Genomics of hypertension

Sandosh Padmanabhan, Anna F Dominiczak

Affiliation:
BHF Glasgow Cardiovascular Research Centre
Institute of Cardiovascular and Medical Sciences
126 University Place
University of Glasgow

Corresponding Author:
Professor Dame Anna F Dominiczak DBE MD FRCP FAHA FRSE FMedSci
Regius Professor of Medicine
Vice-Principal and Head of College of Medical, Veterinary and Life Sciences
University of Glasgow
Wolfson Medical School Building
University Avenue
Glasgow G12 8QQ

Tel No: 0141 330 2738
E-Mail: Anna.Dominiczak@glasgow.ac.uk

Abstract

The genetic architecture of blood pressure now comprises over 30 genes with rare mutations resulting in inherited forms of hypertension or hypotension and 1477 common single nucleotide polymorphisms (SNPs) associated with blood pressure. Monogenic syndromes predominantly involve the renin-angiotensin-aldosterone system, the adrenal glucocorticoid pathway and a smaller fraction due to neuroendocrine tumours of the sympathetic and parasympathetic system. The discovery of somatic mutations causing aldosterone producing adrenal adenomas revealed the critical role of calcium signalling in adrenal aldosterone synthesis. The per-SNP BP effect is small for SNPs from genome wide association studies and all the BP GWAS SNPs explain about 27% of the 30-50% estimated heritability of blood pressure. Whilst there is a paucity of GWAS SNPs mapped to known monogenic genes, a GWAS signal mapped to the uromodulin gene has been shown to affect blood pressure through sodium homeostasis, while another appears to act through endothelin. Majority of the SNPs show pleiotropic associations and unravelling these signals have the potential to understand underpinning biological pathways. In this review, we look at the current state of blood pressure genomics and explore causal pathways from mendelian randomisation studies and opportunities for drug repurposing and pharmacogenomics.

Keyword:

Hypertension; blood pressure; monogenic; repurposing; pharmacogenomics; salt; adrenal; sympathetic system

Introduction

Blood pressure is the pressure exerted by blood on walls of the arteries and is critical to the maintenance of oxygen and nutrient delivery and cardiovascular homeostasis.[1] Physiological regulatory mechanisms maintain blood pressure within a 'normal range' with lower and higher values beyond this range resulting in deleterious consequences – ischemia, myocardial infarction, stroke, kidney disease.[2] Blood pressure is normally distributed in the general population exhibiting a log-linear incremental risk of cardiovascular disease with every 1 mmHg rise in blood pressure.[3] The transition from 'normal' blood pressure to hypertension is currently based on an absolute blood pressure value (that has progressively moved downwards over the last 50 years[2,4]) at the upper end of the distribution of BP "at which the benefits of action (i.e., therapeutic intervention) exceed those of inaction".[5] Hypertension is recognised as the leading modifiable risk factor responsible for the global burden of cardiovascular disease and disability with an estimated 1.5 billion people are affected, and 10.7 million deaths (33.2% of deaths due to all risk factors) in 2015 directly attributable to a systolic BP >140 mm Hg.[6]

Though blood pressure can be parsimoniously defined as the product of cardiac output and peripheral arterial resistance, these two parameters are in turn regulated by a complex network of renal, neural, cardiac, vascular, and endocrine mechanisms under the influence of genetic and environmental factors (Figure 1). Thus, blood pressure is a multifactorial polygenic trait and by extension, hypertension, which is a dichotomisation of the quantitative blood pressure trait is likewise a multifactorial complex trait. This has been aptly illustrated in the 1960's Page model of hypertension and updated in 2014.[7,8] Systolic blood pressure shows a linear age related rise suggesting that increasing blood pressure incites vascular injury or dysfunction, which in turn leads to a vicious cycle of accumulating vascular injury and higher blood pressures.[9] The age-related rise in blood pressure is observed only in industrialised societies and not in non-westernised-tribal populations where routine dietary salt intake and other environmental stressors and exposures that increase BP are absent.[10,11] While there are

clear environmental and occupational factors in addition to salt intake that influence risk of hypertension,[12] there is now accruing evidence for considerable genetic contribution from monogenic syndromes of high and low blood pressure and the exponential rate of identification of validated blood pressure single nucleotide polymorphisms (SNPs) from genome wide association studies (GWAS).[13-15] The causal genetic mutations have been established as necessary and sufficient to cause the blood pressure phenotypes in monogenic syndromes. In contrast, GWAS SNPs may provide the necessary conditions but, by themselves, do not provide sufficient cause for the manifestation of the blood pressure phenotype. In this review, we provide a broad perspective on how genomics has transformed our understanding of blood pressure and hypertension and provide a context for the opportunities and challenges for their full clinical potential to be realised. A detailed description of all the genetic variants and molecular mechanisms is not provided as these areas have been reviewed recently.[13]

Genetic contribution to blood pressure and hypertension

There is now substantial support from multiple lines of observational evidence that indicate genetics play a non-trivial role in the regulation of blood pressure. These are summarised below.

- Family and twin studies indicate a substantial heritable component for blood pressure with heritabilities ranging from 15% to 40% for clinic systolic blood pressure(SBP), and 15% to 30% for clinic diastolic blood pressure (DBP), 69% and 51% for ambulatory SBP and DBP respectively.[16,17] Heritability is a property of the population studied and whilst most of the estimates are obtained from European populations, there is data from African ancestry individuals showing similar levels of heritability.[18]
- Monozygotic twins show a greater correlation of blood pressure compared to dizygotic twins.[19] Family studies have shown risk of hypertension in an individual increases in the presence of parental and grandparental history of hypertension.[20] The familial risk of hypertension is likely to be due to genetic factors after statistical modelling showed that hypertension in grandchildren from grandparents persisted after adjustment for secular

trends, inter-generational differences in lifestyle and behaviour, physical activity and dietary sodium intake.[20]

- The existence of rare monogenic forms of high and low blood pressure with the identification of their underlying causal mutations indicates the role of specific genetic pathways primarily centred in the kidneys and adrenal glands to have a major impact on blood pressure.[13]
- The burst of discoveries in the genome wide era has unequivocally established the polygenic component in the genetic architecture of blood pressure.[14]
- Genetically determined systolic blood pressure based on 12 polymorphisms associated with blood pressure from genome wide association studies was shown to be causally associated with the age-related rise in systolic blood pressure.[21] This supports the hypothesis that increased SBP (inferred from genetic risk alleles) causes vascular injury, which in turn leads to higher SBP longitudinally.

Genetic architecture of hypertension

The genetic architecture of a trait encompasses all genetic factors and their characteristics involved in the expression of the phenotype, and is important for screening for and diagnosing disease as well as enhancing biological understanding, drug development and gene mapping.[22] It comprises the number of variants influencing a phenotype, the magnitude of their effects on the phenotype, the population frequency of these variants and their interactions with each other and the environment. Figure 2 depicts the current genetic architecture of blood pressure including 31 different genes harbouring rare causal variants for monogenic syndromes of high and low blood pressure and over 1477 common SNPs associated with blood pressure traits from GWAS.[13-15] The preponderance of common over rare variants is a reflection of the late onset nature of hypertension making it less susceptible to purifying selection. The multifactorial nature of blood pressure regulation was exemplified by the Page mosaic theory of hypertension[7] of 1960 which posited that essential hypertension (HTN) is not one disease, but several different diseases with different origins and development which included interactions among genetics, environment, adaptive, neural, mechanical, and hormonal perturbations (sympathetic nervous system, renin-angiotensin-aldosterone system). The increasing

availability of large prospective population-based cohorts has enabled genetic association studies to be conducted across a wide range of phenotypes- phenome-wide association studies (PheWAS) revealing pervasive pleiotropy of a majority of the BP SNPs. The transition from the original Page's mosaic model (a wireframe model depicting the multifactorial nature of hypertension) through an update in 2014 with results from early GWAS studies to its latest iteration in Figure 2 showcase the enormous progress that have been made in unravelling the genetic architecture of blood pressure, the eclipsing of monogenic traits by polygenic signals and the scale of integrating evidence from pleiotropic associations with other phenotypes including lifestyle and environmental influences.

Monogenic syndromes

The monogenic blood pressure syndromes all present with the same BP phenotype, but are essentially separate diseases differentiated by additional clinical or laboratory characteristics and the causative genetic mutation. Molecular and clinical details of monogenic syndromes have been reviewed in detail recently and we refer to the reader to these articles.[13,23] The details of pathways and genes involved in monogenic hypertension are presented in Figure 1 and Table 1.The monogenic variants tend to have large effects on blood pressure, around 20-50 mmHg and while not contributing significantly to the public health burden of hypertension, their value lies in helping understand the blood pressure regulatory pathways that they have uncovered. An interesting theory invoking herterozygote advantage to indicate a role for rare variations in hypertension came from a study of pathogenic alleles in SLC12A1, KCNJ1, and SLC12A3 associated with a reduction blood pressure reduced risk of hypertension in the Framingham heart study, though this is yet to be validated.[24]

The mechanisms of salt-sensitive hypertension mediated through aldosterone was elucidated through the mutations causing glucocorticoid-remediable aldosteronism, Liddle syndrome, congenital adrenal hyperplasia (deficiencies of steroid 11β-hydroxylase or 17α-hydroxylase) and apparent mineralocorticoid excess which are all characterised by low plasma renin activity, hypokalaemia, and a degree of metabolic alkalosis.[25,26] About 40% of patients with adrenal

aldosterone-producing adenoma (APA) have somatic gain-of-function mutations in Potassium Inwardly Rectifying Channel Subfamily J Member 5 (*KCNJ5)* gene.[23] Around 7% of APAs are due to somatic mutations in ATPase Na+/K+ Transporting Subunit Alpha 1 (*ATP1A1)*, ATPase Plasma Membrane Ca2+ Transporting 3 (*ATP2B3)*, Calcium Voltage-Gated Channel Subunit Alpha1 D (*CACNA1D)* and Catenin Beta 1 (*CTNNB1)*.[23] Mutations in these genes are less frequent in inherited cases of primary hyperaldosteronism and this raises the possibility that HTN could be due to a multiplicity of uncommon variants.[23] The mutations in *KCNJ5, CACNA1D, ATP1A1* and *ATP2B3* highlight the crucial role of calcium signalling in autonomous adrenal aldosterone production.[27] The mechanisms underlying *CTNNB1*-mediated APA formation have not been elucidated yet.[28]

