Hypertension: Over 1,000 genetic loci influencing blood pressure with multiple systems and tissues implicated

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Abstract

High blood pressure remains the major heritable and modifiable risk factor for cardiovascular disease (CVD). Persistent high blood pressure, or hypertension, is a complex trait with both genetic and environmental interactions. Despite swift advances in genomics, translating new discoveries to further our understanding of the underlying molecular mechanisms remains a challenge. More than 500 loci implicated in the regulation of blood pressure (BP) have been revealed by genome-wide association studies (GWAS) in 2018 alone, taking the total number of BP genetic loci to over 1,000. Even with the large number of loci now associated to BP, the genetic variance explained by all loci together remains low (~5.7%). These genetic associations have elucidated mechanisms and pathways regulating BP, highlighting potential new therapeutic and drug repurposing targets. A large proportion of the BP loci were discovered and reported simultaneously by multiple research groups, creating a knowledge gap, where the reported loci to date have not been investigated in a harmonious way. Here, we review the BP-associated genetic variants reported across GWAS studies and investigate their potential impact on the biological systems using *in silico* enrichment analyses for pathways, tissues, gene ontology and genetic pleiotropy.

Introduction

Cardiovascular diseases, including stroke, renal and heart disease, represent the largest cause of global mortality. The Global Burden of Diseases, Injuries and Risk Factor study calculated ~10.4 million deaths that can be attributed to high systolic blood pressure (SBP) (1) and it is estimated that 25% of the adults have elevated blood pressure (2). To compound this, hypertension is mostly asymptomatic, resulting in the disease being potentially unnoticed until a life-threatening event such as a heart attack or stroke affects the individual.

Individuals with family history of hypertension diagnosed before 55 years of age have been found to have an associated risk to hypertension (odds ratio 2.10 and 1.33 for affected parents and grandparents respectively). These findings reinforce the hypothesis of genetic predisposition to high blood pressure,

independent from the environmental factors (3). Blood pressure is a complex polygenic trait, even discussed as a probable omnigenic trait in previous studies (4). The heritability of the common genetic variation in blood pressure has been observed to be ethnicity-dependent. A study in ~8,900 European ancestry individuals estimated the heritability of SBP to be ~20% and approximately 50% for diastolic blood pressure (DBP), whilst heritability in African ancestry individuals (n=2,860) was estimated at ~27% and ~39% respectively (5). While the expected heritability is between 20-50%, the recent analyses indicated that the BP variants identified thus far explains only 27% of the genetic contribution (4), suggesting many loci are yet to be identified.

Here, we review the blood pressure genetic associations unravelled by GWAS, their implications at a pathway and systems level, and investigate the pleiotropy effects of reported blood pressure loci. Collectively these discoveries may bring new mechanistic insights to the treatment of hypertension.

Blood pressure and genome-wide association studies

Our understanding of genomic regions linked with BP was rapidly expanded with increasingly large and sophisticated GWAS. Up to 2015, there were 64 validated BP loci reported (6-22). Four years later, the number of known BP loci has increased to 1,477 (4, 23-30), including 1,214 lead signals and 263 secondary signals (Supplementary Table 1; a) Lead BP loci; b) Secondary BP loci). The substantial rise in the reported loci is driven by the collaborative work of international consortia, combined with the availability of public datasets such as UK Biobank (UKB) (31). The UKB data has provided a resource of standardised genotypic and phenotypic data from an unprecedented population size (n=502,620). Other large key resources include the US Million Veteran Program (MVP) (n~318,891) (32), the Genetic Epidemiology Research on Adult Health and Aging cohort (GERA) (n~100,000) (33) and the International Consortium of Blood Pressure (ICBP) (29). To date, the ICBP consortium has accumulated 77 cohorts which include ~299,024 individuals. These studies have paved the way to the biggest analysis reported to date including 1 million people and unravelling 535

novel loci in a single study (4). Figure 1 shows the timeline of some of the key BP GWAS in the last decade and their validated loci.

BP candidate genes

The common genetic variants identified as associated with BP continue to improve our understanding of the polygenic nature of blood pressure regulation. Nevertheless, the increased number of loci – and therefore genes – makes the functional investigation of each locus impossible. At the present, there are but a handful of genes followed up by experimental studies (34). While a proportion of the candidate genes at blood pressure loci have been fairly well characterized, many others do not have known links to blood pressure regulation. It is the successes relating to the latter group that highlights the potential to expand our knowledge of the pathophysiology of hypertension. One such example is the transcription factor, Nuclear Receptor 2 Family 2 (*NR2F2*). A murine model with a mutated Nr2f2 protein resulted in lower systolic and diastolic blood pressure, and was more resistant to the hypertensive effects of a high-salt diet. The deletion of a five amino acid hinge region required for the protein-protein interaction with another transcription factor, Fog2 appears to reveal the potential underlying molecular mechanism (35), in particular as the Nr2f2-Fog2 interaction potentially influences expression of the vasorelaxant atrial natriuretic factor (*Anf*) (36).

