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Keywords: Hypertension, Genome-Wide Association Studies (GWAS), Polygenic Risk Scores (PGS), Computational Genomics, Precision Medicine

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Contents

Introduction

The global epidemic of hypertension impacts over 1.13 billion people across the globe, and it has been regarded as a significant risk factor that leads to cardiovascular diseases associated with stroke, heart attack, and the occurrence of kidney failure (Maj et al., 2022). Although it is a widespread disorder, the genetic etiology of hypertension is poorly understood, and

attempts at the prognosis and personalization of treatment plans have been impaired due to the multifactorial nature of the disorder. Genetics and environmental influences play a role in regulating blood pressure; however, understanding how these two factors interact is crucial in the study of hypertension. The discovery of genetic variants that determine hypertension has been the primary target of recent research studies, and there have been enhanced efforts towards the development of predictive models, as well as therapeutic approaches based on genetic knowledge (Khera et al. 2022; Keaton et al., 2024).

This review provides a comprehensive overview of the genomic understanding of high blood pressure, including the most recent breakthroughs in Genome-Wide Association Studies (GWAS) and Polygenic Risk Scores (PGS), as well as original research on candidate genes. Genetic studies initially focused on hypertension, centered on particular genes thought to be important in blood pressure management. The research primarily concentrated on variants in the renin-angiotensin-aldosterone system (RAAS) and other vascular systems. However, the possibility of GWAS opened the doors to a more comprehensive system, revealing hundreds of genetic variations that make a small, independent contribution to the risk of hypertension, but have foundational effects when combined. Such attempts have been complemented by computational genomics, where extensive data are combined to optimize genetic models of prediction and overcome issues of missing heritability (Singh et al., 2023; Keaton et al., 2024).

PGS has so far shown promise in predicting the risk of developing hypertension by simply combining the effects of the many small-effect genetic variants discovered using GWAS (Øvretveit et al., 2024). Although the early PGS models were inferior due to the small sample size and heterogeneity of the population, recent developments have led to PGS models with greater predictive value, particularly those created based on diverse and multi-ancestry samples (Wang et al., 2025). Such genetic findings will transform the problem of hypertension through their prevention and treatment, allowing for the identification of people at the highest genetic risk earlier and the development of more individualized treatment approaches (Khera et al., 2022).

Nevertheless, translating genetic discoveries into clinical applications remains challenging due to concerns about ethnic diversity, gene-environment interactions, and the lack of clinical applications (Wang et al., 2025). Furthermore, combining genetic information with environmental and clinical data through machine learning and other computational analyses offers the potential to refine hypertension risk prediction and improve patient outcomes (Grealey et al., 2024). This review aims to examine developments in genetic research concerning the evolution of hypertension genetics, from candidate gene studies to the present, where GWAS and PGS are currently being developed. It also outlines the future challenges that the field of computational genomics faces, which can transform the direction of hypertension prediction and management.

Methodology:

Search Strategy

This review provides an overview of the genetic understanding of hypertension, with a focus on studies guided by GWAS, PGS, and computational genomics. The studies reviewed are those carried out globally, preferably with studies of different populations, which will capture the genetic spectrum of hypertension. The publications published between January 2015 and the present were also taken into consideration, encompassing both the oldest and the latest publications in the field. The review explains genetic research relating to hypertension, which focuses on loci identification through GWAS, development and construction of PGS, and computer methods to integrate genetic information. All studies that did not relate to the field of hypertension or involved genetic research, or those that involved only animal or non-human subjects, were excluded.

Inclusion and Exclusion Criteria for Studies

Qualitative studies also needed to be established, which is why the issue of study rigor was considered. The quality of the specific study was mentioned regarding the sample size involved, as a minimum of 100 participants is required to obtain reliable and reproducible data. The statistical rigor criterion also played a significant role, prioritizing articles that utilized applicable statistical analyses, such as adjusted regression models, imputation of missing genetic data, and multiple testing adjustments. An exercise was conducted to ensure that the studies could be replicated, i.e., the findings were also established in subsequent cohorts or meta-analyses. Moreover, the methodological clarity of the research has also been considered, and priority was given to studies that provided precise data on data processing, statistical analysis, and possible biases.