Mutations in transporters in different segments of the nephron have enhanced our understanding of sodium and electrolyte regulatory mechanisms in the kidney and their impact on blood pressure. The role of the distal convoluted tubule (DCT) in blood pressure regulation was clarified through dissection of Gordon Syndrome (pseudohypoaldosteronism type II) which causes hyperkalaemic hypertension with mild metabolic acidosis. The major sodium transporter in the DCT is Na^+/Cl^+ ion cotransporter (NCC). Gordon Syndrome is caused by mutations in two serine-threonine kinase (With No Lysine Kinase 1 and 4, *WNK1* and *WNK4*) genes, which inhibit NCC expression and sodium flux. Additionally, mutations in Cullin-3 (*CUL3*) and Kelch3 (*KLHL3*) which are involved in the ubiquitination and degradation of WNK kinases also cause Gordon syndrome. Gitelman and Bartter syndromes are forms of salt losing tubulopathies characterized by hypokalaemic alkalosis with normal to low blood pressure due to dysfunctional transepithelial electrolyte transport in the thick ascending limb of loop of Henle's loop (TAL), the distal convoluted tubule (DCT disorders), or both.[29] Classical Bartter syndrome Type I and II are due to mutations in Solute Carrier Family 12 Member 1 (*SLC12A1)* and Potassium Inwardly Rectifying Channel Subfamily J Member 1 (*KCNJ1)* genes encoding respectively the $Na^+/K^+/2Cl^-$ cotransporter 2 (NKCC2) and the renal outer medullary potassium channel (ROMK) in the TAL, while Bartter Type III and V are DCT disorders due to mutations in the chloride channel ClC-Kb (*CLCNKB*) and calcium sensing receptor (CASR) respectively. Bartter syndrome with

sensorineural deafness is a combined TAL and DCT disorder due to genetic defects of chloride channels ClC-Ka (*CLCNKA*) and *CLCNKB*, and the beta-subunit of barttin (*BSND*). Antenatal Bartter syndrome is a severe form manifesting in utero with foetal polyuria and hydramnios due to mutations in *SLC12A1* and *KCNJ1* genes (NKCC2 and ROMK).[29] Recently a new form of Bartter syndrome (transient antenatal Bartter syndrome) due to mutations in the melanoma-associated antigen D2 (*MAGED2*) which maps to the X chromosome has been identified which is a combined TAL/DCT disorder presenting with polyhydramnios and salt wasting.[30] Autosomal hypertension with type E brachydactyly (HTNB) is a monogenic syndrome that causes hypertension through vascular mechanisms involving phosphodiesterase 3A leading to increased neointimal proliferation and remodelling of the arteries and neurovascular structures.[31] Phaeochromocytomas and paragangliomas (PCC/PGLs) are rare neuroendocrine tumours of the adrenal glands and the sympathetic and parasympathetic paraganglia that cause hypertension through catecholamine hypersecretion. PCC/PGLs are associated with 12 genetic syndromes classified into three clusters pseudohypoxic, Wnt-signaling, and kinase-signaling clusters. Each cluster has unique clinical, molecular and imaging characteristics that can be inform precision medicine.[32,33] The pseudohypoxia group comprises of tricarboxylic acid (TCA) cycle and VHL/EPAS1 -related subgroups. The tricarboxylic acid (TCA) cycle–related subgroup is due to germline mutations in succinate dehydrogenase subunits *SDHA*, *SDHB*, *SDHC*, *SDHD, SDHAF2* (*SDHx*) and fumarate hydratase (*FH*). The VHL/EPAS1-related subgroup is caused by somatic and germline mutations in Von Hippel–Lindau tumour suppressor (*VHL*) and Endothelial PAS domain protein 1(*EPAS1*) genes resulting in multiple and recurrent PGLs. The Wnt signaling group consists of somatic mutations in Cold shock domain containing E1 (*CSDE1*) and Mastermind like transcriptional coactivator 3 (*MAML3*). The kinase signalling group consists of germline or somatic mutations in Ret proto-oncogene (*RET*), Neurofibromin 1 (*NF1*), Transmembrane protein 127 (*TMEM127*), MYC-associated factor X (*MAX*), and HRas proto-oncogene, GTPase (*HRAS*). Approximately, 60% of PCC/PGLs are caused by known genetic mutations. About 10% of PCCs and 35–40% of PGLs are metastatic. The predictors of metastatic disease include size (≥5–6 cm), extra-adrenal location of the primary tumour, noradrenergic/dopaminergic biochemical phenotype, mutations of the succinate

dehydrogenase A and B (*SDHA/B*) genes, tumour multiplicity/recurrence, and age at first presentation (<20 years).[34]

Polygenic hypertension

GWAS have transformed our understanding of complex traits but their clinical impact has been limited. A major limitation has been the difficulty in linking SNP to causal gene and function primarily because a most of the GWAS variants are found in intergenic or intronic regions with only ~10% located in the coding sequence.[35,36] The key aspects of blood pressure GWAS are summarised below.

(1) All the BP GWAS SNPs explain about 27% of the 30-50% estimated heritability of blood pressure and explain about 5.7% of the phenotypic variance of SBP.[14]

(2) The effect size of any SNP on blood pressure is small, approximately 1 mmHg for SBP and 0.5 mmHg for DBP;

(3) GWAS SNPs are tag-SNPs, which means they are likely not causal SNPs, but correlate with the functional variant elsewhere.

(4) Majority of the BP loci are likely to be in novel genes and in blood pressure GWAS with a lower likelihood of identifying signals among known monogenic genes.

(5) Majority of the SNPs identified in GWAS are common with allele frequencies >1% in the population.

(6) The GWAS signals are predominantly from studies of European ancestry subjects with other ancestries under-represented and limiting the generalisability of the findings.

(7) GWAS SNP arrays do not capture rare variants and structural variations in the genome. Information is also limited from regions of low linkage disequilibrium in the genome.

(8) The utility of incorporating all variants into a genetic risk score (GRS) for individual risk prediction is still not established and there is a potential for miss-estimation of risks in non-European ancestries.[37] A one-standard deviation increase in GRS score was associated with a 3.9, 2.4 and 2.6 mmHg increase in SBP respectively among European, African and South-Asian descent individuals in the UK BioBank;[14]

(9) Large scale collaborations using whole genome sequencing in multi-ethnic populations such as Trans-Omics for Precision Medicine (https://www.nhlbi.nih.gov/science/trans-

omics-precision-medicine-topmed-program) are designed to fill the gaps in knowledge base of genomic and other omic markers of hypertension and cardiovascular disease with a view to accelerating precision medicine.

Novel pathways from GWAS

A 5'-promoter SNP, rs13333226, near the uromodulin gene (*UMOD*) was discovered from a GWAS of blood pressure extremes.[38] This SNP affects urinary uromodulin levels the product of *UMOD* which exclusively expressed in the thick ascending limb of the loop of Henle (TAL) in the kidney where 25% of the filtered sodium is reabsorbed. Uromodulin knock-out mice have low blood pressure, absent urinary uromodulin and absent salt-induced rise in BP (shift to the left of the pressure-natriuresis curve).[39] This has identified a novel pathway of blood pressure and renal function regulation through possible interaction with the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in the TAL. NKCC2 is blocked by the commonly used loop-diuretic furosemide, which was shown by Trudu et al[40] to significantly enhance natriuresis and reduce BP levels both in the transgenic mice and in the hypertensive individuals homozygous for the UMOD increasing allele. This is now the basis of a clinical trial (www.clinicaltrials.gov NCT03354897) to reposition a loop diuretic in the hypertension care pathway. Three SNPs from BP GWAS are related to the endothelin pathway – rs9349379 (*PHACTR1*), rs1630736 (*EDN1*), rs10305838 (*EDNRA*). The minor allele of the intronic SNP, rs9349379, in the phosphatase and actin regulatory protein 1 (*PHACTR1*) gene associated with increased risk of coronary artery disease but decreased risk of migraine, cervical artery dissection, fibromuscular dysplasia, and hypertension. This SNP subsequently has been shown to be a distal regulator of *EDN1* expression.[41,42] Endothelin 1 (ET-1) is the most abundant endothelin isoform which acts in a paracrine manner on vascular smooth muscle cells (VSMC) to produce its potent vasoconstrictor effect mediated via ET subtype A (ET_A) and ET subtype B (ET_B) receptors.[43] Endothelin receptor antagonists have demonstrated a blood pressure lowering effect but did not gain traction as an antihypertensive agent because of side-effects or failure to meet clinical trial primary end-points.[43,44] There is encouraging data from phase II study with aprocitentan, a dual ET_A/ET_B endothelin receptor antagonist,[45] and this has now progressed to a phase III trial, the PRECISION study

(www.clinicaltrials.gov NCT02603809). There is also evidence that endothelins play a role in non-obstructive CAD[46] and a genotype directed trial using zibotentan is currently underway (www.clinicaltrials.gov NCT04097314). Other potential targets identified include *NPR3* (natriuretic peptide receptor C) affecting blood pressure through increased vascular smooth muscle cell proliferation, angiotensin II-induced calcium flux and contraction;[47] Two other loci that are of interest include the Sodium Bicarbonate Cotransporter, Member 7 (*SLC4A7)* and Solute Carrier Family 39 (Zinc Transporter), Member 8 (*SLC39A8)* loci.[48,49] The *SLC39A8* locus is associated with an Ala391Thr variation where blood pressure increasing Ala391 variant is associated with increased ERK2 phosphorylation, NFkB activation, cadmium accumulation and reduced vascular endothelial cell viability.[49]

Polygenic risk scores

As the genetic make-up of an individual is largely stable from birth, genetic information has the potential to act as an early risk predictor. Essential HTN is influenced by multiple genetic variants with small individual effect sizes, so meaningful risk prediction necessitates examining the aggregated impact of these multiple variants through calculation of a single metric that represents an individual's overall genetic risk. Initially this was calculated as a simple genetic risk score (GRS) which is a simple additive count of the number of risk alleles (usually from a few SNPs from GWAS, sometimes weighted by effect sizes) carried by each individual.[50] More recently, with the recognition that SNPs that do not meet highly stringent significance thresholds for genome-wide association could also be predictive of disease, a broader range of SNPs, ranging from thousands to millions have been used to generate an enhanced GRS termed polygenic risk score (PRS).[51] It is important to highlight that the risk information provided by the PRS is a probabilistic range and this is different from the risk information from genetic markers of monogenic disorders, which is dichotomous (either high or low probability of disease). Additionally, the rare variant genotype points to specific biological impact of the variant while the PRS is an amalgamation of numerous small-effect variants across the genome with no specific pathway implicated. A PRS constructed using all significant BP GWAS SNPs showed a significant association with stroke, coronary artery disease, heart failure, and left

ventricular mass but not with renal function.[21,52] Compared to the bottom 20% of the GRS distribution, the top 20% was associated with a 35-40% increased risk of cardiovascular disease, MI and stroke.[14] The estimated odds ratio for a 5 mmHg increase in SBP on the risk of coronary artery disease is around 1.30[1.18–1.44] supporting the hypothesis that SBP is causally related to coronary artery disease risk. This aligns with evidence from meta-analysis of clinical trials which show every 10 mm Hg reduction in systolic blood pressure significantly reduced the risk of major cardiovascular disease events by 17%-27%.[53] Lifelong genetic exposure to lower systolic blood pressure using blood pressure GWAS SNPs as genetic instruments showed participants with SBP genetic scores higher than the median had 2.9-mm Hg lower SBP and an OR of 0.82 for major coronary events (95% CI, 0.79-0.85, P < .001).[54] Indeed, this mendelian randomisation study confirms the independent associations of LDL-C and SBP in a dose-dependent log-linear manner with the risk of cardiovascular disease.[54] The lack of association between blood pressure PRS and renal function also suggests that progression of renal damage due to HTN may continue despite control of HTN. Whilst there is considerable interest in the use of PRS as a biomarker for early intervention or preventive strategies, this depends on its ability to motivate healthy behaviour changes for which evidence is not consistent.[55-57] A recent study from the UK BioBank showed that adherence to a healthy lifestyle (including healthy diet, limited alcohol consumption, low urinary sodium excretion, low body mass index, and increased physical activity) was associated with lower blood pressure regardless of the underlying blood pressure genetic risk suggesting that genetically predetermined rise in blood pressure and its complications can be offset at least to some extent by healthy lifestyle.[58] Prospective randomized controlled trials are essential to translate these findings into clinical practice.

