Novel Genetic Indicators of Hypertension Identified Through Genome-Wide Association Studies: Clinical Potential of Endothelin-Related SNPs

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Abstract

Nevertheless, in the field of hypertension genomics, it is likely that new genetic markers will be identified, but until they are, the results are restricted. Following on from this, and by drawing from pharmacogenomic, pleiotropic, and functional studies, the follow-up and clinical translation of these genetic results seems to be very promising. These endothelin-related SNPs, which have gone on to the clinical trial stage, signify further success in the advancement of hypertension precision medicine that has already been discovered through genetic research. Although the use of polygenic risk scores may appear advantageous, further study is required to verify their effectiveness, and this issue must be examined further to determine the potential for these scores to lead to an increase in health inequity.

Introduction

It is vital for sustaining oxygen and nourishment delivery as well as cardiovascular homeostasis1 that blood pressure be kept at a healthy level. Blood pressure can be defined as the force imposed by blood on the inner walls of arteries. Blood pressure is kept within a 'normal range' by physiological regulatory mechanisms, and readings that fall below or above this range are associated with adverse health outcomes such as ischaemia, myocardial infarction, stroke, and renal disease2. In the general population, blood pressure follows a normal distribution, and there is an incremental risk of cardiovascular disease proportional to the logarithm of every one millimeter of mercury that the blood pressure rises by 3. According to Evans and Rose5, the transition from 'normal' blood pressure to hypertension is currently based on an absolute blood pressure value (which has gradually decreased over the past 50 years) 2,4 at the upper end of the blood pressure distribution "at which the benefits of action (i.e. therapeutic intervention) exceed those of inaction." With an estimated 1.5 billion individuals suffering from hypertension, it is acknowledged as the most significant risk factor that can be modified. The Global Burden of Disease report found that a systolic blood pressure (SBP) of 140 mmHg, which is the current clinic SBP threshold for diagnosing hypertension, was responsible for 7.8 million deaths in 2015, whereas an SBP of 110 mmHg was responsible for 10.7 million fatalities (6).

Although it is possible to define blood pressure as the product of cardiac output and peripheral artery resistance, these two parameters are impacted by both hereditary and environmental factors, and they are regulated by a complex network that includes the renal, neuronal, cardiac, vascular, and endocrine systems. Blood pressure can be simply stated as the product of these two characteristics. As a consequence of this, blood pressure is considered to be a multifactorial polygenic trait, and hypertension, which is a dichotomization of the quantitative blood pressure trait, is also considered to be a multifactorial complex trait. The Page model of hypertension, which was developed in the 1960s and updated in 2014, provides a crystal clear illustration of the complex and multifaceted character of hypertension (7,8). In the general population, systolic blood pressure levels rise in a linear, age-related pattern, which suggests that high blood pressure causes vascular injury or malfunction, which leads to a vicious cycle of accumulating vascular injury and rising blood pressure 9The age-related rise in blood pressure level is only seen in industrialized cultures, not in non-Westernized, tribal groups where routine dietary salt intake and other environmental stresses and exposures that raise blood pressure are not present. In addition, the rise in blood pressure Although other environmental and occupational factors, such as salt intake, might increase the risk of hypertension12, accumulating evidence suggests that monogenic syndromes of high or low blood pressure have a major genetic impact.

These syndromes can be inherited and can cause either high blood pressure or low blood pressure. In addition, the number of genome-wide association studies (GWAS), 13, 14, and 15 have shown that the rate of validated single-nucleotide polymorphisms (SNPs) related to blood pressure has increased considerably.

In the case of monogenic blood pressure problems, it has been established that the presence of causal genetic variants is both necessary and sufficient to bring about blood pressure abnormalities. SNPs derived through GWAS, on the other hand, have the ability to provide the necessary conditions; but, they are not sufficient to cause the blood pressure phenotype to become manifest.

Blood pressure can be calculated by taking the product of cardiac output and peripheral vascular resistance. Both of these variables are affected by a wide range of factors. There are various molecular pathways that can have an effect on the eventual phenotype of blood pressure, which suggests that blood pressure is a multidimensional variable. The circos plot in the middle of the diagram illustrates the relationships between organ-specific physiological processes that control blood pressure. The length of each segment indicates a relative representation of known genetic factors that are involved in the blood pressure-regulating pathways of that organ. The density of the connections that link two organs together can be used to estimate the number of blood pressure-regulating pathways or genes that are shared by the two organs. The contribution of polygenic factors to the blood pressure phenotype, in contrast to that of monogenic determinants, is intricate and is mediated by processes that have not yet been identified. The plot in the upper left-hand corner of the page depicts the polygenic architecture of blood pressure. This architecture is shown as a schematic representation of the landscape of genetic variants (blue circles) from genome-wide association studies, in addition to the known environmental and lifestyle factors that influence blood pressure regulation. Chromosomes are represented by the numbered segments. 11-HSD is short for 11-hydroxysteroid dehydrogenase, ACE stands for angiotensin-converting enzyme, ALDOS stands for aldosterone synthase, AME stands for apparent mineralocorticoid excess, Ang is short for angiotensin, ANS is short for autonomic nervous system, APA is short for aldosterone producing adenoma, AT1R is short for angiotensin II type The Jumanji domain is found in the protein known as JMJD, which stands for "Jumanji domain-containing protein." The following abbreviations are used throughout this review: Kir1.1, ATP-sensitive inward rectifier potassium channel 1; Kir3.4, G protein-activated inward rectifier potassium channel 4; KLHL3, Kelch-like protein 3; MC2R, melanocortin receptor 2; MR, mineralocorticoid receptor; NEDD4L, E3 ubiquitin-protein ligase NEDD4-like; NEP, neprily A comprehensive explanation of all the genetic variants and molecular processes is not provided because this information has already been analyzed13 for these regions.