Databases Searched and Keywords Used

A comprehensive search strategy was employed using multiple academic databases to ensure the inclusion of high-quality and relevant studies. Databases searched included PubMed, Scopus, and Web of Science. Keywords and phrases used for the search included: "genetic hypertension," "GWAS and hypertension," "polygenic risk scores for hypertension," "computational genomics in hypertension," "hypertension genetics," and "genetic predictors of blood pressure." The search was refined using Boolean operators (AND, OR) to ensure that all possible articles concerning the genetic basis of hypertension were retrieved. The snowballing and citation tracking were also used to recognize the studies cited in the relevant articles.

Study Quality Assessment

A study rigor assessment was carried out in order to ascertain the inclusion of high-quality studies. The quality of every study was determined by the size of the sample, whereby in most cases, a study was expected to have a minimum sample size of 1,000 participants to be reliable enough to yield a reproducible outcome. Statistical rigor was also a prominent criterion, and studies that used suitable statistical models, including adjusted regressions, imputation to derive missing genetic data, and multiplicity adjustments, were favored. Research studies were considered in the replication endeavors, ensuring that the findings were confirmed in separate cohorts or meta-analyses. Additionally, the transparency of the study methods was taken into account; studies were preferred that provided clear information about the data processing, statistics, and potential sources of bias.

Data Synthesis Approach

The synthesis method of data is used to determine the synthesis approach that will be adopted within the research. The results of the research studies were organized using narrative synthesis, which divided the findings into groups, highlighting essential themes: GWAS, development and validation of PGS, and computational genomics. The studies included are heterogeneous; therefore, it was not possible to carry out a formal meta-analysis. Instead, the comparisons were made across the studies, employing a qualitative approach that involved investigating similarities and differences in the findings. There was an emphasis on identifying patterns in hypertensive genetic loci and evaluating the performance of polygenic risk scores in various populations. A collaboration between them marked the conclusion of the studies, during which the most commonly replicated loci were identified, and the clinical implications of genetic predictors of hypertension were discussed.

Methods for Identifying Patterns and Consensus

Techniques to Detect Patterns and Consensus. To identify patterns and achieve consensus across studies, the most significant genetic single-nucleotide variants associated with hypertension were compared across studies. Special emphasis has been made regarding loci that were replicated in several GWAS and validated in independent populations. Another point the review considered is the performance of the polygenic risk scores (PRS) in predicting hypertension across diverse populations. Common and novel outcomes of studies were summarized, and key methodologies, such as genetic pathway analysis and bioinformatics tools, were scrutinized to compile the data. The results were reoriented in terms of potential gene-environment interplay and population particularity, which provides a unified view of genetic prediction models for high blood pressure.

Genetic Architecture of Hypertension:

Heritability and Genetic Basis

Hypertension is a multifactorial, hereditary disease with some risk being estimated by the family study and by the twin studies. It may vary (Waken et al., 2017). Regulation of blood pressure and hypertension is associated with genetic variants that are classified as non-standard and rare. GWAS have identified hundreds of common single-nucleotide polymorphisms (SNPs) associated with blood pressure characteristics, but the individual effects of these SNPs are only moderate. On the other hand, rare variations may have more pronounced effects and are sometimes associated with solitary hypertension (Carney, 2019). Depending on the interaction with the environment, the outcome is the sensitivity of individuals to hypertension caused by these variants (Ahn and Gupta, 2018).

The primary biological processes contributing to hypertension are associated with the regulation of sodium in the kidneys, vascular tone, and ion transport. The SS equation: The control of blood pressure involving individual genes in the renal system (such as those encoding the protein components of the RAAS) through mediation of fluid and electrolyte homeostasis (Carney, 2019). Vascular health is susceptible to the

pathways of endothelial and smooth muscle contraction. At the same time, ion transporters are crucial in maintaining electrolyte gradients in the cell membrane. More than an opportunity to illustrate the complex genetic properties of hypertension, these pathways present a therapeutic intervention possibility (Maj et al., 2022).