Polygenic scores have mostly been developed in exclusively or majority European populations and there are concerns about the transferability of current PRS derived from European ancestry populations to other ancestries. Preliminary data indicate that PRS can still discriminate between high and low risk groups in other ethnicities,[59] but they don't perform as well, indicating clinical uses of PRS today would systematically afford greater improvement for European-descent populations and thus exacerbate health disparities.[37] The strategies to

address inequities range from recalibration of scores or variant weightings for alternative populations and establishing large GWAS projects in more diverse or non-European populations.[60,61] Until these strategies yield ancestry specific data, currently the applicability of PRS will only be possible in European ancestry populations.

Pleiotropy and causality

Phenome- wide association studies (PheWAS) are similar to a genome-wide association study (GWAS), but here each genetic variant is analysed for association with a multitude of phenotypes. PheWAS permit identification of pleiotropic SNPs and overlapping traits to identify shared pathways that may help prioritise signals for follow-up studies. We performed a look-up of all the 1477 BP SNPs in GWAS catalogue and PhenoScanner to identify all non-blood pressure traits significantly associated with these SNPs using a p-value threshold of $5x10^{-5}$.[62,63] This figure encapsulates the breadth of multi-trait associations of BP SNPs from clearly plausible correlated traits to unexpected novel traits. Surprisingly, cardiovascular complications of hypertension such as coronary artery disease, stroke and atrial fibrillation show fewer pleiotropy with BP compared to adiposity, anthropometric and haematological traits.

As genotypes are determined at conception, they are independent of environmental and life-style factors and cannot be altered by disease. This means genotype variation can be leveraged as a natural experiment to establish causal relationships between risk factors and health outcomes. This is the basis for Mendelian randomisation studies.[64] The next few paragraphs look in detail at the pleiotropic traits through the lens of published mendelian randomisation studies to determine if these pleiotropic traits have a causal role in blood pressure regulation and hypertension.

Figure 3 summarises the scale of pleiotropy of all the BP SNPs from GWAS studies. Only a minority of the over 1400 SNPs are non-pleiotropic and only 6 SNPs lie in genes known to harbour mutations for monogenic blood pressure syndromes. The highest number of pleiotropic signals are for anthropometric traits which includes height, BMI, measures of adiposity and visceral fat. Next are haematological traits which include RBC, WBC and platelet

measurements. Despite the high risk of stroke with hypertension, there are only 4 BP SNPs that also associate with stroke. There are 79 SNPs which also associate with CAD, and a majority of these overlap with lipid trait associations. These pleiotropic associations require further interrogation to determine if these indicate causal relationships with blood pressure or if these associations reflect confounding or reverse causation. In this context, we now summarise various mendelian randomisation studies that have tried to shed light on these associations.

Adiposity

Epidemiological studies show a correlation between BP and BMI with each 5 kg weight reduction reducing SBP by 4 mmHg.[65] In order to establish a causal role of BMI on blood pressure, one mendelian randomisation analysis used two SNPs robustly associated with BMI (rs9939609 in the Alpha-Ketoglutarate Dependent Dioxygenase (*FTO)* and rs17782313 in the Melanocortin 4 Receptor (*MC4R)* genes) and showed a 10% elevation in genotypically determined BMI was associated with a 3 mm Hg increase in systolic BP.[66] While visceral fat is known to be a better marker of cardiovascular risk, there is data to show that higher fat mass index and BMI are similarly associated with higher blood pressure suggesting that BMI may be a useful surrogate for visceral fat.[67]

Alcohol intake

Eighteen BP SNPs show pleiotropic association with alcohol intake. Interventional trials show a strong dose-response between reduction in alcohol intake and BP reduction.[68] A causal link between alcohol intake and blood pressure level has been explored using mendelian randomisation studies employing two indicator variables - rs1229984 mutation in alcohol dehydrogenase 1 (*ADH1*) and rs1229984) and rs671 in aldehyde dehydrogenase 2 (*ALDH2*) genes. The rs1229984 variant common in Caucasians heightens *ADH1* activity leading to more rapid oxidation of alcohol to acetaldehyde, while the rs671 variant common in East Asian populations inhibits metabolism of acetaldehyde by suppressing ALDH2. A large Mendelian randomisation meta-analysis of 56 epidemiological studies with 261,991 participants of European descent using the rs1229984 variant showed lower genotype-predicted alcohol intake was associated with low SBP. Similarly a study from the China Kadoorie Biobank involving 161,498 participants and using both rs1229984 and rs671 showed SBP increased by 4·8 mmHg

per 280 g/week genotype-predicted alcohol intake only in males.[69,70] The gender difference may be explained by male drinkers likely consuming more per drinking session than females. While both epidemiological and mendelian randomisation results show consistent results, a caveat need to be acknowledged that ALDH2 genotype is independently associated with blood pressure as well, independent of alcohol consumption, which renders this variant unsuitable for mendelian randomisation analysis.

Birth weight

There are 28 BP SNPs associated with birth weight out of the 65 SNPs that have been associated with birth weight in genome-wide association studies (GWAS). These results suggest that there are common biological pathways that affect infant survival and future risk of cardio-metabolic diseases in adulthood.[71] The observation that higher blood pressure in later life is associated with low birth weight has two possible explanations from a mendelian randomisation analysis. It shows that maternal BP lowering alleles are associated with lower offspring birth weight (indirect maternal effect), but the same alleles inherited by the foetus result in future higher blood pressure (direct foetal effect). Birth weight-lowering genotypes in the mother does not associate with higher offspring BP implying that the inverse birth weight-blood pressure association is due to genetic effects rather than intrauterine effects.[72]

Height

Height is a pleiotropic association with 199 BP SNPs. Several epidemiological studies have reported inverse association between adult height and blood pressure (BP). One reason for high SBP in short individuals is presumed to be due to early appearance of reflected waves during systole which combines with the forward wave leading to amplification of SBP.[73] In humans, taller height is associated with reduced risk of hypertension and CAD but increased risks of atrial fibrillation, venous thromboembolism, neoplasms.[74] 194 BP SNPs also showed significant association with height. Mendelian randomisation analyses showed a one-standard deviation higher genetically determined height (~6.5 cm) results in a 16% decreased risk of CAD[75] and a 12% decreased risk of hypertension.[74] Height and lung function are closely correlated with a large number of shared genetic loci and lung function has been shown to be the mediator of the effect of height on CAD rather than blood pressure.[75]

Heart rate

Sixty-one BP SNPs show pleiotropic association with heart rate. Observational studies show that increased heart rate is a common feature in hypertensive patients and elevated heart rate is associated with the development of hypertension.[76] Mendelian randomisation studies of SNPs showed only a minor effect of resting heart rate on.[77]

Haematological traits

Blood cells are essential for oxygen transport, haemostasis, innate and acquired immune responses, iron homeostasis, vascular and endothelial function. Observational studies show and association of associations of total white blood cell, granulocyte, and neutrophil counts and RBC traits with CHD risk.[78-84] Mendelian randomisation studies indicate that there is no causal link between red blood cell count, total white blood cell, granulocyte, and neutrophil counts with CHD risk.[85] Interestingly, there is evidence for a weak positive association of CHD risk with reticulocyte indices and the weak inverse association of CHD risk with platelet volume.[85] Reticulocyte count showed a weak direct association with CHD risk,[85] and a possible explanation for this relate to higher reticulocyte count reflecting increased haemolysis with consequent higher circulating free haemoglobin which depletes NO.[86] Furthermore, free haemoglobin in blood substitutes leads to reduced nitrous oxide, increased vasoconstriction, and a higher risk of acute myocardial ischaemia.[87] Increasing platelet volume shows a weak causal relationship with lower CHD risk,[85] in contrast to systematic reviews and observational studies,[88] warranting further investigation.

Education and socio-economic status

Socioeconomic factors such as education have been associated with cardiovascular disease, though educational opportunities are not equitably distributed in the population and interventional studies are difficult.[89] A UK BioBank mendelian randomisation study showed each additional standard deviation of education (3.6 years) was associated with a 37% lower risk of coronary heart disease, and 21% of this protective effect was mediated through systolic blood pressure with BMI and smoking mediating another 21%.[90]

Alzheimer's disease

Inherited lifetime exposure to higher SBP is associated with lower AD risk (odds ratio [OR] per standard deviation [15.4 mm Hg] of SBP [95% CI]: 0.75 [0.62–0.91]; p = 3.4 × 10−3) and with a higher probability of taking antihypertensive medication.

Pharmacogenomics

The goal of genomics is to enable precision medicine through a greater understanding of molecular pathways that regulate BP which can inform new drug development, personalisation of treatment and ultimately leading to a new taxonomy of HTN.[91] But there are significant challenges in realising this goal. Current treatment of HTN have not seen any new drug approval for over two decades. Tailoring of therapy has not progressed beyond considering self-reported African ancestry and serum renin levels.[2,4] The burgeoning list of genomic variants associated with BP and HTN opens opportunities for expanding our understanding of hypertension, revise and update the molecular taxonomy of HTN both of which will feed into hypertension precision medicine. This statement is supported by evidence from studies that showed a 6% improvement of efficacy and safety rates in drug validation efforts.[92] We connected BP GWAS signals to DrugBank[93] and Comparative Toxicogenomics Database[94] and extracted drug-gene interaction data for the plausible genes mapped to GWAS SNPs in previous studies.[14] Strikingly, all the major antihypertensive drug classes are captured by pharmacogenetic interaction with GWAS loci. This may reflect the fact that the putative published genes associated with GWAS SNPs were selected for plausible BP effect. More interestingly, gene-drug interactions revealed a large number of drugs that affect blood pressure. Many of these drugs are licensed for other conditions and have blood pressure decrease or increase as their known side-effect or adverse effect. These raise the possibility that some of the early wins from GWAS may be repurposing or repositioning opportunities for hypertension management.

