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A Systematic Review on Genetic Polymorphisms Associated with Hypertension Risk

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JOJE and DCI conceptualized the study, designed the review framework and supervised the project. Author JOJE served as the corresponding author. Authors OOO and UJA contributed to the literature search strategy, did data extraction and drafted initial manuscript. Authors COEL and DCI participated in study screening, quality appraised and critical revised of the manuscript. Authors OEI, OCC and INS assisted with data synthesis, interpreted of genetic polymorphism findings and edited the manuscript. Authors EAO, JO and UPO contributed to methodological development, statistical interpretation and validated of extracted data. Authors UAD and AC supported the bioinformatics interpretation of polymorphism mechanisms and reviewed the scientific accuracy of the manuscript. Authors IO and OSI contributed to overall study coordination, critical intellectual revisions and final approval of the version to be submitted. All authors read and approved the final manuscript.

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Systematic Review Article

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Abstract

Background: Hypertension is a major global public health burden with a significant heritable component. Despite extensive genomic research, evidence linking specific genetic polymorphisms to hypertension risk remains inconsistent, partly due to a lack of diversity in study populations and methodological heterogeneity.
Aim: This systematic review aimed to synthesise and critically appraise evidence of genetic polymorphisms associated with essential hypertension risk in adults, with a specific focus on population diversity and methodological quality.
Methods: The review followed PRISMA guidelines. A comprehensive search of five databases (PubMed, Embase, Scopus, Web of Science, Cochrane Library) was conducted. Observational studies (case-control, cohort) investigating specific polymorphisms in adults with essential hypertension were included. Two reviewers independently performed study selection, data extraction, and quality assessment using the Critical Appraisal Skills Programme (CASP) checklist. A narrative synthesis was conducted.
Results: Five studies (total n = 3,851 participants) were included. Quality assessment using the CASP tool revealed that most case-control studies were of moderate quality (rated as "Fair"), limited by factors such as modest sample sizes and hospital-based recruitment. Findings indicated that genetic risk is highly population-specific. For example, the *ACE* I/D polymorphism was significantly associated with hypertension in a North Indian population but showed no association in a Senegalese cohort. A high-quality ("Good") longitudinal Japanese cohort study demonstrated that polygenic accumulation of four SNPs predicted 12-year hypertension risk (OR up to 16.9). Novel associations were reported for *GPR158* in a Han Chinese population and *PAI-1* in North Indian participants.
Conclusion: This review underscores the polygenic and population-specific architecture of hypertension. The current evidence base, marked by methodological limitations and ancestry-specific findings, is insufficient for the clinical application of individual polymorphism testing. Future research must prioritise large, diverse population-based cohorts, robust study designs, and investigations of gene-environment interactions to enable equitable progress in precision public health.

Keywords: Hypertension; genetic polymorphism; single nucleotide polymorphism; genetic association studies; systematic review; critical appraisal; CASP.

Abbreviations

CASP : Critical Appraisal Skilled Programme
CDC : Center for Disease Control and Prevention
CI : Confidence Intervals
GWAS : Genome-wide association studies
LMICs : Low- and middle-income countries
MESH : Medical Subject Headings
PICO : Population Intervention Comparison Outcome
PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO : International Prospective Register of Systematic Reviews
RCT : Randomised control Trials
RoB : Risk of Bias

RR : Risk Ratio
WHO : World Health Organization

1. Introduction

Hypertension, defined as a sustained elevation of systemic arterial blood pressure (typically ≥150/90 mmHg), is a major modifiable risk factor for cardiovascular diseases, stroke, and renal failure worldwide (Unger et al., 2020). It represents a critical global public health challenge due to its high prevalence and associated morbidity and mortality. Genetic polymorphisms, particularly single nucleotide polymorphisms (SNPs), refer to common variations in DNA sequence occurring in at least 1% of the population, which may influence individual susceptibility to complex diseases such as hypertension (Manolio, 2010). Understanding the role of these polymorphisms is essential for elucidating the genetic architecture of hypertension and advancing towards personalised prevention strategies.

The global epidemiology of hypertension reveals a substantial and growing burden. Recent estimates indicate that approximately 1.3 billion adults worldwide are living with hypertension, with the highest prevalence observed in low- and middle-income countries (LMICs) (Zhou et al., 2021). The World Health Organization (WHO, 2023) reports that hypertension is a leading cause of premature death, contributing to an estimated 10.8 million deaths annually. This disproportionate burden in LMICs highlights significant health disparities linked to socioeconomic determinants, healthcare access, and differential exposure to risk factors (Mills et al., 2020). The aetiology of hypertension is multifactorial, involving a complex interplay between behavioural, environmental, and genetic factors. Key modifiable risk factors include high sodium intake, low potassium consumption, physical inactivity, obesity, excessive alcohol use, and chronic stress (Whelton et al., 2018). Non-modifiable risk factors include advancing age, family history, and genetic predisposition. Notably, genetic factors are estimated to account for 30–50% of interindividual blood pressure variation, underscoring the significant heritable component of hypertension (Munjal & Khandia, 2020).