Candidate Gene Studies in Hypertension

Candidate gene studies have historically focused on specific genes within the RAAS, such as ACE (angiotensin-converting enzyme), AGT (angiotensinogen), and ADRB1 (β1-adrenergic receptor), due to their roles in blood pressure regulation (Table 1). For instance, the ACE I/D polymorphism has been associated with hypertension risk, with the D allele linked to increased ACE activity and elevated blood pressure levels (Trevisano et al, 2024). Similarly, polymorphisms in the AGT gene, notably M235T and T174M, have been implicated in hypertension susceptibility, with certain alleles showing stronger associations in Asian populations (Fajar et al., 2019). Variants in the ADRB1 gene, such as Arg389Gly, have also been studied for their potential impact on blood pressure regulation and response to antihypertensive medications (Chen et al., 2018). These studies have provided valuable insights into the genetic underpinnings of hypertension, highlighting the involvement of specific genes in its pathogenesis.

Table 1

Key Genes Involved in Hypertension would be placed here, providing a summary of these genes, their polymorphisms, and the biological pathways they influence.

Gene	Key Polymorphisms	Biological Pathway Influenced	Functional Role / Notes	Reference
ACE	I/D (Insertion/Deletion, rs4340)	RAAS	Converts angiotensin I to angiotensin II, regulating vasoconstriction and fluid balance.	Marushchak et al., 2019
AGT	M235T (rs699), T174M	RAAS	Encodes angiotensinogen, precursor of angiotensin I; influences plasma angiotensin levels.	Gunda et al., 2016
ADRB1	Arg389Gly (rs1801253)	Sympathetic Nervous System, Vascular Function	β1-adrenergic receptor; modulates heart rate, cardiac output, and β-blocker response.	Rudemiller and Mattson, 2015
ADD1	Gly460Trp (rs4961)	Sodium Regulation, Renal Function	Influences renal sodium reabsorption; it is associated with salt-sensitive hypertension.	Liao et al., 2015
CYP11B2	-344C/T (rs1799998)	Aldosterone Synthesis (RAAS)	Encodes aldosterone synthase; regulates aldosterone production and sodium retention.	Shah et al., 2023
NOS3	Glu298Asp (rs1799983)	Vascular Function, Nitric Oxide Pathway	Encodes endothelial nitric oxide synthase; regulates vascular tone and endothelial health.	Shnayder et al., 2021
GNB3	C825T (rs5443)	G-Protein Signaling	Influences signal transduction in vascular smooth muscle; associated with hypertension risk.	Sydorchuk et al., 2023
RGS2	1891-1892del TC, G638A	G-Protein Signaling, Vascular Tone	Regulates G-protein signaling; variants linked to hypertension susceptibility.	He et al., 2015
CYP4A11	T8590C (rs1126742)	Fatty Acid Metabolism, Vascular Tone	Involved in 20-HETE synthesis; affects renal sodium transport and vascular constriction.	Zhang et al., 2017
TH	rs2070762	Catecholamine Biosynthesis	The tyrosine hydroxylase gene influences sympathetic nervous system activity.	Lee et al., 2016
ADRB2	Q27E (rs1042714)	Sympathetic Nervous System	β2-adrenergic receptor; modulates vascular smooth muscle relaxation.	Maamor et al., 2024
GRK4	A486V	Dopamine Receptor Signaling, Sodium Balance	G-protein receptor kinase 4 affects renal dopamine receptor function and sodium excretion.	Zhang et al., 2015