Re-purposing or 'multi-purposing'

Drug repositioning or re-purposing is the process of discovering new indications for existing drugs and is becoming increasingly relevant in the current climate of decreasing investments in

new drug development and reduced rates of new drug approvals.[95] One approach that may enhance the likelihood of success is to reposition drugs against a target that has a genetic basis. Indeed, genetic studies have identified a large number of genes whose proteins are already targeted by drugs used in clinical practice (*ESR1* for tamoxifen, *CYP19A1* for aromatase inhibitors, *HMGCR* for statins) and novel drug targets (*PCSK9*).[96,97] Although GWAS SNPs still need to be causally linked to a target gene, there are significant advances in functional genomic and computational methods to accelerate discovery. Table 2 summarises other drugs with potential repurposing potential for hypertension and their pleiotropic associations. Riociguat, a guanylate cyclase (sGC) stimulator, is currently licensed for pulmonary hypertension and it is linked to the BP GWAS hit in *GUCY1A2.* Hypotension is a common side effect reported with with Riociguat, raising the possibility of potential use in blood pressure lowering.[98] Another possibility is Nesiritide is a recombinant B-type natriuretic peptide (interacts with *NPR3*, a BP GWAS locus) which failed in a clinical trial for acute decompensated heart failure and a high incidence of hypotension reported in these patients.[99] Finally, sodium-glucose cotransporter 2 (SGLT2) inhibitors are glucose lowering agents that also lower blood pressure and molecular docking studies show the SGLT2 inhibitor canagliflozin might act as a potent dual inhibitor of *ACHE* (BP GWAS locus) and SGLT2.[100]

Table 2 shows a wide range of drugs that are commonly used for other indications raising hopes for considerably increasing the pool of drugs for repurposing. However, repositioning needs to be carefully performed to ensure that patients are not exposed to off-target effects or side-effects from the wider target range of the drugs. For example, a number of anti-depressant and anti-epileptic drugs feature in Table 2 and a majority of them have hypotension as a known side-effect. Reviewing the pharmacological targets of these drugs raises caution about repositioning these drugs for hypertension. For example, olanzapine interacts with antihypertensive BP GWAS loci (*ADRB1, MTHFR-NPPA, ADRA1A, ADRA1B*), in addition its pharmacological targets include muscarinic acetylcholine receptor (CHRM1-4), histamine receptor (HRH1), 5-hydroxytryptamine receptor, kappa- and mu-type opioid receptor, Sodium-dependent serotonin transporter, HERG human cardiac K+ channel. Topiramate is an antiepileptic which interacts with the BP GWAS loci that are also linked to calcium channel

antagonists (*CACNA1C, CACNA1D, CACNB2*), but in addition its pharmacological targets include gamma-aminobutyric acid receptor, voltage-gated sodium channel, carbonic anhydrase, and glutamate receptors. These two examples highlight the potential risks of repurposing drugs for hypertension, rather we suggest that the opportunities for these drugs are in 'multi-purposing' as the increasing prevalence of multimorbidity in the population requires drugs that can treat multiple conditions. Thus, a hypothetical scenario would be for patients with epilepsy and hypertension or depression and hypertension to be considered for drugs that can benefit both. Whether this strategy will improve adherence and improve outcomes for both conditions need to be assessed through randomised controlled trials.

Conclusions

Hypertension genomics is in midst of a wealth of genomic signals but a poverty of actionable results. Follow up and clinical translation of these genetic data now looks promising with integration of pleiotropic and pharmacogenomic and functional studies. The low hanging fruits, uromodulin and endothelin SNPs that have moved on to clinical trials are harbinger of accelerated advances directly from genetics to hypertension precision medicine. Polygenic risk scores look attractive, but their clinical utility needs controlled studies and the potential ethical impacts on their widespread use exacerbating health disparities need further assessment.[37,101]

Acknowledgements

We thank Dr Stefanie Lip for designing Figure 1.

Funding

Disclosures

None

References

1 Canon, W. B. Organization for physiological homeostasis. *Physiol Rev* **9**, 399-431 (1929).

2 Williams, B. *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* **39**, 3021-3104, doi:10.1093/eurheartj/ehy339 (2018).
3 Lewington, S. *et al.* Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360**, 1903-1913, doi:10.1016/s0140-6736(02)11911-8 (2002).
4 Whelton, P. K. *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **138**, e426-e483, doi:10.1161/CIR.0000000000000597 (2018).
5 Evans, J. G. & Rose, G. Hypertension. *Br Med Bull* **27**, 37-42, doi:10.1093/oxfordjournals.bmb.a070812 (1971).
6 Forouzanfar, M. H. *et al.* Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. *JAMA* **317**, 165-182, doi:10.1001/jama.2016.19043 (2017).
7 Frohlich, E. D., Dustan, H. P. & Bumpus, F. M. Irvine H. Page: 1901-1991. The celebration of a leader. *Hypertension* **18**, 443-445, doi:10.1161/01.hyp.18.4.443 (1991).
8 Padmanabhan, S., Caulfield, M. & Dominiczak, A. F. Genetic and molecular aspects of hypertension. *Circ Res* **116**, 937-959, doi:10.1161/CIRCRESAHA.116.303647 (2015).
9 Franklin, S. S. *et al.* Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* **96**, 308-315, doi:10.1161/01.cir.96.1.308 (1997).
10 Carvalho, J. J. *et al.* Blood pressure in four remote populations in the INTERSALT Study. *Hypertension* **14**, 238-246, doi:10.1161/01.hyp.14.3.238 (1989).
11 Oliver, W. J., Cohen, E. L. & Neel, J. V. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. *Circulation* **52**, 146-151, doi:10.1161/01.cir.52.1.146 (1975).
12 Bursztyn, M. Occupational and environmental influences on hypertension. *J Hum Hypertens* **34**, 202-206, doi:10.1038/s41371-020-0302-z (2020).
13 Padmanabhan, S. & Joe, B. Towards Precision Medicine for Hypertension: A Review of Genomic, Epigenomic, and Microbiomic Effects on Blood Pressure in Experimental Rat Models and Humans. *Physiol Rev* **97**, 1469-1528, doi:10.1152/physrev.00035.2016 (2017).
14 Evangelou, E. *et al.* Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* **50**, 1412-1425, doi:10.1038/s41588-018-0205-x (2018).
15 Giri, A. *et al.* Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat Genet* **51**, 51-62, doi:10.1038/s41588-018-0303-9 (2019).
16 Havlik, R. J. *et al.* Blood pressure aggregation in families. *Am J Epidemiol* **110**, 304-312, doi:10.1093/oxfordjournals.aje.a112815 (1979).
17 Kupper, N. *et al.* Heritability of daytime ambulatory blood pressure in an extended twin design. *Hypertension* **45**, 80-85, doi:10.1161/01.HYP.0000149952.84391.54 (2005).
18 Salfati, E., Morrison, A. C., Boerwinkle, E. & Chakravarti, A. Direct Estimates of the Genomic Contributions to Blood Pressure Heritability within a Population-Based Cohort (ARIC). *PLoS One* **10**, e0133031, doi:10.1371/journal.pone.0133031 (2015).
19 Luft, F. C. Twins in cardiovascular genetic research. *Hypertension* **37**, 350-356, doi:10.1161/01.hyp.37.2.350 (2001).
20 Niiranen, T. J. *et al.* Risk for hypertension crosses generations in the community: a multi-generational cohort study. *Eur Heart J* **38**, 2300-2308, doi:10.1093/eurheartj/ehx134 (2017).
21 Ference, B. A. *et al.* Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. *Hypertension* **63**, 1182-1188, doi:10.1161/HYPERTENSIONAHA.113.02734 (2014).

22 Timpson, N. J., Greenwood, C. M. T., Soranzo, N., Lawson, D. J. & Richards, J. B. Genetic architecture: the shape of the genetic contribution to human traits and disease. *Nat Rev Genet* **19**, 110-124, doi:10.1038/nrg.2017.101 (2018).
23 Funder, J. W. Primary Aldosteronism. *Hypertension* **74**, 458-466, doi:10.1161/HYPERTENSIONAHA.119.12935 (2019).
24 Ji, W. *et al.* Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* **40**, 592-599, doi:10.1038/ng.118 (2008).
25 Baranowski, E. S., Arlt, W. & Idkowiak, J. Monogenic Disorders of Adrenal Steroidogenesis. *Horm Res Paediatr* **89**, 292-310, doi:10.1159/000488034 (2018).
26 Ceccato, F. & Mantero, F. Monogenic Forms of Hypertension. *Endocrinol Metab Clin North Am* **48**, 795-810, doi:10.1016/j.ecl.2019.08.009 (2019).
27 Seidel, E., Schewe, J. & Scholl, U. I. Genetic causes of primary aldosteronism. *Exp Mol Med* **51**, 131, doi:10.1038/s12276-019-0337-9 (2019).
28 Tadjine, M., Lampron, A., Ouadi, L. & Bourdeau, I. Frequent mutations of beta-catenin gene in sporadic secreting adrenocortical adenomas. *Clin Endocrinol (Oxf)* **68**, 264-270, doi:10.1111/j.1365-2265.2007.03033.x (2008).
29 Seyberth, H. W., Weber, S. & Komhoff, M. Bartter's and Gitelman's syndrome. *Curr Opin Pediatr* **29**, 179-186, doi:10.1097/MOP.0000000000000447 (2017).
30 Laghmani, K. *et al.* Polyhydramnios, Transient Antenatal Bartter's Syndrome, and MAGED2 Mutations. *N Engl J Med* **374**, 1853-1863, doi:10.1056/NEJMoa1507629 (2016).
31 Maass, P. G. *et al.* PDE3A mutations cause autosomal dominant hypertension with brachydactyly. *Nat Genet* **47**, 647-653, doi:10.1038/ng.3302 (2015).
32 Dahia, P. L. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nat Rev Cancer* **14**, 108-119, doi:10.1038/nrc3648 (2014).
33 Fishbein, L. *et al.* Comprehensive Molecular Characterization of Pheochromocytoma and Paraganglioma. *Cancer Cell* **31**, 181-193, doi:10.1016/j.ccell.2017.01.001 (2017).
34 Roman-Gonzalez, A. & Jimenez, C. Malignant pheochromocytoma-paraganglioma: pathogenesis, TNM staging, and current clinical trials. *Curr Opin Endocrinol Diabetes Obes* **24**, 174-183, doi:10.1097/MED.0000000000000330 (2017).
35 Gusev, A. *et al.* Integrative approaches for large-scale transcriptome-wide association studies. *Nat Genet* **48**, 245-252, doi:10.1038/ng.3506 (2016).
36 Mancuso, N. *et al.* Integrating Gene Expression with Summary Association Statistics to Identify Genes Associated with 30 Complex Traits. *Am J Hum Genet* **100**, 473-487, doi:10.1016/j.ajhg.2017.01.031 (2017).
37 Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* **51**, 584-591, doi:10.1038/s41588-019-0379-x (2019).
38 Padmanabhan, S. *et al.* Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. *PLoS Genet* **6**, e1001177, doi:10.1371/journal.pgen.1001177 (2010).
39 Graham, L. A. *et al.* Validation of uromodulin as a candidate gene for human essential hypertension. *Hypertension* **63**, 551-558, doi:10.1161/HYPERTENSIONAHA.113.01423 (2014).
40 Trudu, M. *et al.* Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med* **19**, 1655-1660, doi:10.1038/nm.3384 (2013).
41 Gupta, R. M. *et al.* A Genetic Variant Associated with Five Vascular Diseases Is a Distal Regulator of Endothelin-1 Gene Expression. *Cell* **170**, 522-533 e515, doi:10.1016/j.cell.2017.06.049 (2017).
42 Nikpay, M. *et al.* A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* **47**, 1121-1130, doi:10.1038/ng.3396 (2015).

