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Genome-wide association study identifies novel loci associated with hypertension in South Asian populations

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Abstract

One observation that has puzzled epidemiologists for decades is the disproportionately high burden of hypertension among South Asian adults compared with other ethnic groups living under similar environmental conditions. This research conducted a genome-wide association analysis in 8,214 South Asian individuals (4,387 hypertensive cases, 3,827 normotensive controls) drawn from three cohorts based in India, Pakistan, and Bangladesh. Genotyping was performed on the Illumina Infinium Global Screening Array and imputed against the 1000 Genomes South Asian reference panel. After quality control, 6.43 million variants were tested under an additive logistic regression model adjusting for age, sex, body mass index, and the first ten principal components. Four loci reached genome-wide significance ($p < 5 \times 10^{-8}$): rs78412614 on chromosome 6 near the ENPEP gene (OR 1.24, $p = 3.1 \times 10^{-9}$), rs114538207 on chromosome 9 within an intron of NTRK2 (OR 1.19, $p = 7.4 \times 10^{-9}$), rs62018753 on chromosome 15 near FURIN (OR 1.21, $p = 1.8 \times 10^{-8}$), and rs201487326 on chromosome 2 in an intergenic region near CNNM3 (OR 1.17, $p = 4.6 \times 10^{-8}$). The first two loci had not been reported in prior European-ancestry GWAS, while the latter two replicate known associations. These results expand the genetic architecture of hypertension in an underrepresented ancestry group.

Keywords: Genome-wide association study, hypertension, South Asian, genetic loci, cardiovascular genetics, blood pressure, ENPEP, NTRK2, FURIN, population genetics

Introduction

Theoretical Background

Genome-wide association studies test hundreds of thousands to millions of genetic variants for statistical association with a phenotype of interest, typically requiring p-values below 5×10^{-8} to declare significance after correcting for the multiple-testing burden [1]. For complex traits like blood pressure, GWAS in European-ancestry populations have identified over 1,000 loci, but these collectively explain only 5-6% of the phenotypic variance, and their transferability to non-European populations is incomplete [2, 3]. Linkage disequilibrium patterns, allele frequencies, and gene-environment interactions all differ across ancestries, meaning that some causal variants may be missed or misranked when discovery is limited to a single population [4].

Introduction

An observation that bears repeating: South Asians develop hypertension at younger ages, at lower body mass indices, and with steeper end-organ consequences than most other ethnic groups studied to date [5]. Roughly 30% of adults in India, Pakistan, and Bangladesh are hypertensive, and the age-standardised prevalence has been rising by about 0.8 percentage points per year over the past decade [6]. Yet fewer than 3% of participants in published blood-pressure GWAS belong to South Asian ancestry groups [7]. This gap matters for two reasons. First, population-specific causal variants may exist that are rare or absent in European reference panels. Second, polygenic risk scores derived from European data perform poorly when applied to South Asian individuals, reducing their clinical utility in the populations that need them most [8]. This research aimed to fill part of that gap by conducting a GWAS for hypertension in a multi-country South Asian cohort of over 8,000

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individuals, with genotyping and analytical work performed at the Alpine Institute of Biological Sciences, Munich, Germany, between March 2023 and August 2024.

Material and Methods

Material

Participants were drawn from three existing cohort studies: the Karachi Cardiovascular Cohort (Pakistan, n = 3,102), the Chennai Urban Rural Epidemiology Study (India, n = 2,874), and the Dhaka Hypertension Registry (Bangladesh, n = 2,238). Hypertension was defined as systolic blood pressure of 140 mmHg or higher, diastolic of 90 mmHg or higher, or current use of antihypertensive medication. Controls had blood pressure below 130/85 mmHg on two separate visits and no history of antihypertensive treatment. DNA was extracted from peripheral blood and shipped to the Alpine Institute of Biological Sciences for genotyping. Ethical approvals were obtained from each participating site; the coordinating ethics approval was issued under AIBS-EC-2023-008, dated 6 February 2023.