Gene	Key Polymorphisms	Biological Pathway Influenced	Functional Role / Notes	Reference
SELE	rs4656704	Vascular Inflammation	Encodes E-selectin; involved in endothelial adhesion and inflammation.	Xie et al., 2021
PRKG1	rs1904694, rs7897633	Vascular Smooth Muscle Relaxation	Encodes cGMP-dependent protein kinase; regulates vascular tone.	Xie et al., 2021
SLC8A1	rs11893826	Ion Transport, Sodium-Calcium Exchange	Encodes sodium/calcium exchanger; important in vascular smooth muscle function.	Xie et al., 2021

Limitations and Evolution of GWAS

Despite their contributions, candidate gene studies have several limitations. They often suffer from selection bias, as genes are chosen based on prior hypotheses, potentially overlooking other relevant genes. Additionally, these studies typically have small sample sizes, leading to limited statistical power and generalizability of findings. The fact that they are not replicated in other populations also raises doubts about the strength of observed associations. Additionally, studies on candidate genes often tend to consider individual variants, thereby failing to recognize the multifactorial nature of hypertension. Such restrictions have necessitated the use of GWAS, which involve scanning the entire genome to identify associations with hypertension and the potential discovery of many new loci, thereby providing a better understanding of the genetic components of hypertension. In contrast to candidate gene-based studies, GWASs have addressed most of the limitations of such approaches by affording the use of large and diverse sample sets combined with a high-throughput genotyping technology, and hence the profiling of genetic variants that may relate or associate with hypertension in a better manner (Singh et al., 2023; Keaton et al., 2024; Naderi et al., 2025).

Genome-Wide Association Studies (GWAS) in Hypertension:

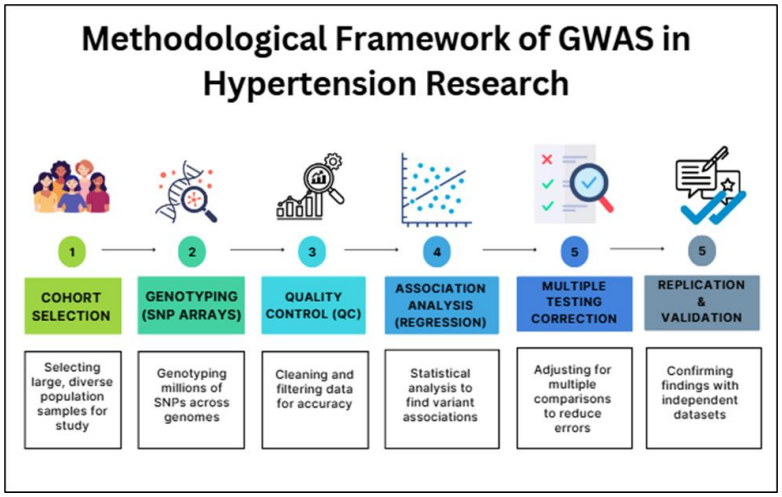
Methodological Framework of GWAS in Hypertension Research

Hypertension GWAS Methodological Framework. As presented in Figure 1, the generic structure of GWAS in the study of hypertension was covered. Hypotension GWAS involve the use of large cohorts to screen the genome at 1000s of possible single-nucleotide polymorphisms (SNPs) to understand variants that contribute to blood pressure. Millions of single-nucleotide polymorphisms (SNPs) to be genotyped are routinely scanned with high-density SNP arrays, and such genotyping is used to probe the field to detect an association purely by accident. The cohorts usually consist of tens or hundreds of thousands of persons with elaborate phenotypes like systolic and diastolic blood pressure or hypertension. These relatively large sample sizes are critical in discovering variants with small effect sizes that describe complex traits, such as hypertension (Wang and Wang, 2019). The quality of the genotyping data is extensively controlled by filtering out problematic SNPs and samples to ensure the reliability of further analyses.