Another candidate gene of interest is *SH2B3* encoding the lymphocyte adaptor protein LNK. This regulator of cytokine signalling and cell proliferation is predominantly expressed in haematopoietic and endothelial cells. *SH2B3*$^{-/-}$ mice had exaggerated hypertensive responses to angiotensin II, and it is noteworthy that haematopoietic cells were the apparent primary driver of the observed vascular inflammation and predisposition to hypertension (37). However, extensive pleiotropy is observed in the *SH2B3-ATXN2* locus, associations with myocardial infraction, multiple sclerosis, juvenile idiopathic arthritis have been reported (38-40). It should also be recognised that while most of the attention is paid to *SH2B3* as the GWAS signal at rs3184504 results in a coding change within

SH2B3, this signal falls within a 1-megabase block of linkage disequilibrium on chromosome 12q24 that encompases at least 15 annotated genes (8).

Other examples include genes that are within pathways with known links to BP regulation, such as *ARHGAP42* (Rho GTPase-activating protein 42 gene) in the RhoA pathway. The deletion of *ARHGAP42* in a murine model enhanced the hypertensive effects of both L-NAME and deoxycorticosterone acetate (DOCA)–salt treatments (41). This was later supported by human studies of balanced chromosomal rearrangement carriers resulting in *ARHGAP42* truncation, leading to age-dependent hypertension (42). Finally, *UMOD* (uromodulin), recently reviewed in more detail (34), is another notable candidate gene identified by GWAS. *UMOD* deficient mice have shown to increase sequestration of the target of loop diuretics, the sodium-potassium-chloride co-transporter 2 (KKCC2), resulting in reduced co-transporter activity. This mimics the effect of diuretic drugs, and with the subsequent lower blood pressure and reduced hypertensive response to increased salt intake. The pharmacological inhibition of uromodulin may have a diuretic effect that may perhaps be synergistic with existing pharmacological options (13, 43-45). This has led to a clinical trial on cardiovascular disease (www.clinicaltrials.gov: NCT03354897) (46), making significant progress towards a novel therapeutic target in hypertension.

Altogether, these are examples of translating GWAS discovery to an improved understanding of biological impact, and providing promise of new therapeutic pathways. However, the identification of a true causal variant and the relevant gene product impacted is rarely straightforward. The lead single nucleotide polymorphism (SNP) typically indicates a chromosomal region usually with tens and sometimes thousands of SNPs in linkage disequilibrium (LD) (47), but it may also mark further-away regions with long-range chromatin interactions (48). For example, following the identification of a BP-associated SNP near the *ANTXR2* (anthrax toxin receptor 2) gene, *ANTXR2*$^{-/-}$ knockout rats were generated. The knockout rats exhibited similar BP to wildtype rats, at both basal and stimulated states with either angiotensin II infusion of high-salt diet (49). This can highlight he difficulty in identifying the causal variant or gene within a locus, particularly since this region also encompasses other genes of interest such as *FGF5* (fibroblast growth factor 5). It is often noted that follow-up mechanistic

studies are time- and resource-heavy endeavours. With this consideration, we expand on our previous *in silico* analyses, aiming to provide candidate genes for prioritisation in future mechanistic studies.

In silico analyses: BP loci pathway and tissue enrichment

Pathway and tissue enrichment analyses can give us a snapshot on the interactions and downstream consequences of blood pressure loci at a systems level. For the purposes of this review, we investigated all published validated blood pressure signals (lead + secondary) and their SNPs in high LD ($r^2 \geq 0.8$). SNPs were annotated to the nearest gene (within 5kb distance) using bedtools (v2.17) (50), and further characterized using ANNOVAR (51). We performed the following analyses on all the genes annotated to the BP-loci a) tissue enrichment using DEPICT (52); b) gene-set enrichment on pathways using GSEA (53); and c) a permutation based gene-set enrichment analysis on gene ontology (GO) terms using GOfuncR (54, 55).

Tissue enhancement analyses - DEPICT

In this tissue enhancement analysis, blood vessels, cardiac and adipose tissues remain in the top most enriched tissues (Table 1), being similar to those presented in Evangelou et al., (2018) (4). The addition of more recently published loci (25) to the analysis, led to an increase of enrichment in mostly all tissues described in previous studies, with the endocrine glands (adrenal cortex, adrenal glands and gonads) and the urogenital system presenting the largest differences between previous studies and the current analysis. The analysis highlighting adrenal tissue is unsurprising with hyperaldosteronism being a well-established secondary cause of hypertension (56), and primary hyperaldosteronism estimated to be responsible for up to 10% of hypertension cases (57, 58). The enrichment in the urogenital system appears driven by genes relating to the myometrium which predominantly consists of uterine smooth muscle cells, which share many similarities with vascular smooth muscle cells. Tissue enrichment analysis also showed for first time enrichment for the exocrine glands and tissues of the digestive system (Table 1). The underlying mechanism of the

enrichment observed in the digestive system may reflect the gastro-endocrine pathways which are discussed later on.

