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REVIEW

Translational medicine

Genes for blood pressure: an opportunity to understand hypertension

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Hypertension (HTN) is quantitatively the major cardiovascular risk factor and responsible for ~50% of cardiovascular morbidity and mortality. Blood pressure (BP) is also a classical complex genetic trait with heritability estimates of 30–50%. Although much is known about BP regulation, the intrinsic origin of essential HTN remains obscure although many environmental factors are known. Analyses of rare monogenic syndromes of HTN have focused attention on pathways that involve renal sodium handling, and steroid hormone metabolism including the mineralocorticoid receptor activity. The genetic basis of common essential HTN on the other hand is only just becoming accessible through high-throughput approaches. Unbiased genome-wide analyses of BP genomics have identified 43 genetic variants associated with systolic, diastolic BP, and HTN. It is highly likely based on current findings that there are hundreds of such loci with small effects on BP, opening a perspective on the genetic architecture of BP that was unknown before. It is our hope that the knowledge of these and further loci will lead to improved understanding of BP pathophysiology and to the identification of new targets for drug therapy.

Keywords Blood pressure genetics • Hypertension • Monogenic disease • Complex genetic disease

Introduction

Persistently elevated blood pressure (BP) or hypertension (HTN) is the most frequent classic cardiovascular risk factor and accounts for a large proportion of cardiovascular mortality, the main cause of death worldwide.[1] Population-based data from North America indicate that 33.5% of the adult general population has HTN,[2] whereas smoking, hypercholesterolaemia, and diabetes are somewhat less frequent. In a large multi-centric European survey on primary prevention outpatients, BP is controlled in only 38% of hypertensives with pharmacological therapy (*Table 1*)[3] and similar numbers have been observed in the NHANES.[4] This is paradoxical because the pharmacological treatment of HTN has been shown to be very effective in decreasing cardiovascular morbidity and mortality in many studies,[5–7] across different age ranges.[8,9]

Blood pressure regulation and risk factors

There are several reasons why BP control is sub-optimal, especially in high-risk subgroups. One of them is far from a complete understanding of the pathophysiologic underpinnings of HTN. At the basic level, BP is controlled by only two variables following Ohm's law: peripheral vascular resistance (modified, e.g. by arterial wall modifications due to ageing, medial hypertrophy due to hyperinsulinaemia of obesity) and blood flow (modified by, e.g. increased fluid volume due to increased salt intake).[10] There are several well-established constitutional and environmental factors that modify BP levels such as dietary salt intake, alcohol consumption, age, BMI (body mass index), and physical activity. Even after adjustment for these major environmental covariates, a large proportion of BP variability remains unexplained for those with essential HTN (>90% of the patient base).

Opportunities by genetics and genomics

Genetics and genomics provide a major opportunity to investigate the remaining variability of BP. Data from family and twin studies suggest that BP is moderately heritable (30–50%).[11] Although the magnitude of heritability of complex genetic traits in general has recently been questioned, it appears unlikely that 'ghost heritability' reduces true heritability greatly.[12] Metrics based on multiple

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Table 1 Prevalence and treatment success for classic cardiovascular risk factors

Risk factor	Prevalence (adults)[2] (%)	Treatment success in practice[3] (%)
HTN	34	38.3[a]
Smoking	20	NA
Hypercholesterolaemia	15[b]	43.3[c]
Diabetes	8	36.7[d]

[a]<140/90 mmHg or <130/80 mmHg in diabetics.
[b]Total cholesterol ≥6.5 mmol/L.
[c]Total cholesterol <5 mmol/L.
[d]Type 2 diabetes: HbA1c < 6.5%.
NA, not available.

measures of BP appear to have a higher heritability (e.g. long-term average values or ambulatory BP measurements).[13] The importance of genetic influence is perhaps best illustrated by the observation that the presence of a family history of HTN increases the risk of developing HTN by approximately four times compared with the general population.[14,15]

The application of genomics in a quest to solve the unknown origins of BP and HTN is attractive because of the unbiased nature of the experimental approach: somewhere in the genome reside genetic determinants that influence the BP level of a given individual and the BP-associated variants considered up to now are of two principal types: (i) variants occurring near exclusively in *rare* familial syndromes that lead to monogenic HTN and that have *large effect sizes*, causing in many cases catastrophically high BP levels with severe cardiovascular morbidity and mortality and (ii) the *frequent* genetic variability underlying common essential HTN that has individually, *small effect sizes*.

In this review, we summarize both types of variation which have been instrumental over the last few years in improving our understanding of BP regulation and HTN. The clinician–cardiologist may never encounter a patient with monogenic HTN because such syndromes remain rare, but the mechanistic insight may still assist more general management. Of course, the clinician–cardiologist encounters individuals with essential HTN every day but the insights from genomic studies only begin to crystallize and their role in the clinic is not yet clear. The genomic methods used for the latter type of experiments are also used for many other diseases and traits and some general conclusions can be drawn.

Insights into blood pressure regulation from rare familial hypertensive syndromes

Hypertensive syndromes are rare but when present a variant in a single gene is sufficient to increase BP greatly, the effect size of the genetic variants being large. In many hypertensive syndromes, individuals develop HTN at an early age (*Table 2*) and for some of the variants the effect sizes are likely to be larger than 10 mmHg of systolic blood pressure (SBP). Strictly speaking, the affected individuals cannot be classified as having essential HTN because they carry a known underlying genetic defect. Nevertheless, insights from these rare families have been of great importance for essential HTN research over the last 20 years because the variants identified in rare HTN syndromes represented the only clearly definable genetic influence on BP in the human before genome-wide association study (GWAS) and were often thought to represent the extremes of the naturally occurring BP variation with the hope of learning also about essential HTN (see below).

Genes causing monogenic hypertension

Studies involving affected families have identified genes for Mendelian forms of HTN and also hypotension.[16,17] In the latter, there is often significant salt wasting associated with severely reduced BP, but these are not described in more detail here.

