Genomic Determinants of Hypertension With a Focus on Metabolomics and the Gut Microbiome

Panayiotis Louca,[1] Cristina Menni,[1] and Sandosh Padmanabhan[2]

Epidemiologic and genomic studies have progressively improved our understanding of the causation of hypertension and the complex relationship with diet and environment. The majority of Mendelian forms of syndromic hypotension and hypertension (HTN) have all been linked to mutations in genes whose encoded proteins regulate salt–water balance in the kidney, supporting the primacy of the kidneys in blood pressure regulation. There are more than 1,477 single nucleotide polymorphisms associated with blood pressure and hypertension and the challenge is establishing a causal role for these variants. Hypertension is a complex multifactorial phenotype and it is likely to be influenced by multiple factors including interactions between diet and lifestyle factors, microbiome, and epigenetics. Given the finite genetic variability that is possible in humans, it is likely that incremental gains from single marker analyses have now plateaued and a greater leap in our understanding of the genetic basis of disease will come from integration of other omics and the interacting environmental factors. In this review, we focus on emerging results from the microbiome and metabolomics and discuss how leveraging these findings may facilitate a deeper understanding of the interrelationships between genomics, diet, and microbial ecology in humans in the causation of essential hypertension.

Keywords: blood pressure; diet; genomics; hypertension; metabolomics; metagenomics; microbiome; salt.

doi:10.1093/ajh/hpaa022

The major risk factor underpinning cardiovascular (CV) diseases is hypertension which directly accounts for up to 10.5 million of the 18 million CV deaths that occur annually or 12% of total global deaths.[1] By 2025, hypertension is projected to affect more than 1.5 billion people globally and modeling indicates that effective control of hypertension through improving treatment rates and lifestyle measures could save more lives than any other clinical intervention.[2] Epidemiologic and genomic studies have progressively improved our understanding of the causation of hypertension and the complex relationship with diet and environment. Family studies have consistently demonstrated a genetic component influencing blood pressure (BP) and hypertension (HTN). The Montreal adoption study[3] demonstrated correlation coefficients of 0.38 and 0.16 between biological and adoptive sibs, respectively, indicating that 61% of the population correlation for systolic BP was due to shared genes and 39% to environment shared by both parents and children. The heritability of clinic systolic BP and diastolic BP is around 15–40% and 15–30%, respectively, whereas for ambulatory night-time systolic and diastolic BP the heritabilities are, respectively, 32–70% and 32–50%.[4,5]

The identification of rare mutations in genes causing monogenic forms of HTN come from linkage analysis of pedigrees exhibiting a Mendelian pattern of inheritance of the BP phenotype. The study of monogenic syndromes has expanded our understanding of some of the pathways that regulate blood pressure. Table 1 summarizes the different forms of monogenic hypertension, their key features, and causal genes and they are detailed in recent authoritative reviews.[6–8] The majority of Mendelian forms of syndromic hypotension and HTN have all been linked to mutations in genes whose encoded proteins regulate salt–water balance in the kidney, supporting the primacy of the kidneys in BP regulation.[8] While these monogenic mutations are germline mutations which are inherited, there is now recognition of somatic mutations that cause aldosteronism and hypertension. A gain-of-function somatic mutation in a K^+ channel, *KCNJ5*, which results in membrane depolarization and enhanced aldosterone production, is a common genetic defect noted for ~40% of aldosterone-producing adenomas (APAs).[6] Mutations in three other genes, encoding the α-subunit of Na^+-K^+-ATPase (*ATP1A1*); *ATP2B3*, a plasma membrane Ca^{2+}-ATPase homologous to the sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPases (SERCA); and *CACNA1D*, encoding an L-type Ca^{2+} channel CaV1.3, are observed in ~7% of the cases.[6]

The era of genome-wide association studies (GWAS) commenced in 2007, resulting in 4,346 publications and 166,103 associations for a wide range of polygenic traits including hypertension and BP (https://www.ebi.ac.uk/gwas/home). The hypothesis underlying GWAS is that common variations (single nucleotide polymorphisms (SNPs)) can have significant impact on common traits and thence

Correspondence: Sandosh Padmanabhan (sandosh.padmanabhan@glasgow.ac.uk).

Initially submitted January 26, 2020; date of first revision February 10, 2020; accepted for publication February 11, 2020; online publication February 15, 2020.