Gene-set enrichment analyses - GSEA

We revisited the pathway enrichment analysis performed using the Gene-set Enrichment Analysis (GSEA) software we conducted in 2015, where only 81 candidate genes in only eight enriched pathways were described (6). In the updated analysis the latest curated list of 1,630 candidate blood pressure genes annotated to gene-sets highlights more than 200 enriched pathways (Supplementary Table 2 GSEA). Whilst all eight pathways enriched in 2015 remain significant, the calcium signalling pathway and the Reactome gene set of genes involved in haemostasis present the strongest increase in overlapping genes, where both gene-sets are in the top 20 highest-ranked enriched gene-sets (Table 2).

The concept of pathways involving G-protein coupled receptors in blood pressure regulation is unsurprising. Among others, this includes receptors for adrenaline, endothelin, cholinergic transmission, serotonin, and histamine. However, there is also a notable contribution from gastro-endocrine regulation, such as gastric inhibitory polypeptide (*GIP*) and its receptor (*GIPR*), the cholecystokinin B receptor (*CCKBR*) and peptide YY (*PYY*) highlighting the interplay between blood pressure and other metabolic processes. From this selection of potential gastro-endocrine therapeutic targets, perhaps *GIP/GIPR* is the closest to translation to patient care with the recent development of a subcutaneous dual GIP/GLP1 agonist (59), currently intended for use in the management of diabetes. The role of *GIP* in the vasculature has been reviewed in detail by Pujadas and Drucker (60). In summary, various *in vitro* studies have shown GIP as pro-proliferative for endothelial cells (61), with increased endothelin-1 secretion (62). In a study of the development of experimental atherosclerosis, GIP infusion reduced lesion formation. Interestingly, GIP infusion did not affect blood pressure in this murine model (63). This is balanced against limited evidence in healthy volunteer studies of GIP

influencing blood flow in some vascular beds during hyperglycaemic phases of a two-step euglycaemic-hyperglycaemic clamp study (64).

There is also a collection of candidate genes involving G-protein coupled receptor pathways that emphasises the key role in neuroregulation of blood pressure, potentially involving gamma-aminobutyric acid (*GABBR1*), opioids (*OPRM1*), neuropeptides (*NPW*) and metabotropic glutamate receptors (*GRM4* and *GRM7*). While there is already some evidence that pharmacological modulation of GABA receptors may influence vascular tone (65), there is no literature thus far on the potential impact of Neuropeptide W and metabotropic glutamate receptors on blood pressure regulation. As G-coupled protein receptors, they represent potentially fruitful avenues for future research.

One other standout result from this pathway analysis is that 48 candidate genes for blood pressure are olfactory receptors. With the caveat that there is hitherto no evidence that genetic variants within olfactory receptors contribute to clinically relevant changes in taste/smell, it has been observed that patients with acquired hyposmia (smell loss) had significant increases in dietary salt intake (66). On a population level, care should be taken when interpreting these results as commonly prescribed antihypertensive and cholesterol-lowering drugs themselves may alter senses of taste and smell (67). Interestingly, there may be a role of olfactory receptors, when ectopically expressed (68), for example in the kidney, where in mouse models *Olfr78* responds to short chain fatty acids with renin secretion, and in turn contributes to blood pressure regulation (69). The human ortholog of *Olfr78* (*OR51E2*) is notably situated near its family member *OR51E1*, which is also blood pressure candidate gene (4).

Another grouping of would-be therapeutic targets may be from the extracellular matrix pathway. This includes gene products within the extracellular matrix itself (e.g. fibronectin, collagen, fibrillin, and thrombospondin), hormones (e.g. transforming growth factor, vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor) and enzymes that regulate the extracellular matrix (e.g. matrix metallopeptidases and ADAM metallopeptidase with thrombospondin enzymes). The potential for many of these candidate genes as therapeutic targets may stem from also being overlapping GWAS candidate genes for ischaemic heart disease (70, 71), allowing for therapeutic agents with the possibility of pleotropic effects.

Gene ontology analyses – GofuncR and REVIGO

Gene ontology enrichment analyses were visualized using REVIGO. This tool calculates the semantic similarity between GO terms and aids their visualization (72). There are two main clusters observed in the GO plot for biological processes (Figure 2). While one cluster (A) is unsurprising, including broad intracellular functions such as regulation of intracellular signal transduction, cell cycle, organelle organization, cellular localization, cellular process and transcription, the second cluster (B) may be more revealing in terms of potential new understanding of the biology underlying blood pressure regulation. Within this cluster, the five major gene ontology terms refer to biosynthesis of nucleobase-containing compounds, organic cyclic compounds, aromatic compounds, cellular nitrogen compounds and heterocyclic compounds. While there are commonly recognised enzymes within these groups contributing to the regulation of blood pressure (e.g. adenylate and guanylate cyclases, and adenosine kinases), there are three other enzymes here which we felt were worth highlighting.