Currently 12 genes have been identified, leading to 8 distinguishable Mendelian syndromes causing HTN. *Table 2* lists the genes affected, and some key features of each clinical syndrome. This is an active area of research, two of the four genes known to cause Gordon syndrome have only been very recently identified.[18,19] Other Mendelian HTN syndromes have been mapped to a genomic region, but a specific defect still remains to be elucidated, leading without doubt to the identification of further linked genes in the future.

Genetic and clinical features of monogenic hypertension

The pathological variants in monogenic HTN genes follow the rules of classical Mendelian genetic inheritance (autosomal dominant and recessive) and are often distinguishable by additional specific phenotypic features, such as electrolyte and hormonal abnormalities.[17,20] The serum potassium level of suspected patients with a strong family history can sometimes provide some guidance to suspect a Mendelian form of HTN, but this is not always the case. A more granular phenotypic analysis may be provided by biological analyses including dosing of aldosterone, renin, and additional hormones. It is of interest that 5 out of the 12 genes present gain-of-function mutations (*Table 2*) leading to increased BP, the remainder are loss-of-function mutations that lead to a reduction of an inhibitory effect on BP or to a positive feedback loop that increases BP. The recognition of a specific disease entity is important because for some diseases these may focus therapy upon a specific drug regimen (e.g. response to steroid therapy in glucocorticoid remediable aldosteronism or response to thiazides in Gordon syndrome). Therefore, it is important to refer patients in whom a monogenic HTN syndrome is suspected to a specialized centre.

Pathways of monogenic hypertension genes and conclusions for essential hypertension

One important overall lesson from monogenic HTN research is that the 12 genes are members of only two groups of pathways: renal sodium handling and steroid hormone metabolism, including mineralocorticoid receptor activity. The specific defects and gene products are shown in context in *Figure 1*. Additional monogenic

Table 2 Monogenic hypertension genes

Gene(s)	Chr	Disease name	Key features of clinical syndrome	Mode of inheritance[a] and genetic mechanism[b]	% HTN (N)—% early-onset HTN (N)[c]	Estimated frequency; occurrence in the general population
CYP11B1[52] (11-beta hydroxylase gene)	8q	(MIM 202010) CAH type IV (congenital adrenal hyperplasia, due to 11-beta-hydroxylase deficiency)	HTN, hypokalaemia, virilization (variable); two of three patients have severe, 'classic form' with HTN in the first years of life, otherwise HTN is usually mild to moderate in intensity; accounts for 5–8% of all CAH cases	AR; LOF	63% (38)—NA[53]	~1/100 000 births ~1/5–7000 in Jewish families of North African origin (Morocco, Tunisia)
CYP11B2[54] (aldosterone synthase gene)	8p	(MIM 103900) Glucocorticoid remediable aldosteronism: familial hyperaldosteronism type I: glucocorticoid suppressible hyperaldosteronism	HTN, low plasma renin, increased aldosterone, response to dexamethasone; high genetic heterogeneity and potassium level often normal; high prevalence of intracranial aneurysms	AD; GOF gene expressed under ACTH control (fusion of the promoter region of the gene for CYP11B1 and the coding sequences of CYP11B2)	88% (8)–41% (12)[55]	Rare defect
WNK1, WNK4[56] (lysine-deficient protein kinase 1 and 4 genes)	12p	Pseudohypoaldosteronism type 2 (PHA2): Gordon syndrome *WNK1*: PHA2C (MIM 614492) *WNK4*: PHA2B (MIM 614491) *KLHL3*: PHA2D (MIM 614495) *CUL3*: PHA2E (MIM 614496)	HTN, hyperkalaemia, response to thiazides	*WNK1*: AR; GOF *WNK4*: AR; LOF; ↑expression of the thiazide-sensitive Na-Cl co-transporter SLC12A3 (NCCT) *KLHL3*: AD or AR; LOF (inhibition of KLHL3 increases the activity of SLC12A3) *CUL3*: AD; LOF	*WNK1*: 84% (12)–13%[18,57] *WNK4*: 50% (18)–10%[18,58] *KLHL3* dominant: 27% (15)–17%[19] *KLHL3* recessive: 100% (5)–14%[19] *CUL3*: NA—94%[18]	Rare defect
KLHL3[18,19] (kelch-like 3 gene)	5q					
CUL3[18] (cullin 3 gene)	2q					
SCNN1B[59], *SCNN1G*[60] (amilorid-sensitive sodium channel, beta and gamma subunit gene encoding two subunits of the ENaC sodium channel)	16p	(MIM 177200) Liddle syndrome[61,62]: pseudoaldosteronism	HTN, hypokalaemia, metabolic alkalosis, low plasma renin, low aldosterone, respond to amiloride	AD; GOF	*SCNN1B*: 100% (18)[61] *SCNN1G*: 100% (6)–50% (6)[60]	Rare defect
CYP17A1[63] (steroid 17-hydroxylase/17,20 lyase gene)	10q	(MIM 202110) Congenital adrenal hyperplasia, due to 17-alpha-hydroxylase deficiency: CAH type V	HTN, hypokalaemia, hypogonadism/ androgen deficiency	AR; LOF	NA[64]	Very rare defect

Continued

Table 2 *Continued*

Gene(s)	Chr	Disease name	Key features of clinical syndrome	Mode of inheritance[a] and genetic mechanism[b]	% HTN (N)—% early-onset HTN (N)[c]	Estimated frequency; occurrence in the general population
HSD11B2[65] (11-beta-hydroxy steroid dehydrogenase 2 gene)	16q	(MIM 218030) Cortisol 11-beta-ketoreductase deficiency: syndrome of apparent mineralocorticoid excess	HTN, hypokalaemia, low plasma renin, responsiveness to spironolactone; severe HTN	AR; LOF	100% (9) to >89% (9)[65]	Very rare defect
NR3C2[66] (mineralocorticoid receptor gene)	4q	(MIM 605115) Early-onset autosomal dominant HTN with exacerbation in pregnancy	HTN, severe HTN in pregnancy	AD; GOF	100%(8)–100% (8)[d] [66]	One large pedigree reported
KCNJ5[67] (potassium inwardly rectifying channel gene, subfamily J, member 5)	11q	(MIM 613677) Familial hyperaldosteronism type III	HTN, hypokalaemia, high aldosterone, high 18-oxocortisol and 18-hydroxycortisol	AD; LOF	100% (3)–100% (3)[67]	One pedigree reported

Genes described to be mutated in monogenic hypertensive syndromes are listed based on the estimated frequency of disease. Key clinical and genetic features are summarized.
[a]AR, autosomal recessive; AD, autosomal dominant.
[b]GOF, gain of function; LOF, loss of function.
[c]The percentage of patients with HTN and with early-onset HTN (≤18 years of age) are indicated if available in the initial report or a related paper.
[d]The age limit for early-onset HTN was <20 years in this report.
NA, not available.