Blood pressure and genetics are closely related.

Several different types of observational data all testify to the significance of genetics in controlling blood pressure. These considerations will be elaborated upon in the following paragraphs.

Studies in families and twins have shown that blood pressure has a large heritable component. The heritability of clinic systolic blood pressure ranges from 15–40%, while the heritability of clinic diastolic blood pressure ranges from 15–30%. Ambulatory systolic and diastolic blood pressure range from 69–51 percent, respectively 16,17. Despite the fact that the majority of the estimations are based on populations from Europe, data from persons of African origin indicate that similar levels of heritability18.

When compared to dizygotic twins, monozygotic twins have a more significant correlation between their blood pressure phenotypes19. According to family studies, an individual's likelihood of developing hypertension is increased by having a hypertensive parent or grandparent20. After taking into account secular trends and intergenerational differences in lifestyle, behavior, physical activity, and dietary sodium intake, statistical modeling revealed that the risk of hypertension in grandchildren of hypertensive grandparents remained after taking into account secular trends and intergenerational differences in lifestyle, behavior, physical activity, and dietary sodium intake.

Certain physiological pathways, most of which are focused in the kidneys and adrenal glands, appear to have a considerable impact on blood pressure13, as suggested by the discovery of unusual monogenic types of high and low blood pressure, as well as the genetic variations that underlie them. These findings support the hypothesis that certain monogenic types of high and low blood pressure are caused by specific genetic differences.

The explosion of data that occurred during the period of genome-wide research unequivocally revealed the polygenic component that is involved in the genetic architecture of blood pressure 14.

SBP levels were found to be causally connected with age-related increases in SBP levels when utilizing genetically determined SBP based on 12 SNPs linked with blood pressure in GWAS21. This finding was made possible by the use of genetically determined SBP. This research lends credence to the notion that having high blood pressure (as a result of having certain genetic risk alleles) can damage blood vessels, which can then result in higher blood pressure in the long run.

Structure of genes responsible for hypertension

The genetic architecture of a trait is comprised of the number of variants that influence the phenotype, the magnitude of their effects, the population frequency of the variants, and their interactions with each other and the environment22. This architecture also includes all genetic factors and their characteristics that are involved in the expression of a given phenotype. It is essential to get an understanding of the etiology of sickness as well as the underlying biological processes in order to successfully screen for and diagnose illness, as well as create new treatments22.

The genetic variations that have been linked to monogenic and polygenic diseases are depicted in the circos plot124. Large full red circles show genetic variations linked to monogenic illnesses, which are linked to their respective clinical syndromes (bottom part of the circle). The smaller purple, dark green, and light green circles represent single-nucleotide polymorphisms (SNPs) discovered by the use of GWAS. The color of the SNPs indicates which type of blood pressure, systolic blood pressure, diastolic blood pressure, or pulse pressure had the best association with the SNP. Chromosomes are often represented by numbered pieces of DNA. The pleiotropic signals from phenome-wide association studies are displayed at the top of the circle. These signals indicate the lifestyle, early-life, and environmental factors that have an effect on blood pressure and are associated to the position of the pleiotropic SNPs. The histogram on the outer ring of the ring plot displays the total number of pleiotropic relationships that can be found between SNPs at that locus. The height of the graph has a direct correlation to the amount of pleiotropy. FH stands for familial hyperaldosteronism; CAH stands for congenital adrenal hyperplasia; AME stands for apparent mineralocorticoid excess; HSD3B2 stands for 3-hydroxysteroid dehydrogenase deficiency; HTNBRACH stands for hypertension with brachydactyly; and MEN stands for multiple endocrine neoplasia type II.

The Page mosaic theory of hypertension7, which was published in 1960, postulated that essential hypertension is a collection of diseases with different origins and development that include interactions between genetics, the environment, adaptive, neural, mechanical, and hormonal (sympathetic nervous system a) mechanisms. This theory proposed that essential hypertension is a collection of diseases with different origins and development. The growing availability of large, prospective, population-based cohorts has made it possible to conduct genetic-association studies across a wide range of phenotypes (phenome-wide association studies, or PheWAS for short). These studies have shown that the vast majority of blood pressure SNPs display pervasive pleiotropy. The progression from the original Page mosaic model, which was a wire model depicting the multifactorial nature of hypertension, to its most recent iteration, which includes an update in 2014 with results from early GWAS studies, demonstrates the enormous progress made in unraveling the genetic architecture of blood pressure. This progression also demonstrates the eclipse of monogenic traits by the identification of polygenic signals, as well as the emergence of polygenic signals as a replacement for monogenic traits.

Syndromes that can be traced back to a single cause

The mutation in the causative gene, in addition to any other clinical or laboratory criteria, is what differentiates monogenic blood pressure diseases from other types of blood pressure problems. There has been prior discussion regarding the genetic and clinical features of monogenic hypertension13,24. Despite the fact that the genetic polymorphisms related with monogenic blood pressure diseases have large impacts on blood pressure (changes of approximately 20–50 mmHg from normal values), their discovery has helped us better understand the fundamental mechanisms that are responsible for blood pressure management.

The observation that participants in the Framingham Heart Study who had pathogenic alleles in KCNJ1, SLC12A1, and SLC12A3 had a lower chance of developing hypertension lends credence to the hypothesis that a heterozygote advantage is at the root of the function that rare genetic variations play in hypertension25.