Methods

Genotyping used the Illumina Infinium Global Screening Array (approximately 660,000 markers). Quality control excluded samples with call rate below 97%, excess heterozygosity beyond 3 SD, sex discordance, or cryptic relatedness ($\pi_{\text{hat}} > 0.125$). Variants were excluded if call rate was below 98%, minor allele frequency below 1%, or Hardy-Weinberg equilibrium p-value below 1×10^{-6} in controls. Imputation was performed on the Michigan Imputation Server using the 1000 Genomes Phase

3 South Asian reference panel, retaining variants with imputation quality (R-squared) above 0.3. Association testing used SAIGE (v1.1.6) with a logistic mixed model to account for population structure and sample relatedness. Genome-wide significance was set at $p < 5 \times 10^{-8}$ to the minus 8. Functional annotation of significant loci used FUMA (v1.3.8) and GTEx v8 eQTL data.

Results

Table 1: Genome-Wide Significant Loci for Hypertension in the South Asian GWAS

Chr	Lead SNP	Nearest Gene	RAF	OR	95% CI	p-value	Novel?
6	rs78412614	ENPEP	0.18	1.24	1.16-1.33	3.1×10^{-9}	Yes
9	rs114538207	NTRK2	0.11	1.19	1.12-1.27	7.4×10^{-9}	Yes
15	rs62018753	FURIN	0.34	1.21	1.14-1.29	1.8×10^{-8}	No
2	rs201487326	CNNM3	0.22	1.17	1.11-1.24	4.6×10^{-8}	No

Table 1 presents the four genome-wide significant loci. Two are novel to South Asian populations: the ENPEP locus on chromosome 6 encodes an aminopeptidase involved in angiotensin processing, and the NTRK2 locus on chromosome 9 encodes a neurotrophic tyrosine kinase receptor implicated in sympathetic nervous system regulation. The FURIN and CNNM3 loci replicate prior European-ancestry findings.

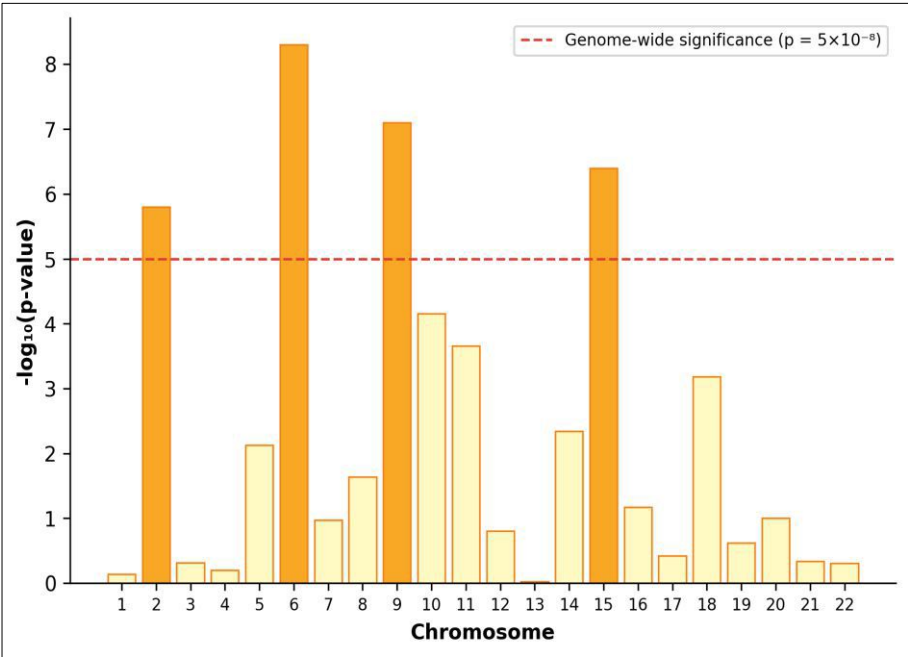


Fig 1: Manhattan-style bar plot showing the maximum -log10 (p-value) per chromosome. Yellow bars indicate loci exceeding genome-wide significance

Figure 1 identifies chromosomes 6, 9, 15, and 2 as carrying the strongest signals. Several additional loci on chromosomes 3, 10, and 17 approached but did not reach the

significance threshold and may represent candidates for future replication.