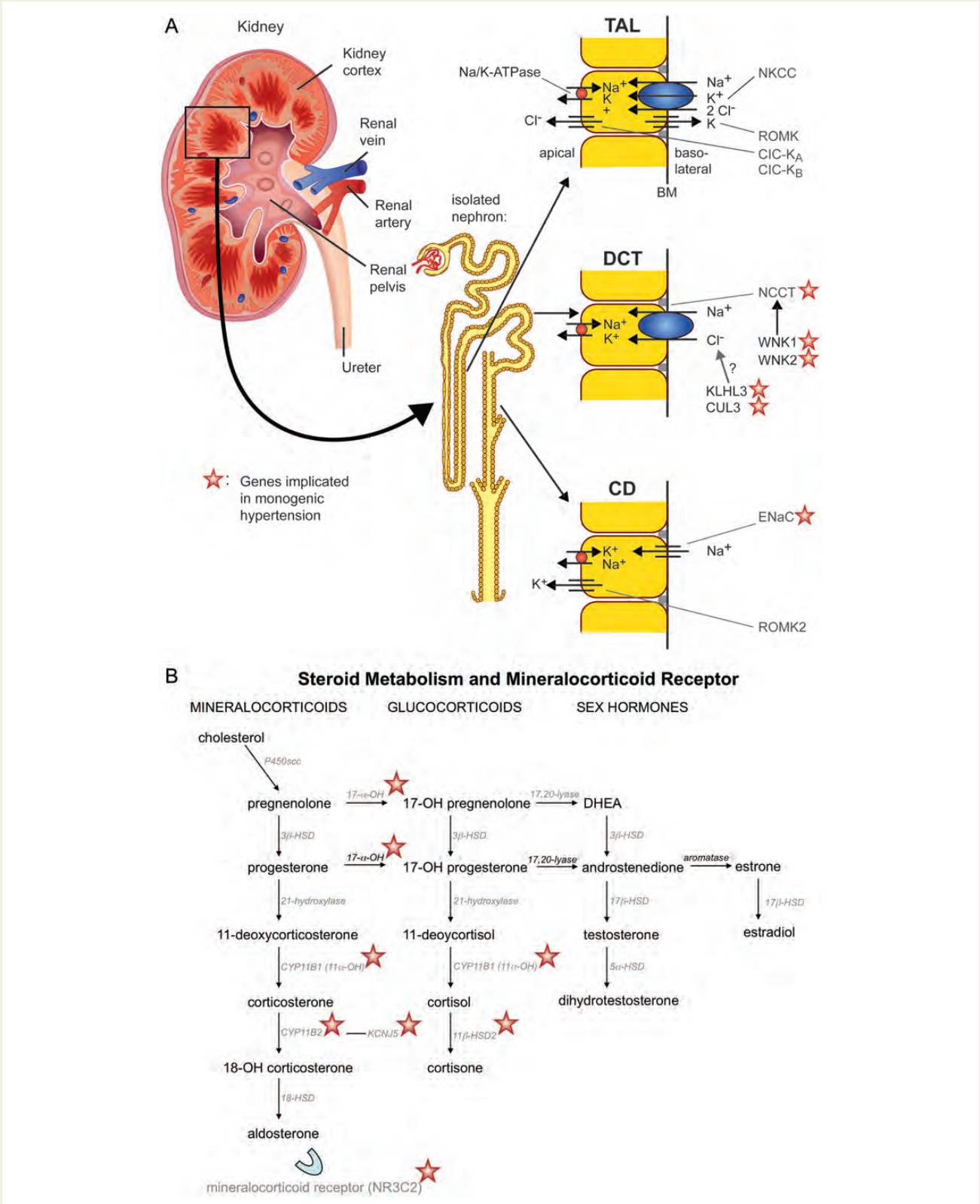

Figure 1 Pathways affected in monogenic hypertensive disease. The location of the mutated gene products in monogenic hypertensive syndromes is shown in the context of their pathway. Two groups of pathways are affected, pathways affecting the kidney (*A*) and pathways affecting steroid metabolism and the mineralocorticoid receptor (*B*). A selection of important structures (ion channels, etc.) or enzymes are labelled in grey. Proteins mutated in monogenic HTN syndromes are marked by a red star. TAL, thick ascending limb of the loop of Henle; DCT, distal-convoluted tubule; CD, collecting duct.

defects are known to lead to HTN such as *PPAR gamma* mutations leading to diabetes and HTN[21] or *RET* gene mutations leading to pheochromocytoma and HTN (and other tumours). These and similar defects are not included in *Table 2* because HTN is not the primary disease phenotype.

The finding that genetic defects in HTN syndromes localize to proteins of the kidney and to steroid hormone activity suggested that similar mechanisms also contribute to the genetic origin of essential HTN. Of note is also the partial overlap between the pathways of monogenic HTN and commonly used anti-hypertensive drugs used to treat essential HTN (e.g. diuretics, aldosterone receptor antagonists). Indeed, rare variants near genes implicated in monogenic hyper- and hypotension syndromes have been shown to influence BP in the general population.[22,23] But causal variants of monogenic HTN syndromes are very unlikely to explain much of the BP variation in the general population and therefore HTN, because of their very low frequencies in the general population based on the studies to date.[17] Our findings in Mendelian forms of HTN genes do, therefore, not appear to significantly help in the understanding of the pathogenesis of essential HTN.