[1]Department of Twin Research, King's College London, London SE1 7EH, UK; [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G12 8TA, UK.

Table 1. Monogenic forms of hypertension and hypotension

Syndrome	Gene	BP	Renin	Aldosterone	Serum K^+	Catecholamines	Treatment
Liddle syndrome MIM 177200	*SCNN1B* *- SCNN1G*	↑↑	↓↓	↓↓	↓↓	—	Amiloride or triamterene
Gitelman syndrome MIM 263800	*SLC12A3*	↓↓	↑↑	-	↓↓	—	Oral potassium and magnesium supplementation with adequate salt and water
Bartter syndrome MIM 601678, 241200, 602522, 613090, 300971	*SLC12A1* *KCNJ1* *CLCNKB* *BSND* *CLCNKA* *CLCNKB* *MAGED2, MAGED, BARTS5*	↓↓	↑↑	↑↑	↓↓	—	Potassium supplementation and use of cyclooxygenase inhibitors, angiotensin converting enzyme (ACE)-inhibitors and potassium sparing diuretics
Familial hyperaldosteronism (FH) MIM 103900, 605635, 613677 "glucocorticoid remediable aldosteronism"	*CYP11B1* *KCNJ5*	↑↑	↓↓	↑↑	↓	—	Dexamethasone
Apparent mineralocorticoid excess (AME) MIM 218030	*HSD11B2*	↑↑	↓↓	↓↓	↓↓	—	Low sodium diet and spironolactone
Pseudohypoaldosteronism (PHA) MIM 177735, 614491, 614492, 614495, 614496 "Gordon syndrome"	*NR3C2* *WNK4* *WNK1* *KLHL3* *CUL3*	↓↓ ↑↑	↑↑ ↓↓	↑↑ ↑	↑↑ ↑	— —	Thiazide diuretics, prostaglandin inhibitors, alkalizing agents, and potassium-binding resins
Sporadic aldosterone-producing adenoma (APA), or primary aldosteronism	*KCNJ5* *ATP1A1* *CACNA1D* *ATP2B3*	↑↑	↓↓	↑↑	↓	—	Surgery, aldosterone antagonists
Hypertension exacerbation in pregnancy MIM 605115	*NR3C2*	↑↑	↓↓	↓↓	↓	—	Spironolactone contraindicated; sodium chloride treatment
11β-hydroxylase MIM 202010	*CYP11B1*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy
3β-hydroxysteroid dehydrogenase OMIM 613890	*HSD3B2*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy
17α-hydroxylase deficiency MIM 202110	*CYP17A1*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy, potassium sparing diuretics
21-Hydroxylase deficiency MIM 201910	*CYP21A2*	↑↑	↓↓	↓↓	↓↓	—	Glucocorticoid therapy
Hypertension and brachydactyly syndrome MIM 112410 "Bilginturan syndrome"	*PDE3A*	↑↑	—	—	—	—	Possible role for PDE3 inhibition
Paragangliomas (PGL1-5) MIM 168000, 601650, 605373, 115310, 614165	*SDHD* *SDHAF2* *SDHC* *SDHB* *SDHA*	↑↑	—	—	—	↑↑	Surgery, adrenergic blockers (alpha blockade followed by beta-blockade)
von Hippel–Lindau syndrome MIM 193300	*VHL*	↑↑	—	—	—	↑↑	
Multiple endocrine neoplasia, type IIA MIM 171400	*RET*	↑↑	—	—	—	↑↑	
NOS3-pregnancy-induced hypertension MIM +163729	*NOS3*	↑↑	—	—	—	↑↑	

human health (common disease/common variant hypothesis). There are more than 1,477 SNPs associated with blood pressure, but these SNPs account for about a third of the estimated 30–50% heritability of blood pressure and explain just about 5.7% of the population phenotypic variance of SBP.[8,9] Multiple reasons have been invoked to explain the missing heritability of blood pressure including gene–gene interactions, gene–environment interactions, diet and lifestyle factors, microbiome, and epigenetics. Furthermore, establishing a causal role for common SNPs from GWAS in essential hypertension has been challenging. Hypertension is a complex multifactorial phenotype and it is likely to be influenced by multiple factors including interactions between these factors. Genome-wide association studies which only look at single marker associations are blind to this complex aspect of hypertension pathogenesis. Given the finite genetic variability that is possible in humans, it is likely that incremental gains from single marker analyses have plateaued and a greater leap in our understanding of the genetic basis of disease will come from integration of other omics and the interacting environmental factors.[10]

In this review, we focus on emerging results from the microbiome and metabolomics and discuss how leveraging these findings may facilitate a deeper understanding of the interrelationships between genomics, diet and microbial ecology in humans in the causation of essential hypertension and identify new interventions to manage hypertension.

