Published in final edited form as:

Circ Genom Precis Med. 2022 June ; 15(3): e003554. doi:10.1161/CIRCGEN.121.003554.

Blood Pressure Polygenic Scores Are Associated with Apparent Treatment-Resistant Hypertension

Joseph H. Breeyear, BS[1],

Megan M. Shuey, PhD[1,2],

Todd L. Edwards, PhD[1,3],

Jacklyn N. Hellwege, PhD[1,2]

[1]Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN

[2]Division of Genetic Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

[3]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Individuals with apparent treatment-resistant hypertension (aTRH) have substantially higher hazards of coronary heart disease and stroke compared to controlled hypertensive individuals.[1] With better prediction of aTRH, hypertensive individuals' therapeutic regimens could more quickly achieve stable blood pressure (BP) control, therefore reducing comorbidity. We examined the associations between the genetic determinants of BP and aTRH by self-reported race/ethnicity to improve identification of individuals at higher risk for aTRH.

Summary statistics for genetic associations with systolic (SBP) and diastolic (DBP) BP were obtained from Giri et al., Liang et al., and Biobank Japan (http://jenger.riken.jp/en/result) (n_{max}=564,851).[2, 3] Results were meta-analyzed and variant weightings were adjusted using PRS-CS, followed by p-value thresholding, selecting the threshold explaining the most outcome variance.[4] Associations between SBP and DBP polygenic risk scores (PRS) and measured BP were validated in the UK Biobank, excluding overlap with Giri et al., (n_{max} = 341,930, SBP $p < 2.31e^{-304}$, DBP $p < 1.17e^{-287}$), adjusted for the covariates: age, age-squared, body mass index (BMI), sex, and the top ten principal components. The study data are available from the corresponding author upon reasonable request. The PRS variants and weights have been uploaded to the PGS Catalog (PGS002238, PGS00229).

Controls, controlled hypertensive individuals, were defined in BioVU, Vanderbilt University Medical Center's DNA biobank, through presence of an HTN ICD-9 or ICD-10 code, treatment with one or two antihypertensive drugs, and BP measurements <135/90 mmHg for three months following the initiation of the last antihypertensive medication. Patients with

Correspondence: Jacklyn N. Hellwege, 2525 West End Ave., Suite 700, Nashville, TN, 37232, Tel: (615) 875-9693, jacklyn.hellwege@vumc.org.

Disclosures: None

aTRH were identified using a previously validated algorithm, based on failure to achieve controlled BP on three antihypertensive drugs, including a thiazide diuretic, or prescribed four or more medications regardless of achieving control, excluding patients with chronic kidney disease stages 4 and 5 as well as causes of secondary hypertension.[5] Data was extracted prior to August 2019. The Vanderbilt Institutional Review Board reviewed this project and deemed it exempt non-human subject research.

Polygenic risk score associations with aTRH were modeled using logistic regression, adjusted for the covariates above and mean estimated glomerular filtration rate (eGFR) in the entire multi-ancestry BioVU population (n_{max} =37,978), as well as non-Hispanic White (NHW) (n_{max}=28,545) and non-Hispanic Black (NHB) (n_{max}=5,026) subsets. To estimate the combined effect of SBP and DBP PRSs on aTRH, we exponentiated the sum of logistic regression coefficients for SBP and DBP PRSs and calculated standard error by taking the square-root of the sum of the variance-covariance matrix of the regression coefficients. Bonferroni corrections are reported as significant ($p < 0.017$), accounting for the 3 PRS models. Effects are presented as odds ratio (OR) and 95% confidence intervals per one standard deviation increase in PRS. The predictive model included both PRSs, covariates listed above, smoking status and mean eGFR, and was developed separately in the NHW, NHB, and multi-ancestry BioVU populations utilizing 10-fold cross validation in STATA 16. Model performance was assessed through calibration and discrimination, utilizing the Brier Score and the area under the receiver operating characteristic curve (AUC) concordance. A smaller Brier Score, which ranges from 0 to 1, describes better model prediction and an AUC greater than 0.8 is generally required for clinical utility.

The SBP PRS was significantly associated with increased aTRH risk in the multi-ancestry (1.08 (1.04 – 1.13)) and NHW (1.08(1.03 – 1.12)) populations (Table 1). The DBP PRS was not associated with aTRH risk in any population. The joint effect of both SBP and DBP PRS was associated with increased aTRH risk in the multi-ancestry (1.27 (1.13 – 1.42)) and NHW (1.20 (1.09 – 1.33)) populations. Brier scores indicated good model fit in all groups, however AUCs were less than 0.8 (Table 1).

We previously observed that genetic determinants of BP are significantly associated with HTN in a phenome-wide association study.[2] In the present study, we found that the genetic determinants of BP are significantly associated with aTRH risk, where increasing PRS is associated with increased aTRH risk in multi-ancestry and NHW populations. However, the PRSs were not associated with aTRH in the NHB population, despite significant prediction of BP in the validation set. The lack of association in the NHB population could be due to limited sample size. Inclusion of PRSs in the predictive model with other significant clinical predictors provides a modest improvement in predictive performance. Calibration and discrimination of the predictive models indicate a good fit in all evaluated populations. While the risk profile for aTRH is complex and the contribution of additional non-genetic factors must be evaluated, we demonstrate that further enhancement of aTRH prediction models is required for clinical application. Refined predictive models may lead to more effective screening strategies, resulting in more rapid BP control, thus reducing the risk of negative cardiometabolic outcomes.

Sources of Funding:

We acknowledge the National Institutes of Health grants F31DK108444, K12HD04348, TL1TR002244, and the BioVU funding sources (https://victr.vumc.org/biovu-funding/).

Nonstandard Abbreviations and Acronyms:

PRS	Polygenic Risk Score
aTRH	Apparent Treatment-Resistant Hypertension
HTN	Hypertension
BP	Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
BMI	Body Mass Index
NHW	non-Hispanic White
NHB	non-Hispanic Black

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Table 1.

Polygenic score associations per standard deviation increase in PRS adjusted for age, age-squared, BMI, sex, and the top ten principal components. Predictive model calibration and discrimination performance results.

Polygenic Risk Score Association Models					Predictive Model	
PRS	**Population**	**aTRH (Cases) & HTN (Controls) (Mean Age, Mean BMI, % Female)**	**Effect (OR (95%CI))**	***p* – value**	**Brier Score**	**AUC (95% CI)**
DBP	NHB	574 Cases (58, 33.4, 62%) 4,452 Controls (50, 32.0, 64%)	1.05 (0.95 – 1.15)	0.35	0.097	0.686 (0.661 – 0.708)
SBP			1.03 (0.94 – 1.14)	0.52		
Combined			1.17 (0.92 – 1.49)	0.21		
DBP	NHW	2,961 Cases (64, 31.4, 49%) 25,584 Controls (58, 29.6, 54%)	1.02 (0.98 – 1.06)	0.34	0.090	0.679 (0.671 – 0.690)
SBP			**1.08 (1.03 – 1.12)**	**0.00037**		
Combined			**1.20 (1.09 – 1.33)**	**0.00042**		
DBP	Multi-Ancestry	3,641 Cases (63, 31.8, 51%) 34,337 Controls (56, 29.9, 56%)	1.04 (0.99 – 1.09)	0.13	0.086	0.691 (0.681 – 0.700)
SBP			**1.08 (1.04 – 1.13)**	**0.00020**		
Combined			**1.27 (1.13 – 1.42)**	**0.000041**		