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GWAS and Replication Analysis of Apparent Treatment-Resistant Hypertension

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BACKGROUND: Resistant hypertension (RH), in which blood pressure remains elevated on ≥3 medications or controlled on ≥4 medications, increases the risk of adverse cardiovascular events nearly 50% more than primary hypertension. We sought to identify genetic drivers of RH in a reliable and generalizable manner.

METHODS: We utilized FinnGen (discovery) and UKBB (UK Biobank, replication) data sets to identify potential genetic drivers of RH. Using standard RH definitions, we developed cohorts in each data set and performed genome-wide (genome-wide association studies) and transcriptome-wide association studies, as well as Mendelian randomization analysis to evaluate potential causal associations.

RESULTS: We replicated 5 genetic loci in *CASZ1, WNT2B, KCNK3, LSP1*, and near the *EVX1/EVX1AS* locus for RH. Of these, *CASZ1* and *WNT2B* are strongly associated with aldosterone homeostasis, while *KCNK3* and *LSP1* are associated with pathways mediating vasodilation. *EVX1/EVX1AS* are involved in mesendodermal lineage differentiation during gastrulation. Gene- and pathway-based analyses identified associations with vascular and cardiac developmental pathways in addition to aldosterone synthesis and secretion pathways. Transcriptome-wide association study analyses identified 37 genes, of which the genetically regulated expression is associated with RH, with particularly strong tissue-specific associations with *KCNK3*. Finally, Mendelian randomization identified possible causal association for 4 vascular risk factors (CRP [C-reactive protein]), triglycerides, waist circumference, and body mass index) with RH, with strong associations with identified lead variants.

CONCLUSIONS: We identified distinct genetic variants associated with RH, including those implicating the role of hyperaldosteronism, highlighting distinct pathways and targets for more effectively treating RH. ***(Hypertension.* 2026;83:00–00. DOI: 10.1161/HYPERTENSIONAHA.125.25719.)** • **Supplement Material**.

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Key Words: genome-wide association study ■ hyperaldosteronism ■ hypertension ■ Mendelian randomization analysis ■ vascular remodeling

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Hypertension remains one of the most common cardiovascular risk factors worldwide, contributing to >10 million excess fatal strokes, heart attacks, and episodes of renal failure annually.[1] Resistant hypertension (RH), defined as uncontrolled blood pressure on ≥3 antihypertensive medications or controlled blood pressure on ≥4 antihypertensive medications, represents a form of hypertension with even greater morbidity and mortality. Compared with those with non-RH, those with RH substantially higher risk of adverse cardiovascular events and a higher risk of death.[2,3] An estimated 10.3% of individuals with hypertension have RH, with even more experiencing apparent RH (aRH), in which factors, such as medication nonadherence, may result in persistently elevated BP and residual cardiac risk.[4] This alarmingly high prevalence of difficult-to-control blood pressure despite adequate antihypertensive pharmacotherapy suggests that understanding the underlying biological processes that contribute to very elevated blood pressure and suboptimal responses to antihypertensive therapy could lead

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NOVELTY AND RELEVANCE

What Is New?

Five genetic loci associated with apparent treatment-resistant hypertension (RH) were identified and replicated using FinnGen (discovery) and UKBB (UK Biobank, replication) data sets: *CASZ1, WNT2B, KCNK3, LSP1*, and near the *EVX1/EVX1AS* locus for RH.

CASZ1 and *WNT2B* are strongly associated with aldosterone homeostasis, whereas *KCNK3* and *LSP1* are associated with pathways mediating vasodilation.

Mendelian randomization identified a possible causal association of RH with 4 vascular risk factors: CRP (C-reactive protein), triglycerides, waist circumference, HDL (high-density lipoprotein), and body mass index.

What Is Relevant?

These findings identify potential biological underpinnings of RH, an increasingly recognized and highly morbid cardiovascular risk factor.

Clinical/Pathophysiological Implications?

Results provide a biological underpinning for the clinically observed usefulness of mineralocorticoid receptor antagonists and novel aldosterone synthesis inhibitors in the treatment of RH, and highlight the important role of hyperaldosteronism as a likely cause of difficult-to-control blood pressure.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
aRH	apparent resistant hypertension
CRP	C-reactive protein
CS	credible set
GWAS	genome-wide association studies
RH	resistant hypertension
TWAS	transcriptome-wide association study
UKBB	UK Biobank

to substantial population health benefits. Although previous genome-wide association studies (GWAS) have pinpointed several genetic variants linked to hypertension,[5,6] a reliable list of genetic contributors to RH has not been presented. Prior studies seeking to evaluate potential genetic underpinnings of RH have been limited by either small sample sizes, lack of replication analyses, or both. We sought to identify genetic drivers of RH in a reliable and generalizable manner, providing insights into the broader physiological mechanisms of RH and paving the way for targeted treatments that can be applied to diverse patient populations.

METHODS

Data for this study were obtained from the Finnish biobank, which can be accessed through the Fingenious services (https://site.fingenious.fi/en/) managed by FINBB. A.K. and T.N. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All participants provided written informed consent. This study protocol was approved by the coordinating ethical committee of the Hospital District of Helsinki and Uusimaa, as described in the Supplemental Material. Ethics approval for the UKBB study (UK Biobank) was obtained from the North West center for Research Ethics Committee (11/NW/0382). The UKBB data are available via the UKBB data access process (http://www.ukbiobank.ac.uk/register-apply/).