INSIGHTS FROM GENOMICS AND DIET ON HYPERTENSION

There is consistent epidemiologic evidence between dietary sodium intake and blood pressure.[11,12] The majority of the Mendelian forms of hypertension and hypotension exert their effect by perturbing renal sodium handling pathways (Table 1).[8] A classic example is Gitelman syndrome (GS), which is a salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria.[13] With a prevalence at 1–10 per 40,000, and potentially higher in Asia, GS is arguably the most frequent inherited tubulopathy. GS is caused by biallelic inactivating mutations in the *SLC12A3* gene encoding the thiazide-sensitive sodium chloride cotransporter (NCC), is usually detected in adolescence or adulthood and exhibits high phenotypic variability.[13] Affected individuals have low blood pressure and may present with salt craving (i.e., preference for salty food or a salted treat during childhood) or in many cases diagnosed incidentally in asymptomatic adults. The first GWAS of gene–salt interaction was conducted in 1,876 Chinese participants of the Genetic Epidemiology Network of Salt-Sensitivity (GenSalt) study with dietary salt intake imputed from overnight urine collections.[14] Single SNP and gene-based analyses identified signals in the following genes—*UST*, *CLGN*, *MKNK1*, *C2orf80*, *EPHA6*, *SCOC-AS1*, *SCOC*, *MGAT4D*, *ARHGAP42*, *CASP4*, and *LINC01478* for gene–sodium intake interaction. A cross-sectional study of 2,728 male Japanese adults where dietary salt consumption was estimated using electronically collected meal purchase data from cafeteria showed a nominally significant association between salt consumption and the rs5063 SNP in the *NPPA* gene.[15]

The most compelling example of gene–salt interaction on blood pressure comes from a GWAS study that identified a 5′-promoter SNP, rs13333226 near the Uromodulin gene (*UMOD*) which is almost exclusively expressed in the thick ascending limb of the loop of Henle in the kidney.[16] The minor G allele of this SNP, rs13333226, was associated with a lower risk of hypertension and reduced urinary UMOD excretion. The main sodium transporter in thick ascending limb is NKCC2 which is blocked by the commonly used loop-diuretic furosemide. Trudu *et al.*[17] showed furosemide treatment significantly enhanced natriuresis and reduced BP levels both in the transgenic mice and in the hypertensive individuals homozygous for the UMOD increasing allele. This has identified a novel pathway of blood pressure and renal function regulation through possible interaction with the sodium transporter NKCC2 in the thick ascending limb of the loop of Henle. This is now the basis of a clinical trial (www.clinicaltrials.gov, NCT03354897) to reposition a loop diuretic in the hypertension care pathway.

There are only a few studies that looked at diet–gene interactions. A study of 723 obese adults showed the risk allele (rs16147-C) in neuropeptide Y (*NPY*) gene was associated with a greater reduction of BP phenotypes in response to low-fat diet, whereas an opposite genetic effect was observed in response to high-fat diet.[18]

THE MICROBIOME AND HYPERTENSION

The human body is colonized by hundreds of trillions of microbes, which collectively possess hundreds of times as many genes as coded in the human genome and is collectively referred to as the "microbiome."[19] The microbiota is involved in energy harvest and storage, as well as in a variety of metabolic functions such as fermenting and absorbing undigested carbohydrates and interaction with the immune system, providing signals for the normal development of immune functions. Advances in high-throughput sequencing technology has allowed for the identification of human-associated microorganisms without the need for culturing.[20] Under physiological conditions, there is a balance between the intestinal bacteria and the host. Disruption of this intricate system (dysbiosis) has been implicated in many human diseases, including cardiometabolic diseases and hypertension.[21–28] The gut microbiota can produce a range of bioactive metabolites, such as enzymes, peptides, antibiotics, amino acids, hormones, and vitamins that can mediate host receptor activation, signaling, and immunomodulatory effects and several of these metabolites have been linked with CV diseases and drug response.[26,29–31] There is compelling evidence that the gut microbiome is modified by diet and this has implications on both health and precision medicine strategies of this is of relevance in hypertension.[32,33]

Metabolomics studies have so far identified numerous circulating metabolites (Supplementary Table) associated with BP and HTN in cohorts of different ethnicities, gender, and age range. The metabolites identified fall into these broad classes: 39% lipids, 27% amino acids, 19% xenobiotic, 7% carbohydrates, 2% energy, 2% nucleotide, 2% peptide, and 2% cofactors and vitamins[26,27,34–44]. These include 24

metabolites produced by the gut microbiome and released into the blood stream. We now describe the most promising metabolites.