Insights by the identification of common genetic variants identified with new genomic tools

Ever since the classic work of Pickering *et al.*,[24] HTN has been considered a multi-factorial (or 'complex') trait. Today, it is known that the genetic origins of essential HTN involve a large number of genetic variants, reflecting the characteristics of the complex genetic trait that BP is known for since long.

Variability of the human genome and principles of genetic mapping

A large fraction of variation of the human genome is contained in single-nucleotide polymorphisms (SNPs): variation in these variants is constituted by two, rarely more, different possible nucleotide bases (alleles) at the same genetic position.[25] Considerable additional variation of the human genome exists, e.g. insertions and deletions (indels), structural variation (e.g. CNVs), and epigenetic modification.[26–28] Although these and other sources of variation are being tested comprehensively, most endeavour in recent years have been centred on SNPs because their interrogation at large scale is now feasible. The microarrays used for these experiments that genotyped tens of thousands of SNPs in their first versions can interrogate more than 5 million variants today.

Two major methods are used for mapping of disease-associated variants: linkage and association mapping.[29] Linkage mapping identifies genetic regions and association mapping individual variants. As described at the beginning of this review, linkage studies have been tremendously successful in rare hypertensive families and have permitted to identify monogenic HTN syndromes. Such studies have also been conducted for essential HTN and genomic regions of interest were identified, but it has been difficult to define associated variants in these regions. Among the studies that have performed large linkage scans on essential HTN were the BRIGHT study and the Family Blood Pressure Program.[30–33] Based on theoretical considerations, association mapping is better suited for complex genetic traits,[34] and although large sample sizes were used in linkage experiments (~10 000 samples), larger numbers are necessary to have suitable power to detect essential HTN-associated variants, and these large sample sizes are difficult to ascertain in families. Much larger sample sizes are available for unrelated, population-based samples and after the technological developments of genotyping described above, very large GWAS became feasible.

Methods of genome-wide association studies

The basic methodology currently used to test for association between BP and hundreds of thousands of SNPs distributed throughout the entire human genome is deceptively simple: an association statistic is calculated between each SNP and the phenotype, typically by linear regression for continuous phenotypes or by logistic regression for dichotomous phenotypes. In the great majority of studies, an additive genetic model is used.

Number of tests

The statistical practice is different from most other biomedical research in the number of tests performed, the total number of tests being identical to the number of SNPs, the number of independent tests is somewhat lower because many SNPs are correlated. This particular aspect of the GWAS is important, because highly significant results can be obtained by chance when performing large numbers of tests. In order to read complete overlap of SNPs between studies, genotypes used for current GWAS are typically imputed to the HapMap datasets, bringing the total number of available variants to ~2.5 million.[26,35] For studies on individuals of European origin, available data indicate that 1 to 2 million effective tests need to be adjusted for[36] in such datasets and $P = 5 \times 10^{-8}$ has become the accepted genome-wide significance threshold.[35,37] GWAS based on the imputed datasets using data from the 1000 Genomes Project have started and will vastly increase the number of variants, particularly at the lower end of the allele frequency (1–5%).[26]

Phenotype adjustments

The phenotype BP is modified by anti-hypertensive pharmacotherapy: several methods to improve the resulting confounding have been proposed and used in recent studies. The most frequently used method is currently the addition of a constant to SBP (15 mmHg) and diastolic blood pressure (DBP) (10 mmHg) in the presence of at least one anti-hypertensive medication.[38] In most association studies the phenotype BP is adjusted by the major readily measurable covariates age, sex, and BMI[38–40] (age^3 was also used as a covariate in many studies) and the residual after correction is used in the association statistic or the co-variates are directly included in the model.

Common disease—common variants

The two alleles of each SNP have different frequencies in the population, the less frequent allele being the minor allele. It is very clear from the HapMap and ENCODE projects that the

total number of SNPs of a population in an allele frequency bin is inversely correlated to the minor allele frequency (MAF) and that most SNPs have a very low MAF.[35] For the currently published GWASs based on imputation on the HapMap backbone, SNPs with allele frequencies <5% are insufficiently covered by the technology, and also have low power. But the currently targeted frequent variants appear particularly attractive targets for complex disease genomics because they are expected to have a particularly strong impact on complex phenotypes, as formalized in the 'common disease—common variant hypothesis'.[41–43]

Statistical power of the genome-wide association on blood pressure

Given the large burden on statistical power incurred by performing ~1 million independent tests, power considerations remain a central issue to GWAS. Statistical power is proportional to the sample size, the MAF, and the effect size of the variant on BP and inversely proportional to the number of tests performed. *Figure 2* shows statistical power in GWASs as a function of the sample size for three allele frequencies and three scenarios of effect sizes. Based on the current findings in the BP GWAS (see *Table 3*), the effect size of the associated frequent variants is ~1 mmHg for SBP and ~0.5 mmHg for DBP, corresponding to 0.05 SD of the phenotypic distribution. It becomes clear from *Figure 2* that even with the largest BP GWAS to date with ~70 000 individuals,[38,44] associated SNPs with an MAF of ~5% have low power (~0.3). For SNPs with more frequent MAF, statistical power is high at these sample sizes. It also becomes clear from *Figure 2* that much larger effect sizes (e.g. 0.5 SD) have excellent statistical power to be detected in experiments even at much lower sample sizes, meaning conversely that not finding those large effect sizes in the current GWASs implies that they very likely do not exist at these allele frequencies.