The most common statistical analyses in GWAS of hypertension are regression models, including linear models for continuous phenotypes (such as blood pressure) and logistic models for case-control status of hypertension. To account for confounders, including population stratification, principal component analysis (PCA) or linear mixed models are used, which correct for ancestral differences and kinship between individuals. The second important point is multiple testing correction, as the number of SNPs analysed is enormous; the established genome-wide significance level is $p < 5 \times 10^{-8}$ to reduce the false positive rate. Although these are methodological safeguards, heterogeneity in the population, phenotypic variability, and rare variants make the interpretation of data challenging, and it is an ongoing effort to improve methods (Kato et al., 2015).

Figure 1

General framework of GWAS in hypertension research.



Key Genetic Loci Identified through GWAS in Hypertension

GWAS have identified many loci implicated in hypertension, and in many cases, they have revealed various biological pathways not typically predicted to play a role. For example, KCNJ5 codes for the renal inward-rectifier potassium channel, which is essential in regulating electrolyte balance and aldosterone secretion. Mutations in this gene are associated with the development of familial hypertension. Other locus, CHRNA3, codes for a subunit of a nicotinic acetylcholine receptor, which is involved in the autonomic regulation of vascular tone, an element that demonstrates the use of neurogenic processes in blood pressure management. Moreover, PDE3A regulates the relaxation of vascular smooth muscle by inhibiting cyclic AMP degradation, which in turn affects vasodilation and blood pressure maintenance (Kato et al., 2015). Other loci involved genes related to renal sodium handling, the functions of vascular endothelium, and hormone regulation, indicating the multifactorial nature of hypertension. A large proportion of these associated variants are located on regulatory regions, implying that they are likely to have impacts on gene transcription instead of protein coding, which is why it is vital to combine both results of GWAS and functional genomics to decipher how they impact the body (Lu et al., 2015; Padmanabhan and Dominiczak, 2021; Alexander et al., 2025).

Statistical Considerations and Interpretation of GWAS Results

The results of GWAS are complex to interpret and demand severe statistical controls to be held firm. The high number of SNPs that are tested requires multiple comparison correction, and the Bonferroni correction is most often used, which yields a conservative genome-wide significance level of $p < 5 \times 10^{(-8)}$. This will decrease false positives but also increase false negatives, particularly in small-effect variants. Other methods, such as controlling the false discovery rate (FDR), offer a compromise by accepting a controlled proportion of false positives, which are particularly suitable for exploratory studies. A recurring issue with hypertension GWAS is the so-called missing heritability problem, as fewer than 1-2 per cent of estimated genetic effects are explained by identified variants. This gap arises because the effect of many loci is too small on an individual, rare variants are not well captured, and gene-gene or gene-environment interactions are not fully accounted for. Polygenic risk scores (PRS) combine the impact of multiple variants to enhance their effect, yet they have limitations in clinical utility (Keaton et al., 2024; Alexander et al., 2025). Therefore, the wide interpretation of GWAS data requires combining statistical evidence with biological meaning and additional information types.

Meta-Analytic Integration of GWAS Data: Advancing Understanding of Hypertension

Progression in the Discovery of Hypertension Meta-analysis in Hypertension Genetics. Meta-analysis has played a crucial role in hypertension genetics by combining GWAS data across cohorts to enhance discovery power. The method combines the results of various studies in their results (that are dichotomous or continuous), resulting in a larger sample size to detect rare variants with smaller effects not otherwise

identified in separate analyses. Huge collaborations, such as the International Consortium for Blood Pressure (ICBP) and the UK Biobank, have collected and compiled data on hundreds of thousands of people or more than a million people, substantially increasing the number of loci associated with hypertension (Biobank, 2020). Besides locus identification, the meta-analysis allows cross-population comparisons to determine both shared and population-specific genetic outcomes. They are also able to fine-map causal variants and are extensively combined with functional annotations, which improve biological interpretation. The outcomes of these collaborations serve as markers of the significance of data sharing and consensus in precision phenotype genetics, as well as the prospect of further genetic information leading to improved hypertension management through precision medicine (Biobank, 2020).