HEXADECANEDIOATE

The dicarboxylic acid hexadecanedioate was significantly associated both with BP and mortality indicating a sustained detrimental effect of higher levels of the metabolite through increased BP.[26] Evidence for a causal role was obtained by feeding this compound to rats resulting in significant increases in BP, indicating that it is not a by-product, but a cause of high blood pressure. Higher hexadecanedioate are associated with stroke in the Women's Health Initiative cohort[45] and the Atherosclerosis Risk In Communities study.[46] GWAS showed hexadecanedioate levels to be associated with genetic variants in *ADH1B* and *SLC01B1*,[47,48] *In vitro* studies confirmed hexadecanedioate was a novel substrate of OATP1B1 (encoded by SLCO1B1) as well as OAT1 and OAT3 indicating that is an endogenous biomarker of OATP1B1 function.[49] A single copy of a loss-of-function variant in *SLC01B1* increased serum hexadecanedioate levels and resulted in a 29% increased risk of heart failure incidence in an African American cohort.[50] A potential pharmacogenetic application of hexadecanedioate is suggested by correlations observed between BP reduction after amlodipine administration with reductions in plasma hexadecanedioate levels.[51] Hexadecanedioic acid is a long chain dicarboxylic acid which is generated during fatty acid ω-oxidation and thence metabolized by β-oxidation in peroxisomes. ω-oxidation is a minor metabolic pathway that occurs in the smooth endoplasmic reticulum and also contributes to 5–10% of total fatty acids metabolism in the liver. Human ω-hydroxylases are all members of the cytochrome P450 family specifically CYP4A and CYP4F. Following addition of the ω-hydroxyl group, the fatty acid becomes a substrate for alcohol dehydrogenase (ADH) which generates an oxo-fatty acid, followed by generation of the corresponding dicarboxylic acid via the action of aldehyde dehydrogenases (ALDH). Furthermore, gene expression of *ADH1A*, *ADH1B* and *CYP4* involved in ω-oxidation pathways were strongly correlated to hexadecanedioate levels indicating a endogenous biomarker for alcohol's effect on BP.[50,52,53] Tang *et al.*[54] recently associated hexadecanedioate with *Lachnospira*, a specific microbial taxon, and linked the metabolite with vitamin E, folate, lutein, zeaxanthin, cheese, and tomato intakes.

SHORT-CHAIN FATTY ACIDS

Short-chain fatty acids (SCFA) are microbially mediated metabolic by-product of dietary fiber fermentation in the colon subsequently absorbed into the bloodstream of the host.[55] SCFAs can bind to and activate host receptors (Gpr41, Gpr43, Gpr109a, and Olfr78), thereby acting as a route of "communication" between gut microbial metabolism and host physiology. The most common SCFA are acetate, propionate, and butyrate, which account for ~80% of all SCFAs and are of significant biological interest, as they have very tangible roles in modulating direct and indirect BP pathways.[56] Studies in animal models with interventions that manipulated levels of SCFAs showed that an increase in SCFA was associated with lower BP.[24,57] Decreases in bacterial taxa thought to produce short chain fatty acids have been reported in two different rat models of hypertension to increase BP,[28] while another study found that rats which received a microbial transplant which increased blood pressure had higher levels of plasma acetate.[58] Chronic acetate intake in animal models was shown to reduce both SBP and DBP by 21 mm Hg, and improved cardiac function in line with the mitigation of inflammatory disorders.[24] Propionate has been shown to increase BP in animal models by stimulating renin secretion through Olfr78 and Gpr41.[57] When wild-type and Olfr78 KO mice were treated with a mixture of antibiotics with blood pressure measurements, wild-type mice had a mild increase in blood pressure on antibiotics, Olfr78 KO mice had a much more dramatic increase indicating Olfr78 and Gpr41 normally act in physiologically opposite roles and balance out wide swings in BP.[57] Additionally, there is evidence for GPR109A and GPR43 activation by SCFAs in controlling inflammation and promoting epithelial repair in the colon with implications for BP regulation through inflammatory pathways.[59] Thus, the role of SCFAs in blood pressure regulation is multi-faceted, involves at least two different SCFA receptors, multiple species of bacteria, and multiple host tissues.[60] There is data showing variants in the host genome can influence the composition of the gut microbiota[61] and causal role for SCFA in metabolic disease was evaluated using Mendelian randomization that showed host genetic-driven increase in gut production of the SCFA butyrate is associated with improved insulin response following an oral glucose test.[62] This opens possibilities for studies to assess the causal relationship between SCFA and blood pressure in the future.