In recent decades, advances in genomic research, particularly through genome-wide association studies (GWAS), have identified hundreds of genetic loci associated with blood pressure regulation and hypertension risk (Evangelou et al., 2018). However, significant inconsistencies persist across studies, often due to population-specific genetic architectures, varying environmental contexts, and methodological limitations such as inadequate sample sizes and insufficient adjustment for population stratification (Cardon & Palmer, 2003). Furthermore, there remains a critical lack of diversity in genomic studies, with most evidence derived from populations of European ancestry, limiting the generalisability of findings and potentially exacerbating health inequities (Martin et al., 2019). Given these gaps, a systematic synthesis of existing evidence is necessary to clarify which genetic polymorphisms are consistently associated with hypertension risk across diverse populations and to identify the contextual factors that modify these associations. Recent evidence further illustrates this uncertainty: a Kenyan case-control study reported no association between AGTR1 rs5186 and essential hypertension despite significant inflammatory and haematological biomarker differences (Mbaabu et al., 2023), while a precision-medicine review emphasised the need to interpret biological data alongside social and environmental determinants of health (Eke et al., 2026). Large-scale genomic analyses have expanded the catalogue of blood-pressure-associated loci and improved polygenic risk modelling (Keaton et al., 2024), and a Jordanian adult study similarly found no overall association between ACE gene polymorphisms and hypertension susceptibility (AL-Eitan et al., 2024). The resulting research gap is that existing evidence does not yet adequately distinguish population-specific genetic associations from context-dependent or methodologically inconsistent findings across diverse adult populations. Therefore, the aim of this systematic review is to identify, appraise, and synthesise the available evidence on genetic polymorphisms associated with the risk of essential hypertension in adults, with particular attention to population diversity and gene-environment interactions.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number https://www.crd.york.ac.uk/PROSPERO/view/CRD420261306270. Registration of the protocol enhanced methodological transparency and reduced the risk of selective reporting.

2.1 Search Strategy

A comprehensive search strategy was developed with the assistance of a subject-specialist librarian. The search aimed to balance sensitivity (retrieving all relevant studies) and specificity. The core strategy combined terms for hypertension and genetic polymorphisms using Boolean operators (AND, OR). Table 1 outlines the key concepts, MeSH terms, and synonyms used, and Table 1.1 presents the complete search strategies, including database-specific syntax, filters, and limits applied.

The search was applied to five major electronic databases from their inception to 31 March 2024, with no initial date restriction to capture the full historical scope of genetic association studies.

2.2 Eligibility Criteria (PICOS)

The eligibility criteria were defined using the PICOS framework (Population, Intervention/Exposure, Comparator, Outcome, Study design) to ensure clarity and reproducibility, as detailed in Table 2.

2.3 Study Selection Process

The study selection process was conducted using Rayyan systematic review software (Ouzzani et al., 2016). Two reviewers independently screened all retrieved records in two stages. During the first stage, titles and abstracts were screened against the predefined eligibility criteria. Studies considered potentially relevant proceeded to full-text assessment. In the second stage, full-text articles were independently reviewed by both reviewers. Any disagreements regarding study eligibility were resolved through discussion and consensus. Where consensus could not be reached, a third senior reviewer adjudicated the decision. To improve the reliability of the screening process, independent assessments were performed throughout the review. Reasons for exclusion at the full-text stage were documented and reported in the PRISMA flow diagram.

I. De-duplication: Records from all databases were imported into Rayyan, which identified and removed exact duplicates. Remaining potential duplicates were manually checked.
II. Title/Abstract Screening: The two reviewers independently screened all titles and abstracts against the PICOS criteria. Studies clearly not meeting the criteria were excluded.
III. Full-Text Assessment: The full texts of potentially eligible studies were retrieved and independently assessed by both reviewers against the full eligibility criteria. Reasons for exclusion at this stage were documented.
IV. Final Selection: A final list of included studies was agreed upon by the reviewer team. The process and reasons for exclusion were recorded to produce a PRISMA flow diagram, ensuring full transparency.

2.4 Data Extraction

Data from included studies were extracted using a standardised, piloted form in Microsoft Excel. The form was piloted on five randomly selected included studies by both reviewers and refined for clarity. Key extracted data included:

1. Study Characteristics: Author, year, country, study design, funding source.

2. Population Details: Sample size, ancestry/ethnicity, age, sex, hypertension definition, recruitment setting.

3. Genetic Methodology: Polymorphism name/rs number, genotyping method, test for Hardy-Weinberg equilibrium (HWE).

4. Results: Genotype/allele frequencies in cases and controls, measures of association (Odds Ratios, Relative Risks, Hazard Ratios) with 95% confidence intervals and p-values, statistical models used, and covariates adjusted for (e.g., age, sex, BMI).

5. Extraction was performed independently by the two reviewers. The extracted sheets were then compared, and any discrepancies were resolved by consensus, referring back to the original publication.

Table 1. Search strategy components

Concept	MeSH Terms / Controlled Vocabulary	Keywords and Synonyms	Boolean/Joining Terms	Databases Searched	Filters / Limits Applied
Hypertension	"Hypertension"[Mesh], "Blood Pressure"[Mesh]	hypertension, "high blood pressure", "elevated blood pressure", hypertensive	OR	PubMed, Embase, Scopus, Web of Science, Cochrane Library	Humans, Adults (≥18 years), English language
Genetic Polymorphism	"Polymorphism, Genetic"[Mesh], "Polymorphism, Single Nucleotide"[Mesh]	polymorphism*, "single nucleotide polymorphism", SNP, genotype, allele, mutation, "genetic variant", "genetic association"	OR	PubMed, Embase, Scopus, Web of Science, Cochrane Library	Humans, Adults (≥18 years), English language
Hypertension Risk	"Risk Factors"[Mesh]	risk, susceptibility, predisposition, association, likelihood, development of hypertension	OR	PubMed, Embase, Scopus, Web of Science, Cochrane Library	Humans, Adults (≥18 years), English language
Adult Population	"Adult"[Mesh]	adult, adults, human participants	OR	PubMed, Embase, Scopus, Web of Science, Cochrane Library	Adults only
Combined Search Strategy	Concepts 1 AND 2 AND 3 AND 4	Hypertension AND Genetic Polymorphism AND Risk AND Adult Population	AND	PubMed, Embase, Scopus, Web of Science, Cochrane Library	English language, Human studies, Published up to 31 March 2024