43 Dhaun, N. & Webb, D. J. Endothelins in cardiovascular biology and therapeutics. *Nat Rev Cardiol* **16**, 491-502, doi:10.1038/s41569-019-0176-3 (2019).

44 Barton, M. & Yanagisawa, M. Endothelin: 30 Years From Discovery to Therapy. *Hypertension* **74**, 1232-1265, doi:10.1161/HYPERTENSIONAHA.119.12105 (2019).

45 Iglarz, M. *et al.* Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther* **327**, 736-745, doi:10.1124/jpet.108.142976 (2008).

46 Ford, T. J. *et al.* Genetic dysregulation of endothelin-1 is implicated in coronary microvascular dysfunction. *Eur Heart J*, doi:10.1093/eurheartj/ehz915 (2020).

47 Ren, M. *et al.* The biological impact of blood pressure-associated genetic variants in the natriuretic peptide receptor C gene on human vascular smooth muscle. *Hum Mol Genet* **27**, 199-210, doi:10.1093/hmg/ddx375 (2018).

48 Ng, F. L. *et al.* Increased NBCn1 expression, Na+/HCO3- co-transport and intracellular pH in human vascular smooth muscle cells with a risk allele for hypertension. *Hum Mol Genet* **26**, 989-1002, doi:10.1093/hmg/ddx015 (2017).

49 Zhang, R. *et al.* A blood pressure-associated variant of the SLC39A8 gene influences cellular cadmium accumulation and toxicity. *Hum Mol Genet* **25**, 4117-4126, doi:10.1093/hmg/ddw236 (2016).

50 International Schizophrenia, C. *et al.* Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748-752, doi:10.1038/nature08185 (2009).

51 Torkamani, A., Wineinger, N. E. & Topol, E. J. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet* **19**, 581-590, doi:10.1038/s41576-018-0018-x (2018).

52 International Consortium for Blood Pressure Genome-Wide Association, S. *et al.* Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **478**, 103-109, doi:10.1038/nature10405 (2011).

53 Ettehad, D. *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* **387**, 957-967, doi:10.1016/S0140-6736(15)01225-8 (2016).

54 Ference, B. A. *et al.* Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease. *JAMA*, doi:10.1001/jama.2019.14120 (2019).

55 Khera, A. V. *et al.* Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *N Engl J Med* **375**, 2349-2358, doi:10.1056/NEJMoa1605086 (2016).

56 Knowles, J. W. *et al.* Impact of a Genetic Risk Score for Coronary Artery Disease on Reducing Cardiovascular Risk: A Pilot Randomized Controlled Study. *Front Cardiovasc Med* **4**, 53, doi:10.3389/fcvm.2017.00053 (2017).

57 Loos, R. J. Genetics: genome-wide risk profiles - will they change your life(style)? *Nat Rev Endocrinol* **7**, 252-254, doi:10.1038/nrendo.2011.41 (2011).

58 Pazoki, R. *et al.* Genetic Predisposition to High Blood Pressure and Lifestyle Factors: Associations With Midlife Blood Pressure Levels and Cardiovascular Events. *Circulation* **137**, 653-661, doi:10.1161/CIRCULATIONAHA.117.030898 (2018).

59 Marquez-Luna, C., Loh, P. R., South Asian Type 2 Diabetes, C., Consortium, S. T. D. & Price, A. L. Multiethnic polygenic risk scores improve risk prediction in diverse populations. *Genet Epidemiol* **41**, 811-823, doi:10.1002/gepi.22083 (2017).

60 Gurdasani, D., Barroso, I., Zeggini, E. & Sandhu, M. S. Genomics of disease risk in globally diverse populations. *Nat Rev Genet* **20**, 520-535, doi:10.1038/s41576-019-0144-0 (2019).

61 Chatterjee, N., Shi, J. & Garcia-Closas, M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nat Rev Genet* **17**, 392-406, doi:10.1038/nrg.2016.27 (2016).

62 Kamat, M. A. *et al.* PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*, doi:10.1093/bioinformatics/btz469 (2019).
63 MacArthur, J. *et al.* The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* **45**, D896-D901, doi:10.1093/nar/gkw1133 (2017).
64 Pingault, J. B. *et al.* Using genetic data to strengthen causal inference in observational research. *Nat Rev Genet* **19**, 566-580, doi:10.1038/s41576-018-0020-3 (2018).
65 Neter, J. E., Stam, B. E., Kok, F. J., Grobbee, D. E. & Geleijnse, J. M. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* **42**, 878-884, doi:10.1161/01.HYP.0000094221.86888.AE (2003).
66 Timpson, N. J. *et al.* Does greater adiposity increase blood pressure and hypertension risk?: Mendelian randomization using the FTO/MC4R genotype. *Hypertension* **54**, 84-90, doi:10.1161/HYPERTENSIONAHA.109.130005 (2009).
67 Bell, J. A. *et al.* Associations of Body Mass and Fat Indexes With Cardiometabolic Traits. *J Am Coll Cardiol* **72**, 3142-3154, doi:10.1016/j.jacc.2018.09.066 (2018).
68 Roerecke, M. *et al.* The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. *Lancet Public Health* **2**, e108-e120, doi:10.1016/S2468-2667(17)30003-8 (2017).
69 Cho, Y. *et al.* Alcohol intake and cardiovascular risk factors: A Mendelian randomisation study. *Sci Rep* **5**, 18422, doi:10.1038/srep18422 (2015).
70 Holmes, M. V. *et al.* Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ* **349**, g4164, doi:10.1136/bmj.g4164 (2014).
71 Horikoshi, M. *et al.* Genome-wide associations for birth weight and correlations with adult disease. *Nature* **538**, 248-252, doi:10.1038/nature19806 (2016).
72 Warrington, N. M. *et al.* Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet* **51**, 804-814, doi:10.1038/s41588-019-0403-1 (2019).
73 London, G. M., Guerin, A. P., Pannier, B. M., Marchais, S. J. & Metivier, F. Body height as a determinant of carotid pulse contour in humans. *J Hypertens Suppl* **10**, S93-95 (1992).
74 Lai, F. Y. *et al.* Adult height and risk of 50 diseases: a combined epidemiological and genetic analysis. *BMC Med* **16**, 187, doi:10.1186/s12916-018-1175-7 (2018).
75 Marouli, E. *et al.* Mendelian randomisation analyses find pulmonary factors mediate the effect of height on coronary artery disease. *Commun Biol* **2**, 119, doi:10.1038/s42003-019-0361-2 (2019).
76 Palatini, P. Role of elevated heart rate in the development of cardiovascular disease in hypertension. *Hypertension* **58**, 745-750, doi:10.1161/HYPERTENSIONAHA.111.173104 (2011).
77 Larsson, S. C., Drca, N., Mason, A. M. & Burgess, S. Resting Heart Rate and Cardiovascular Disease. *Circ Genom Precis Med* **12**, e002459, doi:10.1161/CIRCGEN.119.002459 (2019).
78 Wheeler, J. G., Mussolino, M. E., Gillum, R. F. & Danesh, J. Associations between differential leucocyte count and incident coronary heart disease: 1764 incident cases from seven prospective studies of 30,374 individuals. *Eur Heart J* **25**, 1287-1292, doi:10.1016/j.ehj.2004.05.002 (2004).
79 Lassale, C. *et al.* Elements of the complete blood count associated with cardiovascular disease incidence: Findings from the EPIC-NL cohort study. *Sci Rep* **8**, 3290, doi:10.1038/s41598-018-21661-x (2018).
80 Shah, A. D., Denaxas, S., Nicholas, O., Hingorani, A. D. & Hemingway, H. Low eosinophil and low lymphocyte counts and the incidence of 12 cardiovascular diseases: a CALIBER cohort study. *Open Heart* **3**, e000477, doi:10.1136/openhrt-2016-000477 (2016).