TRIMETHYLAMINE N-OXIDE

Similar to SCFAs, trimethylamine N-oxide (TMAO) is generated by gut microbes from choline, betaine, and carnitine through dietary phosphatidylcholine oxidation. The plasma level of TMAO is determined by several factors including diet, gut microbial flora, drug administration and liver flavin monooxygenase activity.[63] There is accruing evidence that TMAO is associated with inflammation and atherosclerosis, though it is unclear whether it is proatherogenic or just a biomarker of increased cardiovascular disease.[64,67] In Sprague-Dawley rats, infusion of TMAO did not affect BP in normotensive animals, but it prolonged the hypertensive effect of Ang II.[68] Genomic studies indicate that TMAO levels are not determined by genetic variation, rather they reflect the influence diet and gut microbiota.[69]

4-HYDROXYHIPPURATE

A microbial metabolite of benzoate, 4-hydroxyhippurate, is the most widely detected urinary metabolite of host-microbial origin in humans and its urinary concentrations are modulated by diet, stress, disease, and microbial presence or activity.[34] Zheng *et al.*[35] showed 4-hydroxyhippurate was associated with incident hypertension in a small study of 896 black normotensive subjects.

INDOLES

Indoles are products of gut bacterial metabolism of tryptophan and have been shown to impact homeostatic processes including inflammatory pathways,[70] gut barrier permeability,[71] and impact arterial blood pressure pathways via the inhibition of serotonin receptor blockers.[72]

PHENYLACETYLGLUTAMINE

Phenylacetylglutamine is involved in amino acid metabolism and has been associated with CV disorders including diastolic blood pressure, incidence of heart failure,[73] carotid femoral pulse wave velocity,[74] and overall mortality in chronic kidney disease patients.[75] However, findings appear to be dependent on kidney status and glomerular filtration rate.

Gut microbiota and blood pressure

Studies in animal models of HTN have been instrumental in understanding the role of gut microbiota and metabolites and its association with hypertension (Figure 1).[24,76] High salt intake affects the gut microbiome in mice, particularly by depleting *Lactobacillus murinus* and treatment of mice with *L. murinus* prevented salt-sensitive hypertension by modulating TH17 cells.[77] Rat models of HTN showed a reduction in the proportion of Bacteroidetes and an increase in *Firmicutes* in the gut with a corresponding shift of the metabolic profile.[28] In humans, a greater percentage of *Prevotella* and reduced abundance of *Bacteroidetes* were observed in patients with HTN and prehypertension compared with healthy controls along with a different metabolic profile.[27] In particular, the metabolites 3,4,5-trimethoxycinnamic and S-carboxymethyl-L-cysteine were lower in prehypertension and HTN compared with controls. 3,4,5-Trimethoxycinnamic acid suppresses cell adhesion molecules in vascular endothelium protecting against dysregulated inflammatory disorders. S-carboxymethyl-L-cysteine, on the other hand, has been shown to mitigate inflammatory damage.[27,78] In the Coronary Artery Risk Development in Young Adults (CARDIA) study, gut microbial diversity was inversely associated with both hypertension and systolic BP.[79] Finally, antibiotic therapy in the Dahl salt-sensitive (S) rat and the spontaneously hypertensive rat (SHR) appeared to increase systolic BP in the former but decrease in the latter accompanied by significant alterations in gut microbiota.[80] This highlights potential interactions between host genome and interventions that modify the gut microbiome and blood pressure. These results illustrate the interconnection between potential hypertensive pathways and microbial metabolites that merit further validation and elucidation of underpinning mechanisms.