Study Sample

Our study sample was drawn from the FinnGen Data Freeze 12, which consists of 520 210 individuals, including patients from Finland's national hospital biobanks, and randomly selected participants from Finnish cohort studies.[7] Briefly, FinnGen represents a public-private partnership that longitudinally collects and manages anonymous nationwide health information from across Finland, including diagnoses, medications, clinical events, health registry, and genomic data. All participants provided written informed consent. This study protocol was approved by the coordinating ethical committee of the Hospital District of Helsinki and Uusimaa, as described in the Supplemental Material. For replication, we used the UKBB, which is a large-scale biomedical database containing genetic and health information from 502 355 UK participants.[8]

Hypertension Diagnosis

Hypertension status was defined based on the presence or absence of a diagnosis in registries. In FinnGen, hypertension diagnosis (FinnGen code I9_HYPTENS) was identified from *International Classification of Diseases (ICD)* codes from the nationwide hospital discharge and causes-of-death registers (*ICD*, *Tenth Revision*: I1 [0–5]|I67.4; *ICD*, *Ninth Revision*: 4019X|4029 [A–B]|4039A|4040A| 4059 [A–B]|4372A|4059X; *ICD*, *Eighth Revision*: 40 [0–4]), and drug reimbursement register (code 205). Codes were linked by personal nationwide identification number. These *ICD* code–based diagnoses are made by the attending physician, and the accuracy of these codes is robust and has been described in detail previously.[9] For UKBB replication, we used baseline data: Self-reported hypertension diagnoses by a doctor (field 6150), self-reported medication use (field 20 003), and systolic and diastolic blood pressure measurements with automated reading (fields 4080 and 4079, respectively).

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Number of Antihypertensive Medications

Antihypertensive medication prescription was defined by the Anatomical Therapeutic Chemical codes via the drug purchase register (available from 1992 to 2023). Antihypertensive medications were divided into 6 classes: diuretics, ACE (angiotensin-converting enzyme) inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta-blockers, and other medications. For each individual, we determined the maximum number of different antihypertensive classes prescribed during any 3-month period, corresponding with the maximum 3-month supply that can be reimbursed at one transaction by the Finnish pharmacies. For UKBB data, antihypertensive medications were divided into 6 classes, similar to FinnGen.

Hypertension Subclassification: Mild and Apparent RH

We used standardized protocols to cohort patients with hypertension into either mild hypertension (control group) or aRH (case group). Mild hypertension was defined as a patient with hypertension prescribed maximally only 1 antihypertensive class at a time. This definition was true for both FinnGen and UKBB data sets.

aRH was defined by contemporary guidelines as blood pressure above target despite the use of at least 3 antihypertensive medications from different classes or controlled blood pressure using at least 4 drugs from different classes.[10] Importantly, FinnGen does not include blood pressure values, while UKBB does. As such, conservative yet slightly different definitions were used to classify patients in each data set. In FinnGen, we used a conservative definition of aRH, requiring a prescription of at least 4 drug classes, as we were unable to determine blood pressure control to meet lower prescription thresholds. For UKBB data, we used 2 alternative definitions for aRH: (1) patient with hypertension with a simultaneous prescription of at least 4 drug classes (same as FinnGen), and (2) a clinical definition, in which individuals simultaneously receiving at least 3 antihypertensive classes and with a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or receiving at least 4 antihypertensive medication classes regardless of blood pressure level (as in definition 1). The FinnGen definition of aRH was used for discovery, and the more inclusive UKBB definition was used for replication. We additionally performed sensitivity analyses to evaluate for differences in replication if we applied either one of the subsets of the more inclusive definition: (1) 4 medications regardless of blood pressure, or (2) 3 medications with uncontrolled BP.

Genotyping and Imputation

FinnGen samples were genotyped with Illumina and Affymetrix arrays and genotype calls with zCall or GenCall (for Illumina) and AxiomGT1 (for Affymetrix) at the Institute for Molecular Medicine Finland.[7] Reference genomes were lifted over to build GRCh38. Quality control exclusions were performed sample-wise: ambiguous gender, missingness >5%, heterozygosity >4 SD, or non-European ancestry; and variant-wise: missingness >2%, Hardy-Weinberg equilibrium $P<1\times10^{-6}$, and minor allele count <3. Samples were first prephased with Eagle 2.3.5 and then imputed genotypes with Beagle 4.1 using a Finnish population–specific SISu v4 reference panel. Variants with imputation INFO <0.6 and MAF <0.00001 were excluded. Finally, to account for population structure in downstream analyses, genetic principal component analysis was performed using a pruned set of SNPs of unrelated individuals.

UKBB genotype calling was performed at Affymetrix on purpose-designed arrays with 805 426 markers and quality controlled.[8] The positions of markers are in GRCh37 coordinates (field 22 418). We used Genomics England high coverage imputation lifted to GRCh38 (field 21 008; https://doi.org/10.1101/2023.11.06.23298035).

Genome-Wide Association Studies

We used regenie (FinnGen: v2.2.4; UKBB: v3.1.1) to perform GWAS.[11] In the first step of regenie, the whole genome regression model was fit to the traits (bsize 1000). In FinnGen, we included variants imputed with an INFO score of 0.95, 97% nonmissing genotypes, and MAF >1%. In UKBB, we used unimputed data (field 22 418) that was lifted to GRCh38 and quality controlled using PLINK (maf 0.01, mac 20, geno 0.1, hwe 1×10^{-15}, and mind 0.1).[12] In the second step of regenie, imputed SNPs (Genomics England, field 21 008) were tested for associations using a Firth logistic regression model and output of the first step (bsize 400). We used sex, age, and 10 genetic principal components as covariates. In FinnGen, genotyping batches were included as covariates (Figure 1).