However, this discovery needs to be verified by other research in the future. The genetic variants that cause familial hyperaldosteronism type I (also known as glucocorticoid-remediable aldosteronism), Liddle syndrome, congenital adrenal hyperplasia (deficiency of steroid 11-hydroxylase or 17-hydroxylase), and apparent mineralocorticoid excess have been identified and studied. Additionally, the mechanism of salt-sensitive hypertension mediated by aldosterone has been elucidated. In comparison, somatic gain-of-function variants in ATP1A1, ATP2B3, CACNA1D, or CTNNB1 are only identified in approximately 7% of patients with adrenal aldosterone-producing adenoma (.24). KCNJ5 somatic gain-of-function variants are detected in approximately 40% of patients with adrenal aldosterone-producing adenoma. There were fewer genetic variants in these genes in inherited kinds of primary hyperaldosteronism, which raises the possibility that hypertension is caused by a large number of rare genetic variants24. As shown by polymorphisms in ATP1A1, ATP2B3, CACNA1D, and KCNJ5, calcium signaling is essential for the independent synthesis of adrenal aldosterone28. It is currently unknown which processes are responsible for the development of aldosterone-producing adenomas in the adrenal gland as a result of CTNNB1-mediated signaling.

Our knowledge of the mechanisms by which the kidney regulates salt and electrolytes, as well as the impact these mechanisms have on blood pressure, has been expanded thanks to the discovery of variants in genes that code for transporter proteins that can be found in different parts of the nephron. The condition known as Gordon syndrome, which also goes by the name pseudohypoaldosteronism type II and is characterized by hyperkalaemic hypertension together with mild metabolic acidosis, elucidates the function of the distal convoluted tubule in the regulation of blood pressure. The Na–Cl cotransporter, which is coded by the gene SLC12A3, is the primary sodium transporter in the distal convoluted tubule (NCC). Gordon syndrome is brought on by mutations in two serine/threonine kinase genes (WNK1 and WNK4). These mutations make it such that WNK4 is unable to limit normal sodium flow and NCC activity as it should. Mutations in the CUL3 and KLHL3 genes, which are responsible for encoding proteins involved in the ubiquitylation and degradation of WNK kinases, are what lead to the development of Gordon syndrome.

Gitelman syndrome and Bartter syndrome are examples of salt-losing tubulopathies. These conditions are characterized by hypokalaemic alkalosis and normal-to-low blood pressure. Gitelman syndrome and Bartter syndrome are caused by dysfunctional transepithelial electrolyte transport in the thick ascending limb of the loop of Henle, the distal convoluted tubule (distal convoluted tubule disorders), or both30. Both type I and type II of thick ascending limb anomalies are caused by variants in the genes SLC12A1 (encoding solute carrier family 12 member 1; also known as NKCC2) and KCNJ1 (encoding ATP-sensitive inward rectifier potassium channel 1). Bartter syndrome type III and type V are both disorders of the distal convoluted tubule.

These conditions are caused by variations in the genes that code for the chloride channel ClC-Kb (CLCNKB) and the extracellular calcium-sensing receptor (CASR). Gene defects in the chloride channel proteins ClC-Ka (CLCNKA), CLCNKB, and the subunit of Barttin are the root cause of Bartter syndrome, which is characterized by sensorineural hearing loss. The thick ascending limb as well as the distal convoluted tubule (BSND) are also impacted by this condition. In utero manifestations of prenatal Bartter syndrome include polyuria and hydramnios in the developing fetus. This syndrome is caused by mutations in the SLC12A1 and KCNJ1 genes. It has been discovered that there is a novel form of Bartter syndrome called transitory prenatal Bartter syndrome. It is caused by mutations in MAGED2, which maps to the X chromosome, and it is characterized by a mix of thick ascending limb and distal convoluted tubule abnormalities, as well as polyhydramnios and salt wasting31.

Autosomal hypertension with type E brachydactyly is a monogenic syndrome that causes increased neointimal proliferation and remodelling of arteries and neurovascular structures. This is because vascular processes that involve phosphodiesterase 3A32 are responsible for causing the disorder. Phaeochromocytomas and paragangliomas are rare neuroendocrine tumors of the adrenal glands and sympathetic and parasympathetic paraganglia. Phaeochromocytomas and paragangliomas (PPGLs) are responsible for hypertension because of the hypersecretion of catecholamines. Known genetic variants are responsible for approximately 60% of PPGLs33. Metastatic phaeochromocytomas and paragangliomas are responsible for approximately 10% of phaeochromocytomas and 35–40% of paragangliomas33. Metastatic disease can be predicted by a number of factors, including tumor size (five to six centimeters in diameter), extra-adrenal location of the primary tumor, noradrenergic or dopaminergic biochemical profile, genetic polymorphisms in SDHA and SDHB, tumor multiplicity and/or recurrence, and age at first presentation (twenty years). 33. There are a total of 12 genetic disorders that have been associated to PPGLs. These diseases can be broken down into three categories: pseudohypoxia, WNT signaling, and kinase signaling. Each cluster possesses unique clinical, genetic, and imaging characteristics that can serve as a foundation for the practice of precision medicine 35,36. The pseudohypoxia group is composed of subgroups that are linked to the tricarboxylic acid cycle and the von Hippel–Lindau disease tumour suppressor (VHL) – endothelial PAS domain-containing protein 1 (EPAS1) axis. The tricarboxylic acid cycle-related PPGL subgroup (FH) is created by germline changes in the genes that produce succinate dehydrogenase subunits (SDHA, SDHB, SDHC, and SDHAF2) and fumarate hydratase. These variants occur in the SDHA, SDHB, SDHC, and SDHAF2 genes. Somatic and germline mutations in EPAS1 and VHL in the VHL–EPAS1-related PPGL subgroup are responsible for the development of multiple and recurring paragangliomas. The WNT signaling PPGL group is produced by somatic mutations in CSDE1 and MAML3, respectively. The kinase signaling PPGL group can be induced by either germline or somatic mutations in the HRAS, MAX, NF1, RET, and TMEM127 genes.