81 Jae, S. Y. *et al.* Higher blood hematocrit predicts hypertension in men. *J Hypertens* **32**, 245-250, doi:10.1097/HJH.0000000000000029 (2014).
82 Paul, L. *et al.* Hematocrit predicts long-term mortality in a nonlinear and sex-specific manner in hypertensive adults. *Hypertension* **60**, 631-638, doi:10.1161/HYPERTENSIONAHA.112.191510 (2012).
83 Atsma, F. *et al.* Hemoglobin level is positively associated with blood pressure in a large cohort of healthy individuals. *Hypertension* **60**, 936-941, doi:10.1161/HYPERTENSIONAHA.112.193565 (2012).
84 Schaffer, A. *et al.* Impact of red blood cells count on the relationship between high density lipoproteins and the prevalence and extent of coronary artery disease: a single centre study [corrected]. *J Thromb Thrombolysis* **40**, 61-68, doi:10.1007/s11239-015-1174-x (2015).
85 Astle, W. J. *et al.* The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. *Cell* **167**, 1415-1429 e1419, doi:10.1016/j.cell.2016.10.042 (2016).
86 Gladwin, M. T., Crawford, J. H. & Patel, R. P. The biochemistry of nitric oxide, nitrite, and hemoglobin: role in blood flow regulation. *Free Radic Biol Med* **36**, 707-717, doi:10.1016/j.freeradbiomed.2003.11.032 (2004).
87 Natanson, C., Kern, S. J., Lurie, P., Banks, S. M. & Wolfe, S. M. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. *JAMA* **299**, 2304-2312, doi:10.1001/jama.299.19.jrv80007 (2008).
88 Sansanayudh, N. *et al.* Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol* **175**, 433-440, doi:10.1016/j.ijcard.2014.06.028 (2014).
89 Davies, N. M., Dickson, M., Davey Smith, G., van den Berg, G. J. & Windmeijer, F. The Causal Effects of Education on Health Outcomes in the UK Biobank. *Nat Hum Behav* **2**, 117-125, doi:10.1038/s41562-017-0279-y (2018).
90 Carter, A. R. *et al.* Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. *BMJ* **365**, l1855, doi:10.1136/bmj.l1855 (2019).
91 Padmanabhan, S., Aman, A. & Dominiczak, A. F. Recent Findings in the Genetics of Blood Pressure: How to Apply in Practice or Is a Moonshot Required? *Curr Hypertens Rep* **20**, 54, doi:10.1007/s11906-018-0863-1 (2018).
92 Nelson, M. R. *et al.* The support of human genetic evidence for approved drug indications. *Nat Genet* **47**, 856-860, doi:10.1038/ng.3314 (2015).
93 Wishart, D. S. *et al.* DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* **46**, D1074-D1082, doi:10.1093/nar/gkx1037 (2018).
94 Davis, A. P. *et al.* The Comparative Toxicogenomics Database: update 2019. *Nucleic Acids Res* **47**, D948-D954, doi:10.1093/nar/gky868 (2019).
95 Pushpakom, S. *et al.* Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov* **18**, 41-58, doi:10.1038/nrd.2018.168 (2019).
96 Jhamb, D., Magid-Slav, M., Hurle, M. R. & Agarwal, P. Pathway analysis of GWAS loci identifies novel drug targets and repurposing opportunities. *Drug Discov Today* **24**, 1232-1236, doi:10.1016/j.drudis.2019.03.024 (2019).
97 Tragante, V. *et al.* Druggability of Coronary Artery Disease Risk Loci. *Circ Genom Precis Med* **11**, e001977, doi:10.1161/CIRCGEN.117.001977 (2018).
98 Stasch, J. P., Pacher, P. & Evgenov, O. V. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation* **123**, 2263-2273, doi:10.1161/CIRCULATIONAHA.110.981738 (2011).
99 O'Connor, C. M. *et al.* Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* **365**, 32-43, doi:10.1056/NEJMoa1100171 (2011).

100 Rizvi, S. M. *et al.* Invokana (Canagliflozin) as a dual inhibitor of acetylcholinesterase and sodium glucose co-transporter 2: advancement in Alzheimer's disease- diabetes type 2 linkage via an enzoinformatics study. *CNS Neurol Disord Drug Targets* **13**, 447-451, doi:10.2174/18715273113126660160 (2014).
101 Minari, J., Brothers, K. B. & Morrison, M. Tensions in ethics and policy created by National Precision Medicine Programs. *Hum Genomics* **12**, 22, doi:10.1186/s40246-018-0151-9 (2018).
102 Krzywinski, M. *et al.* Circos: an information aesthetic for comparative genomics. *Genome Res* **19**, 1639-1645, doi:10.1101/gr.092759.109 (2009).

Table 1: Monogenic syndromes of blood pressure dysregulation with causal genes, key features and treatment.

Syndrome	Gene	Treatment
11β-hydroxylase deficiency	*CYP11B1*	Glucocorticoid therapy
17a-hydroxylase deficiency	*CYP17A1*	Glucocorticoid therapy, Potassium sparing diuretics
21-Hydroxylase deficiency	*CYP21A2*	Glucocorticoid therapy
3β-hydroxysteroid dehydrogenase	*HSD3B2*	Glucocorticoid therapy
Apparent Mineralocorticoid Excess (AME)	*HSD11B2*	Low sodium diet and spironolactone
Bartter syndrome	*CLCNKA* *CLCNKB* *KCNJ1* *MAGED2* *SLC12A1*	Potassium supplementation and use of cyclooxygenase inhibitors, angiotensin converting enzyme (ACE)-inhibitors and potassium sparing diuretics.
Familial Hyperaldosteronism (FH I)	*CYP11B1* *CYP11B2*	Dexamethasone
Familial Hyperaldosteronism (FH II)	Linkage to Chr 7p22, *KCNJ5*	Adrenalectomy is performed in case of APA, and medical therapy with aldosterone antagonists in case of BAH.
Gitelman syndrome	*SLC12A3* *CLCNKB*	Oral potassium and magnesium supplementation with adequate salt and water.
Hypertension and brachydactyly syndrome	*PDE3A*	Possible role for PDE3 inhibition
Hypertension exacerbation in pregnancy	*NR3C2*	Spironolactone contraindicated; sodium chloride treatment. Delivery of the foetus ameliorates hypertension
Liddle Syndrome	*SCNN1B* *SCNN1G*	Low sodium diet. Amiloride or triamteren.

Multiple endocrine neoplasia, type IIA neoplasia, type IIA	*RET*	Alpha adrenergic blockers for pheochromocytoma
Paragangliomas (PGL1-5)	*SDHA* *SDHAF2* *SDHB* *SDHC* *SDHD*	Surgery, adrenergic blockers (alpha blockade followed by beta-blockade)
Pseudohypoaldosteronism (PHA II- Gordon syndrome)	*CUL3* *KLHL3* *NR3C2* *WNK1* *WNK4*	Thiazide diuretics, prostaglandin inhibitors, alkalising agents, and potassium-binding resins. Na^+ and K^+ restricted diet
Sporadic aldosterone-producing adenoma (APA), or primary aldosteronism	*ATP1A1* *ATP2B3* *CACNA1D* *KCNJ5*	Surgery, aldosterone antagonists
von Hippel-Lindau syndrome	*VHL*	

Table 2: Pharmacologically active gene loci from genome wide association studies, their pleiotropic associations, key drug-gene interactions with their indications and blood pressure effect.

GWAS Locus	Pleiotropic Associations	Antihypertensive License	BP reduction as side effect	Effect on BP	Therapeutic context/indication
ACE	Non-pleiotropic	Angiotensin Converting Enzyme Inhibitors		↓↓↓↓	Hypertension; Heart Failure; DM Nephropathy
			Omapatrilat	↓↓	(Hypertension; Heart Failure – Failed because of ADR)
ACVR2A	Basophils, Eosinophils, Neutrophils, Renal.Function, Urate		Sotatercept	↓	(Pulmonary Hypertension – Phase II)
ADORA1	Non-pleiotropic		Adenosine	↓↓	Supraventricular tachycardias
			Pentoxifylline	↓↓	Peripheral vascular disease
ADRB1	Birth Weight		Bethanidine	↓↓	(Sympatholytic)
		Beta Blockers		↓↓↓↓	Hypertension; Angina; Arrhythmia; Heart Failure
			Dobutamine	↓↓	Inotropic support; cardiac stress testing
			Amiodarone	↓↓	Arrhythmia

AKR1A1	Basophil, Granulocytes, Height, Hematocrit, Haemoglobin, Neutrophils, Platelet traits, RBC traits, Reticulocytes, WBC		Tolrestat	↓	(Diabetes complications – Failed trials)
AKR1B10	Non-pleiotropic				(Diabetes complications – Failed trials)
BCL2	Adiposity, BMI, BMR, CAD, Glycemia, Hematocrit, RBC traits, Reticulocytes, T2DM, Visceral fat, Weight		Docetaxel	↓↓	Solid tumours
CACNA1C	Hematocrit, Hemoglobin, RBC traits		Cinnarizine	↓	Ménière's disease
		Spironolactone		↓↓↓↓	Hyperaldosteronism; Oedema; Heart Failure; Hypertension
			Drotaverine	↓↓	Antispasmodic
			Topiramate	↓	Epilepsy; Migraine
		Calcium Channel Blockers		↓↓↓↓	Angina; Hypertension
CACNA1D	Monogenic, Non- pleiotropic		Cinnarizine	↓	Ménière's disease
		Spironolactone		↓↓↓↓	Hyperaldosteronism; Oedema; Heart Failure; Hypertension
		Calcium Channel Blockers		↓↓↓↓	Angina; Hypertension

CACNB2	Non.Pleiotropic	Spironolactone		↓↓↓↓	Hyperaldosteronism; Oedema; Heart Failure; Hypertension
		Calcium Channel Blockers		↓↓↓↓	Angina; Hypertension
CHRM2	Heart Rate		Pizotifen	↓↓	Migraine
			Disopyramide	↓↓	Arrhythmia
			Cinnarizine	↓	Ménière's disease
			Acetylcholine	↓↓	
			Amitriptyline	↓↓	Depression; Neuropathic pain; Migraine
CSK	Cholesterol, Granulocytes, Hematocrit, Monocytes, Platelet.traits, RBC.traits, Renal.Function		Dasatinib	↓↓	Chronic myeloid leukaemia
CYP11B2	Height	Spironolactone		↓↓↓↓	Hyperaldosteronism; Oedema; Heart Failure; Hypertension
DBH	Non.Pleiotropic		Ascorbic acid	↓	Scurvy
DDAH1	Adiposity		Esomeprazole	↓	Peptic ulcer disease
EDNRA	CAD		Ambrisentan	↓↓	Pulmonary hypertension
ESR1	Adiposity, Height		Dobutamine	↓↓	Inotropic support; cardiac stress testing
FGR	BMI		Dasatinib	↓↓	Chronic myeloid leukaemia
FRK	Adiposity, Cholesterol, CRP, Height, LDL		Dasatinib	↓↓	Chronic myeloid leukaemia

GUCY1A2	CAD		Riociguat	↓↓	Pulmonary hypertension
HDAC7	Allergy, Asthma, Platelet.traits, Reticulocytes		Belinostat	↓	(T-cell lymphoma)
HDAC9	Adiposity, CAD, CVA				
HDAC9	Adiposity, CAD, CVA		Valproic acid	↓	Epilepsy; Bipolar Disorder; Migraine
HRH1	Adiposity, BMD, Neoplasm		Mirtazapine	↓↓	Depression
			Pizotifen	↓↓	5-HT, Muscarinic, H1, Alpha Adrenergic Antagonist
			Dimenhydrinate	↓	Vertigo
			Histamine	↓↓	
			Cinnarizine	↓	Ménière's disease
			Amitriptyline	↓↓	Depression; Neuropathic pain; Migraine
INSR	Adiposity, HDL, Height, Triglycerides, Urate, Visceral.fat		Insulin	↓	Diabetes Mellitus
KCNJ11	Adiposity, BMI, Glycemia, Height, T2DM		Diazoxide	↓↓	Hypoglycemia
LIMK1	Lung.function		Dabrafenib	↓↓	Melanoma
MTHFR-NPPB	CAD, RBC.traits, Visceral.fat	Carvedilol		↓	Hypertension; Angina; Heart Failure
NPR3	Adiposity, BMR, Height, Lung.function, Visceral.fat,		Nesiritide	↓↓	(Heart Failure – Failed clinical trial)