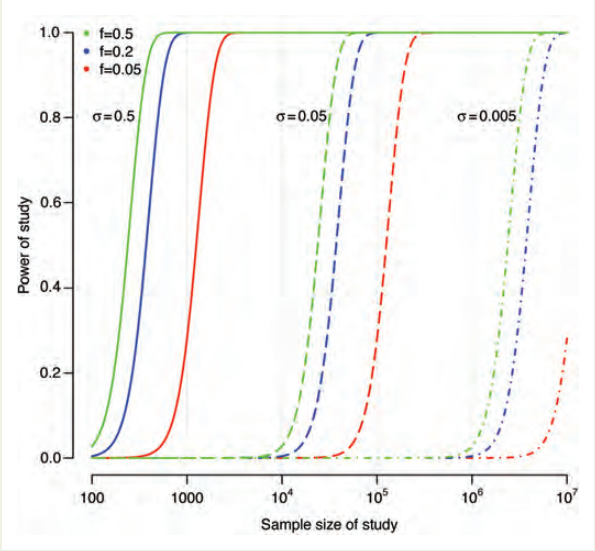

Figure 2 Statistical power in GWAS on continuous traits. The power of the study is plotted as a function of the sample size for three different minor allele frequencies (MAFs): MAF 50% (green), MAF 20% (blue), MAF 5% (red) and for three different effect sizes expressed in standard deviations (SD) of the phenotype: 0.5 SD (continuous line), 0.05 SD (dashed line), and 0.005 SD (dot-dashed line). An alpha of 5×10^{-8} was used.

Current genome-wide association studies on systolic blood pressure and diastolic blood pressure

The first large-scale attempt to identify HTN variants by GWAS was carried out by the Welcome Trust Case Control Consortium in 2007, but did not identify genome-wide significant variants using 2000 cases and 3000 shared controls.[45] Since then, and recognizing the need for much larger sample sizes, several consortia and individual studies have published 43 variants associated with SBP, DBP, or HTN that could be replicated in independent samples (see *Table 3*) using GWAS or similar methods. Reflecting the availability of samples, most discovery efforts were carried out using the samples of European origin, such as the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium www.chargeconsortium.com, the Global BP Gen (Global BP Genetics) consortium, and the ICBP (International Consortium for BP GWAS). Among the large discovery efforts involving participants of Asian origin are the studies by the Korea Association REsource consortium and the Asian Genetic Epidemiology Network, and are experiments using participants of African origin the CARe (Candidate-gene Association Resource) consortium.

The largest contribution to date in terms of number of loci discovered for SBP, DBP, and HTN is by the ICBP,[38] although many other studies have contributed additional variants and also important additional information. The ICBP experiment of 2011 included total discovery GWAS data on 69 395 individuals and further replication genotyping/look-ups in up to 133 661 subjects. The study convincingly replicated 13 loci identified in previous, largely overlapping studies.[40,46] In total, the study described 29 SNPs with genome-wide significance. Interestingly, all of the alleles increasing SBP/DBP also increased the risk of HTN. Panel A of *Figure 3* shows the effect sizes for the 29 SNPs for SBP and DBP. Based on these 29 SNPs, it can be seen that with few exceptions all variants are associated with both SBP and DBP, although differential effects have been identified in a separate ICBP study.[44] Panel B shows the effect sizes as a function of the allele frequencies. There is a trend towards larger effect sizes in variants with lower MAFs, although some of these observations might be primed by the feature that for lower MAF SNPs with larger effect sizes are more likely to be detected if the sample size remains constant.

Some of the 43 BP SNPs in *Table 3* have been identified using a candidate gene focused array[47] and others have used additional similar technologies. Interestingly, these other experiments illustrate that there is more than one strategy to identify gene loci for common complex cardiovascular disease.

Conclusions from 43 variants for essential hypertension

Several interesting conclusions can be drawn on the genetics of essential HTN based on all significant and replicated variants identified by the GWAS so far.

(1) The effect sizes are small for each individual genetic variant, typically 1 mmHg for SBP and 0.5 mmHg for DBP (see

Table 3 Genetic variants associated with blood pressure by unbiased investigation