There are many different things that might lead to hypertension.

The genome-wide association study (GWAS) has completely transformed our understanding of intricate traits, but its therapeutic application has been severely limited. The fact that the bulk of genetic variations detected by GWAS are found in intergenic or intronic areas, with only 10% found in the coding sequence 37,38, has been a significant limitation. This has made it difficult to relate SNPs to the genes and functions that are responsible for the condition in question. These are the aspects of GWAS on blood pressure that are considered to be the most significant.

All of the blood pressure-related SNPs that were discovered by GWAS account for around 27% of the estimated heritability of the blood pressure phenotype, which ranges from 30–50%, and approximately 5.7% of the phenotypic variation of SBP14. It is anticipated that the remaining unaccounted heritability will be accounted for by SNPs whose impact values fall substantially below the significance threshold for the entire genome.

Any given SNP only has a marginal impact on blood pressure, measuring approximately 1 mmHg for systolic blood pressure and 0.5 mmHg for diastolic blood pressure 14.

In GWAS, single nucleotide polymorphisms (SNPs) known as tag SNPs are used to tag common variations in the genome that are caused by linkage disequilibrium. These arrays do not cover rare or structural variants, and the information for genomic regions with low linkage disequilibrium is severely limited. SNPs that are significant over the entire genome are not likely to be causal SNPs; rather, they correspond with a nearby functional genetic variation. This variation can be discovered by utilizing trans-ethnic data and representative imputation panels.

The majority of blood pressure loci revealed through the use of GWAS are mutations in non-coding regions that are considered to influence gene regulation. On the other hand, GWAS loci in recognized genes that are known to cause monogenic disorders appear to be sparse. Mendelian illness genes are significantly overrepresented in GWAS loci40, according to investigations that looked at 62 additional complex features and their corresponding monogenic syndromes.

The vast majority of SNPs that were found to be connected to blood pressure and other complicated variables through the use of GWAS are common variations that had allele frequencies of more than 1% in the general population 41. In genome-wide association studies (GWAS) on blood pressure, people of European ancestry have been overrepresented, which reduces the findings' capacity to be generalized to a wider population.

The use of merging all discovered genetic variations into a single genetic risk score for the purpose of predicting an individual's level of risk has not yet been demonstrated, and doing so could result in an incorrect risk assessment among people of non-European ancestry42. In the UK Biobank, an increase of one standard deviation in the genetic risk score for blood pressure was connected to increases in systolic blood pressure of 3.9 mmHg, 2.4 mmHg, and 2.6 mmHg, respectively, among people of European, African, and South-Asian descent14. This was the case for people of European, African, and South-Asian origin.

For example, the Trans-Omics for Precision Medicine program is a large-scale collaboration that uses whole-genome sequencing in multi-ethnic populations to fill knowledge gaps on genomic and other omic markers of hypertension and cardiovascular disease, with the aim of speeding up the implementation of precision medicine. This program's primary objective is to fill knowledge gaps on genomic and other omic markers of hypertension and cardiovascular disease.

The GWAS led to the identification of previously unknown pathways.

Only a small fraction of the SNPs found by GWAS have been connected to the processes that cause the disease or clinical applications43. The haplotype structure of the genome, the fact that the majority of GWAS signals occur in the non-coding region of the genome, and the presence of ubiquitous pleiotropy39,43 are all factors that make it difficult to establish a link between a gene and its function. This section provides a description of the pathophysiological processes that have emerged as a result of GWAS conducted on blood pressure. These mechanisms are involved in the control of blood pressure.

Uromodulin and NKCC2 make up the axis.

The minor allele of an SNP that is located in the promoter region of the gene that produces uromodulin (UMOD) (rs13333226) is connected to lower blood pressure and urine uromodulin levels44, according to a GWAS that looked at blood pressure extremes. The only location where uromodulin is expressed is in the thick ascending limb, which is also the location where 25 percent of the sodium that has been filtered is reabsorbed. In mice lacking uromodulin, there is a low blood pressure symptom, there is no uromodulin in the urine, and there is no salt-induced elevation in blood pressure (as shown by a shift to the left of the blood pressure–natriuresis curve). According to the findings of this study, a potential new mechanism for the regulation of blood pressure and renal function may involve the interaction of uromodulin with the renal cotransporter NKCC2 in the thick ascending limb.

Loop diuretic furosemide, which is used extensively, has been shown to block NKCC2. Furosemide treatment led to significantly increased natriuresis and reduced blood pressure levels in transgenic mice that overexpressed uromodulin, as well as in patients with hypertension who were homozygous for UMOD risk variants that increased UMOD expression compared to other patients with hypertension46. This discovery is the foundation for a clinical trial that is currently under way to reposition a loop diuretic into the hypertension therapeutic pathway47.