	Weight				
PDE10A	Non.Pleiotropic		Dipyridamole	↓↓	Adenosine deaminase and phosphodiesterase Inhibitor
			Papaverine	↓↓	(Antispasmodic)
PDE1A	Adiposity, BMR, Weight	Calcium Channel Blockers		↓↓↓↓	Angina; Hypertension
			Bepridil	↓↓	Angina(withdrawn)
PDE3A	CAD, Monogenic		Amrinone	↓	Heart Failure
PDE5A	Basophil, CAD, Granulocytes, Platelet.traits, WBC		Dipyridamole	↓↓	Antiplatelet
			Pentoxifylline	↓↓	Peripheral vascular disease
SCN10A	Heart.Rate, Neoplasm		Tetracaine	↓	Local anaesthetic
			Lidocaine	↓↓	Local anaesthetic; Ventricular arrhythmia
			Valproic acid	↓	Epilepsy; Bipolar Disorder; Migraine
			Brivaracetam	↓	Epilepsy
SCN2A	Adiposity		Zonisamide	↓↓	Epilepsy
			Tetracaine	↓	Local anaesthetic
			Valproic acid	↓	Epilepsy; Bipolar Disorder; Migraine
			Brivaracetam	↓	Epilepsy
VEGFA	Hematocrit, Hemoglobin, RBC.traits, Renal.Function, Urate	Carvedilol		↓↓↓↓	Hypertension; Angina; Heart Failure
YES1	Non.Pleiotropic		Dasatinib	↓↓	Chronic myeloid leukaemia

All pleiotropic associations of BP GWAS SNPs were extracted and categorised into groups of correlated traits. Some SNPs did not show any non-BP associations and were classified as non-pleiotropic. The genes linked to GWAS SNPs were determined by proximity to the SNP and cardiovascular plausibility. Only one gene per loci was included. Drug-gene interactions were obtained from Drug Bank and Comparative Toxicogenomics Database and drug indications were obtained from the British National Formulary and FDA labelled indications.

Legends to Figures.

Figure 1: Blood pressure regulation – blood pressure is the product of cardiac output and peripheral vascular resistance and these are regulated by a multitude of factors. This figure shows the spectrum of rare genomic mutations affecting blood pressure by perturbing specific physiological systems. Additionally, the role of polygenic variants are complex and integral to blood pressure regulation through pathways that are yet to be characterised. Blood pressure is a multifactorial trait and the circos background plot represents both the landscape of genetic variants and environmental and other factors that have a role in blood pressure regulation. The inner circle, represents the organ specific physiological pathways that affect blood pressure. The length of each segment is a relative representation of known genetic factors involved in that pathway. The outer circle represents the polygenic background and known environmental factors that influence multiple physiological pathways leading to the final blood pressure phenotype.

Figure 2: Genetic architecture of blood pressure and hypertension. The circos[102] plot shows depicts the monogenic and polygenic genetic variants identified by linkage, sequencing and genome wide association studies. Monogenic variants are large filled red circles and they are connected to their Clinical syndromes. The smaller blue, green and yellow filled circles are SNPs identified from genome wide association studies. The colour of the SNPs indicates whether the best association of the SNP was for systolic, diastolic or pulse pressure. FH – Familial hyperaldosteronism; AME – Apparent mineralocorticoid excess; PHA – Pseudohypoaldosteronim II; APA – Aldosterone producing adenoma; CAH – Congenital adrenal hyperplasia; HTNBRACH – Hypertension with brachydactyly; HSD3B2 - 3β-hydroxysteroid dehydrogenase deficiency; PGL1-5 – Paraganglioma; VHL – Von Hippel Lindau Syndrome; MEN – Multiple Endocrine Neoplasia II.
The top of the plot shows pleiotropic signals from PheWAS, which indicate lifestyle, environmental and early life influences on blood pressure linked to the location of the pleiotropic SNPs.
The histogram on the outer ring indicates the number of pleiotropic associations SNPs in that locus have. The taller the graph, the greater the number of pleiotropy.

Figure 3: Pleiotropic signals from phenome wide association studies. The Venn diagrams show the number of blood pressure SNPs that are significantly associated with other traits. The top panel is the global pleiotropic landscape of different phenotypic groups with the number of BP SNPs that overlap

with them shown within brackets. Here overarching phenotypic groups were condensed from a range of traits that fall under this category. More detailed representation of the constituents of the major phenotypic groups are represented in the bottom panel showing the contribution of individual traits and the degree of pleiotropy with blood pressure and the level of overlap between them.

Figure 1

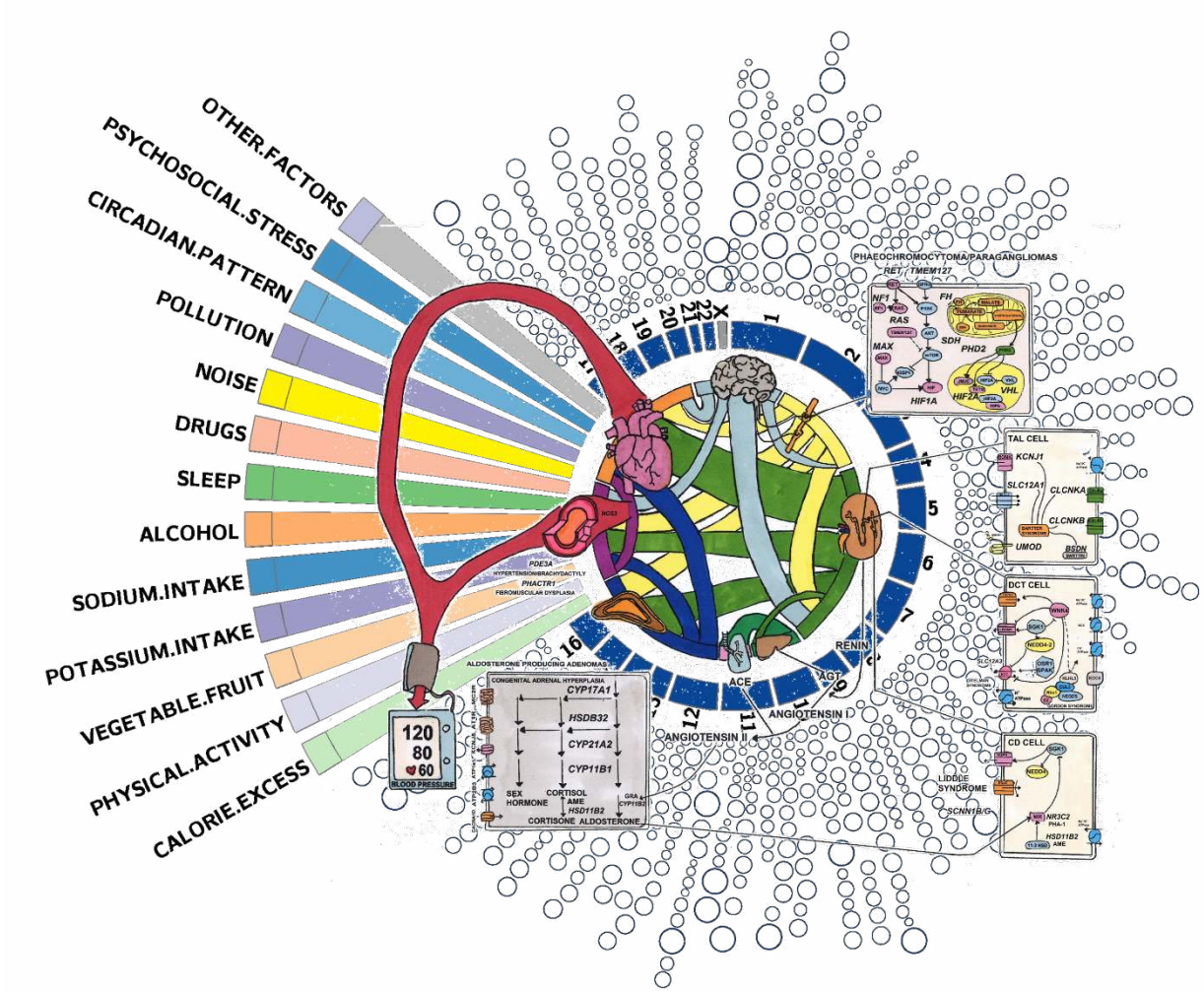

OTHER.FACTORS
PSYCHOSOCIAL.STRESS
CIRCADIAN.PATTERN
POLLUTION
NOISE
DRUGS
SLEEP
ALCOHOL
SODIUM.INTAKE
POTASSIUM.INTAKE
VEGETABLE.FRUIT
PHYSICAL.ACTIVITY
CALORIE.EXCESS
120
80
60
BLOOD PRESSURE
PHAEOCHROMOCYTOMA/PARAGANGLIOMAS
RET, TMEM127
NF1
RAS
FH
SDH
PHD2
MAX
HIF1A
HIF2A
VHL
TAL CELL
KCNJ1
SLC12A1
CLCNKA
CLCNKB
UMOD
BSDN
DCT CELL
NEDD4-2
CD CELL
LIDDLE SYNDROME
SCNN1B/G
NR3C2
PHA-1
HSD11B2
AME
RENIN
AGT
ACE
ANGIOTENSIN I
ANGIOTENSIN II
ALDOSTERONE PRODUCING ADENOMAS
CONGENITAL ADRENAL HYPERPLASIA
CYP17A1
HSDB32
CYP21A2
CYP11B1
SEX HORMONE
CORTISOL
CORTISONE
ALDOSTERONE
PDE3A
HYPERTENSIONBRACHYDACTYLY
PHACTR1
FIBROMUSCULAR DYSPLASIA

