Pulse

Review Article

Pulse 2024;12:19–26
DOI: 10.1159/000536505

Received: January 3, 2024
Accepted: January 19, 2024
Published online: January 27, 2024

# Genetic Variants Associated with Hypertension Risk: Progress and Implications

David Curtis

UCL Genetics Institute, University College London, London, UK



**Keywords**
GWAS · Exome · *DNMT3A* · *FES* · *NPR1* · *GUCY1A1* · *GUCY1B1* · *DBH* · *INPPL1* · *REN* · *ASXL1* · *SMAD6*

**Abstract**
***Background:*** Genetic variants causing diseases with hypertension as a secondary feature have previously been identified. Studies focussing on primary hypertension have utilised common and latterly rare genetic variants in attempts to elucidate the genetic contribution to the risk of primary hypertension. ***Summary:*** Using genome-wide association studies (GWASs), associations of hypertension with hundreds of common genetic variants have been reported, implicating thousands of genes. Individual variants have small effect sizes and cumulatively account for around 6% of genetic risk. The common variant signal is enriched for relevant tissues and physiological processes, while some variants are associated with traits expected to have secondary impacts on hypertension risk, such as fruit intake, BMI, or time watching television. Studies using rare variants obtained from exome sequence data have implicated a small number of genes for which impaired function has moderate effects on blood pressure and/or hypertension risk. Notably, genetic variants which impair elements of guanylate cyclase activation, stimulated by either natriuretic hormones or nitric oxide, increase hypertension risk. Conversely, variants impairing dopamine beta-hydroxylase or renin production are associated with lower blood pressure. Variants for which a definite effect can be designated remain cumulatively extremely rare and again make only a small contribution to overall genetic risk. Although these results are of interest, it is not clear that they provide radical new insights or identify drug targets which were not previously known. Nor does it seem that genetic testing could be useful in terms of quantifying disease risk or guiding treatment. ***Key Messages:*** Research has increased our knowledge about the relationship between naturally occurring genetic variation and risk of hypertension. Although some results serve to confirm our understanding of underlying physiology, their value in terms of potentially leading to practical advances in the management of hypertension appears questionable.



## Introduction

Human beings are 99.9% genetically identical with each other, but errors in copying DNA can introduce variations in genetic sequence which may impact susceptibility to disease. Variants with zero or minimal impacts which occurred early in human evolution can, through a process called genetic drift, grow to become common so that they may nowadays be observed in a substantial proportion of people. By contrast, any variant

karger@karger.com
www.karger.com/pls



Correspondence to:
David Curtis, d.curtis@ucl.ac.uk

which causes severe disruption of a vital physiological process will tend to be quickly weeded out of the population through the process of natural selection, and hence, variants with large effects on disease risk are expected to be very rare. Common variants which have small effects on risk can be detected through genome-wide association studies (GWASs), which typically use the genotypes of around a million common variants called single nucleotide polymorphisms (SNPs) to test for association with a disease phenotype in thousands of cases and controls. However, as the human genome consists of three thousand million DNA bases, GWASs are unable to detect the extremely rare variants which may have large effects on risk in the individuals who carry them, and these variants can only be detected by techniques which directly interrogate DNA sequence changes [1]. Methods to localise and identify variants responsible for severe genetic diseases, often occurring in families, have been available for several years, but it has only recently become possible to obtain the full sequence of all genes. This approach, termed whole exome sequencing if applied only to the coding regions of genes or whole genome sequencing if applied to all chromosomal regions, allows the detection of all variations in DNA sequence, common or rare, and hence facilitates attempts to discover the relationship between disruption of functioning of specific genes and effects on disease risk. Large-scale studies involving whole exome and genome sequencing of many thousands of people are now yielding important new results.

Here, we review the relationship between naturally occurring genetic variants and risk of hypertension with a special emphasis on the new insights which have been derived from the studies of large exome-sequenced samples. We consider how these findings impact our understanding of the pathogenesis of hypertension and what might be relevant clinical implications.