Endothelin's Molecular Pathway

SNPs rs9349379 (in PHACTR1), rs1630736 (in EDN1), and rs10305838 (in EDNRA) 14 are associated with the endothelin pathway. These SNPs were discovered through genome-wide association studies (GWAS) on blood pressure. A lower risk of migraines, cervical artery dissections, fibromuscular dysplasia, and hypertension are associated with having the minor allele of the PHACTR1 gene's intronic SNP rs9349379, whereas a higher risk of coronary artery disease is associated with having the major allele. 48 and 49. After that, it was found out that this SNP was a distal regulator of the EDN1 expression 48,49. Endothelin 1 is the most prevalent form of the endothelin isoform, and it exerts a potent vasoconstrictor effect by acting in a paracrine manner on vascular smooth muscle cells. This effect is mediated by endothelin receptor subtype A (ETA) and endothelin receptor subtype B (ETB) (.50). Despite the fact that endothelin-receptor antagonists lower blood pressure, they have not been widely used as antihypertensive drugs due to the fact that they cause adverse effects or fail to meet the primary objective of clinical trials 50,51. A phase II trial of aprocitentan, a dual ETA–ETB antagonist52, produced encouraging results53, which prompted the initiation of a phase III trial known as the PRECISION study54, which is now being conducted. According to the research, endothelins could potentially play a role in non-obstructive coronary artery disease55. Zibotentan is currently being studied in those who have microvascular angina as part of a clinical trial that is being driven by genotype56.

Alternate possibilities

The use of GWAS has indicated that NPR3, which encodes the natriuretic peptide receptor C, is another viable target for blood pressure management. NPR3 causes an increase in blood pressure by increasing vascular smooth muscle cell proliferation, angiotensin II-induced calcium flux, and vessel contraction57. This target is a potential blood pressure regulator. Two other genes have been connected to the regulation of blood pressure, and those genes are SLC4A7 and SLC39A8 (58,59). Increased ERK2 phosphorylation, nuclear factor-B activation, cadmium accumulation, and reduced vascular endothelial cell viability59 have all been linked to the Ala391Thr mutation in the SLC39A8 gene.

levels of risk due to many genes

Because an individual's genetic make-up remains mostly unchanged from birth to adulthood, genetic information has the potential to be utilized as an early risk predictor. In order to make a meaningful risk prediction for essential hypertension, it is necessary to examine the aggregated effect of the various variations by developing a single measure that represents the individual's entire genetic risk. This is because essential hypertension is caused by a number of genetic variants, each of which has a relatively little influence on its own. This genetic risk was initially assessed as a simple genetic risk score, which was an additive tally of the number of risk alleles carried by an individual60 (usually from a few SNPs from GWAS, occasionally weighted by effect sizes). This was the first method that was used to calculate this genetic risk.

As a result of the discovery that single nucleotide polymorphisms (SNPs) that do not satisfy extremely stringent significance thresholds for genome-wide association can also be predictive of disease, over the course of the past ten years, a wider variety of SNPs, numbering anywhere from thousands to millions, has been used to produce an improved genetic risk score that has been dubbed a polygenic risk score61. The risk information that is obtained from genetic markers of monogenic disorders is binary, meaning that it either indicates a high chance of disease or a low probability of sickness, but the polygenic risk score offers a probabilistic range of risk. In addition, the presence of a rare genetic variant is indicative of the variant's one-of-a-kind biological impact, whereas the polygenic risk score is an accumulation of numerous variants with little effects that are dispersed throughout the genome, and there is no specific pathway that is implicated. A polygenic risk score for blood pressure that was derived from all of the important genome-wide SNPs that were discovered in GWAS revealed a meaningful association with stroke, coronary artery disease, heart failure, and left ventricular mass, but not renal function21,62. The fact that there is no correlation between this blood pressure polygenic risk score and renal function demonstrates that even with successful treatment of high blood pressure, progression to renal impairment brought on by hypertension may still occur. The highest 20% of a person's genetic risk score was associated with a 35–40% higher risk of cardiovascular disease, myocardial infarction, and stroke when compared to the lowest 20% of a person's genetic risk score. 14th. Indicating that SBP is causally connected to the risk of coronary artery disease62, the computed odds ratio for a 5 mmHg rise in SBP on the risk of coronary artery disease is 1.30 (95 percent confidence interval: 1.18–1.44). These findings are in line with the findings of a meta-analysis of clinical research, which discovered that a reduction in systolic blood pressure of 10 mmHg resulted with a 17–27% reduction in the risk of major cardiovascular events. Number 63. Using GWAS SNPs related to blood pressure and LDL cholesterol, a Mendelian randomization study was conducted to assess the association between lifetime exposure to the combination of lower LDL-cholesterol levels and lower SBP and the lifetime risk of cardiovascular disease. The study found that participants with SBP genetic scores higher than the median had lower blood pressure (2.9 mmHg) and a lower risk of major coronary artery disease. This was the conclusion of the study. Our analysis verified the independent relationships between LDL-cholesterol levels and SBP and the risk of cardiovascular disease64 in a dose-dependent and log-linear fashion. Furthermore, we found that these associations increased with higher SBP.

The use of polygenic risk scores as biomarkers to guide early intervention or preventive strategies has piqued the public's interest. However, the effectiveness of these strategies is contingent on whether or not knowledge of a higher genetic risk of a disease will motivate individuals to adopt a healthier lifestyle, for which there is conflicting evidence. 65, 66, and 67. A study that was conducted by the UK Biobank and published in 2018 found that living a healthy lifestyle (which included eating healthy, limiting alcohol consumption, having a low urinary sodium excretion, having a low BMI, and increasing physical activity) was linked to lower blood pressure regardless of the underlying blood pressure genetic risk.

This suggests that genetically predetermined high blood pressure and the complications that come with it can be avoided. It will be necessary to conduct prospective, randomized, controlled investigations before these findings can be implemented into clinical practice.

