressure. They also performed an in silico meta-analysis with data from the CHARGE consortium [6]. All four of these associations demonstrated genome-wide levels of significance. These novel loci will require confirmation in an independent population.

Levy et al. [6] for the CHARGE group consortium (Cohorts for Heart and Aging Research in Genome Epidemiology) performed a meta-analysis in 29,136 participants from six different cohort studies. A meta-analysis was

Table 1 Details of novel hypertension and blood pressure genes identified from genome-wide association studies

Gene	Phenotype	Risk allele frequency	Association p value	SNP ID
CDH13	HYP [40]	0.60	8×10^{-6}	rs11646213
STK39	SBP [39]	Na	1.6×10^{-7}	rs6749447
MTHFR	SBP [5]	0.86	1.2×10^{-13}	rs17367504
MTHFR	HYP [5]	0.86	2×10^{-9}	rs17367504
CYP17A1	SBP [5]	0.91	7×10^{-23}	rs11191548
CYP17A1	HYP [5]	0.91	3×10^{-13}	rs11191548
Intron PLCD3	SBP [5]	0.28	1×10^{-8}	rs12946454
PRDM8/FGF5	DBP [5]	0.21	1×10^{-21}	rs16998073
PRDM8/FGF5	HYP [5]	0.21	7×10^{-10}	rs16998073
Intron c10orf107	DBP [5]	0.81	1×10^{-9}	rs1530440
SH2B3	DBP [5]	0.47	3×10^{-18}	rs653178
Intron CSK	DBP [5]	0.36	1×10^{-23}	rs1378942
Intron CSK	HYP [5]	0.36	2×10^{-14}	rs1378942
ZNF652	DBP [5]	0.39	5×10^{-9}	rs16948048
CYP17A1	SBP [6]	0.90	1.2×10^{-10}	rs1004467
PLEKHA7	SBP [6]	0.26	1.8×10^{-9}	rs381815
ATP2B1	SBP [6]	0.80	3.7×10^{-11}	rs2681492
SH2B3	SBP [6]	0.48	4.2×10^{-9}	rs3184504
ULK4	DBP [6]	0.17	2.5×10^{-9}	rs9815354
CACNB2	DBP [6]	0.46	1.2×10^{-8}	rs11014166
ATP2B1	DBP [6]	0.83	1.4×10^{-9}	rs2681472
SH2B3	DBP [6]	0.48	2.6×10^{-14}	rs3184504
TBX3-TBX5	DBP [6]	0.65	3.7×10^{-8}	rs2384550
CSK-ULK3	DBP [6]	0.42	1.8×10^{-10}	rs6495122
ATP2B1	HYP [6]	0.83	1.7×10^{-11}	rs2681472

performed with the population from GBP-gen (n=34,443), and many novel loci for systolic and diastolic blood pressures were identified. Novel variants for SBP at genome-wide levels of significance from CHARGE and Global BPgen, Stage-2; $p=5\times10^{-8}$ were located in *CYP17A1*, *PLEKHA7*, *ATP2B1*, and *SH2B3* loci. The lone genetic variant associated with hypertension (odds ratio= 1.17 for $p=1.7\times10^{-8}$) was identified at the *ATP2B1* locus. Novel genetic variants for DBP were located at the *ULK4*, *CACNB2*, *ATP2B1*, *SH2B3*, *TBX3-TBX5*, and *CSK-ULK3* loci (Table 1, Fig. 1). In the meta-analysis of CHARGE and GBP-GEN, it is of note that only one locus from the GBP-GEN eight loci reached genome-wide significance. Nevertheless, five novel loci with genome-wide significance were identified. While these five loci have not been replicated in an independent population, the results are strongly suggestive since the meta-analysis involved a large population of over 60,000. These loci have frequencies in the general population similar to that observed in the GWAS for CAD and also have similar modest risk effects.

Results from recent GWAS studies indicate the importance of achieving near complete genetic coverage and high statistical power using meta-analysis approaches. The number of genes identified by meta-analysis studies by the Global BPgen and the CHARGE consortia has taken the number of Systolic BP, Diastolic BP, and Hypertension genes identified to date to 8, 11, and 6, respectively (Table 1, Fig. 2).

Future Studies and Pharmacogenomics

Inter-individual variation in response to antihypertensive agents is common. Reasons for this variation include adherence, differential dosing, and possibly genetic variation. As antihypertensive drugs act on specific systems to lower blood pressure, selection of candidate gene SNPs for analysis often focuses on genes acting in these systems. Gene–blood pressure associations have been tested for at least 22 drugs. For example, polymorphisms in genes encoding blood pressure-regulating receptors, receptor response pathways and renin–angiotensin–aldosterone systems have been obvious candidates for pharmacogenetic analysis of hypertension and cardiovascular disease [41]. The renin–angiotensin system genes have been widely studied. Specifically the ACE I/D (ACE Insertion/Deletion Polymorphism) polymorphism was included in up to 50% of the studies performing pharmacogenetic analysis of