## Genetic Associations

Prior to the availability of large-scale studies, targeted investigations of genetic diseases with hypertension as a prominent feature led to the identification of rare variants causing diseases such as congenital adrenal hyperplasia, familial hyperaldosteronism, and pseudohypoaldosteronism in the genes *CYP11B1*, *CYP11B2*, *WNK1*, *WNK4*, *KLHL3*, *CUL3*, *SCNN1B*, *SCNN1G*, *CYP17A1*, *HSD11B2*, *NR3C2*, and *KCNJ5* [2]. Subsequently, variants in *CACNA1H*, *CACNA1D*, and *CLCN2* were also identified as causes of familial hyperaldosteronism, while somatic mutations in *ATP1A1* or *ATP2B3* can produce aldosterone-producing adrenal adenomas with consequent hypertension [3]. Recessively acting variants in *GUCY1A1* (previously named *GUCY1A3*) can cause moyamoya disease, in which risk of hypertension is increased, and two unrelated subjects with moyamoya disease who also had achalasia and hypertension were reported to have compound heterozygote variants in this gene [4, 5]. Polycystic kidney disease, which may result in hypertension, can be caused by dominantly acting variants in *PKD1*, *PKD2*, or *GANAB* or by recessively acting variants in *PKHD1*, *DZIP1L*, or *CYS1* [6, 7].

The first study to convincingly demonstrate association between genetic variants and blood pressure at the population level focused on the *PPNA-PPNB* locus, comprising the natriuretic peptide precursor A and natriuretic peptide precursor B genes which code for atrial natriuretic peptide (ANP) and beta-type natriuretic peptide (BNP) [8]. This found alleles of two SNPs, rs5068 and rs198358, which were associated with higher levels of ANP and BNP and with lower blood pressure levels. A later study concluded that it was variants affecting ANP rather than BNP levels which were associated with blood pressure [9].

The largest GWAS of blood pressure traits to date involved over one million people and identified 901 associated genetic loci [10]. Typically, the SNPs implicated in a GWAS may not be located within genes, and it can be difficult to characterise their specific effects. However, it is possible to use statistical techniques to study their distribution across chromosomes, and the study authors reported that there was a tendency for these associated SNPs to be near genes expressed in relevant tissues (blood vessels, heart, adrenal tissue, and adipose tissue) and/or to be involved in relevant physiological processes (angiotensinogen, calcium channels, progesterone, natriuretic peptide receptor, angiotensin converting enzyme, angiotensin receptors, and endothelin receptors). The authors also noted that some SNPs had been reported to be associated with traits which might secondarily impact hypertension risk, such as fruit intake, BMI, or time watching television. Cumulatively, SNPs at these 901 loci explained 5.7% of the variance in systolic blood pressure. Effect sizes of individual SNPs were small, with the mean absolute value for beta being 0.22 and the maximum value for beta being 1.1 for rs11191548, meaning that possessing one variant allele of this SNP is associated with a 1.1 mm Hg increase in systolic blood pressure. When SNPs from all loci were combined to produce a genetic risk score (GRS), there was a mean 10.4 mm Hg

difference in systolic blood pressure between top and bottom quintiles of GRS and a sex-adjusted odds ratio (OR) for hypertension of 3.34 between top and bottom deciles of GRS. Using a variety of functional annotation and functional enrichment methods, the authors identified 2,605 genes as being associated with these SNPs, representing around 10% of all genes. They note that 21 of these genes overlap with the 145 genes which are currently target genes for the treatment of blood pressure.

In an attempt to address the issue that GWAS analyses rely on common variants, most of which are not located in genes and do not obviously affect gene function, a study of 327,288 individuals was undertaken using an alternative genotyping platform called an Exome Chip [11]. This includes 247,039 variants, of which more than 90% are nonsynonymous or splice-modulating variants and hence are expected to alter the gene product. Two nonsynonymous variants with low frequency in genes *NPR1* and *SVEP1*, rs35479618 and rs111245230, were associated with systolic blood pressure with moderate effect sizes (beta = 1.11 and 0.70), while a low-frequency nonsynonymous variant in *PTPMT1*, rs11537751, was associated with hypertension, although the magnitude of the effect was not stated. Additionally, a rare, nonsynonymous variant in *DBH*, rs3025380, was associated with 1.8 mm Hg reduction in mean arterial blood pressure. Because very rare variants may have little power to detect association individually, analyses were undertaken in which all rare, nonsynonymous variants within a gene were considered jointly, and these analyses implicated *PTMT1*, *NPR1*, and *DBH*.