Polygenic Risk Scores (PGS) for Hypertension:

Development and Construction of PGS

The PGS consists of the combination of results from hundreds or thousands of genetic variants identified through GWAS. Each of these variances is weighed by its effect, with the most frequent being the GWAS slope (beta) or risk ratio, and its total sum is viewed as the hereditary predisposition of this particular individual to the elevated blood pressure or hypertension (Øvretveit et al., 2024). Multiple statistical methods are employed in the implementation of PGS, where several of them involve pruning and thresholding (P+T), whereby independent SNPs are selected using a significance threshold and linkage disequilibrium, as well as a Bayesian approach, where linkage disequilibrium (LD) patterns are defined to improve score prediction (Wang et al., 2023).

PRS strategies that combine multiple scores across GWAS datasets have also been able to increase predictive performance in more heterogeneous populations (Wang et al., 2023). This is achieved through the construction pipeline, which utilizes SNPs based on their merit, compatibility of their linking elements, and weights. This leads to the PGS, which can be verified and even standardized through independent cohorts to conclude on its utility in prediction. At the same time, the importance of population-specific development of PGS is also growing, as genetic architecture and allele frequencies differ across ancestries, which affects the accuracy of scores (Kalafati et al., 2025; Wang et al., 2025). To illustrate, PRS models developed on African populations have demonstrated better predictive value compared to those developed solely on European ancestry GWAS, emphasizing the importance of having diverse reference groups (Wang et al., 2025).

Validation and Predictive Performance of PGS

The use of hypertension PGS has been validated in studies to show that hypertension PGS can be used to stratify the population based on gene risk in various populations. As an example, people with the highest frequency of PGS in the population have an extremely high blood pressure and a higher risk of hypertension development than other members of lower deciles, and the difference can be detected even in early childhood and maintained even when the person arrives at adulthood (Khera et al., 2022; Øvretveit et al., 2024). Measures usually employed in the evaluation of predictive performance include the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and net reclassification improvement. Those published recently show a modest yet significant improvement in the prediction of hypertension with the addition of PGS to existing clinical risks (Khera et al., 2022; Wang et al., 2023). Nonetheless, the predictive accuracy across all populations is ancestry-specific, and PGS varies in terms of the populations or ancestries in which it is most accurate. The transferability of Multi-ancestry PRS approaches has increased; nevertheless, some challenges remain (Wang et al., 2025). Moreover, PGS on the traits of hypertension has been associated not only with the risk of hypertension but also with associated cardiovascular and renal outcomes, clearly referring to their broader clinical utility (Khera et al., 2022). These results suggest the potential usefulness of PGS in identifying individuals at risk early on, allowing for targeted interventions.

Despite the great prospects, the clinical application of the hypertension PGS is hampered by several issues. One of the most critical issues is that the accuracy of various ethnicities is reduced. Current disparities in allele frequencies can cause it, the structure of linkage disequilibrium, and dissimilarity in the genetic blueprint, which can lead to health disparities unless addressed (Wang et al., 2025; Karsten Øvretveit et al., 2024). That issue has been ameliorated to some extent because of population-specific PGS and multi-ancestry PGS development efforts, which are also based on larger and more diverse GWASs. One of the limitations

is that gene-environment interactions are other important factors in hypertension pathogenesis that are mostly not taken into account by PGS. The environmental factors that are causing changes to genetic risk include environmentally sensitive factors associated with diet, physical activity, and stress, which can also influence alterations in PGS predictive ability (Spandidos et al., 2025). The newer integrating methods are developed to integrate PGS with medical and lifestyle data, enhancing risk evaluation and personalizing approaches to prevention (Spandidos et al., 2025). Overall, PGS may be applied to improve the prediction of hypertension risk; however, their accuracy needs to be refined further to leverage their equity and clinical utility.