Fine-Mapping and Replication

First, we defined a fine-mapping region by taking a 3 Mb window around a lead variant for each genome-wide significant locus ($P<5\times10^{-8}$) and merging overlapping regions. The dosage linkage disequilibrium (LD) is computed for each fine-mapping region using LDstore2.[13] After extracting variants present in the LD panel, the default settings of SuSiE v.0.11.92 were used with the maximum number of 10 putative causal variants in a locus.[14]

We considered a credible set (CS) lead variants successfully replicated if the P value of the variant in UKBB survived Bonferroni correction by the total number of CSs, and the effect direction was concordant with FinnGen. The FinnGen definition of aRH was used for discovery, and the more inclusive UKBB definition was used for replication.

Gene- and Pathway-Based Analysis

We performed gene-based and pathway-based analyses using VEGAS2 with default parameters.[15] VEGAS2 considers variants in the gene or within 10 kb on either side of a gene's transcription site to compute a gene-based P value. We used 1000 Genomes phase 3 reference samples of European ancestry to compute the LD between variants for gene-based analyses. Gene-wide significance was defined as $P<1.9\times10^{-6}$, correcting for 26 056 autosomal protein-coding genes tested. The output from the gene-based association analysis was used as an input for VEGAS2 pathway analysis with Biosystems pathways.[16] We used empirical $P<0.05$ as the significance level for pathway analysis.

Transcriptome-Wide Association Study

We carried out a transcriptome-wide association study (TWAS) using TWAS-FUSION[17] on GWAS summary statistics to identify genes whose expression is associated with the risk of aRH.

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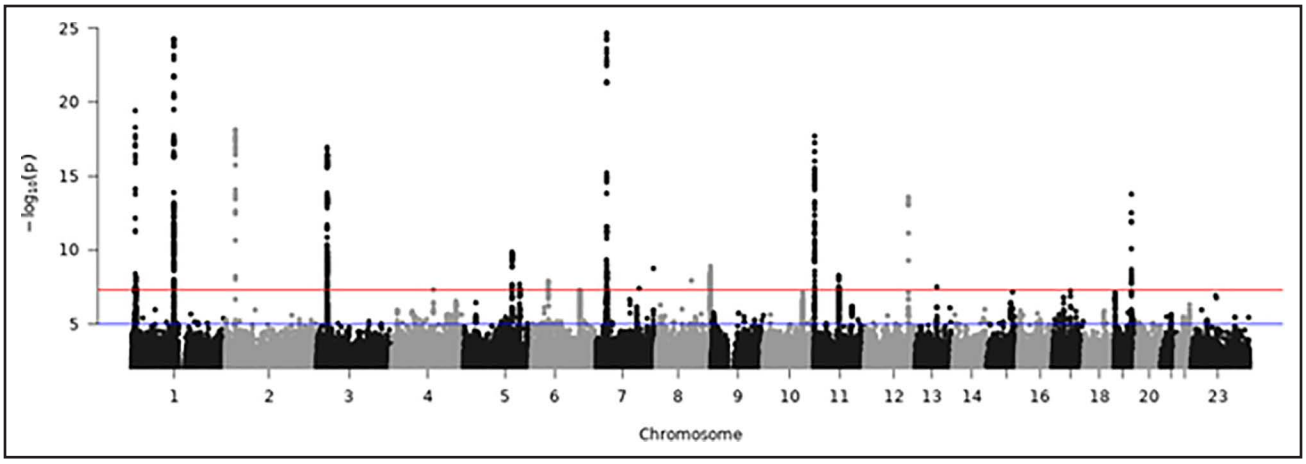

Figure 1. Discovery Manhattan plot for resistant hypertension genome-wide association studies.

TWAS-FUSION integrates expression quantitative trait locus reference data with an LD panel to construct gene expression prediction models, which are then applied to GWAS summary statistics to test gene-level associations between genetically predicted expression and the trait of interest.[17] We performed the analysis in 9 tissues considered to be relevant for hypertension (adipose visceral omentum, adrenal gland, artery aorta, artery coronary, artery tibial, heart atrial appendage, heart left ventricle, kidney cortex, and liver) using expression quantitative trait locus reference panels from the GTEx v.8 database.[18] Transcriptome-wide significance was defined as $P<5.0\times10^{-6}$ determined using a Bonferroni correction based on the highest number of expressed genes in a single tissue type (9905 genes in adipose tissue; Table S1).

Mendelian Randomization and Risk Traits

To elucidate the causal clinical factors underlying RH, we performed 2-sample Mendelian randomization using the R package TwoSampleMR. We extracted exposure data from the IEU OpenGWAS database,[19–21] with the exception of urine albumin-to-creatinine ratio data for which we downloaded better-powered summary statistics from the GWAS catalog, specifically data from the CKDGen Consortium (Teumer et al[22]). For the outcome, we used discovery GWAS summary statistics for aRH from FinnGen. We constructed genetic instruments for 16 vascular risk traits: CRP (C-reactive protein), triglycerides, waist circumference, body mass index, blood glucose, low-density lipoprotein cholesterol, estimated glomerular filtration rate, alcohol usage, neuroticism, urine albumin-to-creatinine ratio, urate, glycated hemoglobin, height, HDL (high-density lipoprotein) cholesterol, total cholesterol, and smoking. The lead variants for instruments were selected based on genome-wide significant associations ($P<5\times10^{-8}$) after clumping by P value in 10 000 kb windows using an r^2 threshold of 0.001 and 1000 Genomes Project (ancestry EUR) as an LD reference panel. After data harmonization, we ran MR using all available methods to ensure robustness: inverse variance weighting, weighted median, MR Egger, simple mode, and weighted model. In addition, we visualized associations between risk traits and the UKBB-replicated SuSiE lead variants. Details of harmonized risk trait GWAS summaries are listed in Table S2.