The ability to carry out exome sequencing in large samples has now made it possible to identify every coding variant in every gene, rather than only those variants which were prespecified on the Exome Chip or those in specific genes sequenced in targeted studies. An early implementation of this approach was to identify variants using the first wave of 50,000 exome-sequenced participants in the UK Biobank study and then to impute these variants into the full cohort of 500,000 [12]. These analyses yielded 1,189 associations judged likely to be causative between rare coding variants and a variety of different phenotypes, with the following genes having single variant associations reported for systolic and/or diastolic blood pressure: *GPR137B*, *CACNA1D*, *PHC3*, *NR3C2*, *DBH*, *SLC9A3R2*, *GATA5*, *NPR1*, *PHC3*, *GEM*, *PDE3A*, *TNS2*, *TBX5*, *SLC9A3R2*. As exome sequence data for more UK Biobank participants became available, subsequent studies made use of directly genotyped variants, rather than those obtained by imputation, to test for association with a variety of phenotypes, including some related to blood pressure [13–15]. Although these studies carried out broadly similar analyses, variations in the methods used mean that the results obtained differ somewhat. Additionally, it can be somewhat problematic to interpret their overall statistical significance because of the multiple testing issues arising from the analysis of different but non-independent phenotypes as well as the use of different analytic methods. It should also be noted that, because they used multiple phenotypes and did not focus on hypertension specifically, relevant results are not reported in the main text but need to be gleaned from supplementary material. The first of these studies again identified the rs3025380 variant within *DBH* as associated with diastolic blood pressure and rs200383755 in *GATA5* as being associated with self-reported hypertension, while gene-level associations of variant burden were reported for *TTN*, *COL21A1*, *ZFAT*, *SLC9A3R2*, *FES*, and *PKD1* [14]. Another study using thousands of binary and quantitative phenotypes again implemented single variant tests as well as gene-based collapsing analyses [13]. Their supplementary material lists 325 associations of a single variant with systolic or diastolic blood pressure and 399 with a hypertension phenotype significant at $p < 5 \times 10^{-8}$. In their gene-based tests, loss of function (LOF) variants in *PKD1* were associated with hypertension. A third study used a novel nonsynonymous variant effect predictor called PrimateAI-3D to select variants to be included in gene-based collapsing analyses [15]. The following genes were significantly associated with systolic and/or diastolic blood pressure at $p < 10^{-6}$: *GEM*, *GUCY1A1*, *NPR1*, *REN*, *SMAD6*, *FES*, *LZTR1*, and *SVEP1*. Variants in *REN* were associated with lower blood pressure. Two additional studies of the same dataset focused exclusively on hypertension as a phenotype and performed gene-based collapsing analyses with variants being weighted more highly if they were rarer and/or more likely to damage gene function [16, 17]. The second of these, utilising data from 470,000 exome-sequenced UK Biobank participants, analysed genes achieving suggestive results in the first, based on 200,000 participants, and after correction for multiple testing results for the following genes were declared to be statistically significant: *DNMT3A*, *FES*, *NPR1*, *GUCY1A1*, *ASXL1*, *SMAD6*, *DBH*, *INPPL1*. For *DBH* and *INPPL1*, rare coding variants impairing gene function were associated with reduced rather than increased risk of hypertension. *GUCY1A1* codes for a subunit of a soluble guanylate cyclase, and it was noted that *GUCY1B1*, which codes for a different subunit of the same enzyme, had an uncorrected $p$ value of <0.0001. LOF variants in the risk genes exerted moderate effects,

with ORs ranging from 1.33 for *SMAD6* to 1.96 for *FES*, and were very rare, with cumulative allele frequency less than 0.001 for each gene. Nonsynonymous variants tended to have smaller effects and to be slightly less rare. LOF variants in *DBH* had cumulative frequency of 0.002 with OR 0.90 and those in *INPPL1* had cumulative frequency of 0.0004 and OR 0.75.

### Functional Mechanisms

Arguably, the results which most readily lend themselves to biological interpretation are those obtained from gene-based analyses, where there is a consistent effect from multiple different variants impairing gene function. By contrast, single-variant associations tend to be associated with small effects on phenotype, and the mechanism of action may be less clear. Some implicated genes are known to be involved in the pathogenesis of diseases which have hypertension as part of the phenotype, such as congenital adrenal hyperplasia or polycystic kidney disease, and we will not consider these further. Other gene-based results seem to point very clearly to key elements of blood pressure control, and in some cases, mirror results obtained from animal and cellular models. These provide good examples of the mechanisms whereby genetic variation can impact disease risk.