Computational Genomics in Hypertension:

Role of Bioinformatics in GWAS and PGS

Bioinformatics Tools and Databases in GWAS Analysis

GWAS in research related to hypertension generate vast amounts of data, necessitating the use of bioinformatics resources to manage and analyze this data effectively. Computation features, such as those of PLINK, execute quick data cleansing, quality control, and statistical relatedness calculations on a set of information, allowing scholars to order millions of one-bulb cerebral cortex improvements (SNPs) in groups (Chang et al., 2015). The versatility of PLINK enables the filtering of low-quality variants, assessment of population stratification, and regression analysis, among other key strategies in GWAS pipelines. At the same time, SNPTEST possesses more specificities concerning the association testing on imputed information; the probabilities of genotypes allow investigators to increase the statistical strength. The emergence of the cloud-based structures, including the HAIL, has also changed the interpretation of genomic information by enabling distributed, scalable computation over datasets dispersed across biobanks and allowing swift execution of GWAS, as well as PGS (Das et al., 2016).

These tools have been integrated into standardized pipelines, bringing convenience and ease to GWAS analyses and enhancing their replicability by alleviating computational bottlenecks. Moreover, the availability of public data sources, such as the 1000 Genomes Project and gnomAD, provides access to valuable reference panels for annotating variants and imputing genotypes, thereby making genotype calls more reliable and facilitating downstream analyses. Such bioinformatic materials are helping researchers to break down the genetic map of hypertension in considerably greater detail and to a much greater magnitude than previously, closer to creating functional PGS and identifying new variants (Chang et al., 2015; Das et al., 2016).

Computational Tools for Imputation, Quality Control, and Fine-Mapping

In GWAS, genotype imputation is important in imputing pseudo-tying variants and expanding genomic coverage beyond the SNP profiled. Tools such as IMPUTE2, Beagle, and Minimac4 utilize panels of reference haplotypes derived from large-scale sequencing efforts to statistically infer unknown genotypes, thereby increasing the power to identify associations with hypertension (Das et al., 2016). Imputation is also useful in meta-analysis to harmonize sets of variants across genotyped studies using different platforms. In addition to imputation, rigorous quality control measures are implemented using tools such as PLINK and bcftools, which include the removal of the poorest genotyped samples and variants, adjustment for small-batch effects, and verification of data integrity (Chang et al., 2015).

Fine-mapping methods such as FINEMAP, CAVIAR, or SuSiE are crucial in identifying causal variants within the associated loci and reducing the number of associated loci as well (Benner et al., 2016). Rather than analyzing the genotype-phenotype association at the summary level only, these approaches combine summary-level statistics of association with linkage disequilibrium (LD) patterns to allocate probability to candidate variants, allowing researchers to focus their efforts on functional follow-up. Fine-mapping enhances the biological understanding and translation of GWAS studies to mechanistic understanding and therapeutic targets by narrowing down the list of implicated variants that may have causal mechanisms (Das et al., 2016).

Integrating Multi-Omic Data

Hypertension genetics is more complicated than DNA variants, and multilayered omics will be required to study the disease mechanism comprehensively. The integration of genomic data with transcriptomic, proteomic, epigenomic, and metabolomic data, utilizing bioinformatics techniques, can be used to identify the mechanisms by which genetic variation affects molecular pathways relevant to blood pressure management (Zhang et al., 2025). Here, an illustrative example is the expression quantitative trait loci (eQTL) analyses, which relate GWAS-identified variants to

tissue-specific gene expression in the kidney and vasculature, thereby providing a functional context for the GWAS association signals (Gamazon et al., 2015).

Proteomic data also explain the influence of genetic variation on protein abundance and post-translational modification, which are pivotal in vascular activity and hormonal balance. Modelling gene-environment interactions as a risk factor for hypertension is possible by incorporating environmental and lifestyle factors with multi-omic data. Such integrative analyses are supported by computational platforms such as PrediXcan and OmicSoft, which predict the genotype-based gene expression against clinical phenotypes. This type of systems biology can be used to help define new biomarkers and drug targets, taking the field closer to the direction of precision medicine, which involves genetic susceptibility, as well as molecular and environmental factors (Zhang et al., 2025).