Because the majority of the people who contributed to the development of current polygenic risk scores are of mostly or mostly European ancestry, there have been questions raised about the degree to which these scores may be transferred to populations with diverse ancestral backgrounds. Clinical use of current polygenic risk scores would systematically afford greater improvements to European-descent populations, exacerbating health disparities. Preliminary data show that polygenic risk scores can still discriminate between high-risk and low-risk groups in other ethnicities69, but not as well as in European-ancestry populations. The options for addressing health disparities range from recalibrating scores to developing large GWAS projects in more diverse populations. Polygenic risk scores can currently only be employed in populations of European ancestry, and this limitation will remain in place until these approaches provide data that is specific to individual ancestries.

PheWAS is quite similar to GWAS, with the main difference being that PheWAS analyzes each genetic variation for correlations with a wide range of phenotypes, whereas GWAS normally analyzes just one trait at a time. This is due to the fact that GWAS investigates just one phenotype at a time. PheWAS makes it possible to find pleiotropic SNPs and overlapping traits, which can help with the prioritizing of identified signals to be tested in subsequent study. The universal pleiotropy of blood pressure-associated GWAS SNPs was demonstrated by the fact that we were able to extract all phenotypic correlations of 1,477 GWAS blood pressure SNPs by using a P value threshold of 5 10–5. This was accomplished by searching the GWAS Catalog72 and PhenoScanner73. There are around 1,400 SNPs that are associated to blood pressure, however only a small number of those SNPs are not pleiotropic, and there are only six SNPs that are located in genes that are linked to monogenic blood pressure diseases. The most pleiotropic signals can be found in anthropometric variables like height and body mass index (BMI), as well as assessments of adiposity and visceral fat. Then there are the haematological aspects, which comprise measurements of the number of platelets, white blood cells, and red blood cells in the patient's blood. Only four of the SNPs related to blood pressure are linked to an increased risk of stroke, despite the fact that hypertension is associated with a higher risk of stroke. A total of 79 SNPs associated to blood pressure have also been connected to coronary artery disease, with the majority of these associations overlapping with lipid characteristics. The number of SNPs that have been linked to coronary artery disease totals 79. It is necessary to do additional research into these pleiotropic connections in order to determine whether or not they are indicative of confounding, reverse causation, or whether or not they reveal causal interactions with blood pressure management.

The number of single-nucleotide polymorphisms (SNPs) connected to blood pressure that are also linked to other variables is represented by the number of overlapping circles in the Venn diagrams. All of the pleiotropic connections for the 1,477 SNPs that were reported as being connected with blood pressure in genome-wide association studies (GWAS) were obtained by querying the GWAS Catalog72 and PhenoScanner73 with a P value cutoff of 5 tens of thousands. This was done in order to meet the criteria for the study. a panorama of pleiotropy depicting the world, showing the different phenotypic categories that exist and the number of blood pressure-related SNPs that overlap with each group (in brackets). The general phenotypic classifications were made by compressing a wide range of characteristics that may be grouped together under each heading. b | A detailed depiction of the members of the important phenotypic categories, highlighting the contribution of individual traits as well as the degree of pleiotropy associated with blood pressure-related SNPs and the overlap between them. CAD is for coronary artery disease; CVA stands for cerebrovascular accident; NT-proBNP stands for N-terminal pro-B-type natriuretic peptide; RBC stands for red blood cell. BMD stands for bone mineral density; CAD stands for coronary artery disease; CVA stands for cerebrovascular accident.

The genotype is fixed from the moment of conception onward and cannot be changed. As a consequence of this, variation in the genotype can serve as a natural experiment to demonstrate the existence of causal connections between risk factors and health consequences. Variation in a person's genome is unaffected by factors such as their environment or lifestyle, and illness is not able to have an effect on it. Mendelian randomization studies74 are conducted with the presumption that this is the case. The pleiotropic traits that are associated with SNPs related to blood pressure from GWAS are described in detail in the following subsections. These descriptions are based on published Mendelian randomization studies that aim to determine whether or not these pleiotropic traits have a causal role in the regulation of blood pressure and hypertension.

The accumulation of fat in the body is what defines obesity.

There is a correlation between blood pressure and body mass index (BMI), and epidemiological research indicates that for every 5 kg of body weight lost, there is a corresponding drop of 4 mmHg in SBP75. To evaluate the causal impact of BMI on blood pressure control, a Mendelian randomization study used two SNPs that are reliably associated to BMI (rs9939609 in FTO and rs17782313 in MC4R). The study indicated that a 10% increase in genetically determined BMI was related to a 3 mmHg rise in SBP76. Studies have shown that a higher visceral fat mass index as well as a higher BMI are both connected to higher blood pressure, which suggests that BMI might be a suitable proxy for visceral fat77. This is the case despite the fact that visceral fat is a stronger indication of the risk of developing cardiovascular disease.

Ingestion of alcoholic beverages

The use of alcohol was affected in a pleiotropic way by a total of 18 SNPs that were connected to blood pressure. A strong dose–response association between lower alcohol consumption and lower blood pressure levels has been discovered by interventional clinical research78. Researchers have used Mendelian randomization trials with two indicator variables, namely the variants rs1229984 in ADH1B and rs671 in ALDH2, as will be discussed further below, in order to determine whether or not there is a causal connection between alcohol use and blood pressure levels. The rs1229984 SNP is quite common in white individuals. It is responsible for an increase in the activity of alcohol dehydrogenase 1B, which ultimately leads to a quicker oxidation of alcohol to acetaldehyde79. The rs671 mutation is extremely common in East Asian cultures. This polymorphism suppresses mitochondrial aldehyde dehydrogenase, which in turn limits acetaldehyde metabolism. A correlation between having a low SBP81 and having a lower genotype-predicted alcohol intake was discovered using an exhaustive Mendelian randomization meta-analysis of the rs1229984 variation in 56 epidemiological studies including a total of 261,991 people of European origin. SBP rose by 4.8 mmHg per 280 g per week of genotype-predicted alcohol intake, according to research from the China Kadoorie Biobank that involved 161,498 people and analyzed both rs1229984 and rs671. Men are likely to consume more alcohol per drinking session than women, which might explain the gender disparity. In spite of the fact that the findings of epidemiological and Mendelian randomization research are consistent with one another, there is one important qualification to make. Because the ALDH2 genotype is linked to blood pressure regardless of whether or not a person drinks alcohol, this variation cannot be used in a Mendelian randomization study.