Dietary interventions to modify the microbiome and blood pressure

Gut microbiota composition and function is shaped from infancy and persists into adulthood, but it retains some degree of flexibility that allows modulation through exposure

Microbiome Marker	Microbiome marker trend	BP trait	Ref
Acetanaerobacterium		HTN	87
Acetobacteroides		HTN	87
Acidaminobacter		HTN	87
Adlercreutzia		HTN	87
Adlercreutzia equolifaciens	↑	HTN	88
Aeromicrobium massiliense	↓	HTN	88
Alistipes		HTN	87
Anaerotruncus		HTN	87
Asteroleplasma		HTN	87
Bacteroidales	↓	HTN	88
Bacteroides	↓	SBP & DBP	89
Bacteroides		HTN	87
Bacteroides (genus)	↑	HTN	88
Bacteroides (genus)	↑	HTN	88
Bacteroides cellulosilyticus	↑	HTN	88
Bacteroides dorei	↓	HTN	88
Bacteroides eggerthii	↑	HTN	88
Bacteroides nordii	↓	HTN	88
Bacteroides uniformis	↓	HTN	88
Barnesiella		HTN	87
Bifidobacterium (genus)	↑	HTN	88
Bifidobacterium dentium	↓	HTN	88
Bilophila	↓	Pre-HTN	27
Blautia	↓	SBP & DBP	89
Blautia hansenii	↓	HTN	88
Blautia product	↓	HTN	88
Butyricimonas (genus)	↑	HTN	88
Clostridiaceae	↓	SBP & DBP	89
Clostridiales	↓	HTN	88
Clostridium citroniae	↓	HTN	88
Clostridium hathewayi	↓	HTN	88
Clostridium IV		HTN	87
Collinsella aerofaciens	↓	HTN	88
Coprococcus	↓	Pre-HTN	27
Desulfovibrio		HTN	87
Dorea	↑	Pre-HTN	27
Dorea longicatena	↑	HTN	88
Eggerthella lenta	↑	HTN	88
Eisenbergiella		HTN	87
Enterobacter	↓	HTN	27
Enterococcaceae	↑	HTN	90
Faecalibacterium prausnitzii	↓	HTN	88
Faecalitalea		HTN	87
Faecalitalea		HTN	87
Faecalitalea (genus)	↓	HTN	88
Flavonifractor plautii	↓	HTN	88
Fusobacterium (genus)	↓	HTN	88
Guggenheimella		HTN	87
Haemophilus parainfluenzae	↓	HTN	88
Holdemania filiformis	↓	HTN	88
Intestinibacter bartlettii	↓	HTN	88
Intestinimonas		HTN	87
Klebsiella (genus)	↑	HTN	88
Klebsiella (genus)	↑	HTN	88
Klebsiella (genus)	↑	HTN	88
Klebsiella pneumoniae	↑	HTN	88
Klebsiella variicola	↑	HTN	88
Lachnoclostridium	↓	Pre-HTN	27
Lactobacillaceae	↑	HTN	90
Lactobacillus		HTN	87
Macellibacteroides		HTN	87
Megasphaera (genus)	↓	HTN	88
Megasphaera (genus)	↓	HTN	88
Megasphaera micronuciformis	↓	HTN	88
Mitsuokella		HTN	87
Mitsuokella multacida	↑	HTN	88
Mollicutes	↓	HTN	90
Odoribacter	↓	SBP & DBP	89
Odoribacteraceae	↓	SBP & DBP	89
Olsenella		HTN	87
Olsenella		HTN	87
Parabacteroides		HTN	87
Parabacteroides		HTN	87
Parabacteroides merdae	↑	HTN	88
Paraprevotella		HTN	87
Paraprevotella		HTN	87
Parasutterella		HTN	87
Prevotella		HTN	87
Prevotella (genus)	↑	HTN	88
Prevotella (genus)	↓	HTN	88
Prevotella bivia	↓	HTN	88
Proteiniborus		HTN	87
Pyramidobacter piscolens	↑	HTN	88
RF3	↓	HTN	90
Robinsoniella	↓	SBP	70
Romboutsia		HTN	87
Roseburia hominis	↓	HTN	88
Roseburia intestinalis	↓	HTN	88
Roseburia intestinalis	↓	HTN	88
Ruminococcus		HTN	87
Ruminococcus (genus)	↓	HTN	88
Shanon index	↓	HTN	90
Sporobacter		HTN	87
Sporobacterium		HTN	87
Streptococcaceae	↑	HTN	90
Streptococcus (genus)	↑	HTN	88
Streptococcus (genus)	↑	HTN	88
Streptococcus infantarius	↑	HTN	88
Streptococcus pasteurianus	↑	HTN	88
Streptococcus salivarius	↑	HTN	88
Sutterella		HTN	87
Sutterella		HTN	87
Sutterella wadsworthensis	↑	HTN	88
Vampirovibrio		HTN	87
Victivallis		HTN	87