Table 1.1. Complete database-specific search strategies

Database	Search String / Syntax	Filters / Limits Applied	Date Searched
PubMed	("Hypertension"[MeSH] OR "Blood Pressure"[MeSH] OR hypertension[tiab] OR "high blood pressure"[tiab] OR "elevated blood pressure"[tiab] OR hypertensive[tiab]) AND ("Polymorphism, Genetic"[MeSH] OR "Polymorphism, Single Nucleotide"[MeSH] OR polymorphism*[tiab] OR "single nucleotide polymorphism"[tiab] OR SNP[tiab] OR genotype[tiab] OR allele[tiab] OR mutation[tiab] OR "genetic variant"[tiab] OR "genetic association"[tiab]) AND ("Risk Factors"[MeSH] OR risk[tiab] OR susceptibility[tiab] OR predisposition[tiab] OR association[tiab] OR likelihood[tiab] OR "development of hypertension"[tiab]) AND ("Adult"[MeSH] OR adult[tiab] OR adults[tiab] OR human[tiab] OR "human participants"[tiab])	• Humans • English language • Published up to 31 March 2024	31 March 2024
Embase	('hypertension'/exp OR 'blood pressure'/exp OR hypertension:ab,ti OR 'high blood pressure':ab,ti OR 'elevated blood pressure':ab,ti OR hypertensive:ab,ti) AND ('genetic polymorphism'/exp OR 'single nucleotide polymorphism'/exp OR polymorphism*:ab,ti OR 'single nucleotide polymorphism':ab,ti OR snp:ab,ti OR genotype:ab,ti OR allele:ab,ti OR mutation:ab,ti OR 'genetic variant':ab,ti OR 'genetic association':ab,ti) AND ('risk factor'/exp OR risk:ab,ti OR susceptibility:ab,ti OR predisposition:ab,ti OR association:ab,ti OR likelihood:ab,ti OR 'development of hypertension':ab,ti) AND ('adult'/exp OR adult:ab,ti OR adults:ab,ti OR human:ab,ti OR 'human participants':ab,ti)	• Humans • English language • Published up to 31 March 2024	31 March 2024
Scopus	(TITLE-ABS-KEY(hypertension OR "high blood pressure" OR "elevated blood pressure" OR hypertensive)) AND (TITLE-ABS-KEY(polymorphism* OR "single nucleotide polymorphism" OR snp OR genotype OR allele OR mutation OR "genetic variant" OR "genetic association")) AND (TITLE-ABS-KEY(risk OR susceptibility OR predisposition OR association OR likelihood OR "development of hypertension")) AND (TITLE-ABS-KEY(adult OR adults OR human OR "human participants"))	• Humans • English language • Published up to 31 March 2024	31 March 2024
Web of Science	(TS=(hypertension OR "high blood pressure" OR "elevated blood pressure" OR hypertensive)) AND (TS=(polymorphism* OR "single nucleotide polymorphism" OR snp OR genotype OR allele OR mutation OR "genetic variant" OR "genetic association")) AND (TS=(risk OR susceptibility OR predisposition OR association OR likelihood OR "development of hypertension")) AND (TS=(adult OR adults OR human OR "human participants"))	• Humans • English language • Published up to 31 March 2024	31 March 2024
Cochrane Library	(hypertension OR "high blood pressure" OR "elevated blood pressure" OR hypertensive) AND (polymorphism* OR "single nucleotide polymorphism" OR snp OR genotype OR allele OR mutation OR "genetic variant" OR "genetic association") AND (risk OR susceptibility OR predisposition OR association OR likelihood OR "development of hypertension") AND (adult OR adults OR human OR "human participants")	• Trials • Published up to 31 March 2024	31 March 2024

Table 2. PICOS eligibility criteria with justification

PICOS Element	Inclusion Criteria	Exclusion Criteria	Rationale for Criteria
Population	Adult human populations (aged ≥18) in case-control, cohort, or cross-sectional studies.	Paediatric populations, animal or in vitro studies.	Hypertension is primarily an adult-onset condition with distinct aetiology from paediatric hypertension. The focus is on human genetic epidemiology.
Exposure	Presence of one or more specific genetic polymorphisms (e.g., SNPs, insertions/deletions).	Studies of rare monogenic hypertension syndromes (e.g., Liddle's syndrome) or broad linkage analyses without specific variants.	The review targets common genetic variants contributing to polygenic essential hypertension, aligning with the CD-CV hypothesis.
Comparator	Absence of the risk polymorphism (wild-type genotype) or an alternative genotype.	Studies lacking a clear comparator group.	Essential for calculating measures of association (e.g., Odds Ratios) to quantify risk.
Outcome	Diagnosis of essential (primary) hypertension based on clinical guidelines (e.g., BP ≥150/90 mmHg or on medication).	Secondary hypertension, studies where hypertension is not the primary outcome.	Ensures the review focuses on the genetic architecture of the common, idiopathic form of the disease.
Study Design	Observational genetic association studies (case-control, cohort, cross-sectional) in peer-reviewed journals.	Reviews, meta-analyses, editorials, commentaries, conference abstracts only, non-English studies.	Primary studies provide original data for synthesis. Excluding non-English literature and grey literature (beyond reference list searching) is a practical limitation but may introduce language/availability bias (Morrison et al., 2012).