Carbamoyl-phosphate synthase 1 (*CPS1*) is the enzyme that catalyses the rate-limiting step in the urea cycle and L-citrulline production. This reaction allows vascular endothelial cells to recycle the by-product of nitric oxide synthesis, L-citrulline, by using components of the urea cycle. The naturally occurring T1405N variation within *CPS1* is already known to vascular dynamics in an experimental setting (73). *MTAP* (encoding S-methyl-5'-thioadenosine phosphorylase) is also an interesting potential target as an important in the salvage of adenine and methionine. It also resides in the 9p21 region, with the strongest GWAS signal for coronary artery disease and myocardial (74, 75). Mice heterozygous for *MTAP* shows increased predisposition to atherosclerotic lesions (76), which may allow for the development of therapeutic options that has pleotropic effects. It should however be recognised that there are also multiple other genes of interest in the 9p21 region, including the tumour suppressor genes *CDKN2A* and *CDKN2*, and the long non-coding RNA *ANRIL*. *DBH* encodes dopamine β-hydroxylase which catalyses the conversion of dopamine to norepinephrine. It is predominantly expressed in neural and adrenal tissues, and is involved in noradrenergic transmission of central and peripheral nervous systems. More recently, its expression has been detected in

endothelial cells, where dopamine β-hydroxylase inhibition reduces *in vitro* angiogenesis (77). This enzyme also potentially plays a role in vascular wall remodelling, where *DBH*$^{-/-}$ mice has attenuated vessel injury-induced medial hypertrophy compared to wildtype littermates (78).

Multi-trait BP associations

BP-variants have been reported to have many other genetic associations (4, 6, 79). Here, we interrogated the GWAS Catalog for all traits associated with the BP-variants (n=45.9k) (80). After applying a stricter p-value association threshold (–log10 p-value < 10.5), these results were manually curated and summarized on the mapped genes. After excluding blood pressure traits (e.g. SBP, DBP, and PP), cardiovascular disease, red blood cell counts, body mass index and type 2 diabetes were the traits with increased numbers of BP-variant associations. The co-occurrence observed between BP variants and other traits could be highlighting pleiotropy effects, where the associated variant impacts overlapping causal pathways for each phenotype. However, this co-occurrence could also possibly be due to BP being affected by other traits. Figure 3 shows all BP loci with more than five associations with at least four traits. Two clusters of interest can be observed, with several genes demonstrating potential such as cholesterol levels, diabetes, obesity, and cardiovascular disease itself. These genes include *APOE, LDLR, FGF5, SLC39A8*, *FUT2, FTO and SH2B3-ATXN2*. Our group has previously demonstrated the role of the blood-pressure associated non-synonymous polymorphism at *SLC39A8* influencing *in vitro* intracellular cadmium accumulation and subsequent toxicity (81).

The landscape and future of BP genetics

The genetic research community realised at early stages of GWAS that the sample sizes needed to be very large and also dependent on the number of SNPs been tested (82). As the sample sizes increased, substantial number of loci associated to traits and disease started to be uncovered. The ~1,477 validated blood pressure associations reported to date have been achieved by analysing over 1 million individuals (4, 7-29). Yet, approximately 73% of the genetic variance remains unaccounted for (4).

The genetics of hypertension and blood pressure prove to be highly complex. The associated BP loci are localized across the whole genome, and their annotations revealed enrichment in some obvious blood pressure pathways, but they also revealed hundreds of other pathways and tissues with no direct known connections to BP. Here, we only observed two pathways previously enriched (the calcium signalling pathway and genes involved in haemostasis) maintaining their status as "top" enriched pathways. These discoveries are contrary to the initial idea that the unravelling of new loci would first fill in the gaps of the already known pathways, and instead we observe the enrichment of systems and tissues with no prior knowledge on BP regulation. However, BP loci have been found to have multiple associations across traits (e.g. Type II diabetes, obesity, and cholesterol among others) showing strong evidence of pleiotropy (83) and this is challenging for the characterization of loci specific to BP.

The number of genes and variants uncovered by GWAS means there is a great challenge for traditional functional studies. There seems to be only a few successful follow up studies on candidate genes identified through GWAS relative to the numerous loci reported. However, this should be viewed in context of the lag-time between GWAS and publication of mechanistic studies that is often in the range of 3-5 years. With that, it may be reasonable to suggest more mechanistic studies are to follow with the massively expanded candidate gene list. *In silico* follow-up, the utilization of resources such as ENCODE (84) and GTEx (85), are becoming increasingly more important, where the next task is to prioritise the genes that may be most likely to bear fruitful clinical translation. For example, the application of deep neural networks to prioritise blood pressure genes, converging data from a range of genomic annotation resources on the blood pressure associated genes identified by GWAS; providing model training and testing datasets. Exploring the systems biology of these prioritised genes may offer new mechanistic insights and therapeutic targets.

BP genetic associations have shed light into mechanisms and the architecture of blood pressure. However, there are two main drawbacks on most of these GWAS studies, 1) they are largely based on individuals with European descent and 2) due to most GWAS based on imputed SNP arrays, where imputation performs poorly in regions with low LD (86), they are generally restricted to the analysis

of common variants (minor allele frequency > 1%). Expanding research into rare variants proved to be extraordinarily fruitful for Wainshctein and colleagues, who succeeded to recover all the heritability from height using whole-genome sequencing, but there has been limited research to date on the impact of rare variants on blood pressure regulation (27, 28). The missing heritability in height was unearthed from rare variants in regions of low LD (87). The availability of whole genomes and initiatives such as Genomics England could pave the way to investigate all variants, including structural and non-coding variants, allowing us to expand our knowledge and discover the hidden genetic variance in blood pressure.