Figure 1. Gut microbiome and blood pressure traits.

to a variety of environmental factors, the most important of which is diet.[81,82]

The Mediterranean diet is understood to exert a cardioprotective effect, including mitigating blood pressure. This beneficial effect may be partially dependent on changes to the gut microbiome, two recent studies suggest that adhering to a Mediterranean diet is associated with a more favorable gut microbiome composition and increased SCFA generation potential (increased *Faecalibacterium prausnitzii* and *Clostridium* cluster XIVa).[83]

The OmniHeart study was a randomized crossover study of three dietary patterns—OmniCarb diet (58% kcal from carbohydrates, 15% from protein, and 27% from fat), OmniProt (10% of the kcal from carbohydrates replaced by mainly vegetable sourced protein), or OmniMFA (10% of the kcal from carbohydrates replaced by unsaturated fat).[36] An inverse association was observed for proline–betaine with SBP and DBP in OmniCarb and OmniMFA diets. Carnitine was directly associated with SBP in OmniProt, hippurate with both SBP and DBP in OmniCarb. Comparisons between OmniProt and OmniMFA diets identified inverse associations for BP with 4-cresyl sulfate and with phenylacetylglutamine, metabolites of tyrosine, and phenylalanine. A metabolite of tryptophan-NAD, *N*-methyl-2-pyridone-5-carboxamide was also inversely associated in the OmniCarb diet compared with baseline.[36]

Derkach *et al.*[84] randomly assigned 119 participants a 12-week DASH diet or a 12-week typical American diet (control). Each participant was randomly assigned high-, medium-, or low-versions of their respective diets, crossing over after 30 days. They identified six metabolic pathways associated with higher sodium intake. The strongest associations were generated from fatty acid, benzoate, methionine, and tryptophan pathways. Moreover, switching from high- to low-sodium intake had a greater effect on metabolites in comparison to switching from high- to medium-sodium, this effect was particularly apparent for metabolites involved in the γ-glutamyl amino acid pathway.[84] The enzyme responsible for γ-glutamyl metabolite formation γ-glutamyl transferase has previously been positively associated with prehypertension.[85] The key finding from the study does not relate to BP and comes from the strongest associated metabolite 4-ethylphenylsulfate, which increased with sodium restriction. This metabolite is generated by gut bacteria and related to numerous disorders, highlighting this gut–diet-health interaction.

Lee *et al.*[86] investigated serum metabolites associated with incident HTN within a Korean cohort (n = 1,529), grouping participants into tertiles of MUFA intake. They reported an inverse association between the highest MUFA intake group and risk of HTN when compared with the lowest MUFA intake. Moreover, researchers associated MUFA intake with metabolite concentration, higher MUFA intake was associated with an increase in the metabolite phosphatidylcholine-diacyl (PC aa) C 38:1.

CONCLUSIONS

Advances in high throughput genomics, metabolomics and other omics have vastly increased our understanding of the complex architecture of BP and hypertension. The burgeoning list of genomic variants associated with BP and hypertension provides a realistic basis for refining the molecular taxonomy of hypertension, but this requires incorporation of other characteristics including lifestyle and environmental influences in addition to molecular and genomic information. This step is critical in realizing the potential of genomics and other omics in precision hypertension prevention and therapy.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

ACKNOWLEDGMENTS

C.M. is funded by the MRC Aim-Hy project grant and Chronic Disease Research Foundation. P.L. is funded by the Chronic Disease Research Foundation. S.P. is funded by the Medical Research Council (MRC) (MR/M016560/1; Ancestry and biological Informative Markers for stratification of Hypertension [AIM-HY] Study), the British Heart Foundation (BHF) (CS/16/1/31878) and BHF Centre of Excellence (RE/18/6/34217).

DISCLOSURE

The authors declared no conflict of interest.

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