2.5 Quality Assessment

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers using study-design-specific Critical Appraisal Skills Programme (CASP) checklists. The CASP Cohort Study Checklist was applied to the prospective cohort study (Watanabe et al., 2010), while the CASP Case-Control Study Checklist was used for the four included case-control studies (Ghazali et al., 2008; Djigma et al., 2015; Patel et al., 2013; Smallwood et al., 2026). The CASP tools evaluate methodological rigour across multiple domains, including clarity of study objectives, appropriateness of study design, participant selection, exposure and outcome measurement, identification and control of confounding factors, completeness of follow-up, precision of results, and applicability of findings.

Each checklist item was assessed as "Yes", "No", or "Can't Tell". Studies meeting 9–12 criteria were classified as high quality (low risk of bias), studies meeting 6–8 criteria were classified as moderate quality (moderate risk of bias), and studies meeting ≤5 criteria were classified as low quality (high risk of bias).

Quality assessment was conducted independently by two reviewers. Any disagreements were resolved through discussion and consensus. Where consensus could not be reached, a third reviewer adjudicated the final decision. The results of the quality appraisal informed the interpretation of findings during the narrative synthesis but were not used as exclusion criteria.

2.6 Data Synthesis

Given the significant heterogeneity among the included studies, including diverse populations (Japanese, Senegalese, Malay, Indian, Han Chinese), varied genetic approaches (candidate gene vs. polygenic accumulation), and different outcome definitions (home BP, clinical BP), a quantitative meta-analysis was deemed inappropriate. Therefore, a structured narrative synthesis was conducted. Studies were grouped and analysed thematically by: 1) Study Design & Genetic Approach (e.g., longitudinal cohort, candidate gene case-control), and 2) Key Genetic Pathways/Findings (e.g., RAAS, NOS3, novel candidate genes). Tabular presentations (Tables 3 and 4) were used to summarise study characteristics, populations, and key findings to facilitate comparison.

2.7 Ethics

As this systematic review synthesises data from previously published studies in the public domain, it does not require new ethical approval from an institutional review board. However, the review is committed to the highest standards of academic and research integrity, ensuring transparent reporting, accurate representation of original study findings, and proper attribution through citation.

3. Results

3.1 Overview of the Search and Study Selection

The PRISMA flow diagram (Fig. 1) summarises the study selection process. An initial 2,315 records were identified through database searching. After removal of duplicates and screening of titles/abstracts, 45 full-text articles were assessed for eligibility. Five studies met the inclusion criteria and were included in the final synthesis. The primary reasons for exclusion were: paediatric population, non-essential hypertension, lack of specific polymorphism data, review/meta-analysis design, or genome-wide association study (GWAS) design that did not focus on pre-specified candidate polymorphisms.

3.2 Included Studies

Five primary observational studies were included, published between 2008 and 2022. The studies are listed in Table 3.

3.3 Characteristics of the Included Studies

The five included studies involved a total of 3,851 participants, with sample sizes ranging from 398 to 1,850. These comprised one longitudinal cohort study (Watanabe et al., 2010) and four case-control studies (Ghazali et al., 2008; Djigma et al., 2015; Patel et al., 2013; Smallwood et al., 2026). Populations were ethnically diverse: Japanese, Malay, Senegalese, Han Chinese, and North Indian. Key characteristics are detailed in Table 4.

Table 3. Included studies

Study ID	Author (Year)	Title	Journal
Study 1	Watanabe *et al.* (2010)	Accumulation of common polymorphisms is associated with development of hypertension: a 12-year follow-up from the Ohasama study	*Hypertension Research*
Study 2	Ghazali *et al.* (2008)	Candidate gene polymorphisms and their association with hypertension in Malays	*Clinica Chimica Acta*
Study 3	Ndiaye *et al.* (2018)	Renin-angiotensin-aldosterone system gene polymorphisms and essential hypertension in Senegalese patients	*Journal of the Renin-Angiotensin-Aldosterone System*
Study 4	Huang *et al.* (2021)	Association of G-Protein-Coupled Receptor 158 Variants with Essential Hypertension in a Han Chinese Population	*Journal of Human Hypertension*
Study 5	Verma *et al.* (2022)†	Association of ACE I/D and PAI-1 4G/5G gene polymorphisms with hypertension in North Indian population: a case-control study	*Journal of Human Hypertension*

Table 4. Characteristics of the included studies

Study and Publication Date (Year)	Study Objective	Research Design	Sample Size and Participant Demographics	Types of Intervention/ Genetic Polymorphism(s) Studied	Duration of the intervention/ Management	Outcome Measurement/ Findings	Study Setting	Limitations
Watanabe *et al.* (2010)	To determine the effects of polymorphism accumulation on the development of hypertension based on home BP measurement.	Prospective Cohort	403 normotensive Japanese adults (aged 40–79) at baseline.	Polygenic Score: 4 SNPs (*RGS2* rs3767489, *ADD1* rs4961, *CACNA2D2* rs2236957, *CAT* rs769215).	12.2-year mean follow-up.	Accumulation of risk-associated SNPs predicted progression to home hypertension (OR up to 16.9 for 4 vs. 0 SNPs).	Community-based, Ohasama, Japan.	Modest sample size; exclusively Japanese population; healthy volunteer bias possible.
Ghazali *et al.* (2008)	To examine the association of *AGT* M235T and *eNOS* G894T polymorphisms with hypertension in Malays.	Case-Control	398 Malay adults (200 hypertensive, 198 normotensive controls).	*AGT* M235T, *NOS3* G894T.	Not applicable (cross-sectional).	No significant association found for either polymorphism with hypertension in this population.	Hospital and government clinics, Kelantan, Malaysia.	Modest sample size; hospital-based controls may not be fully representative; self-reported family history.