All statistical tests were 2-sided in nature.

RESULTS

A total of 153 023 and 92 163 individuals with hypertension with complete data were obtained from FinnGen and the UKBB, respectively. Of these, 15 996 (10%) in FinnGen and 31 028 (34%) in UKBB met the definition for mild hypertension (control group), while 39 737 (26%) in FinnGen and 5979 (6.5%) in UKBB met cohort-specific definitions for aRH (case group; Table 1).

Using FinnGen as our primary cohort, we first identified genome-wide significant loci for the aRH phenotype (Figure 1), followed by statistical fine-mapping, which resulted in 21 CSs from which lead variants were selected from each CS based on the posterior inclusion probability (for reliable CSs) or P value (Table 2). Replication in UKBB was performed, with individuals classified as aRH if they met either the FinnGen or UKBB aRH-specific criteria. A total of 5 CS lead variants identified in FinnGen were replicated in UKBB: rs880315 (intron variant, *CASZ1*), rs12037987 (intron variant, *WNT2B*), rs1275984 (upstream variant, *KCNK3*), rs612652 (intron variant, *LSP1*), and rs4722681 (intergenic variant, near *EVX1/EVX1AS*). Specifically, these include proximity of genes involved in mineralocorticoid receptor activity (*WNT2B* [odds ratio 1.21; $P=6.3\times10^{-25}$], *CASZ1* [1.14; $P=4.0\times10^{-20}$]), endothelial function (*LSP1* [1.13; $P=2.0\times10^{-18}$], and ion transport (*KCNK3* [0.88; $P=7.9\times10^{-19}$]). LocusZoom plots for discovery GWAS loci containing the replicated CS lead variants are provided in the Supplemental Material (Figure S1). We secondarily performed sensitivity analyses by separately applying the individual subcomponent definitions of aRH (1) 4 medications regardless of blood pressure, or (2) 3 medications with uncontrolled BP to the UKBB cohort, with similar results (Table S3).

Gene- and Pathway-Based Analysis

We performed gene-based and pathway-based analyses using VEGAS2 first for the control group (mild

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Table 1. Demographic and Clinical Characteristics Overall and by Cohort

	FinnGen		UKBB	
	Resistant	Mild	Resistant	Mild
N	39737	15996	5979	31028
Female sex, n (%)	18464 (46.5)	7691 (48.1)	2409 (40.3)	16137 (52.0)
Clinical events, n (%)				
Coronary heart disease	11986 (30.2)	1901 (11.9)	370 (6.2)	1316 (4.2)
Stroke	5897 (15.9)	1816 (12.0)	293 (4.9)	901 (2.9)
Heart failure	10344 (26.0)	1098 (6.9)	756 (12.6)	1738 (5.6)
Cardiovascular disease	15893 (40.0)	3557 (22.2)	627 (10.5)	2125 (6.8)
Max no. of simultaneous antihypertensive medications, n (%)				
1	0	15996 (100)	0	31028 (100)
2	0	0	0	0
3	33092 (83.3)	0	4515 (75.7)	0
4	6189 (15.6)	0	1300 (21.7)	0
≥5	456 (1.1)	0	154 (2.6)	0
Patients with controlled BP by max no. of simultaneous antihypertensive medications, n (%)*				
1 medication				9250 (29.8)
3 medications			0	
≥4 medications			546 (9.1)	

BP indicates blood pressure; and UKBB, UK Biobank.
*BP controlled defined both systolic BP<140 mm Hg and diastolic BP <90 mm Hg.

hypertension) and again for those with aRH. Among patients with mild hypertension, associations with whole genes and numerous vascular and cardiac developmental pathways were identified (Table S4). Similar associations of vascular and cardiac developmental pathways were found among aRH patients. aRH associations also revealed an association with aldosterone synthesis and secretion pathways.

Transcriptome-Wide Associations

We performed TWAS analyses to infer associations between aRH and gene expression. We identified 37 genes whose genetically predicted expression was associated with aRH with transcriptome-wide significance in at least 1 tissue (22 genes in arteries and heart; 13 genes in subcutaneous or visceral adipose tissue; 11 genes in the adrenal gland). *KCNK3* expression in the heart atrial appendage, *TNNT3* in the left ventricle, and *NEK10* in the aorta were most strongly associated with increased aRH prevalence. Conversely, expression of *MRPL23-AS1* in the left ventricle, *PRR33* in subcutaneous adipose tissue, and *NEK10* in the liver were most strongly associated with decreased aRH prevalence (Figure 2). One of the genes identified through TWAS, *KCNK3*, overlapped with those identified in the GWAS analysis. As noted, *KCNK3* expression in the atrial appendage was associated with increased aRH prevalence, while its expression in subcutaneous adipose was negatively associated with aRH.

Mendelian Randomization

Using 2-sample Mendelian randomization, we found evidence for a possible causal association for 5 vascular risk traits with aRH: CRP, triglycerides, waist circumference, HDL, and body mass index (Figure 3; Table S5). We additionally evaluated for associations between risk traits and replicated lead variants identified via fine-mapping. We found *KCNK3* to be positively associated with low-density lipoprotein cholesterol and triglycerides, *CASZ1* positively associated with urine albumin-to-creatinine ratio and negatively associated with low-density lipoprotein cholesterol and triglycerides, *WNT2B* negatively associated with triglycerides, and *LSP1* negatively associated with height (Figure 4).