Figure 2

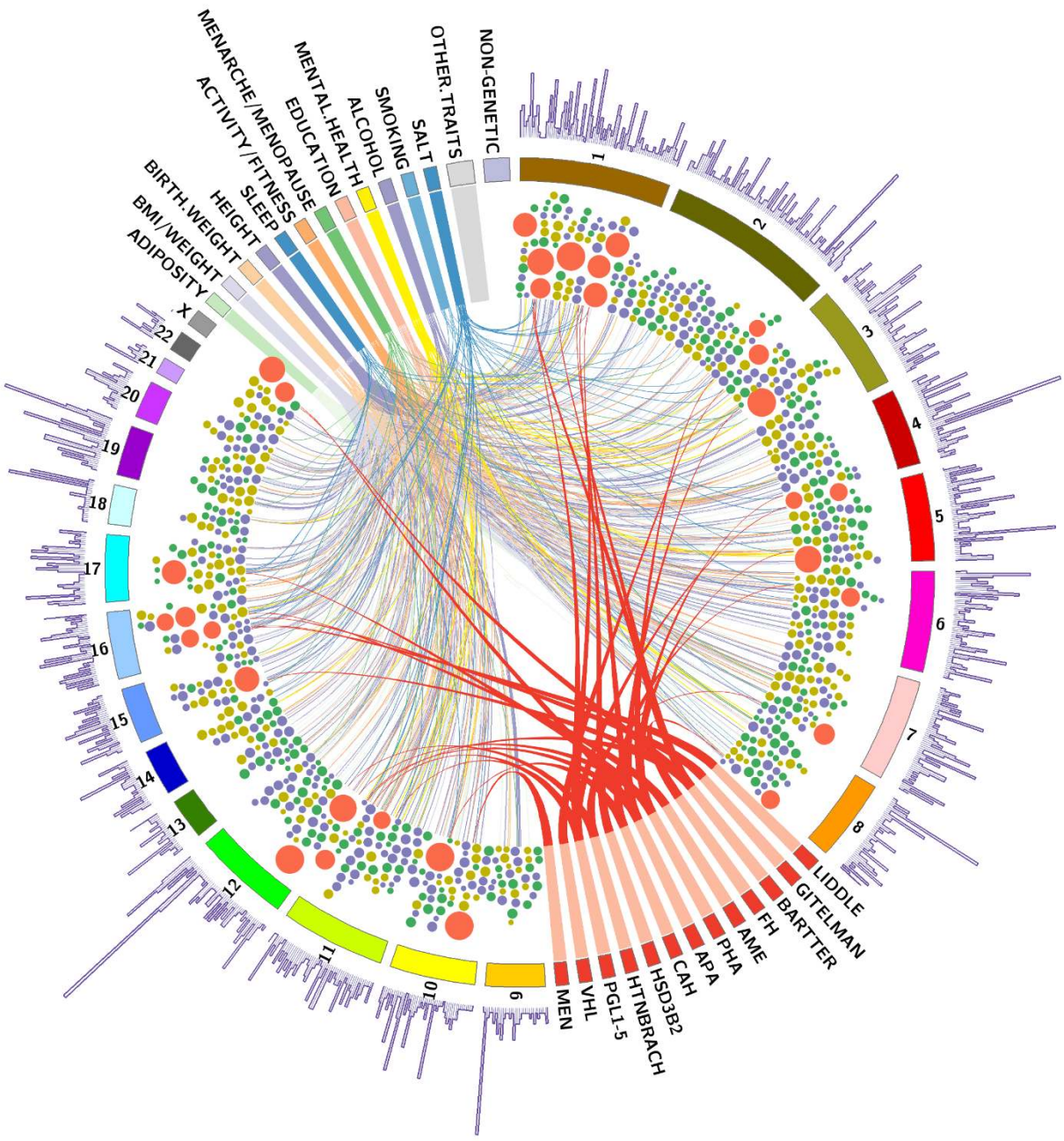
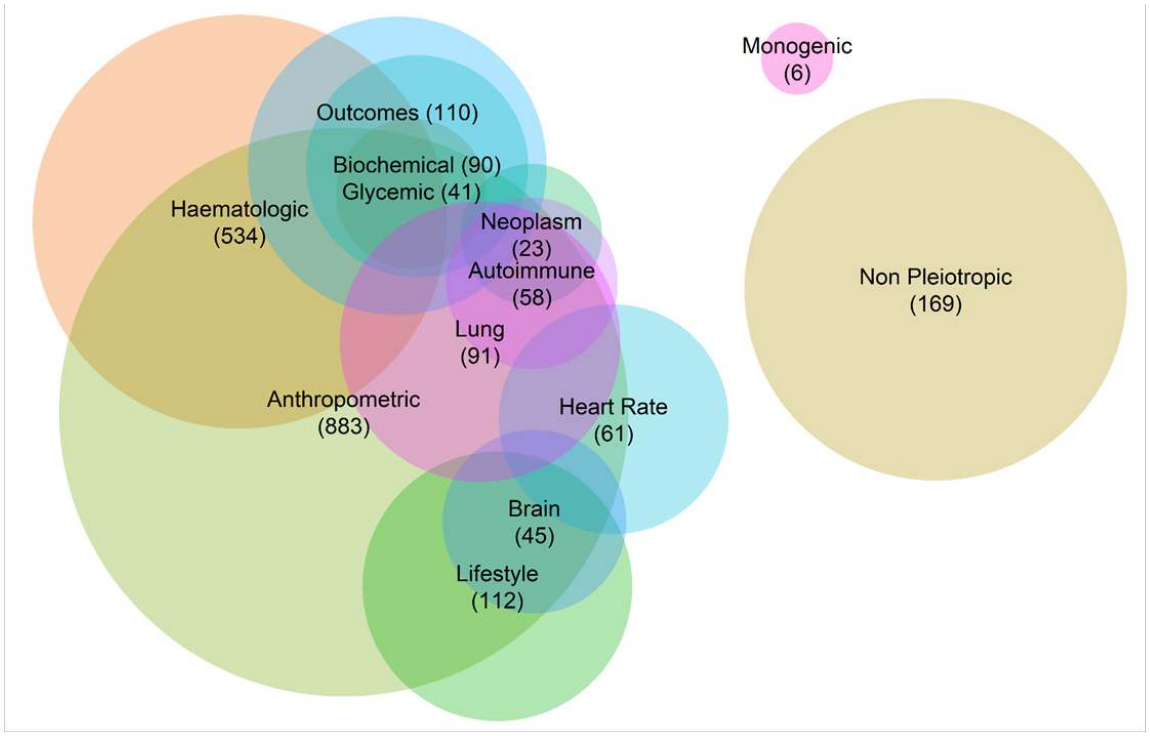
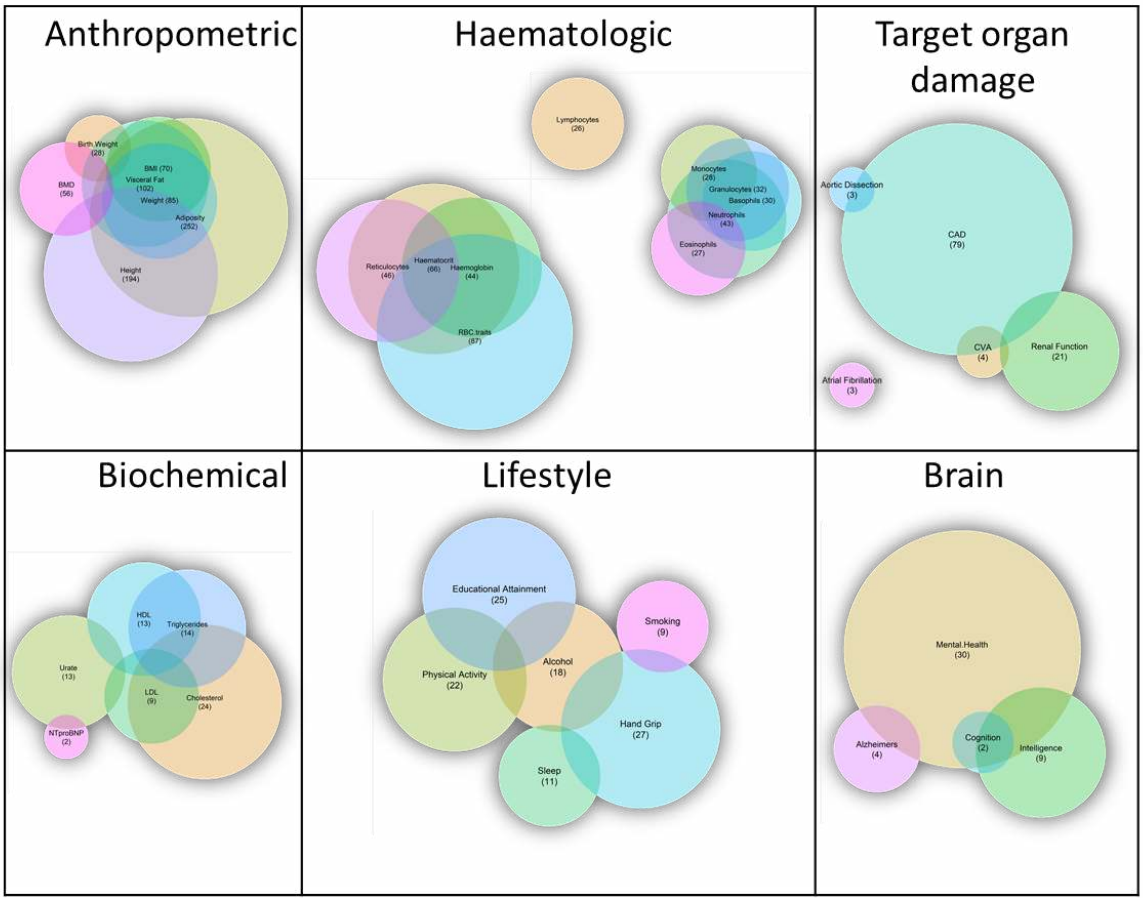

NON-GENETIC
OTHER.TRAITS
SALT
SMOKING
ALCOHOL
MENTAL.HEALTH
EDUCATION
MENARCHE/MENOPAUSE
ACTIVITY/FITNESS
SLEEP
HEIGHT
BIRTH.WEIGHT
BMI/WEIGHT
ADIPOSITY
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
LIDDLE
GITELMAN
BARTTER
AME
FH
PHA
APA
CAH
HSD3B2
HTNBRACH
PGL1-5
VHL
MEN

Figure 3


Monogenic
(6)
Outcomes (110)
Biochemical (90)
Glycemic (41)
Haematologic
(534)
Neoplasm
(23)
Autoimmune
(58)
Lung
(91)
Non Pleiotropic
(169)
Anthropometric
(883)
Heart Rate
(61)
Brain
(45)
Lifestyle
(112)


Anthropometric
Birth Weight (28)
BMD (56)
BMI (70)
Visceral Fat (102)
Weight (85)
Adiposity (252)
Height (194)
Haematologic
Lymphocytes (26)
Monocytes (26)
Granulocytes (32)
Basophils (30)
Neutrophils (43)
Eosinophils (27)
Reticulocytes (46)
Haematocrit (66)
Haemoglobin (44)
RBC.traits (87)
Target organ damage
Aortic Dissection (3)
CAD (79)
CVA (4)
Renal Function (21)
Atrial Fibrillation (3)
Biochemical
HDL (13)
Triglycerides (14)
Urate (13)
LDL (9)
Cholesterol (24)
NTproBNP (2)
Lifestyle
Educational Attainment (25)
Smoking (9)
Physical Activity (22)
Alcohol (18)
Hand Grip (27)
Sleep (11)
Brain
Mental Health (30)
Alzheimers (4)
Cognition (2)
Intelligence (9)