The baby's weight at birth

According to GWAS, 28 of the 65 SNPs that are associated to an individual's birthweight are also linked with their blood pressure. The finding that having a low birthweight is associated with a larger chance of developing high blood pressure later in life 83,84 offers two possible explanations, as indicated by a study based on the Mendelian randomization method 85. Both an indirect maternal effect, in which alleles that elevate maternal blood pressure also diminish the birthweight of the offspring, and a direct fetal effect, in which these same alleles produce high blood pressure in the offspring when they are inherited, are involved. The fact that maternal genotypes connected to low birthweight in kids were not linked to higher blood pressure in kids was identified by the researchers. This finding indicates that the inverse association between birthweight and blood pressure is attributable to genetic factors rather than intrauterine effects85.

A particular elevation

There was a pleiotropic association between height and blood pressure in 199 SNPs that were linked to blood pressure. Several epidemiological research 86, 87 have come to the conclusion that an adult's height and their blood pressure levels are inversely associated to one another. According to Mendelian randomization analysis, taller people have a lower risk of hypertension and coronary artery disease, but a higher chance of atrial fibrillation, venous thromboembolism, and neoplasms89. The early development of lected waves in blood flow during systole, which mix with the forward wave, resulting in the amplification of SBP88, could be one cause of the higher SBP observed in people of short stature. With a significant number of common genetic loci91, height and lung function are strongly linked, and it has been demonstrated that lung function (rather than blood pressure) is the mediator of the influence of height on the risk of coronary artery disease. A one standard deviation increase in genetically determined height (6.5 cm) lowers the risk of coronary artery disease by 16% and hypertension by 12%89. 91.

beats per minute of a pulse

It has been discovered that a total of 61 SNPs that are associated to blood pressure also have a pleiotropic relationship with heart rate. According to observational studies, those who have hypertension tend to have a faster heart rate than those who do not have the condition. Furthermore, having a faster heart rate has been associated to the development of hypertension92. In Mendelian randomization studies93, the researchers found that the relationship of resting heart rate on hypertension was only moderate.

Blood's defining traits and characteristics

Blood cells are necessary for oxygen transfer, maintaining blood flow and clotting, regulating both innate and acquired immune responses, maintaining iron homeostasis, and maintaining proper vascular and endothelial function. Observational studies have found a correlation between the total white blood cell, granulocyte, and neutrophil counts, as well as features of red blood cells, and the risk of developing coronary heart disease. 9 Despite this, a Mendelian randomization study did not find any correlation between total white blood cell count, granulocyte count, neutrophil count, or red blood cell count with the risk of coronary heart disease 101. The researchers were surprised to find that there was a slight positive connection between reticulocyte indices and platelet volume and the risk of coronary heart disease101.

Higher reticulocyte counts indicate a higher level of hemolysis, which leads to increased levels of free haemoglobin in circulation and lower levels of nitric oxide102. Nitric oxide is an important vasoprotective factor that is produced by the endothelium. It has hypertensive, antithrombotic, and antioxidant properties, and nitric oxide depletion has been associated to atherosclerosis103. In addition, the presence of free haemoglobin in blood substitutes has been associated with decreased amounts of nitrous oxide, increased vasoconstriction, and an increased risk of acute myocardial infarction 104.

The fact that there is no causal association between greater platelet volume and a reduced risk of coronary heart disease101 contradicts the findings of systematic reviews and observational studies 105, which suggests that additional study is required.

Educational level and social standing both play a role.

Research106 has found a correlation between the risk of cardiovascular disease and education as well as other socioeconomic factors. Nevertheless, educational possibilities are not dispersed equitably among the general population, which makes it challenging to do interventional research 107. According to the findings of a Mendelian randomization study that used data from the UK Biobank, each additional standard deviation of educational attainment (3.6 years) was associated with a 37% lower risk of coronary heart disease. SBP mediation accounted for 21% of the total risk reduction, while BMI and smoking mediation accounted for another 21% of the total risk reduction. 108 is the correct answer.

Alzheimer's disease is a form of dementia that can impact a person's

A lower risk of Alzheimer's disease is associated with genetic lifetime exposure to high SBP levels (odds ratio per standard deviation (15.4 mmHg) of SBP 0.75, 95 percent confidence interval (CI) 0.62–0.91, P = 3.4 103) and a greater likelihood of using antihypertensive medication109. This association was found in a study conducted by the Alzheimer's Association.