DISCUSSION

In this study, we identified 6 genome-wide significant loci associated with aRH. Notably, the gene variants at these loci are heavily involved in pathways related to vascular remodeling, primary aldosteronism, and endothelial dysfunction—all known contributors to RH. We report 5 gene variants that were identified in FinnGen and subsequently replicated in UKBB: rs880315 (*CASZ1*), rs12037987 (*WNT2B*), rs1275984 (*KCNK3*), rs612652 (*LSP1*), and rs4722681 (near *EVX1/EVX1AS*). The identified gene variants provide valuable insights into the molecular mechanisms underlying RH and are consistent with the framework set by previous studies investigating their roles in other forms of hypertension.

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Table 2. Fine-Mapping Results From FinnGen and UKBB Cohorts

rsID	Chr:Pos*	EA	Non-EA	EAF (%)	Nearest gene	FinnGen discovery		UKBB replication	
						OR (95% CI)	*P* value	OR (95% CI)	*P* value
Replicated									
rs880315	1:10736809	C	T	41	*CASZ1*	1.14 (1.11–1.17)	4.0×10^{-20}	1.12 (1.07–1.17)	1.4×10^{-7}
rs12037987	1:112500200	C	T	17	*WNT2B*	1.21 (1.17–1.25)	6.3×10^{-25}	1.15 (1.07–1.24)	1.2×10^{-4}
rs1275984	2:26688641	C	A	55	*KCNK3*	0.88 (0.86–0.91)	7.9×10^{-19}	0.90 (0.86–0.93)	1.5×10^{-7}
rs4722681	7:27280700	C	T	14	*EVX1/EVX1AS*	1.15 (1.11–1.20)	2.5×10^{-12}	1.17 (1.09–1.24)	2.2×10^{-6}
rs612652	11:1865986	C	T	57	*LSP1*	1.13 (1.10–1.16)	2.0×10^{-18}	1.09 (1.05–1.14)	1.4×10^{-5}
Not replicated									
rs55892892	1:11836799	A	C	8.8	*CLCN6*	0.87 (0.82–0.91)	6.3×10^{-9}	0.93 (0.84–1.01)	9.8×10^{-2}
rs3790611	1:112525170	G	A	24	*ST7L*	0.89 (0.86–0.91)	7.9×10^{-14}	0.95 (0.91–1.00)	5.0×10^{-2}
rs7624512	3:27426806	G	C	39	*SLC4A7*	0.89 (0.86–0.91)	1.3×10^{-17}	0.94 (0.90–0.98)	2.7×10^{-3}
rs6815273	4:110416322	A	G	45	*ZNF969P*	0.93 (0.90–0.95)	5.0×10^{-8}	0.95 (0.91–0.99)	1.7×10^{-2}
rs4385259	5:128479760	C	G	35	*FBN2*	1.10 (1.07–1.13)	1.3×10^{-10}	1.06 (1.02–1.10)	5.7×10^{-3}
rs13154725	5:148515142	A	G	39	*HTR4*	1.08 (1.05–1.11)	2.0×10^{-8}	1.02 (0.98–1.07)	2.5×10^{-1}
rs2270860	6:43302413	T	C	30	*SLC22A7*	1.09 (1.06–1.12)	1.3×10^{-8}	1.05 (1.00–1.10)	2.9×10^{-2}
rs1859168	7:27202740	C	A	90	*HOTTIP*	1.28 (1.22–1.35)	2.5×10^{-25}	1.12 (1.03–1.21)	8.3×10^{-3}
rs57239204†	7:113130492	CA	C	6.5	*AC073346.1*	0.86 (0.81–0.91)	4.0×10^{-8}	1.08 (0.93–1.26)	3.0×10^{-1}
rs3918226	7:150993088	T	C	7.0	*NOS3*	1.17 (1.11–1.23)	1.6×10^{-9}	1.05 (0.97–1.12)	2.2×10^{-1}
rs59122069	8:92599599	‡	G	0.5	*AC091096.1*	0.57 (0.47–0.69)	1.0×10^{-8}	§	§
rs61276460	8:142983465	T	C	48	*LY6E-DT*	0.92 (0.89–0.94)	1.3×10^{-9}	0.97 (0.93–1.01)	1.1×10^{-1}
rs1308020	11:65730087	A	G	28	*KRT8P26*	0.91 (0.89–0.94)	5.0×10^{-9}	0.98 (0.94–1.02)	3.2×10^{-1}
rs35427	12:115118502	G	T	37	*RP11-25E2.1*	0.90 (0.87–0.92)	2.5×10^{-14}	0.94 (0.90–0.98)	5.9×10^{-3}
rs9573144	13:73247350	A	G	12	*RNY1P8*	1.13 (1.08–1.17)	3.2×10^{-8}	1.03 (0.97–1.10)	3.5×10^{-1}
rs429358	19:44908684	C	T	18	*APOE*	0.87 (0.84–0.90)	1.6×10^{-14}	0.98 (0.93–1.04)	5.5×10^{-1}

In UKBB replication, we considered 2-sided $P<0.0025$ as statistically significant, corresponding to a Bonferroni correction over 20 variants available for replication. OR indicates odds ratio; and UKBB, UK Biobank.

*Positions in GRCh38/hg38.

†Variant not available in UKBB. Proxy rs73198900 utilized with $R^2=0.58$.

‡GAGATAGATAGATAGATAGATAGAT.

§Missing from UKBB without an available proxy. Not considered part of the multiple-testing burden.