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Conflict of Interest Statement

No conflicts of interest to disclose

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Figure 1. Timeline of validated blood pressure GWAS associations of the last 10 years. The total sample size (left vertical axis) used for the discovery analysis is represented by the blue long-dotted line, whilst the replication sample size represented by the green short-dotted line. The total number of loci is represented by the bars (right vertical axis). The yellow bars represent the number of novel loci reported without independent replication and in pink the total number of novel loci with replication. The numbers in parenthesis after the study (horizontal axis) show the numbers for the novel without replication and the novel loci with replication respectively (yellow/pink).

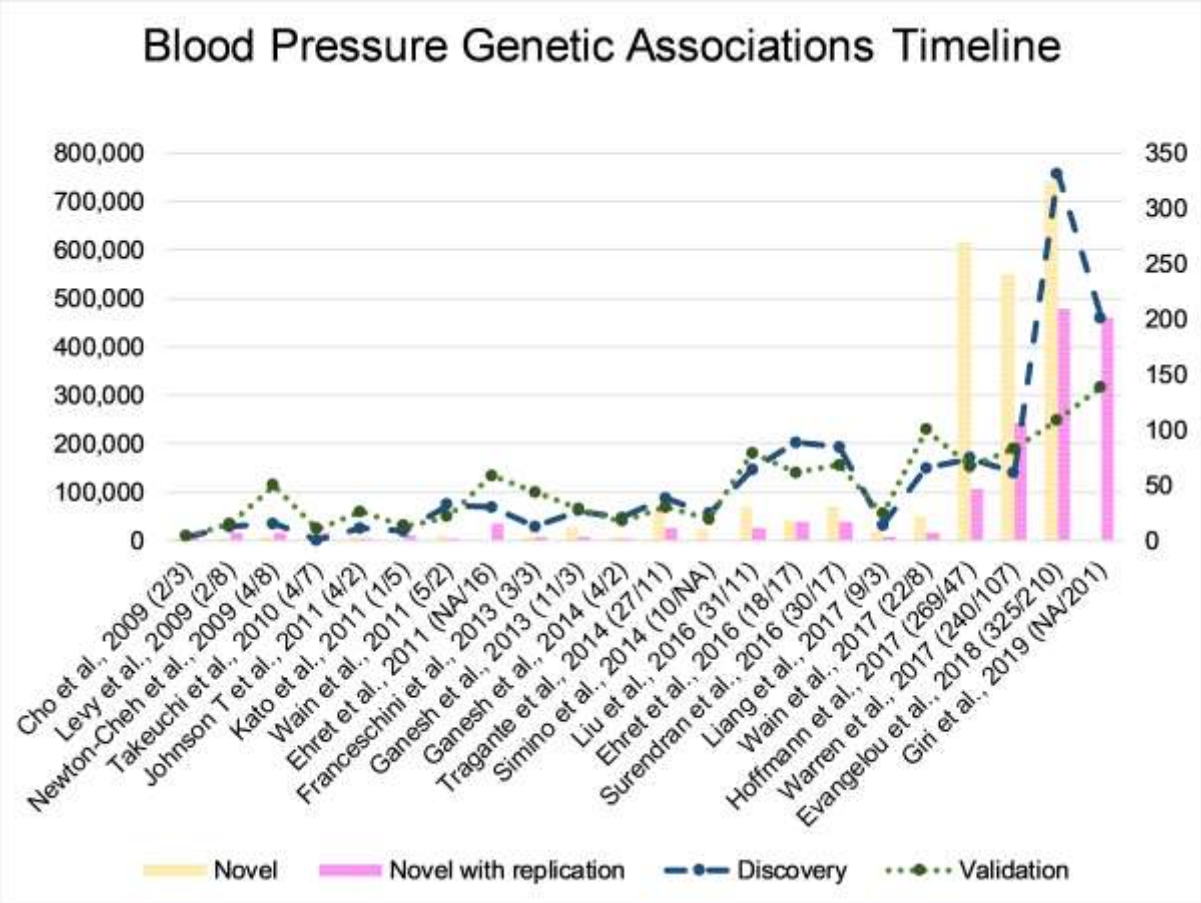


Figure 2. Gene ontology enrichment analysis. The REVIGO graph displays the biological process GO enrichment. Each sphere represents a GO term coloured by the GOfuncR enrichment in the –log10(p-value) scale. The semantic similarity of each GO term is represented by the position of each sphere on the graph. Plot size (sphere size) indicates the frequency of each GO term in which is found in the gene ontology database (i.e. the larger the sphere is the more general the term is). Two clusters are highlighted: A) includes broad intracellular functions such as regulation of intracellular signal transduction, cell cycle, organelle organization, cellular localization, cellular process and transcription; B) the second cluster revealing terms of potential new understanding of the biology underlying blood pressure regulation. Within this cluster, the five major gene ontology terms refer to biosynthesis of nucleobase-containing compounds, organic cyclic compounds, aromatic compounds, cellular nitrogen compounds and heterocyclic compounds.