Machine Learning and Predictive Modeling

Machine Learning (ML) algorithms have become increasingly popular in hypertension studies due to the demonstration of having strong model-fitting capabilities to complex non-linear parameters observed in genetic variants, clinical measurements, and environmental exposures. Other machine learning techniques, such as Random Forests, Support Vector Machines (SVMs), and Neural Networks, can scan high-dimensional data and identify certain interactions that a regular statistical model might miss (Grealey et al., 2024). ML models have been able to achieve greater levels of precision and accuracy in predicting the risk and stratification of the dangers posed by hypertension when combined with clinical and multi-omic data, as well as polygenic risk scores. In addition to risk prediction, ML strategies enable feature selection and biomarker discovery by highlighting the most informative genetic and molecular predictors. These models also support personalized medicine, as they enable the tailoring of prevention and treatment to individuals according to their risk profile. Nonetheless, issues such as overfitting, interpretability, and the need for large and diverse training datasets persist. The work on explainable AI, with strong validation frameworks, must be continued to realize ML-driven insights into clinical practice (Layton, 2024).

Future Directions: AI-Driven Models in Hypertension Risk Stratification

With the aid of AI, combining artificial intelligence (AI) and deep learning, tools will be developed to enable the utilization of the rich complexity of multi-omics and clinical discoveries, marking a significant step forward in the future of hypertension genomics. According to emerging AI systems that introduce federated learning approaches, data can be utilized to conduct collective analyses between institutions without compromising the privacy of the data, thereby broadening the training data size and diversity (Kalafati et al., 2025). Convolutional and recurrent neural networks are deep learning systems that have the potential to reveal subtle relationships in genomic and phenotypic data, supporting the existence of hypertension risk. In addition, explainable AI innovations are intended to increase the transparency and medical credibility of predictive models, making them more applicable to healthcare. Combined with genomics, transcriptomics, proteomics, electronic health records, and environmental exposures, AI-driven models will be able to provide a more comprehensive and personalized assessment of risk, directing specific management. The innovations will accelerate precision medicine practices, enhancing the prevention, diagnosis, and treatment outcomes of hypertension among diverse populations (Al Kuwaiti et al., 2023).

Conclusion

To sum up, the genetic perspectives on hypertension have improved so much in the last several decades that they have changed our perception of the complex, multifactorial character of hypertension. This was initially established through the study of candidate genes, with the RAAS providing the major activity variants associated with blood pressure regulation. Nevertheless, small sample sizes, choice biases, and a narrow focus on a limited number of candidate genes limited these studies. The advent of GWAS represented an important change, as it allowed for the identification of hundreds of minor genetic variations that explain the modest risk of developing hypertension. These variants also provide fascinating insights into the biological mechanisms underlying the disease, as well as issues related to missing heritability and the polygenic nature of hypertension. PGS were developed, offering an encouraging approach to predict individual risk, especially when relevant to various groups. Although PGS has proven to hold potential in stratifying individuals based on their genetic risk, specific issues need to be addressed regarding its precision when applied to various ethnic groups and its clinical utility.

Additionally, the combination of computational genomics and recent technological breakthroughs,

including machine learning, holds promise for optimizing predictive models and addressing existing drawbacks, particularly in the integrative inclusion of gene-environment interactions, as well as enhancing predictive performance. In the future, the future of hypertension genetics will be more defined by the ongoing and further detailed assessment of genetic risk tool refinement, where the size of the sample and issues of data diversity, as well as multi-omics integration, are primary factors. Ultimately, the goal is to translate these genetic discoveries into clinical applications, enabling the development of precision medicine that will facilitate the management and possibly prevention of hypertension more efficiently. With the development of computational technology and the accumulation of an increasingly rich amount of data, it is becoming a reality that personalized, genetically based treatments can radically reduce hypertension both in terms of prevention and control on a global scale. Ultimately, the integration of genetic, environmental, and clinical data, along with the advancement of computational genomics, will revolutionize the field of hypertension research, enabling more accurate risk predictions, targeted treatments, and enhanced patient outcomes in the years to come.

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