As stated above, variants in the *PPNA-PPNB* locus are associated with higher levels of the natriuretic peptides ANP and BNP and variants which increase ANP levels are associated with lower blood pressure [8, 9]. In mice, reduced expression of the gene coding for ANP is associated with salt-sensitive hypertension, while overexpression lowers systolic blood pressure [18, 19]. *NPR1* codes for the membrane-bound guanylate cyclase NPR-A, ANP receptor 1, which in response to ANP or BNP produces increased levels of cGMP, and the studies referred to above consistently show that variants impairing *NPR1* function are associated with increased risk of hypertension. In cell culture experiments, it has been shown that two nonsynonymous *NPR1* variants which were associated with increased blood pressure caused reduced guanylate cyclase activity, while a variant associated with decreased blood pressure caused enhanced guanylate cyclase activity [20]. Taken together, these results demonstrate that genetic variation affecting either levels of ANP itself or the activity of the guanylate cyclase receptor it acts on lead to the expected effects, whereby reduced cGMP production increases hypertension risk.

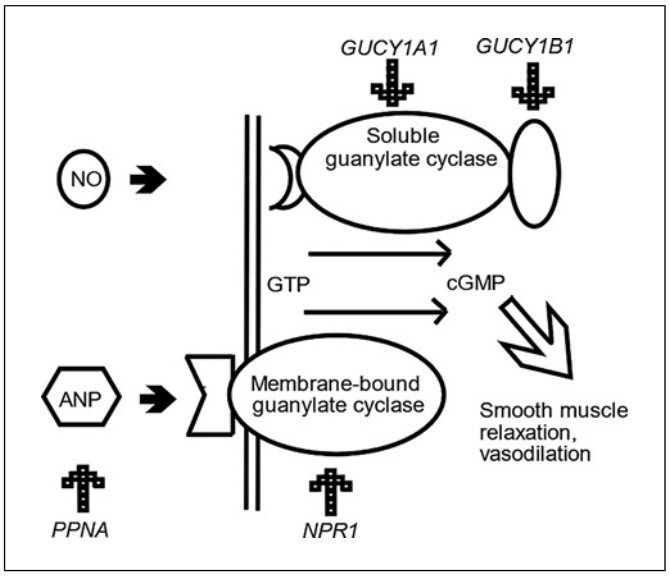


**Fig. 1.** Either membrane-bound or soluble guanylate cyclase can convert GTP to cGMP, producing smooth muscle relaxation and vasodilation, exerting a hypotensive effect. *GUCY1A1* and *GUCY1B1* code for subunits of a soluble guanylate cyclase responding to NO signalling. *NPR1* codes for a membrane-bound guanylate cyclase responding to ANP, which is coded for by *PPNA*. Genetic variants damaging function of *GUCY1A1*, *GUCY1B1*, *NPR1*, or *PPNA* are associated with increased risk of hypertension, presumably through reduced guanylate cyclase activity.

The results reported for *GUCY1A1* and *GUCY1B1* imply that genetic variants which lead to impaired functioning of soluble, rather than membrane-bound, guanylate cyclase also increase risk of hypertension. These genes code for subunits of a soluble guanylate cyclase which responds to nitric oxide (NO) signalling in order to increase cGMP, leading to vasodilation and other responses, and the central role of this pathway in the control of blood pressure is well established from animal studies, while guanylate cyclase stimulators have been developed as treatments for pulmonary hypertension [21]. The mechanisms whereby genetic variants impairing guanylate cyclase activity could lead to hypertension are illustrated in Figure 1.

The observation that variants in the *REN* gene are associated with lower blood pressure is unsurprising, given that this gene codes for renin. One can easily understand how variants resulting in abnormal forms of the protein could lead to a weaker hypertensive effect of this hormone.