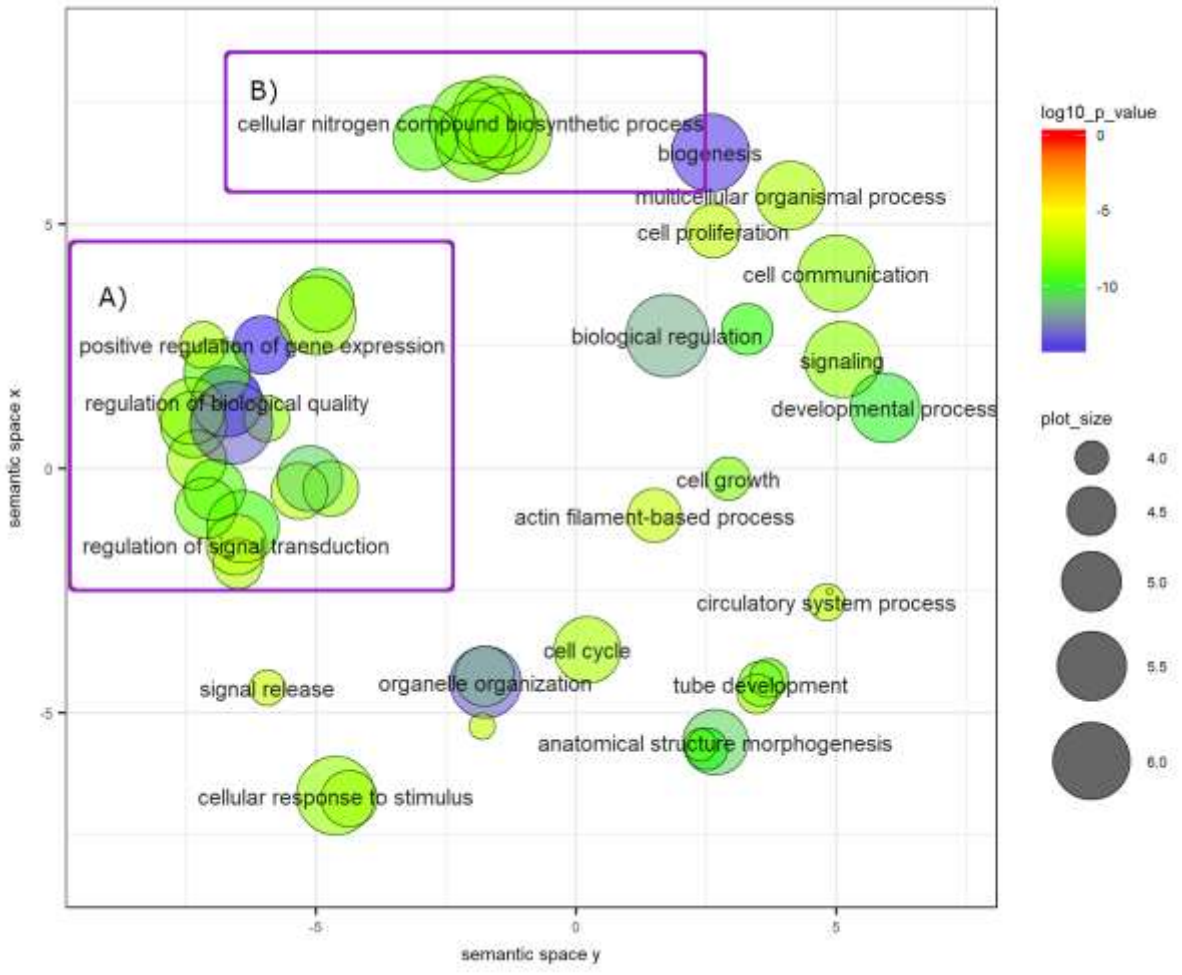
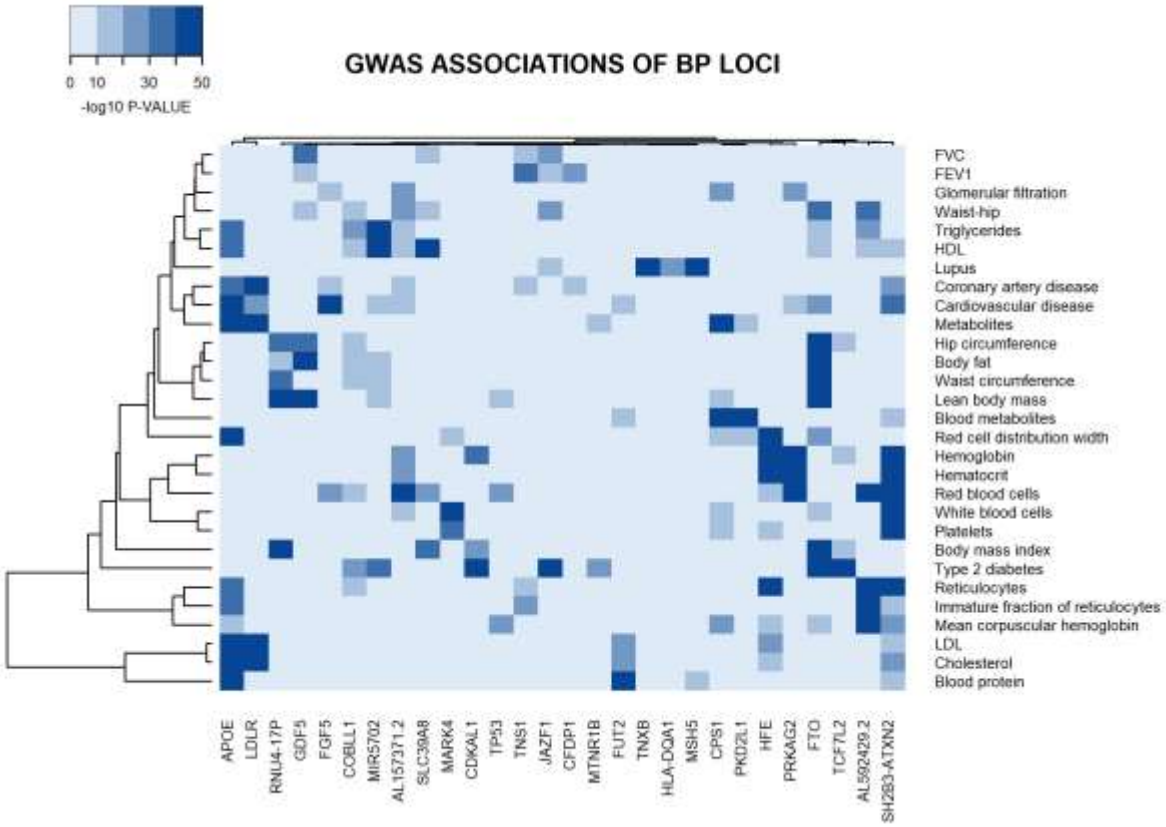