Locus name	Sentinel SNP	chr	Position (hg19)	CA	SBP		DBP		HTN		ethnicity	max *N*
					beta	*P*-value	beta	*P*-value	beta	*P*-value		
CASZ1[68,69]	rs880315	1	10 796 866	C	0.61	5.20×10^{9}	NA	NA	NA	NA	EU, AS	52 155
MTHFR(3′)-NPPB[47]	rs4846049	1	11 850 365	T	NA	NA	−0.34	3.00×10^{10}	NA	NA	EU	84 467
MTHFR(5′)-NPPB[38,40,70,71]	rs17367504	1	11 862 778	G	−0.90	8.72×10^{22}	−0.55	3.55×10^{19}	−0.10	2.34×10^{10}	EU	125 000
ST7L-CAPZA1[72]	rs17030613	1	113 190 807	C	0.49	8.40×10^{8}	0.38	1.20×10^{8}	NA	NA	AS	49 952
MOV10[38]	rs2932538	1	113 216 543	G	0.39	1.17×10^{9}	0.24	9.88×10^{10}	0.05	2.89×10^{7}	EU, AS	195 000
AGT[47,73,74]	rs2004776	1	230 848 702	T	0.42	3.80×10^{6}	0.32	5.00×10^{8}	0.08	3.70×10^{7}	EU, AS	86 588
FIGN_GRB14[44,72]	rs16849225	2	164 906 820	C	0.75	3.50×10^{10}	0.29	2.70×10^{5}	NA	NA	AS, EU	49 511
SLC4A7[38]	rs13082711	3	27 537 909	T	−0.32	1.51×10^{6}	−0.24	3.77×10^{9}	−0.03	3.56×10^{4}	EU	198 000
ULK4[38,39]	rs3774372	3	41 877 414	T	−0.07	3.95×10^{1}	−0.37	9.02×10^{14}	−0.02	1.81×10^{1}	EU	162 000
MAP4[44]	rs319690	3	47 927 484	T	−0.423	4.74×10^{8}	−0.265	6.88×10^{9}	NA	NA	EU	93 496
MECOM[38]	rs419076	3	169 100 886	T	0.41	1.78×10^{13}	0.24	2.12×10^{12}	0.03	3.06×10^{4}	EU	194 000
FGF5[38,40,69,72,75]	rs1458038	4	81 164 723	T	0.71	1.47×10^{23}	0.46	8.46×10^{25}	0.07	1.85×10^{7}	EU, AS	140 000
SLC39A8[38]	rs13107325	4	103 188 709	T	−0.98	3.27×10^{14}	−0.68	2.28×10^{17}	−0.10	4.89×10^{7}	EU	151 000
ENPEP[72]	rs6825911	4	111 381 638	C	0.6	7.30×10^{8}	0.39	9.00×10^{9}	NA	NA	AS	49 515
GUCY1A3-1B3[38]	rs13139571	4	156 645 513	C	0.32	1.16×10^{6}	0.26	2.17×10^{10}	0.04	2.49×10^{5}	EU	185 000
NPR3-C5orf23[38,72]	rs1173771	5	32 815 028	G	0.50	1.79×10^{16}	0.26	9.11×10^{12}	0.06	3.23×10^{10}	EU, AS	159 000
EBF1[38]	rs11953630	5	157 845 402	T	−0.41	3.02×10^{11}	−0.28	3.81×10^{13}	−0.05	1.68×10^{7}	EU	161 000
HFE[38]	rs1799945	6	26 091 179	G	0.63	7.69×10^{12}	0.46	1.45×10^{15}	0.09	1.76×10^{10}	EU	144 000
BAT2-BAT5[38]	rs805303	6	31 616 366	G	0.38	1.49×10^{11}	0.23	2.98×10^{11}	0.05	1.12×10^{10}	EU	202 000
PIK3CG[44]	rs17477177	7	106 411 858	T	−0.552	5.67×10^{11}	−0.081	1.40×10^{1}	NA	NA	EU	112 996
NOS3[47,76]	rs3918226	7	150 690 176	T	NA	NA	0.78	2.20×10^{9}	NA	NA	EU	84 467
BLK-GATA4[68]	rs2898290	8	11 433 909	C	−0.53	3.40×10^{9}	NA	NA	NA	NA	EU	52 155
CYP11B2[74]	rs1799998	8	143 999 600	T	0.91	1.50×10^{5}	0.53	1.80×10^{5}	NA	NA	AS	19 426
CACNB2(5′)[38]	rs4373814	10	18 419 972	G	−0.37	4.81×10^{11}	−0.22	4.36×10^{10}	−0.05	8.53×10^{8}	EU	188 000
CACNB2(3′)[38,39,77]	rs1813353	10	18 707 448	T	0.57	2.56×10^{12}	0.41	2.30×10^{15}	0.08	6.24×10^{10}	EU, AS	102 000
C10orf107[38,40]	rs4590817	10	63 467 553	G	0.65	3.97×10^{12}	0.42	1.29×10^{12}	0.10	9.82×10^{9}	EU	111 000
PLCE1[38]	rs932764	10	95 895 940	G	0.48	7.10×10^{16}	0.18	8.06×10^{7}	0.06	9.35×10^{9}	EU	161 000
CYP17A1-NT5C2[39,40,69,72,75,77,78]	rs11191548	10	104 846 178	T	1.10	6.90×10^{26}	0.46	9.44×10^{13}	0.10	1.40×10^{5}	EU, AS	162 000
ADRB1[73]	rs1801253	10	115 805 056	G	−0.57	4.70×10^{10}	−0.36	9.50×10^{10}	−0.06	3.30×10^{4}	EU	86 588
ADM[38]	rs7129220	11	10 350 538	G	−0.62	2.97×10^{12}	−0.30	6.44×10^{8}	−0.04	1.11×10^{3}	EU	183 000
PLEKHA7[38,46,78]	rs381815	11	16 902 268	T	0.57	5.27×10^{11}	0.35	5.34×10^{10}	0.06	3.41×10^{6}	EU, AS	97 000
FLJ32810-TMEM133[38]	rs633185	11	100 593 538	G	−0.56	1.21×10^{17}	−0.33	1.95×10^{15}	−0.07	5.41×10^{11}	EU, AS	160 000
ATP2B1[38,39,69,75,78–80]	rs17249754	12	90 060 586	G	0.93	1.82×10^{18}	0.52	1.16×10^{14}	0.13	1.13×10^{14}	EU, AS	96 000
SH2B3[38,40,44,81]	rs3184504	12	111 884 608	T	0.60	3.83×10^{18}	0.45	3.59×10^{25}	0.06	2.62×10^{6}	EU, AF	121 000
ALDH2[72]	rs11066280	12	112 817 783	T	1.56	7.90×10^{31}	1.01	1.30×10^{35}	NA	NA	AS	46 957
TBX5-TBX3[38,46,72,81]	rs10850411	12	115 387 796	T	0.35	5.38×10^{8}	0.25	5.43×10^{10}	0.05	5.18×10^{6}	EU, AS	161 000

CYP1A1-ULK3[38–40,80,81]	rs1378942	15	75 077 367	C	0.61	5.69×10^{-23}	0.42	2.69×10^{-26}	0.07	1.04×10^{-8}	EU, AS, AF	163 000
FURIN-FES[38]	rs2521501	15	91 437 388	T	0.65	5.20×10^{-19}	0.36	1.89×10^{-15}	0.06	7.02×10^{-7}	EU, AS, AF	127 000
UMOD[82]	rs13333226	16	20 365 654	G	−0.49	2.60×10^{-5}	−0.3	1.50×10^{-5}	NA	1.50×10^{-13}	EU	79 133
GOSR2[38]	rs17608766	17	45 013 271	T	−0.56	1.13×10^{-10}	−0.13	1.66×10^{-2}	−0.02	7.99×10^{-2}	EU	152 000
ZNF652[38,40]	rs12940887	17	47 402 807	T	0.36	1.79×10^{-10}	0.27	2.29×10^{-14}	0.05	1.20×10^{-7}	EU	188 000
JAG1[38]	rs1327235	20	10 969 030	G	0.34	1.87×10^{-8}	0.30	1.41×10^{-15}	0.03	4.57×10^{-4}	EU, AS	158 000
GNAS-EDN3[38]	rs6015450	20	57 751 117	G	0.90	3.87×10^{-23}	0.56	5.63×10^{-23}	0.11	4.18×10^{-14}	EU, AS	159 000

The table includes loci associated with SBP, DBP, or HTN that were replicated in independent samples. Only data from unbiased experiments as the GWAS and similar experiments are included and only single marker analyses were considered. Only SNPs discovered using an additive model were included and the maximal r^2 between two pairs of SNPs was set to be 0.3. The locus name is the name of the nearest gene or a composite of the flanking genes if several genes are near.[38]

CA, coded allele; EU, individuals of European ancestry; AF, individuals of African-American or African origin; AS, individuals of Asian origin; NA, not available; DBP, diastolic blood pressure; SBP, systolic blood pressure. The effect sizes and *P*-values are taken from the report with the larger sample size if several reports were available.