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The existing literature on aRH often relies on single databases and concentrates on specific demographics, limiting both sample sizes and the generalizability of findings to the broader population. For example, one prior study focused on the prevalence of aRH solely in a Japanese population, limiting its generalizability due to its reliance on data from a single genomic database.[23] In addition, the absence of a replication analysis from this study prevents validation of the reported results. A more recent analysis has a similar limitation, focusing primarily on Chinese patients with RH.[24] Other work has included validation analysis; however, it specifically extracts data from a small subset of White and Hispanic patients with RH and simultaneous coronary artery disease, which may introduce collider bias.[25]

Primary aldosteronism is well-established as a common cause of RH and target for established and novel therapeutics such as mineralocorticoid receptor antagonists and novel aldosterone synthase inhibitors.[26,27] It is known that increased aldosterone production leads to excessive sodium retention and potassium excretion, triggering an elevation in blood pressure that remains refractory to standard antihypertensive therapies. *CASZ1* is a zinc finger protein that has been implicated in primary aldosteronism due to its role as a corepressor of the mineralocorticoid receptor, a crucial mediator of aldosterone's effects across different tissues. A previous study demonstrated that expression of *CASZ1* in a specific cell line derived from a human adrenocortical carcinoma led to a significant reduction in aldosterone synthase expression,[28] suggesting that *CASZ1* suppresses aldosterone production and consequently plays a key role in lowering blood pressure. Another of our 5 identified genes, *WNT2B*, a key player in the Wnt/β-catenin signaling pathway, was previously found to be strongly associated with primary aldosteronism in Japanese individuals with essential hypertension.[29] This pathway is crucial for the development of the zona glomerulosa in the adrenal cortex, which is responsible for aldosterone production.

In addition, 2 of the identified genes are known to be involved in the control of vascular tone, which is crucial in the pathophysiology of RH. The *KCNK3* gene,

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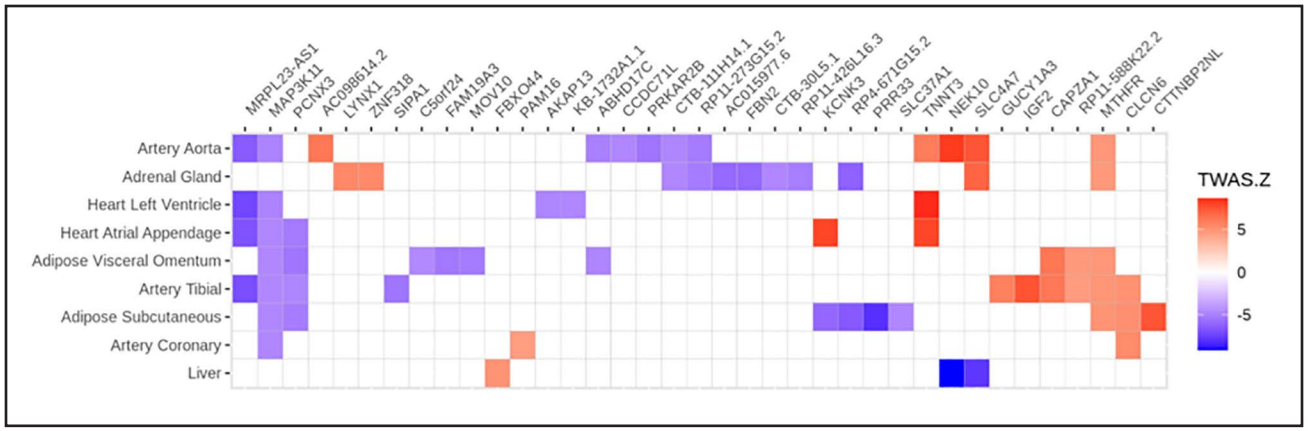

Figure 2. Transcriptome-wide association study (TWAS) results identifying genes with expression across 9 tissues significantly associated with the risk of apparent resistant hypertension.
TWAS-Fusion was used to estimate the association statistics between predicted gene expression and aRH. We plot those gene-aggregated *Z* scores that survive Bonferroni correction ($P<5.0\times10^{-6}$). TWAS-Fusion aggregates *Z* scores from single-variant test Z scores and standardizes them by linkage disequilibrium. Larger *Z* score deviations from zero correspond to higher levels of statistical evidence.

encoding a potassium (K^+) efflux channel, plays a critical role in regulating vascular tone within pulmonary vessels by limiting the proliferation of smooth muscle cells in the pulmonary vasculature. *KCNK3* inhibition is associated with pulmonary artery constriction,[30] demonstrating a synergistic effect that increases pulmonary arterial pressure. This suggests that SNPs resulting in the downregulation of *KCNK3* function could potentially have a similar effect on systemic vasculature, predisposing patients to RH. The *LSP1* gene has been widely implicated in NO-mediated vasodilation due to its role in leukocyte extravasation and endothelial cell permeability.[31] Variations in the *LSP1* locus that reduce *LSP1* expression could contribute to RH by decreasing nitric oxide synthesis and reducing the sensitivity of vascular smooth muscle cells and endothelial cells to its vasodilatory effects. Of note, although rs4722681 initially maps to *RPL35P4*, which is a nonfunctional pseudogene, the closest true gene locus is *EVX1/EVX1AS*. In this pair, *EVX1AS* is a divergent lncRNA that promotes transcription of *EVX1*, which is itself involved in mesendodermal lineage differentiation during gastrulation.[32,33]

A recent large-scale GWAS of standard hypertension published in 2024 identified multiple loci that were also observed in our study of RH.[34] The concordance of these loci delineates the reproducibility and the robust nature of these genetic associations across both standard and