The finding that impaired functioning of *DBH* is associated with reduced hypertension risk is also readily explained. *DBH* codes for dopamine beta-hydroxylase,

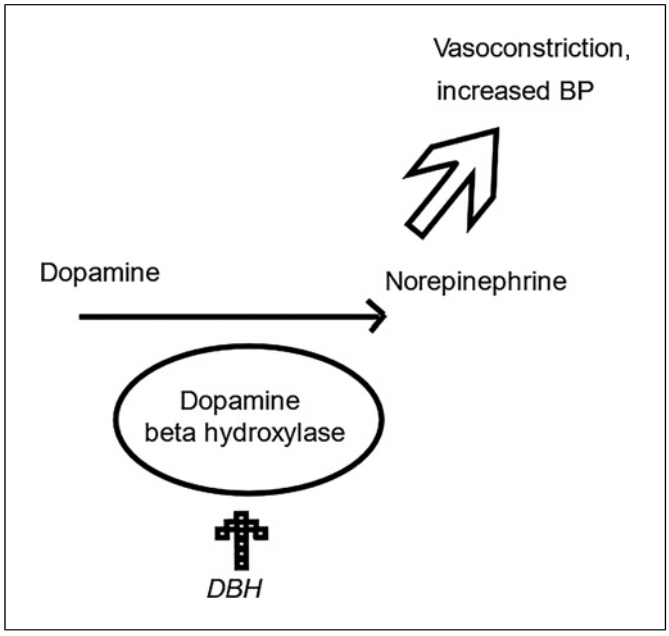


**Fig. 2.** Dopamine beta-hydroxylase converts dopamine to norepinephrine, which has a hypertensive effect. Genetic variants damaging function of *DBH*, which codes for dopamine beta-hydroxylase, are associated with reduced risk of hypertension, presumably through reduced production of norepinephrine.

which is the enzyme required for the production of norepinephrine from dopamine, and recessively acting variants in it have been reported to cause norepinephrine deficiency syndrome, characterised by orthostatic hypotension among other symptoms [22]. This mechanism is illustrated in Figure 2.

The causal mechanism for the association of impaired *DNMT3A* function with hypertension is somewhat less obvious. The function of DNMT3A is to methylate DNA in order to reduce the expression of specific genes [23, 24]. In mice, *Dnmt3a* deficiency results in reduced methylation of the gene for angiotensin receptor type 1a, *Agtr1a*, leading to increased *Agtr1a* expression along with salt-induced hypertension [25]. This is illustrated in Figure 3. It is possible that a similar mechanism could be active in humans, whereby genetic variants impairing *DNMT3A* could result in reduced methylation of genes such as those coding for angiotensin receptors, resulting in inappropriately high expression of these genes and an increased sensitivity to angiotensin. For other implicated genes, including *ASXL1*, *FES*, *SMAD6*, *GEM*, *LZTR1*, *SVEP1*, and *INPPL1*, the mechanisms whereby altered functioning might affect risk of hypertension are unclear, and insights must await further experimental work.

## Clinical Implications

Broadly speaking, the identification of association between genetic variants and disease risk might have clinical implications in one of three ways. Firstly, new insights into pathogenic mechanisms might be obtained, leading to improved therapeutics. Secondly, genetic testing might be used to quantify risk of disease. Thirdly, genetic testing might be useful to guide treatment.

The results obtained to date seem to illustrate that genetic variation leading to impairment of natriuretic peptide or NO signalling with reduced guanylate cyclase activity increases risk of hypertension, while abnormalities in renin or reduced dopamine beta-hydroxylase activity, with lower synthesis of norepinephrine, are protective. However, it could be argued that these findings are unsurprising and do not provide new insights into the physiological control of blood pressure. Likewise, if the mechanism by which reduced DNMT3A activity increased hypertension risk is through enhancing expression of angiotensin receptors, then again, this would not really tell us something new about physiology or suggest novel drug targets. If the mechanisms involved in blood pressure regulation had been unknown prior to this genetic research, then the findings would have been very impactful. As it is, the findings to date seem to be more confirmatory than revelatory. It is not impossible that elucidating the mechanisms underlying the association of other implicated genes could lead to novel physiological insights. But this is far from guaranteed.