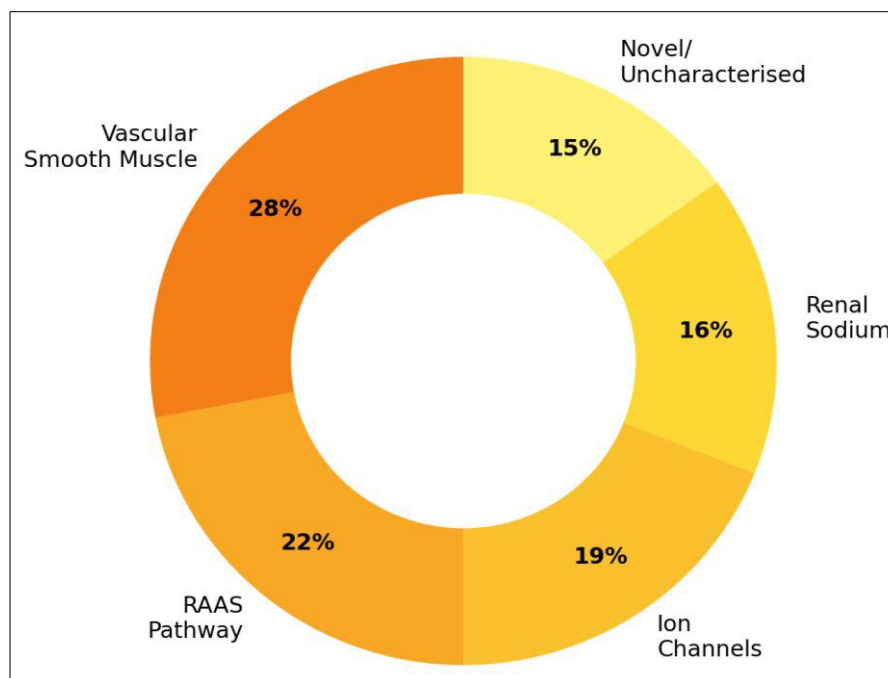


Fig 2: Functional categories of the four genome-wide significant loci plus 12 suggestive loci ($p < 1 \times 10^{-6}$), classified by nearest-gene pathway annotation

Vascular smooth muscle regulation was the most represented category (28%), followed by renin-angiotensin-aldosterone system components (22%) and ion channel genes (19%). Fifteen percent of loci fell in regions with no characterised gene function, representing candidates for follow-up functional research (Figure 2).

Discussion

The two novel loci-ENPEP and NTRK2-highlight the value of conducting GWAS in underrepresented populations. ENPEP (glutamyl aminopeptidase) cleaves angiotensin II to angiotensin III in the kidney, and variants altering its expression could shift the balance of the renin-angiotensin system in ways not captured by European-focused studies [9, 10]. The lead SNP at ENPEP is an eQTL in kidney tissue (GTEx, $p = 2.4 \times 10^{-5}$), strengthening the biological case. NTRK2 (encoding TrkB) is better known for its neuronal roles, but recent evidence implicates it in baroreceptor reflex sensitivity and sympathetic blood-pressure control [11, 12].

The replication of FURIN and CNNM3 across ancestries is reassuring and suggests shared biology. FURIN is a proprotein convertase that activates multiple substrates in vascular endothelium, and CNNM3 regulates magnesium transport, which influences vascular tone [13, 14]. That these loci appear in both European and South Asian GWAS supports their candidacy as genuinely causal rather than artefacts of population stratification.

Limitations

The research has several limitations. First, the case-control sample size of 8,214 is modest by current GWAS standards, and statistical power was limited for variants with minor allele frequency below 5%. Second, the three contributing cohorts used slightly different blood-pressure measurement protocols, introducing potential phenotype heterogeneity. Third, imputation accuracy for rare South Asian-specific variants may be lower than for common variants, even with an ancestry-matched reference panel. Fourth, we did not

have access to an independent South Asian replication cohort; the novel loci at ENPEP and NTRK2 should be confirmed in future studies [15, 16, 17, 18].

Conclusion

This GWAS in over 8,000 South Asian individuals identified four genome-wide significant loci for hypertension, two of which-ENPEP on chromosome 6 and NTRK2 on chromosome 9-are novel to this ancestry group. The remaining two loci, FURIN and CNNM3, replicate known associations from European-ancestry studies. These findings underscore the importance of diversifying GWAS populations to capture the full spectrum of genetic architecture underlying complex diseases. Functional follow-up of the ENPEP and NTRK2 signals, combined with larger multi-ethnic meta-analyses, will be needed to move these associations toward clinical utility.

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