Table 3 and *Figure 3* for a subset of SNPs). Even collectively, the 29 variants tested in one experiment explain only 1–2% of SBP and DBP variance.[38] With the uncertainty that only a subset of all BP-associated SNPs has been evaluated collectively, the heritability of BP is ~25× larger than the variation currently explained by GWAS SNPs. The observation that only little of the total heritability can currently be explained by the GWAS is also found for many other traits and has led to the term 'missing heritability'.[48] It is expected that many more yet undiscovered loci, possibly including variants in the rare allele spectrum that might have larger effect sizes, will contribute to explain the missing heritability. For SNPs with effect sizes similar to those in *Table 3*, the total number of variants underlying BP variation has been estimated to be 116.[38] A risk score of the combined effects of the 29 SNPs is clearly associated with BP and HTN in multiple populations,[38] but as it explains only little of the overall phenotypic variance it is unlikely to be useful in HTN risk prediction at this point, although this has not yet been formally tested. More likely immediate use in addition to mechanistic insights and discovery of targets for intervention is to come from Mendelian randomization experiments (see below).

(2) Of the 43 variants significantly associated with SBP, DBP, and HTN listed in *Table 3*, a minority is near a gene that is known to be related to BP. The remaining variants are localized in genomic regions that were previously completely unsuspected for their link with BP. Other GWAS consortia could identify over-represented biological pathways in analyses using GWAS SNPs,[49] but these efforts have not been successful for BP until now, potentially due to intrinsic properties of the phenotype or to the limited number of variants identified so far.

(3) Many variants identified are associated not only with individuals of European origin, but also with people of Asian and African origin (see *Table 3*) and although testing in multiple ethnicities is far from complete, many identified variants have an impact across ethnicities and the hypothesis of transethnic validity appears valid.

Mendelian randomization

A genetic risk score associated with BP can be used to investigate whether the same genetic risk profile is also associated with target organ damage of BP, notably stroke, heart failure, myocardial infarction, and renal failure, or other phenotypes. Such an experiment was conducted based on the 29 ICBP SNPs[38] and a significant association of the genetic risk score with stroke, coronary artery disease, and left ventricular wall thickness could be shown. In contrast, there was interestingly no association with five phenotypes of renal disease (prevalent chronic kidney disease, prevalent microalbuminuria, serum creatinine, estimated glomerular filtration rate, and urinary albumin/creatinine ratio). This is an intriguing observation that might indicate that the impact of HTN on renal failure is less clear than previously thought. Similar examples of unanticipated absence of association between GWAS-derived genetic scores and phenotypes have been published, e.g. recently a report casting further doubt on the causal role of low HDL in myocardial infarction.[50]