Another frequently cited potential benefit of genetic research is that it could assist in quantifying disease risk. This might range from identifying babies with Mendelian disease amenable to early treatment, such as cystic fibrosis, through to using polygenic risk scores to classify individuals at high or low risk of outcomes such as cardiovascular disease or breast cancer [26–28]. In certain clinical situations, there might be indications for testing for rare coding variants causing the Mendelian diseases resulting in secondary hypertension mentioned above, but this does not seem to apply to primary hypertension since the most impactful variants are both extremely rare and also still have only moderate effect sizes. Alternatively, it would be possible to combine information from common variants to produce a GRS to quantify risk of hypertension. However, the clinical utility of GRSs in general remains controversial. Arguably, the phenotype for which a GRS might potentially have most utility is cardiovascular

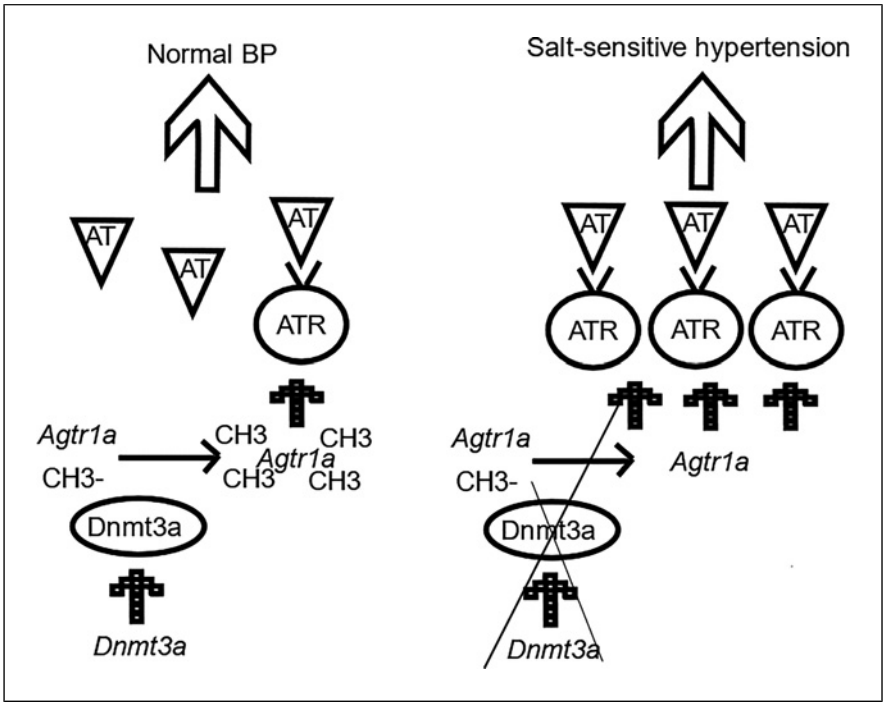


**Fig. 3.** In mice, Dnmt3a methylates *Agtr1a*, the gene which codes for angiotensin receptor type 1a (ATR). This methylation keeps *Agtr1a* expression under control, producing normal levels of ATR and a normal response to angiotensin (AT) with normal blood pressure. If Dnmt3a function is reduced then *Agtr1a* is hypomethylated, leading to abnormally increased expression and higher levels of ATR. The subsequent angiotensin receptor overactivity causes salt-sensitive hypertension. In humans, genetic variants damaging function of *DNMT3A* are associated with increased risk of hypertension, perhaps through a similar mechanism of loss of control of genes coding for angiotensin receptors.

disease, because risk is moderately heritable, because there is a future outcome which is serious and not uncommon, and because there are modifiers of risk, such as statins, which have differential benefits for patients at high risk [26, 29]. However, even in this context, there are claims that such risk scores are of minimal utility, as well as being problematic in other ways [30–32]. For hypertension, the case for clinical benefit is much weaker. For one thing, the GRS for hypertension is a substantially poorer predictor than that for cardiovascular disease [10]. However, an even stronger objection is that there does not seem to be much value in "predicting" hypertension when one can simply measure it. One would not be assessing risk of a future outcome but of a current, measurable condition which itself acts as risk factor for future outcomes. And one would not be contemplating treating somebody for hypertension pre-emptively on the basis that they might be at modestly increased risk of developing it later. Overall, it is difficult to see how using genetic information to quantify risk of hypertension could have clinical utility.