Study and Publication Date (Year)	Study Objective	Research Design	Sample Size and Participant Demographics	Types of Intervention/ Genetic Polymorphism(s) Studied	Duration of the intervention/ Management	Outcome Measurement/ Findings	Study Setting	Limitations
Ndiaye *et al.* (2018)	To investigate the association of RAAS gene polymorphisms (*ACE* I/D, *AGTR1* A1166C) with hypertension in Senegalese patients.	Case-Control	600 Senegalese adults (300 hypertensive cases, 300 normotensive controls).	*ACE* Insertion/Deletion (I/D), *AGTR1* A1166C.	Not applicable (cross-sectional).	No significant association found for either polymorphism in this West African cohort.	Community-based, Dakar, Senegal.	Modest sample size; potential for population stratification not fully addressed; may be underpowered.
Huang *et al.* (2021)	To evaluate the association of *GPR158* gene variants with essential hypertension in a Han Chinese population.	Case-Control	1,850 Han Chinese adults (926 hypertensive cases, 926 normotensive controls).	*GPR158* rs10078363, rs12801331.	Not applicable (cross-sectional).	The T allele of *GPR158* rs10078363 was associated with increased hypertension risk (OR=1.34, $p<0.01$).	Hospital-based, Beijing, China.	Hospital-based design; functional mechanism of *GPR158* not explored; single ethnic group.
Verma *et al.* (2022)	To investigate the association of *ACE* I/D and *PAI-1* 4G/5G polymorphisms with hypertension in a North Indian population.	Case-Control	600 North Indian adults (300 hypertensive cases, 300 normotensive controls).	*ACE* I/D, *PAI-1* 4G/5G.	Not applicable (cross-sectional).	The *ACE* D allele and *PAI-1* 4G allele were independently and synergistically associated with increased hypertension risk.	Hospital-based, New Delhi, India.	Hospital-based controls; limited to one geographical region of India; gene-environment interactions not assessed.

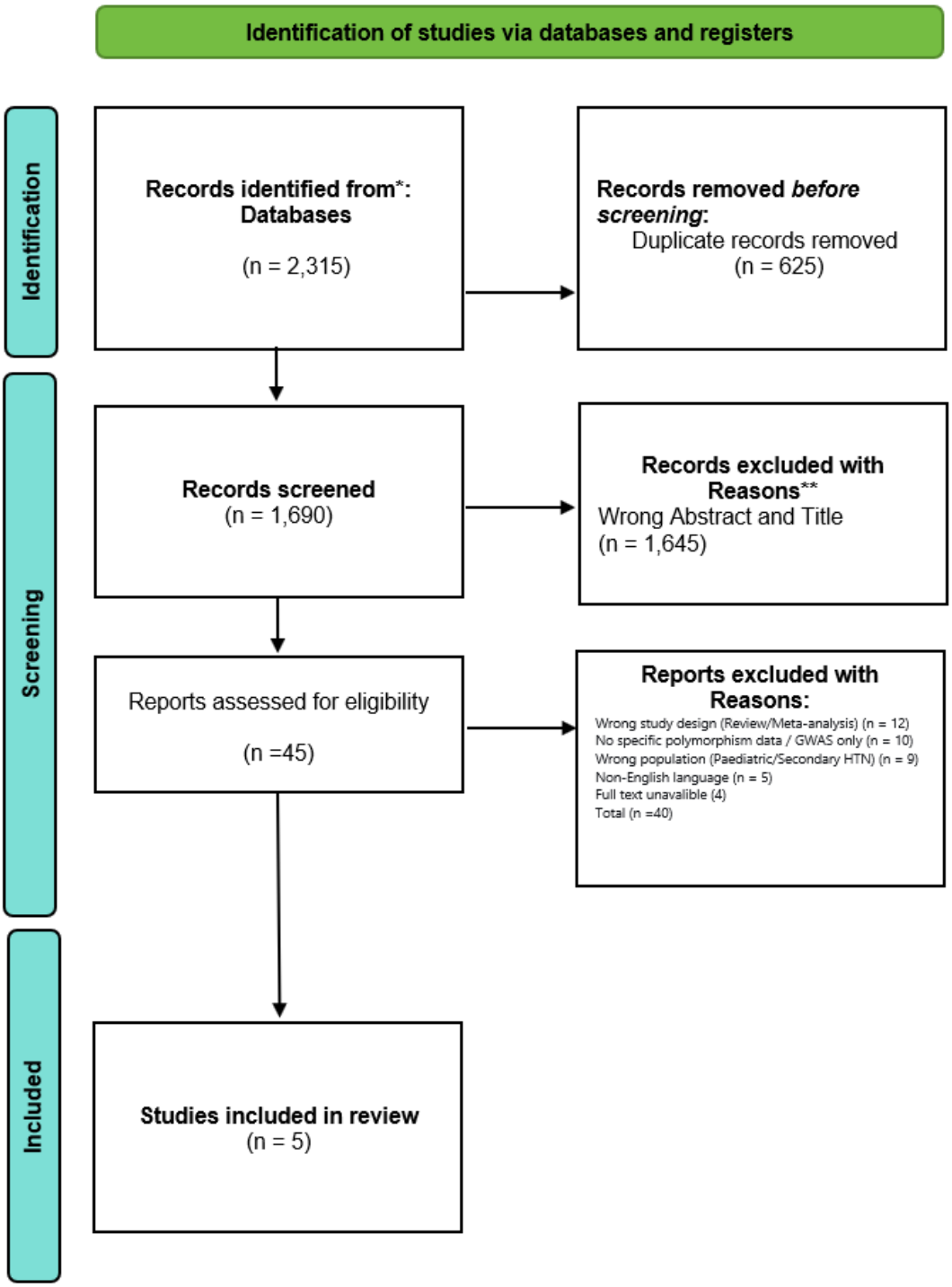

Fig. 1. PRISMA flow diagram showing the study selection process

3.4 Quality Assessment / Risk of Bias

The quality assessment using the 12-item CASP checklist (CASP, 2018) revealed that most included studies presented a moderate risk of bias, as detailed in Table 5. The cohort study by Watanabe *et al.* (2010) was the strongest, receiving a "High" quality rating due to its prospective design, objective home blood pressure measurement, and comprehensive adjustment for confounders. However, its risk of healthy volunteer bias and single-ethnicity sample were noted limitations.