Pharmacogenomics

The purpose of genomics is to facilitate the practice of precision medicine by increasing one's understanding of the molecular pathways that govern blood pressure. This increased understanding has the potential to result in the discovery of new medications, the customization of treatments, and ultimately the development of a new taxonomy for hypertension110. However, there are still a great number of challenges that stand in the way of accomplishing this objective. Since the beginning of the 21st century, there has not been a single new hypertension drug that has been approved for use. Beyond taking into account the patient's self-reported level of African ancestry and serum renin levels2,4, there has been no progress made toward individualizing treatment for each patient. The ever-expanding number of genetic polymorphisms that have been connected to hypertension and blood pressure opens up new options for improving our understanding of the etiology of hypertension and rewriting and updating the disease's molecular taxonomy, both of which will contribute to the development of more precise treatments for hypertension. This assumption is supported by research that indicated an increase of 6% in effectiveness and safety rates in pharmaceutical validation efforts when genetic data was included 111. The findings of this study provide credence to the aforementioned assertion.

We connected all SNPs related with blood pressure in GWAS to the DrugBank database112 and the Comparative Toxicogenomics Database113 in order to extract gene–drug interactions for the likely genes that were mapped to the area of the SNPs in past studies14. This allowed us to extract gene–drug interactions for the likely genes that were mapped to the area of the SNPs. All of the major types of antihypertensive medications are represented in the pharmacogenetic interaction with the GWAS loci that were investigated. This conclusion may suggest that the putative published genes that are connected to the SNPs that are related to blood pressure in GWAS were selected for their fair blood pressure impact. Interactions between genes and drugs revealed a considerable number of pharmaceuticals that modify blood pressure. Many of these medicines are already authorized for the treatment of other conditions, but many are known to have the unintended side effect of either lowering or raising blood pressure. Based on these data, it appears that one of the earliest potential benefits of GWAS could be the repurposing of existing drugs for the treatment of hypertension.

Repurposing, sometimes known as multitasking

In the current climate of decreased financing for new drug research and lower rates of new drug approvals114, the process of identifying new indications for existing treatments, which is known as drug repositioning or repurposing, is becoming an increasingly significant aspect of the pharmaceutical industry. One option that could increase the likelihood of successful therapeutic development and approval is to repurpose existing drugs so that they are used to treat a target that has a genetic basis. Indeed, genetic research has uncovered a sizeable number of genes whose products (encoded proteins) are targeted by pharmacological agents that are already in use as well as those that are in the process of being developed (for example, ESR1 for tamoxifen, CYP19A1 for aromatase inhibitors, and HMGCR for statins) 115,116. Significant advances in functional genomics and computational methods can assist speed up the process, despite the fact that GWAS SNPs must still be shown to have a causal connection to a target gene. Riociguat, a guanylate cyclase stimulator, has recently been given the green light for use in the treatment of pulmonary arterial hypertension. This drug has been linked to the GUCY1A2 region, which is a part of the genome that has been linked to blood pressure in genome-wide association studies. Hypotension is a common side effect of riociguat117, which brings attention to the possibility of using riociguat as a treatment for decreasing blood pressure. Another medicine that has the potential to be repurposed is nesiritide, which is a recombinant B-type natriuretic peptide connected to NPR3, a gene associated to blood pressure that was discovered through the use of GWAS. Nesiritide, on the other hand, was not successful in treating acute decompensated heart failure in a clinical investigation and was associated with an increased risk of hypotension118. Inhibitors of sodium–glucose cotransporter 2 (SGLT2) lower blood pressure while simultaneously lowering glucose levels. 119. Molecular docking studies suggest that the SGLT2 inhibitor canagliflozin may serve as a dual inhibitor of acetylcholinesterase and SGLT2 (120-267). This finding is supported by the fact that the encoding gene for acetylcholinesterase has been identified as a blood pressure locus in GWAS.

But the process of repurposing pharmaceuticals needs to be carried out with extreme caution in order to protect patients from being exposed to unintended side effects or problems that result from the treatments' more widespread application. The majority of antidepressant and antiepileptic medications, for example, include hypotension as a side effect, which means they could potentially be repurposed to treat hypertension. This presents an opportunity to develop new treatments for the condition. Concerns arise when these drugs are repurposed for use in the treatment of hypertension because of the pharmacological goals of these medications.

For instance, the antipsychotic medication olanzapine interacts with multiple GWAS blood pressure loci (ADRB1, APOE, BCL2, CHRM2, CTNNB1, IL6, and MTHFR–NPPA); additionally, olanzapine's pharmacological targets include the muscarinic acetylcholine receptors M1–M4, the histamine receptor, the 5-hydroxytryptamine receptor, the-type and-Topira Topiramate acts on a number of different pharmacological targets, including glutamate receptors122, the voltage-gated sodium channel, carbonic anhydrase, and the aminobutyric acid receptor.

The outcomes of these two cases highlight the risks associated with repurposing drugs for the treatment of hypertension. Instead, we believe that the potential for these treatments lies in a process known as "multipurposing." This is because the increasing prevalence of multimorbidity in the general population makes it necessary to develop medicines that can treat a number of different conditions. As a consequence of this, there is a possibility that persons who suffer from epilepsy and hypertension, or depression and hypertension, could be screened for drugs that treat both conditions at the same time. It is necessary to conduct randomized controlled studies in order to determine whether or if the use of this method improves treatment adherence and the results for both disorders.

Conclusion

In the study of hypertension genomics, there have been many genetic markers discovered; nevertheless, there have been very few outcomes that can be acted upon. The follow-up and clinical translation of these genetic findings appear to have a bright future as a result of the confluence of pharmacogenomic research, pleiotropic research, and functional research. The fact that endothelin-related SNPs have made it to the clinical trial stage is an indication of the greater success being made in hypertension precision medicine, which is directly translated from genetic research. Even if the utilization of polygenic risk scores seems intriguing, their clinical efficacy needs to be evaluated in controlled study, and the potential ethical challenge posed by their widespread application leading to an increase in health disparities needs to be examined further.

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