A third possible impact on clinical practice would be if genetic findings could be used to guide treatment choices. Genetic variation can have pharmacokinetic effects, impacting the speed with which drugs are absorbed or metabolised and hence potentially influencing levels achieved, efficacy, and risk of adverse effects. Taking account of such variation has not been proven to be clinically useful in most situations, and while the authors of a recent large study claimed such testing produced benefits, critics claimed that the actual results demonstrated that the testing was ineffective [33–35]. Alternatively, genetic variants may have disease-specific or medication-specific effects which can be broadly grouped as pharmacodynamic. Naively, it might be thought that patients with a specific genetic variant underlying their condition might benefit from a treatment targeting the biologic process which is disrupted. However, evidencing that this is actually the case would require focussed clinical trials which are rarely, if ever, carried out in practice. To take a real-world example, patients with familial hyperlipidaemia, whose disease is due to specific, identifiable genetic variants, are still likely to be treated simply with generic lipid-lowering medications [36]. In the case of hypertension, we see that only a very small proportion of patients carry an identifiable variant which might moderately influence risk, and the vast majority of patients would not have any specific treatment target. Alternatively, it might be the case that certain variants had effects on response to particular medications, but again, variants with large effect sizes would be expected to be very rare, and it is difficult or impossible to see how they would be

identified in practice. Overall, there does not seem to be any clear role for using rare variants to guide treatment choices in hypertension.

An alternative approach would be incorporate information from common variants in order to use a GRS approach to inform treatment. It is entirely conceivable that if one were to carry out a careful clinical trial involving thousands of patients then one might identify common SNPs associated with small effects on response to treatment, and one would then be able to combine these to achieve a score with (probably) modest predictive value. However, if one wished to use genetic information to guide treatment choice, one would not want simply to predict who would respond more or less well to a given intervention, which, in the case of hypertension, one can simply discover by measuring response. Rather, one would want to know that a patient would respond worse to one drug and better to another. Devising scores which would differentially favour one treatment rather than another is conceivable but would require clinical trials which were very large indeed. Once studies had been carried out in order to generate such scores, one would then need to carry out further clinical trials to evidence that incorporating the scores into practice actually produced better outcomes. Given that, realistically, any effect sizes are likely to be modest, it does not seem that such studies would be worth the resources required to undertake them. We can draw contrasts between cancer and hypertension with regard to the potential value of genetic testing to guide treatment choices. For breast cancer, there are particular genetic subtypes which are not uncommon with interventions which are effective in one subtype but not another in terms of impacting risk of future recurrence [37]. In the case of hypertension, there are no clear subtypes, and one can instead quite reasonably use a trial and error approach to assess the tolerability and efficacy of a treatment on measured blood pressure and modify prescribing accordingly. One is not concerned with quantifying the risk of some possible future event but with the current condition of the patient. In this context, treatment can be titrated in real time, and neither rare nor common genetic variants seem likely to be able to provide information which would yield additional utility.

To summarise, insofar as hypertension is concerned, genetic findings nicely confirm some known physiology but do not seem to have utility as either informing risk estimates or guiding treatment choices. Genetic research into hypertension has increased our knowledge of the way naturally occurring genetic variation can affect risk, but it seems difficult to claim that it has had, or is likely to have, a substantial clinical impact.

## Conclusion

The risk of developing hypertension is modified by genetic variation as well as by environmental factors. Hundreds of common genetic variants have been identified, each associated with a small effect on risk, and between them, they suggest thousands of genes as potentially having a causal effect. Cumulatively, these common variants account for about 6% of the total genetic contribution to risk, and when they are considered jointly, they can be used to generate a risk score which is weakly predictive. By contrast, rare variant studies implicate just a handful of genes, some of which have clear physiological roles in control of blood pressure. Variants with an identifiable role remain cumulatively very rare and, again, would only explain a small fraction of the contribution to genetic risk. Presumably the residual genetic risk could be accounted for, at least in part, by large numbers of rare variants without obviously predictable effects, occurring both within and outside coding regions.

From the literature to date, it seems difficult to argue that findings of genetic research are likely to have a major clinical impact on the management of hypertension. The interpretable genetic results seem to fit in well with known biology but do not offer radical, novel insights. There seems little value in predicting the risk of developing hypertension before it emerges, and genetic testing would anyway have poor predictive power. Nor is it easy to see how genetic testing might be used to guide treatment. Hypertension provides an example of how research can provide increased knowledge about the relationships between genetic variation and risk of developing a common, clinically important phenotype.

## Conflict of Interest Statement

The author declares no conflict of interest.


## Funding Sources

This study was not supported by any sponsor or funder.


## Author Contributions

D.C. reviewed the literature and prepared the manuscript.

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