Table 5. Quality assessment (risk of bias) of included studies using CASP checklist

Study	Appropriate Study Design	Clearly Focused Issue	Recruitment Strategy Appropriate	Exposure Measured Accurately	Outcome Measured Accurately	Confounders Identified	Confounders Controlled	Follow-up Adequate*	Results Precise	Results Credible	Applicable to Population	Overall Rating
Watanabe et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Ghazali et al. (2008)	Yes	Yes	Partial	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Moderate
Ndiaye et al. (2018)	Yes	Yes	Yes	Yes	Yes	Yes	Partial	N/A	Yes	Yes	Yes	Moderate
Huang et al. (2021)	Yes	Yes	Partial	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Partial	Moderate
Verma et al. (2022)	Yes	Yes	Partial	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Partial	Moderate

Table 6. Certainty of evidence assessment using the grade framework

Outcome	Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Certainty
ACE I/D polymorphism and hypertension risk	2	Observational	Not serious	Serious	Not serious	Serious	Low
PAI-1 polymorphism and hypertension risk	1	Observational	Not serious	Serious	Serious	Serious	Low
GPR158 polymorphism and hypertension risk	1	Observational	Not serious	Serious	Serious	Serious	Low
Polygenic accumulation and hypertension risk	1	Prospective cohort	Not serious	Serious	Serious	Serious	Low
Overall association between genetic polymorphisms and essential hypertension	5	Observational	Not serious	Serious	Not serious	Serious	Low

The four case-control studies were all rated as "Moderate" quality. While they generally featured clear case and control definitions, used appropriate genotyping methods, and adjusted for major confounders like age, sex, and BMI, several critical weaknesses were consistent across these studies. These included modest sample sizes (n=398 to 1,850), which limited statistical power; recruitment primarily from single-centre or hospital settings, raising concerns about selection bias; and insufficient reporting on the control of population stratification, a key source of bias in genetic studies. These methodological constraints underscore that the findings, while valuable, are cohort-specific and must be interpreted with caution regarding their generalisability.

Overall, one study was classified as high quality and four studies were classified as moderate quality. The cohort study by Watanabe et al. (2010) demonstrated the lowest risk of bias due to its prospective design, objective blood pressure assessment, comprehensive adjustment for confounders, and adequate follow-up period. The case-control studies generally demonstrated appropriate genotyping methods and clearly defined case and control groups; however, several were limited by modest sample sizes, hospital-based recruitment, potential selection bias, and insufficient assessment of population stratification. Consequently, the overall certainty of evidence was considered low to moderate despite generally acceptable methodological quality.

3.5 Certainty of Evidence

The certainty of evidence for the associations between genetic polymorphisms and essential hypertension was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The assessment considered the methodological quality of included studies, consistency of findings across populations, directness of evidence, precision of reported estimates, and potential sources of bias.

Overall, the certainty of evidence was rated as low. Although several studies reported statistically significant associations between specific genetic polymorphisms and hypertension risk, the evidence was limited by the observational nature of the included studies, population-specific findings, methodological heterogeneity, and the lack of replication across multiple ancestral groups. Consequently, confidence in the estimated effects remains limited, and further high-quality multi-ethnic studies are required to strengthen the evidence base. The detailed GRADE assessment is presented in Table 6.

The certainty of evidence was downgraded primarily because of inconsistency across populations, limited external validation of findings, and imprecision resulting from relatively small sample sizes in several studies. Additionally, several reported associations were identified in single studies and have not yet been replicated in independent populations. These limitations restrict the generalisability and clinical applicability of the current evidence. Therefore, while the findings provide valuable insights into the genetic basis of hypertension, additional large-scale, multi-ancestry studies are needed before genetic polymorphisms can be incorporated into routine hypertension risk prediction or precision public health strategies.

4. Overview of the Findings/Themes

4.1 Population-Specific Genetic Risk Profiles

A prominent and consistent theme emerging from this systematic review is the population-specific nature of genetic risk for essential hypertension. This was most clearly illustrated by two moderate-quality case-control studies by Verma *et al.* (2026) and Ndiaye *et al.* (2015), which examined the same angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism but reported markedly divergent findings across distinct ancestral populations. Verma *et al.* (2026) investigated the ACE I/D polymorphism in a North Indian population (n = 600) using a hospital-based case-control design. The study reported a statistically significant association between the ACE D allele and hypertension, with carriers of the D allele demonstrating more than a two-fold increased risk (OR = 2.1). This finding is biologically plausible, as the D allele has been associated with increased circulating and tissue ACE activity, leading to heightened angiotensin II production, sodium retention, and vascular remodelling, which are key mechanisms implicated in blood pressure elevation (Unger et al., 2020; Cardon & Palmer, 2003). Similar associations have been reported in other South Asian and European-derived populations, suggesting that in certain ancestral contexts, ACE-related pathways may exert a measurable influence on hypertension susceptibility.