Figure 3. Multi-trait associations of blood pressure loci. BP loci were searched in the GWAS catalog to investigate the pleiotropy of the loci. The heatmap displays a subset of the BP loci with five or more gene associations with at least four traits (excluding blood pressure traits). Ward hierarchical clustering was applied on rows and columns (genes and traits).



Tables

Table 1 DEPICT tissue enrichment results across all validated blood pressure loci to date and compared to the reported enrichment in Evangelou et al (2018). Results are shown for tissue enrichments with an FDR < 0.05 ordered by nominal -log10 p-value

Name	MeSH second level term	Nominal -log10(p-value)	Evangelou et all -log10(p-value)
Myometrium	Genitalia	14.66	9.50
Arteries	Blood Vessels	13.72	10.84
Cartilage	Cartilage	10.53	9.03
Adipose Tissue	Connective Tissue	10.36	8.01
Genitalia Female	Genitalia	10.04	4.89
Subcutaneous Fat	Connective Tissue	9.62	7.56
Adipose Tissue White	Connective Tissue	9.62	7.56
Genitalia	Genitalia	9.59	4.48
Uterus	Genitalia	9.48	4.88
Joint Capsule	Skeleton	9.19	7.12
Joints	Skeleton	9.19	7.12
Synovial Membrane	Skeleton	9.19	7.12
Subcutaneous Fat Abdominal	Connective Tissue	8.60	6.09
Abdominal Fat	Connective Tissue	8.60	6.09
Endocrine Glands	Endocrine Glands	8.38	3.67
Fallopian Tubes	Genitalia	7.86	3.83
Ovary	Genitalia	7.76	3.30
Adnexa Uteri	Genitalia	7.75	3.31
Serous Membrane	Membranes	7.26	4.76
Gonads	Endocrine Glands	7.07	2.92
Aortic Valve	Heart	6.97	4.91
Heart Valves	Heart	6.97	4.91
Endometrium	Genitalia	6.97	3.44
Adipocytes	Connective Tissue Cells	6.03	4.24
Adrenal Glands	Endocrine Glands	5.76	2.99
Adrenal Cortex	Endocrine Glands	5.70	3.44
Blood Vessels	Blood Vessels	5.19	4.85
Stomach	Gastrointestinal Tract	5.12	3.37
Upper Gastrointestinal Tract	Gastrointestinal Tract	5.09	3.23
Heart	Heart	4.89	4.57
Stromal Cells	Connective Tissue Cells	4.45	3.56
Serum	Blood	4.40	2.92
Muscle Smooth	Muscles	4.38	3.45
Heart Atria	Heart	4.17	3.82
Heart Ventricles	Heart	4.10	4.03
Veins	Blood Vessels	4.09	3.67
Lung	Lung	3.89	2.40
Atrial Appendage	Heart	3.87	3.43
Pancreas	Pancreas	3.70	3.81
Mesenchymal Stem Cells	Stem Cells	3.59	2.97
Chondrocytes	Connective Tissue Cells	3.54	2.00
Fibroblasts	Connective Tissue Cells	3.52	2.45
Umbilical Veins	Blood Vessels	3.50	3.13
Portal System	Blood Vessels	3.50	3.13