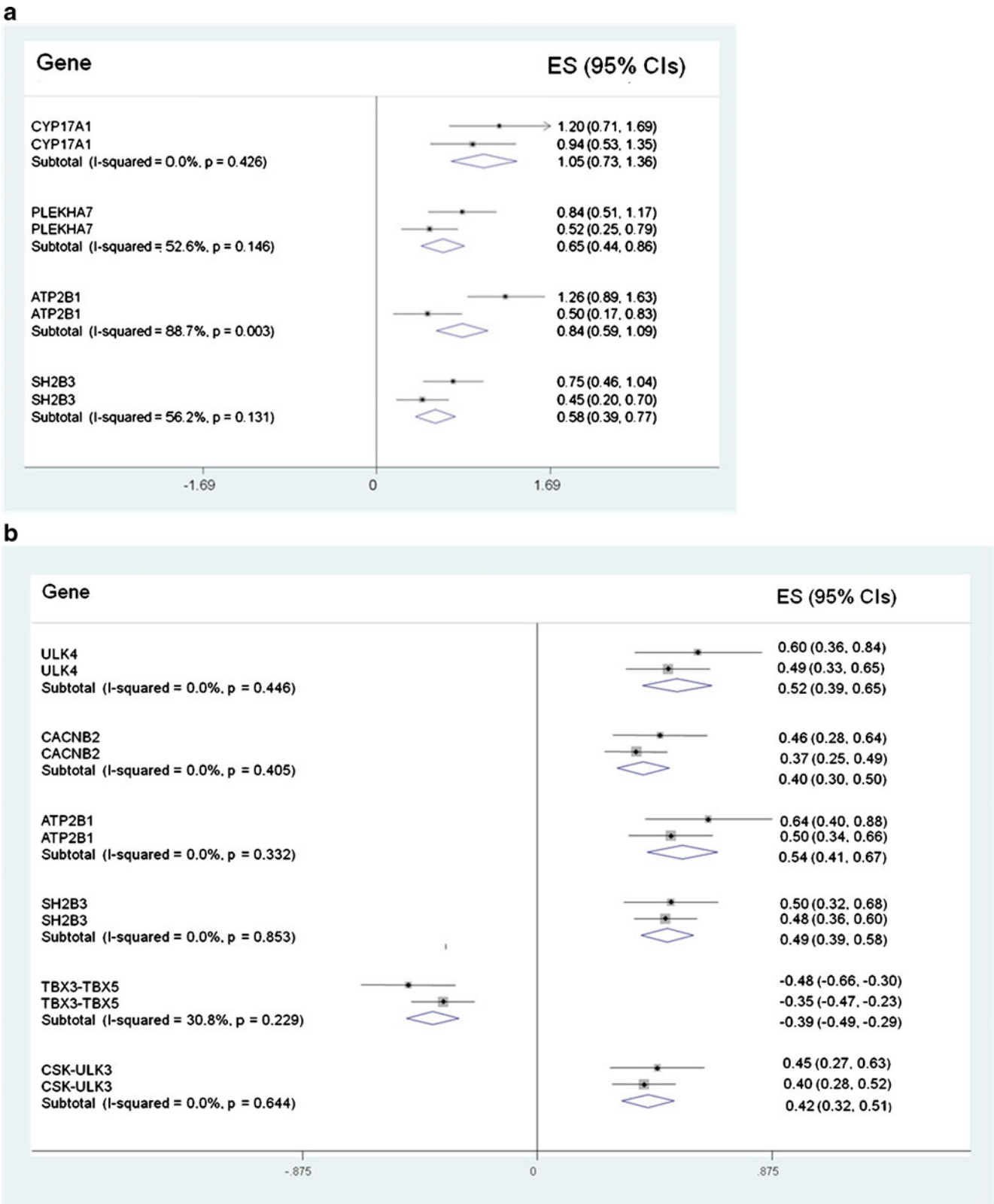

Fig. 1 **a** Forest plot for genetic effects on systolic blood pressure, across the CHARGE, and Global BPgen consortia. **b** Forest plot for genetic effects on diastolic blood pressure, across the CHARGE, and Global BPgen consortia