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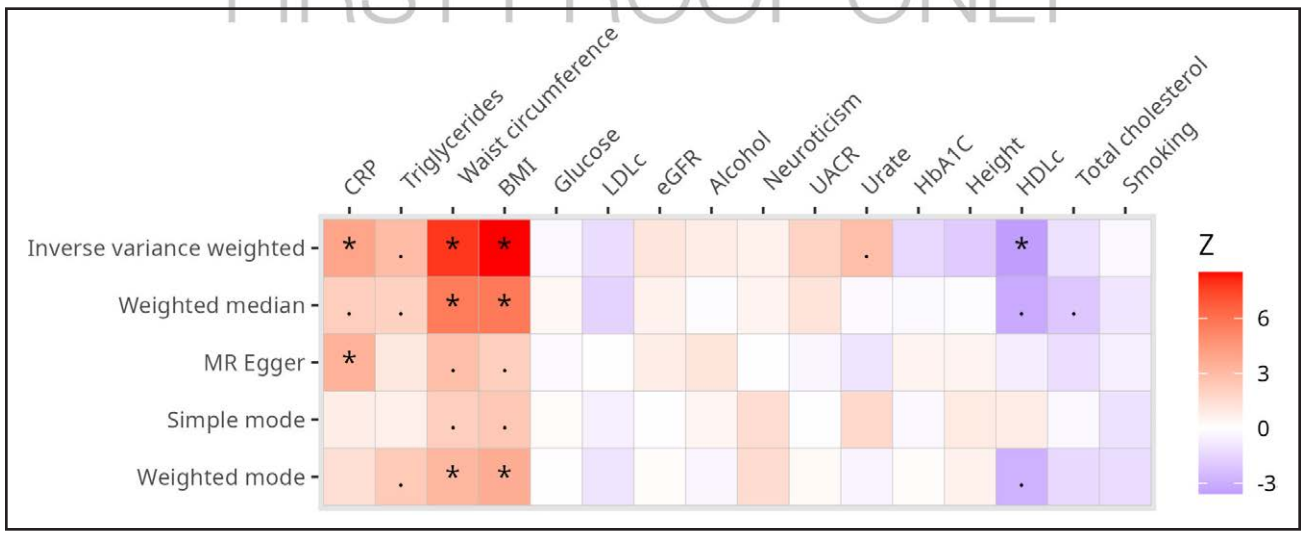

Figure 3. Heatmap of 2-sample Mendelian randomization causal estimates of vascular risk factors on apparent resistant hypertension across 5 methods.
We plot the *Z* scores corresponding to the MR test statistics. The coloring on the heatmap represents the magnitude and directionality of the *Z* scores. BMI indicates body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; HDLc, calculated high-density lipoprotein; LDLc, calculated low-density lipoprotein; and UACR, urine albumin:creatinine ratio. Dots denote *Z* score with $P<0.05$; **Z* score with $P<0.01$.

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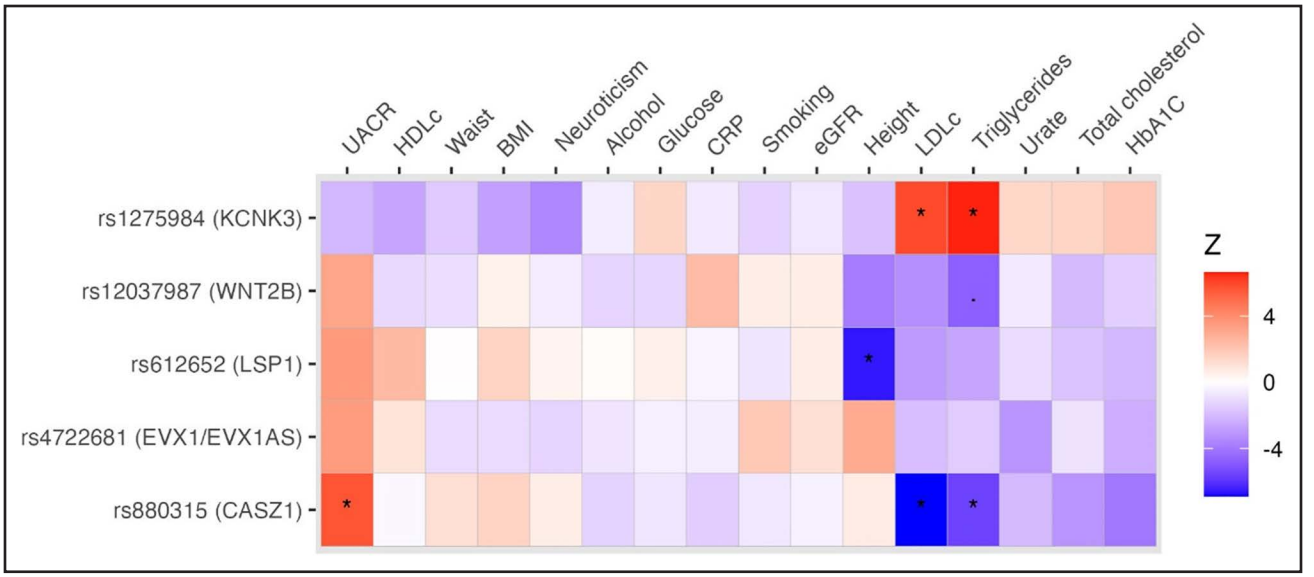

Figure 4. Heatmap of associations between replicated fine-mapping lead variants and vascular risk factors.
We plot the *Z* score, calculated as beta divided by SE, derived from publicly available genome-wide association study summary statistics (Table S2). The coloring on the heatmap represents the magnitude and directionality of the *Z* scores. BMI indicates body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; HDLc, calculated high-density lipoprotein; LDLc, calculated low-density lipoprotein; and UACR, urine albumin:creatinine ratio. Dots denote *Z* score with corresponding $P<0.05$; *Z score with corresponding $P<0.01$.