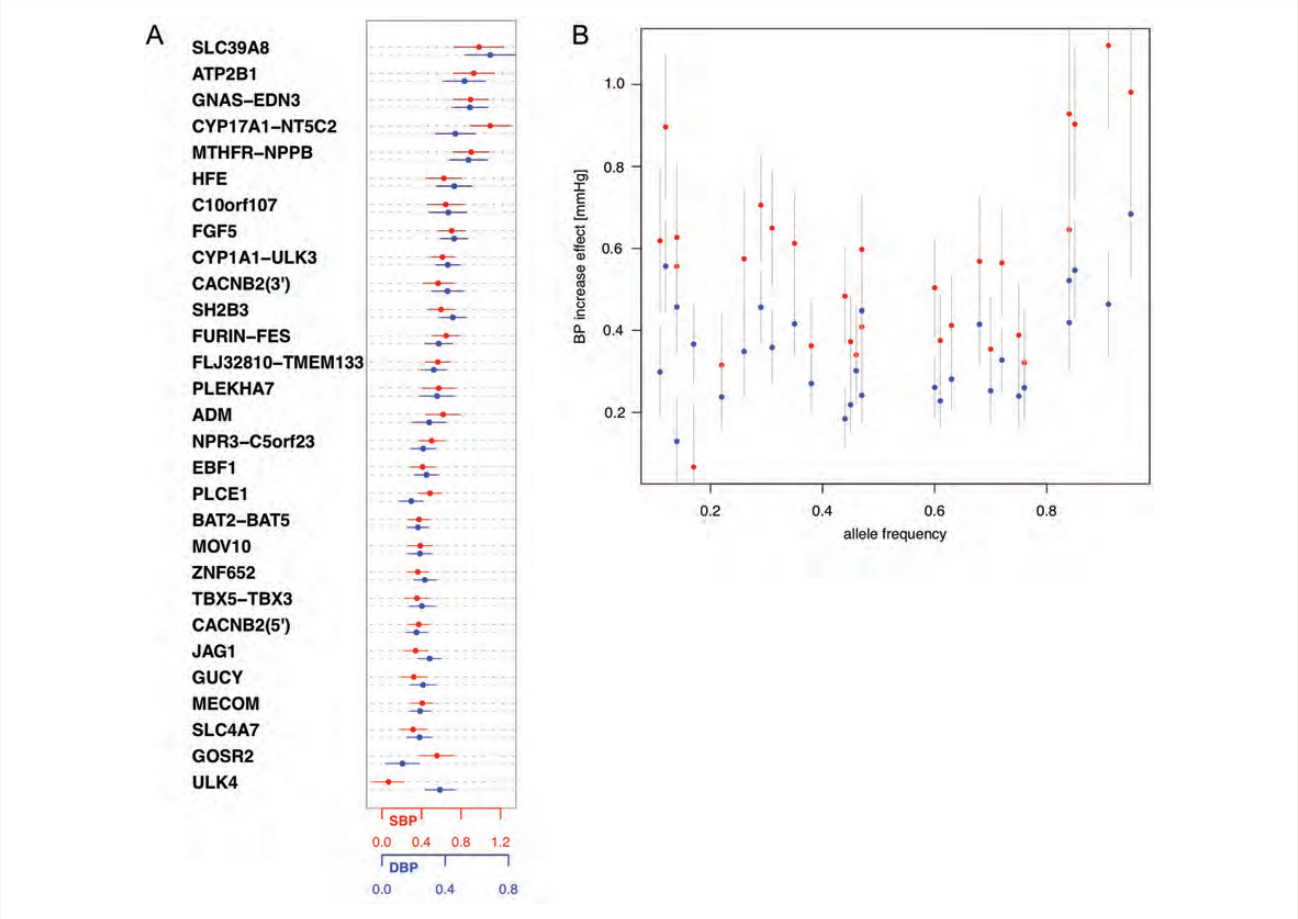

Figure 3 Effect sizes of 29 BP and HTN variants identified by the ICBP consortium. (*A*) shows the effect sizes for SBP (red) and DBP (blue) for 29 BP variants identified by the ICBP.[38] The locus name is indicated to the left and the effect size ($\pm$SD) is indicated on a mmHg scale. (*B*) shows the effect size for SBP (red) and DBP (blue) as a function of the risk allele frequency for the same 29 BP variants identified by the GWAS.

Limitations of current blood pressure genome-wide association studies by genetic and phenotype heterogeneity

A major limiting factor of GWAS is statistical power and the main approach to overcome this limitation has been to use the largest possible sample size in meta-analyses with inclusion of many different studies. Twenty-nine different studies were used for the discovery effort of the ICBP[38] and other recent GWAS have used many more studies. Adding many different studies in meta-analyses can introduce heterogeneity just as heterogeneity can also be observed in very large single studies. Although the association results do not show statistical significance in heterogeneity tests,[38] there is potential for population substructure that is partially corrected for by applying genomic control, but it is not impossible that unrecognized substructure persists.

Blood pressure phenotypes are particularly prone to systematic measurement differences, either due to different measurement technology or due to differences in measurement methods. Although all studies of the current analyses[38] ascertained BP according to a standard protocol and many of the studies have the best BP phenotype available in BP epidemiology, there are slight differences in ascertainment with potential impact on the association results. But again, given the large sample sizes necessary, the phenotype is probably close to optimal for single visit analyses, but potentially a more precise adjustment of the BP values might be possible if primary data were shared across studies. One striking example on the precision of the phenotype the Womens' Genome Health Study that ascertained BP by patient history in categories (nine for systolic and seven for diastolic). Although the study was not included in the discovery effort of ICBP, the 29-SNP genetic score is strongly associated with SBP, DBP, and HTN, suggesting that the phenotype is as precise as the phenotype carefully ascertained according to the standard methods in the BRIGHT study.[38] It will be interesting to see the impact of large-scale analyses on more precise BP measurements (e.g. analyses based on long-term average BP traits or on ambulatory BP measurement) and such efforts are underway.

Future studies

Given that only a small fraction of the BP heritability is currently explained, new experiments are underway to capture additional trait variability (see *Table 4*). It is desirable that these efforts are conducted using large sample sets of European- and non-European origin. New BP GWAS efforts with increased sample sizes, using

Table 4 New investigations in hypertension genomics

Project type	Genotyping platform	Number of variants genotyped	Allele frequency spectrum
Larger GWAS	Affymetrix and Illumina	>250 k SNPs, genome-wide	Mainly >0.05
Refined BP phenotypes	Idem	Idem	Idem
Cardio-MetaboChip	Illumina	~200 k SNPs, targeted	Mainly >0.05
Exome chip	Affymetrix and Illumina	~300 k SNPs, exome-wide	Mainly low frequency variants
Targeted sequencing	Next generation sequencing	Dependent on target	Entire frequency spectrum
Whole exome and genome sequencing	Next generation sequencing	All variants	Entire frequency spectrum

A selection of current and planned experiments with key features such as genotyping platforms, number of markers, and targeted allele frequency spectrum is indicated.

the newly available imputation backbone of the 1000 Genomes project, will increase statistical power and extend the allele frequency spectrum analysed. Refined phenotypes such as long-term average and ambulatory BP measurements are interesting to consider. The Illumina Cardio-MetaboChip is a collection of SNPs from all major cardiovascular, metabolic, and antropometric GWAS efforts, including BP tagging SNPs up to a *P*-value of ~0.01.[51] A large number of study participants have been genotyped on this platform, and it is likely that a sizeable number of new BP loci are discovered when using these data for association mapping. To capture the entire spectrum of variants, sequencing or genotyping has been proposed (targeted sequencing, whole exome sequencing, whole genome sequencing) and several studies and consortia [e.g. CHARGE-S, NHLBI Grand Opportunity Exome Sequencing Project (ESP-GO)] have taken up these challenges. Very large sample sizes will be necessary to reach sufficient statistical power. An interesting alternative approach is genotyping of exomic variants on a microarray because very large sample sizes can be reached at lower cost. Such experiments are underway (see *Table 4*).

Conclusion

Analyses of Mendelian HTN syndromes and GWAS on essential HTN have contributed and continue to contribute to our understanding of the genetics of BP in very different ways. One type of disease is very rare that it might never be encountered by the practicing cardiologist, and the other is so frequent that most colleagues see it several times every day.

Mendelian syndromes are important to recognize because such knowledge might lead to specific forms of pharmacotherapy for the affected individual. The clinical impact of findings of GWAS on essential HTN is currently undefined, but the knowledge will help us to understand the mechanisms once genes near the associated variants will be identified, which can be used as targets for pharmacological intervention. Much of the variability still remains to be explained and many more variants will be identified. For essential HTN, the magnitude of the missing heritability could suggest that there is a yet unrecognized, but major, mechanism that remains to be discovered and this mechanism may or may not be discovered by GWASs.

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Conflict of interest: Both authors are members of the ICBP. G.B.E. is co-chair of the CHARGE BP working group and member of the Family Blood Pressure Program Essential HTN Genome-Wide Association Studies (FEHGAS) group. Parts of this text will be used in the privat-docent thesis of Georg Ehret.

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