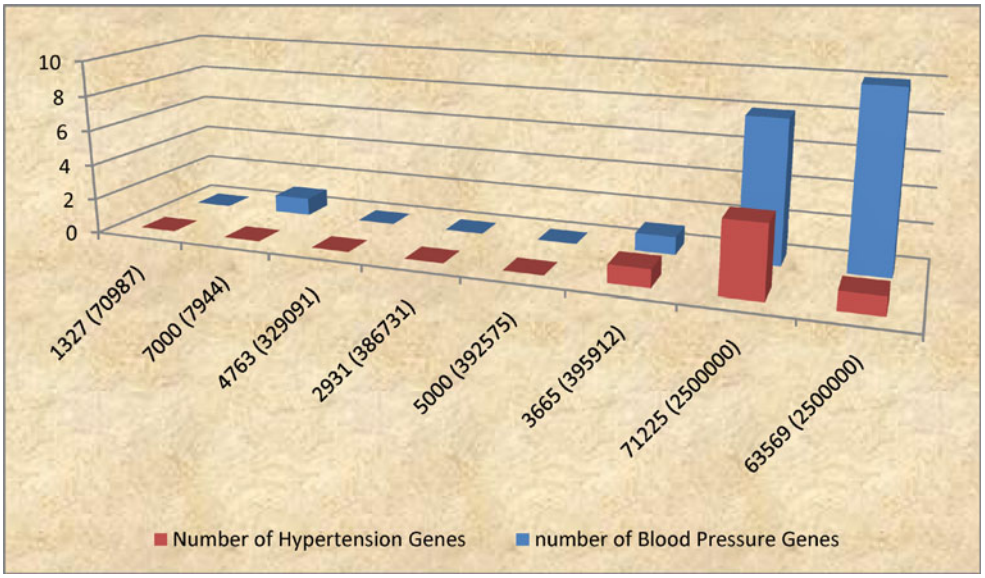

Fig. 2 A plot of the number of blood pressure and hypertension genes identified from eight genome-wide association studies (*x* axis) in relation to sample size and (SNP density)

hypertension [41]. In a study of nearly 40,000 individuals from the GenHAT study Arnett et al. did not observe any interaction of the ACE I/D polymorphism with antihypertensive drug usage in relation to coronary heart disease risk predisposition [42]. A recent study investigated the association of renin–angiotensin–aldosterone system polymorphisms in the angiotensin-converting enzyme encoding gene (insertion/deletion), angiotensin II type 1-receptor gene (A1166C), aldosterone synthase gene (−344C/T) and the angiotensinogen (−6A/G) encoding gene. No associations of any of the studied polymorphisms with essential hypertension and blood pressure response were observed in the entire cohort or following a randomization experiment using fosinopril 20 mg/day in 191 patients [43].

Psaty et al. [44] reported a study that described an interaction of the Gly460Trp variant in the α-adducin gene with use of diuretic medication finally altering cardiovascular disease risk. While the wild-type allele carriers of the Gly460Trp variant did not demonstrate any interaction with use of diuretics, the minor allele carriers of the α-adducin gene were at lower risk of suffering from cardiovascular disease (OR=0.49; 95% CI, 0.32–0.77). Further, a recent analysis in the Rotterdam study demonstrated an association of the Gly460Trp allele with higher risk of stroke (HR=1.22; 95% CI, 1.02 to 1.45) and myocardial infarction (HR=1.33; 95% CI, 1.05 to 1.69). However, a recent study did not find an interaction effect of the Gly460Trp variant with thiazide diuretics treatment in either the wild-type or the minor allele carriers [45].

Recently Lynch et al. described a landmark study, which demonstrated an interaction of the T-allele at the *NPPA* T2238C variant with diuretic (chlorthalidone) treatment to predispose individuals to higher risk of cardiovascular disease and stroke [46]. The *NPPA* genes encode for the atrial natriuretic precursor A, which itself acts as a diuretic. Previous studies of this variant had identified association of the minor allele at the T223C variant with cardiovascular disease and stroke in some studies. Lynch et al. identified an association of the minor allele of the *NPPA* T2238C variant with lower systolic BP in individuals who were treated with chlorthalidone vs. the other drugs (p=0.001).

The recently identified novel polymorphisms, which are associated with blood pressure and hypertension, are excellent candidates for pharmacogenetic analysis. These genetic variants have been identified without setting an a priori hypothesis to select polymorphisms in specific physiological sub-systems. Initial clues from genome-wide association studies implicate genes in a variety of pathways including biosynthesis of mineralocorticoids and glucocorticoids that effect sodium exchange in the kidney, genes encoding proteins with vasodilatory and natriuretic properties, genes encoding proteins altering renal function and peripheral vascular tone, enzymes regulating alcohol metabolism, and genes associated with Type 1 diabetes and celiac disease, suggesting an inflammatory component for hypertension [5, 6]. Future selection of these genes from genome-wide association studies of hypertension for pharmacogenetic analysis will mean that their effects are unlikely to be modulated by obesity and type 2 diabetes. Furthermore, novel designs, such as GWAS of extremes of the blood pressure trait, in responders versus non-responders to drug therapy, may increase the yield of genetic variants and blood pressure.

Pharmacogenetic experiments reported in literature rarely consider the possibility of variation in drug effect sizes or the interaction effects of SNP's with drug dosage varying between ethnically diverse individuals. Pharmaceutical companies operate on "a one-drug-fits-all" ideology and

consider low financial incentives in marketing drugs for different ethnic sub-groups. Future studies will need to consider the possibility of gene–ethnicity and drug–ethnicity interactions and propose suitable methodologies as an incentive for pharmaceutical companies.

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