Esophagus	**Gastrointestinal Tract**	**3.39**	**2.00**
Urinary Bladder	**Urinary Tract**	**3.26**	**2.84**
Chorion	**Membranes**	**3.16**	**2.68**
Extraembryonic Membranes	**Membranes**	**3.16**	**2.68**
Ileum	**Gastrointestinal Tract**	**3.09**	**3.15**
Endothelial Cells	**Epithelial Cells**	**3.09**	**2.80**
Urinary Tract	**Urinary Tract**	**3.02**	**3.21**
Osteoblasts	**Connective Tissue Cells**	**3.01**	**3.46**
Exocrine Glands	**Exocrine Glands**	**2.92**	
Kidney Cortex	**Urinary Tract**	**2.89**	**2.07**
Prostate	**Exocrine Glands**	**2.80**	
Kidney	**Urinary Tract**	**2.76**	**2.97**
Intestine Small	**Gastrointestinal Tract**	**2.75**	**2.81**
Genitalia Male	**Genitalia**	**2.61**	
Cecum	**Gastrointestinal Tract**	**2.46**	
Islets of Langerhans	**Pancreas**	**2.13†**	
Cervical Vertebrae	**Skeleton**	**2.06†**	
Spine	**Skeleton**	**2.01†**	
Cervix Uteri	**Genitalia**	**1.70†**	
Skin	**Skin**	**1.70†**	
Lower Gastrointestinal Tract	**Gastrointestinal Tract**	**1.70†**	

FDR: False discovery rate; Significant tissue enrichment threshold set at an FDR < 5%. † MeSH terms with an FDR ≥ 1% and below 5%, all others represent an FDR < 1% MeSH term: Medical Subject Heading term.

Table 2. GSEA: Gene set enrichment analysis. Results shown for the top 20 enriched gene sets. All sets observed with an at an FDR threshold below or equal to 0.05.

Gene Set Name	# Ge	Description	# Ge	k/ K	p-valu
REACTOME_SIGNALING_BY_GPCR	92	Genes involved in Signalling by GPCR	107	0.1	4.87 E
REACTOME_GPCR_DOWNSTREAM_SIG NALING	80	Genes involved in GPCR downstream signalling	98	0.1	2.32 E
KEGG_PATHWAYS_IN_CANCER	32	Pathways in cancer	51	0.1	8.23 E
REACTOME_DEVELOPMENTAL_BIOLO GY	39	Genes involved in Developmental Biology	54	0.1	3.07 E
NABA_MATRISOME	10 28	Ensemble of genes encoding extracellular matrix and extracellular matrix-associated proteins	95	0.0 92	3.06 E-
REACTOME_OLFACTORY_SIGNALING_ PATHWAY	32	Genes involved in Olfactory Signalling Pathway	45	0.1	1.06 E
KEGG_PROSTATE_CANCER	89	Prostate cancer	23	0.2	4.72 E
REACTOME_HEMOSTASIS	46	Genes involved in Hemostasis	54	0.1	3.28 E
KEGG_OLFACTORY_TRANSDUCTION	38	Olfactory transduction	48	0.1	8.33 E
KEGG_DILATED_CARDIOMYOPATHY	92	Dilated cardiomyopathy	23	0.2	1.02 E
KEGG_HYPERTROPHIC_CARDIOMYOP ATHY_HCM	85	Hypertrophic cardiomyopathy (HCM)	22	0.2 58	1.62 E-
KEGG_ARRHYTHMOGENIC_RIGHT_VE NTRICULAR_CARDIOMYOPATHY_ARV C	76	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	20	0.2 63 2	1.45 E- 12
NABA_CORE_MATRISOME	27 5	Ensemble of genes encoding core extracellular matrix including ECM glycoproteins, collagens and	38	0.1 38	9.75 E-
KEGG_WNT_SIGNALING_PATHWAY	15	Wnt signalling pathway	27	0.1	4.32 E
KEGG_CHRONIC_MYELOID_LEUKEMI A	73	Chronic myeloid leukemia	19	0.2	6.48 E
KEGG_FOCAL_ADHESION	20	Focal adhesion	31	0.1	6.60 E
KEGG_MAPK_SIGNALING_PATHWAY	26	MAPK signalling pathway	35	0.1	3.43 E
KEGG_CALCIUM_SIGNALING_PATHW AY	17	Calcium signalling pathway	28	0.1	4.21 E

KEGG_SMALL_CELL_LUNG_CANCER	**84**	**Small cell lung cancer**	**19**	**0.2**	**9.28**
KEGG_ADHERENS_JUNCTION	**75**	**Adherens junction**	**18**	**0.2**	**1.01**

Abbreviations

Blood pressure (BP)

Cardiovascular disease (CVD)

Diastolic blood pressure (DBP)

Gene ontology (GO)

Gene-set Enrichment Analysis (GSEA)

Genetic Epidemiology Research on Adult Health and Aging cohort (GERA)

Genome-wide association studies (GWAS)

International Consortium of Blood Pressure (ICBP)

Linkage disequilibrium (LD)

MAF minor allele frequency

Million Veteran Program (MVP)

Single nucleotide polymorphism (SNP)

Systolic blood pressure (SBP)

UK Biobank (UKB)