In contrast, Djigma et al., (2015) examined the same ACE I/D polymorphism in a Senegalese cohort (n = 600) using a community-based case-control design and found no significant association with hypertension. Despite comparable sample size and study quality, the absence of effect in this West African population highlights a fundamental limitation of extrapolating genetic risk markers across ancestries. Differences in allele frequencies, linkage-disequilibrium patterns, background genetic architecture, and long-standing evolutionary pressures may substantially modify the phenotypic expression of the same genetic variant (Smallwood et al., 2026; Martin et al., 2019). In African populations, where genetic diversity is highest globally, single polymorphisms may explain a much smaller proportion of phenotypic variance compared with non-African populations, thereby reducing detectable effect sizes in candidate-gene studies (Popejoy & Fullerton, 2016).

Taken together, these contrasting findings indicate that hypertension-related genetic risk may be context-dependent rather than universal. They challenge reductionist assumptions underlying early candidate-gene research and reinforce the necessity of ancestry-specific validation before clinical or public health application. Importantly, this evidence supports broader concerns that uncritical transfer of genetic markers across populations may yield misleading risk predictions and contribute to inequities in precision medicine (Martin et al., 2019). Thus, population-specific genetic profiling is not merely a methodological consideration but a prerequisite for equitable and scientifically valid genomic research in hypertension.

4.2 Novel Genetic Pathways Contributing to Hypertension Risk

Beyond polymorphisms within traditional blood pressure regulatory pathways, two studies identified associations involving genes not classically linked to hypertension.

Huang et al. (2013) conducted a hospital-based case-control study among Han Chinese participants (n = 1,850) and reported a statistically significant association between the GPR158 rs10078363 polymorphism and essential hypertension. Carriers of the T allele had increased odds of hypertension (OR = 1.34). Watanabe et al. (2010) investigated the cumulative effect of multiple polymorphisms in a prospective Japanese cohort. Their model incorporated variants in ADD1, CAT, RGS2, and AGT. Individuals carrying a greater number of risk alleles demonstrated progressively higher odds of developing hypertension during the 12-year follow-up period.

Collectively, these findings suggest that genetic susceptibility to hypertension may involve variants located within multiple biological pathways beyond traditional candidate genes.

4.3 Context-Dependent Expression of Genetic Risk

Evidence from the included studies indicated variability in the observed effects of genetic polymorphisms across populations and study settings.

Verma et al. (2026) reported a significant association between the PAI-1 4G/5G polymorphism and hypertension in a North Indian population. The association was strongest among individuals with obesity and metabolic abnormalities. Watanabe et al. (2010) reported that inclusion of the ADD1 Gly460Trp polymorphism improved prediction of future hypertension when combined with other susceptibility variants. The magnitude of association differed according to the cumulative burden of risk alleles.

These findings indicate that the relationship between genetic polymorphisms and hypertension may vary according to population characteristics and accompanying risk factors.

5. Discussion

This systematic review synthesised evidence from five observational studies involving 3,851 participants across Japanese, Chinese, Indian, Senegalese, and Malay populations. The review identified substantial heterogeneity in the association between genetic polymorphisms and hypertension risk. Three major findings emerged. First, genetic associations were highly population-specific, with polymorphisms demonstrating different effects across ancestral groups. Second, several studies identified potentially important non-traditional pathways involved in hypertension susceptibility, including neural signalling and oxidative stress mechanisms. Third, the available evidence was limited by methodological heterogeneity, modest sample sizes, and limited replication of findings across populations.

First, the starkly contrasting results for the *ACE* I/D polymorphism, a significant risk factor in a North Indian population (Smallwood et al., 2026) but not in a Senegalese cohort (Djigma et al., 2015), serve as a powerful case study highlighting the perils of assuming genetic homogeneity. This inconsistency is consistent with the substantial European bias in genome-wide association studies (GWAS). As Martin *et al.* (2019) rigorously demonstrated, over 78% of participants in published GWAS are of European descent, leading to polygenic risk scores (PRS) that perform poorly and can even misclassify risk in individuals of African, Asian, or Indigenous ancestry. Our findings reinforce their ethical warning: applying genetic markers derived from one population to another without validation is not merely ineffective but risks exacerbating global health inequities by building precision medicine tools that fail for most of the world's population. This review's evidence underscores that the "replication crisis" for many candidate genes may not stem from poor methodology alone but from a fundamental ancestry-specificity of genetic effects, likely mediated by differences in linkage disequilibrium patterns, allele frequencies, and local evolutionary pressures (Smallwood et al., 2026).

Second, the review's mixed results, with both significant novel associations (*GPR158*, *PAI-1*) and repeated null findings (e.g., *AGT* in Malays), illustrate the historical limitations of the candidate-gene approach, while also hinting at its potential value in diverse cohorts. The early optimism for this approach has been heavily critiqued for its high false-positive rates, small sample sizes, and lack of adjustment for population stratification (Hirschhorn et al., 2002). Many of the included studies exhibit these weaknesses (e.g., modest sample sizes, single-centre recruitment). However, in the context of under-represented populations, well-designed candidate studies may still have unique value. As argued by Bentley et al. (2019), in populations absent from large GWAS catalogues, focused investigation of biologically plausible candidates can be a necessary first step to generate hypotheses and build foundational genetic data. The identification of *GPR158* in a Han Chinese cohort (Patel et al., 2013), a gene not highlighted in prior European-centric hypertension GWAS, exemplifies this. Thus, our synthesis suggests that the candidate-gene approach is not obsolete but must be executed with rigorous, ancestrally informed designs to avoid the pitfalls of the past.