American Heart Association.

RH. However, several loci identified in the standard hypertension GWAS were not identified as significant hits in our analysis of RH. Several known medication targets for hypertension, such as the product of the *ADRA1A* gene discussed in the 2024 GWAS analysis on hypertension, were not part of the significant loci identified in our RH analysis. This reflects the notion that unique biological pathways, including hyperaldosteronism, endothelial dysfunction, and altered vascular tone, exist that drive resistance to antihypertensive medications or a more difficult-to-control/more extreme clinical phenotype. These pathways may be different from the classical mechanisms that influence blood pressure in the general population and could explain the divergence in loci identified in our study and those identified in the large-scale GWAS on standard hypertension published in 2024. Overall, these differences highlight the importance of performing phenotype-specific GWAS for RH, as some loci relevant to treatment-resistant populations may be less applicable to standard hypertensive cohorts.

Our study has both strengths and inherent limitations. One of the key strengths is the large sample size, which consists of 55 733 individuals from FinnGen and thus provides substantial statistical power for genetic analyses. Our use of the UKBB as an independent replication cohort with a sample size of 37 007 individuals further strengthens the validity of our findings. However, there are also limitations to consider. The primary cohort is specific to the Finnish population, which may limit the generalizability of our findings to other populations. Furthermore, as with any observational study, there may be unmeasured confounding factors that could influence the results. For instance, the distinct genetic backgrounds, environmental factors, and socioeconomic determinants within the Finnish and UK populations could affect future replication of findings. Similarly, although we leveraged 2 large and well-established biobank cohorts, data availability, particularly the lack of BP data in FinnGen, limits the depth of clinical phenotyping of aRH. As such, for discovery, we used a conservative assessment of aRH in the FinnGen cohort, defined as taking at least 4 antihypertensive medications regardless of BP. In replication analyses in the UKBB cohort, we used a more inclusive definition of RH to increase robustness and clinical accuracy, where RH was defined by the simultaneous use of at least 4 antihypertensive medications (same as in FinnGen) or the presence of uncontrolled blood pressure on at least 3 antihypertensive medications.

In addition, the use of large data sets necessitated the use of *ICD* codes, self-reported hypertension diagnoses, and medication records to classify hypertension. This approach carries an implicit assumption that all individuals in the study were treated sufficiently and equally, with their medication use increased until their blood pressure was adequately controlled. However, this assumption may not always hold true, particularly when comparing different healthcare systems. For example, there is a clear difference in the proportion of individuals classified as resistant in the FinnGen and UKBB data sets. It is possible that, due to differences in healthcare access and treatment algorithms applied to patients in the UKBB data set compared

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with the FinnGen data set, individuals in the UK were more likely to remain on fewer medications regardless of hypertension status, thereby reducing the likelihood of being classified as resistant. Furthermore, the use of cohort data precludes the assessment of medication nonadherence, a key factor that should be excluded before the diagnosis of true RH. As such, we have been sure to label cases as apparent RH, highlighting the importance of excluding alternative causes for uncontrolled blood pressure clinically. These limitations highlight the need for cautious interpretation of our cross-cohort comparisons. In addition, it paves the way for future studies to incorporate more granular treatment and adherence data to eliminate the possibility of confounding in this manner.

PERSPECTIVES

In sum, our findings identify genes highly associated with RH and suggest several potential pathways through which genetic variants may influence this condition. In particular, the results provide a biological underpinning for the clinically observed usefulness of mineralocorticoid receptor antagonists and aldosterone synthase inhibitors in the treatment of RH and highlight the important role of hyperaldosteronism as a likely cause of difficult-to-control blood pressure. Further research is needed to validate these associations and to explore their potential for guiding the development of targeted treatments for RH.

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ARTICLE INFORMATION

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Author Contributions

J.E. Ebinger contributed to the conceptualization, methodology, formal analysis, writing–original draft, writing–review and editing, visualization, project administration, and funding acquisition for the manuscript. A. Kauko contributed to the methodology, software, validation, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, and visualization for the manuscript. F. Vaura contributed to the methodology, formal analysis, writing–original draft, and writing–review and editing for the manuscript. P. Hage contributed to the writing–original draft, writing–review and editing, and visualization. J. Sundström contributed to writing–review and editing. FinnGen collaborators participated in the methodology, software, investigation, resources, and data curation for the manuscript. S.Y. Joung participated in the formal analysis, writing–original draft, and writing–review and editing for the manuscript. S. Cheng participated in the conceptualization, formal analysis, writing–original draft, writing–review and editing, visualization, supervision, and project administration for the manuscript. T. Niiranen participated in the conceptualization, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, project administration, and funding acquisition for the manuscript.

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Disclosures

T. Niiranen has stock ownership in Mineralys Therapeutics and has received speaking honoraria from AstraZeneca and Orion Finland. J. Sundström reports direct or indirect stock ownership in companies (Anagram kommunikation AB, Sence Research AB, Symptoms Europe AB, MinForskning AB) providing services to companies and authorities in the health sector, including Amgen, AstraZeneca, Bayer, Boehringer, Eli Lilly, Gilead, GSK, Göteborg University, Itrim, Ipsen, Janssen, Karolinska Institutet, LIF, Linköping University, Novo Nordisk, Parexel, Pfizer, Region Stockholm, Region Uppsala, Sanofi, STRAMA, Takeda, TLV, Uppsala University, Vifor Pharma, WeMind. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Tables S1–S5
Figure S1

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