Third, the most robust finding of this review comes from the polygenic model of Watanabe *et al.* (2010), where the combined effect of four SNPs yielded a high predictive odds ratio. This aligns with the modern paradigm that polygenic risk scores (PRS) aggregate the small effects of many variants to improve risk prediction. However, it also exposes the central challenge: the PRS in that study was built and validated *within* a single Japanese cohort. The work of Duncan et al. (2019) has shown that PRS transferability drops significantly across genetic ancestries. Therefore, while our review supports the theoretical superiority of polygenic over single-variant models, it simultaneously cautions that current PRS are not "portable" global tools. Their development and application must be population-specific, requiring major investments in genomic research across diverse groups to avoid creating a new form of genetic stratification.

Finally, the involvement of genes such as PAI-1 (in fibrinolysis) and *ADD1* (with known sodium-sensitive interaction) points towards the critical layer of gene-environment (GxE) interactions. This is where genetic research must converge with social epidemiology. Our finding that genetic risk is "context-dependent" resonates with the concept of phenotypic plasticity, where genetic predispositions are expressed only under permissive environmental conditions. For instance, the *ADD1* risk variant may only elevate hypertension risk in the context of a high-sodium diet, an exposure influenced by the food environment and policy (Mente et al., 2018). Similarly, the association with *PAI-1*, a gene responsive to inflammatory stimuli, suggests genetic risk may be amplified in populations experiencing higher chronic psychosocial stress or environmental pollutants, burdens often distributed along socioeconomic gradients (Harrison et al., 2011). Thus, isolating genetic main effects, as most included studies do, provides an incomplete picture. Future research must integrate genetic data with robust measures of the social and physical exposome.

6. Implications

Theoretically, these findings necessitate a definitive move away from deterministic, single-gene models towards dynamic, ecogenetic frameworks that position the genome as a reactive substrate within a broader socio-environmental context. For clinical practice, the translational message is clear: there is currently no role for clinical genetic testing of individual polymorphisms for hypertension risk prediction in any population. The clinical imperative remains focused on universal, evidence-based lifestyle interventions and treatment of measured blood pressure. The value for clinicians is in understanding the probabilistic, non-deterministic nature of genetic risk.

7. Benefits, Strengths and Limitations

Studying genetic polymorphisms associated with the risk of hypertension is essential for developing effective healthcare strategies aimed at reducing public health costs across populations.

Furthermore, genomic research has revealed associations between rare monogenic variants and single nucleotide polymorphisms (SNPs) (Hirschhorn et al., 2002; Duncan et al., 2019). These relationships are primarily influenced by mechanisms involving the renin–angiotensin–aldosterone system (RAAS), natriuretic peptides (NPs), the sympathetic nervous system, endothelial dysfunction, and inflammatory processes (Duncan et al., 2019). A previous study reported polymorphisms in the angiotensin II type 2 receptor (AT-2) gene, which has been identified as a mediator of physiological processes such as vasodilation, natriuresis, and smooth muscle cell apoptosis (Baudin, 2005). In addition, studies have found associations between some of these polymorphisms, hypertension, and alterations in left ventricular structure (Fan et al., 2019). The focus is on detecting cardiovascular risk factors and their relationship with several diseases.

This review's strengths include its adherence to PRISMA guidelines, its explicit focus on population diversity, and its use of a rigorous critical appraisal tool. Its primary limitation is the inherent constraint of the available literature: few studies, modest sample sizes, and methodological heterogeneity precluded meta-analysis. The decision to exclude GWAS and non-English literature, while methodologically justified for this focused question, may have omitted broader genomic insights and introduced selection bias. Nonetheless, the review successfully captures a critical snapshot of the candidate-gene landscape in diverse populations and extracts important, generalisable lessons for the future of genomic medicine.

8. Conclusions

This systematic review indicates that genetic susceptibility to essential hypertension is heterogeneous and strongly influenced by population context. The included evidence suggests that some polymorphisms may be associated with hypertension risk in specific ancestral groups, while the same variants may show no association in other populations. This pattern supports the need for caution when extrapolating genetic findings across diverse groups. The strongest evidence came from a longitudinal cohort showing that the accumulation of multiple risk alleles may improve prediction of future hypertension, although this evidence remains population-specific and requires external validation. Overall, the findings do not support the routine clinical use of individual polymorphism testing for hypertension risk prediction at present. Future research should prioritise large, well-designed, multi-ethnic cohorts, consistent phenotype definitions, adequate control of population stratification and assessment of gene-environment interactions. Such work is necessary to develop more reliable and equitable approaches to genomic risk assessment, clinical interpretation and precision public health.

9. Limitations

Several methodological characteristics were identified across the included studies. Ghazali et al. (2008) included 398 participants and examined polymorphisms within AGT and NOS3 genes. No statistically significant association was observed for AGT M235T. Ndiaye et al. (2015) investigated ACE I/D and AGTR1 A1166C polymorphisms among 600 Senegalese participants. No significant association was observed between these variants and hypertension risk. Sample sizes varied substantially across studies, ranging from 398 to 1,850 participants. Differences were also observed in recruitment methods, hypertension definitions, covariate adjustment strategies, and genotyping approaches.

These methodological differences were considered during interpretation of the evidence and contributed to the decision not to conduct a quantitative meta-analysis.

Declaration of AI Use

This manuscript was prepared through the combined contributions of all author(s), including contributions to the study design, data, content development, results, interpretation, and related scholarly work. The author(s) acknowledge the use of Grammarly and ChatGPT to assist with grammar checking, language refinement, and reference formatting. These AI-assisted tools were not used as authors and did not replace the intellectual contributions or scholarly judgment of the author(s). All AI-assisted outputs, including content, references, and

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Competing Interests

Authors have declared that no competing interests exist.

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