BRIEF COMMUNICATION

Genome-Wide Association Study of Apparent Treatment-Resistant Hypertension in the CHARGE Consortium: The CHARGE Pharmacogenetics Working Group

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BACKGROUND
Only a handful of genetic discovery efforts in apparent treatment-resistant hypertension (aTRH) have been described.

METHODS
We conducted a case–control genome-wide association study of aTRH among persons treated for hypertension, using data from 10 cohorts of European ancestry (EA) and 5 cohorts of African ancestry (AA). Cases were treated with 3 different antihypertensive medication classes and had blood pressure (BP) above goal (systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg) or 4 or more medication classes regardless of BP control (n_{EA} = 931, n_{AA} = 228). Both a normotensive control group and a treatment-responsive control group were considered in separate analyses. Normotensive controls

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Initially submitted July 19, 2019; date of first revision September 10, 2019; accepted for publication September 13, 2019; online publication September 23, 2019.

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were untreated (n_{EA} = 14,210, n_{AA} = 2,480) and had systolic BP/diastolic BP < 140/90 mm Hg. Treatment-responsive controls (n_{EA} = 5,266, n_{AA} = 1,817) had BP at goal (<140/90 mm Hg), while treated with one antihypertensive medication class. Individual cohorts used logistic regression with adjustment for age, sex, study site, and principal components for ancestry to examine the association of single-nucleotide polymorphisms with case–control status. Inverse variance-weighted fixed-effects meta-analyses were carried out using METAL.

RESULTS

The known hypertension locus, *CASZ1*, was a top finding among EAs ($P = 1.1 \times 10^{-8}$) and in the race-combined analysis ($P = 1.5 \times 10^{-9}$) using the normotensive control group (rs12046278, odds ratio = 0.71 (95% confidence interval: 0.6–0.8)). Single-nucleotide polymorphisms in this locus were robustly replicated in the Million Veterans Program (MVP) study in consideration of a treatment-responsive control group. There were no statistically significant findings for the discovery analyses including treatment-responsive controls.

CONCLUSION

This genomic discovery effort for aTRH identified *CASZ1* as an aTRH risk locus.

Keywords: blood pressure; hypertension; genome-wide association study; severe hypertension; treatment-resistant hypertension

doi:10.1093/ajh/hpz150

INTRODUCTION

Apparent treatment-resistant hypertension (aTRH) is an extreme form of hypertension (HTN) characterized by the use of 4 or more antihypertensive (AHT) medication classes to achieve blood pressure (BP) control. The estimated prevalence of aTRH in population-based studies is between 12 and 15% among adults with HTN and higher among clinic-based populations, e.g. >25% in those with chronic kidney disease.[1,2] Risk factors for aTRH are increasing age, obesity, reduced kidney function, and African-American race.[1] Research shows that individuals with aTRH are at an increased risk for cardiovascular disease events when compared with individuals with controlled HTN, demonstrating a need to understand the cause of nonresponse to improve BP control.[3] We hypothesized that identifying the genetic architecture may shed light on distinct underlying pathobiology.

Published genetic studies of aTRH have reported limited findings and are lacking in comparison to HTN.[4–7] The present study comprises European ancestry (EA) and African ancestry (AA) studies from the *Cohorts for Heart and Aging Research in Genomic Epidemiology* (CHARGE) consortium, for a case–control study of aTRH that capitalizes on epidemiological data characterized by deep phenotyping. Common genetic variants in 931 EA aTRH cases were compared with 14,210 normotensive controls and separately to 5,266 treatment-responsive controls, whereas 228 AA aTRH cases were compared with 2,480 normotensive controls and separately to 1,817 treatment-responsive controls. Results were replicated in an aTRH case–control data set from the Million Veterans Program (MVP).

METHODS

Ten studies contributed data on EA participants, whereas 5 studies contributed data on AA participants (Supplementary Section 1). Data on medication use were extracted by medication inventory, self-report, or computerized databases once for cohorts with cross-sectional data, or at each BP measurement for those with longitudinal data (Supplementary Section 1). AHT medications counted toward the sum of classes are described in Supplementary Table 1. Combination products were therapeutically co-classified based on their active ingredients. All diuretics were counted as one class including potassium-sparing diuretics.

Participants with conditions that may lead to secondary forms of HTN (including estimated glomerular filtration rate < 30 ml/min/1.73 m^2 or body mass index > 40 kg/m^2) were excluded. aTRH cases were defined as those treated with 3 AHT medication classes and BP above goal (systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg) or 4 or more AHT medication classes regardless of BP control. aTRH cases fitting the above definition who were not treated by a diuretic were excluded.[8] The analysis included 2 control groups: (i) *Normotensive controls*: participants not hypertensive and not treated with an AHT medication and (ii) *Treatment-responsive controls*: participants who had BP at goal (<140/90 mm Hg) on treatment with one AHT medication class. Details of the case and control definition in cohorts with longitudinal data are described in Supplementary Section 1.

Genome-wide single-nucleotide polymorphism (SNP) genotyping was performed within each study using commercial genotyping arrays (Supplementary Table 2). Cohorts most commonly imputed to the 1000 Genomes version 3 reference panel. After imputation cohorts filtered out SNPs with imputation quality score < 0.3. SNPs with minor allele frequency < 5% and which were not represented in 2 or more cohorts were filtered out at the meta-analysis stage.

Statistical Analysis

Logistic regression models or generalized estimating equations were used for case–control association analysis (Supplementary Table 3). The variable of interest was SNP dosage of the effect allele. Models were adjusted for age, sex, and study-specific covariates (e.g., study site, principal components for ancestry and, if applicable, exchangeable correlation matrices to account for family relatedness). For cohorts with longitudinal data, the average age across the visits included was used as the covariate. In total, there were 4 models, one for each control group and one for each ancestry grouping. Inverse variance-weighted, fixed-effects meta-analysis was performed for each of the 4 strata, using METAL software (www.sph.umich.edu/csg/abecasis/metal/). Statistical heterogeneity across studies was evaluated using Cochran's χ^2 test (Q-test). P-values < 5×10^{-8} indicated genome-wide significant results. Results of the race-stratified analyses from METAL were then combined using

a similar approach (one meta-analysis per control group). Linkage disequilibrium was evaluated using the rAggr tool (http://raggr.usc.edu/). Regional plots were created using Locus Zoom with a window of 500 kb (v0.4.8).[9] In a sensitivity analysis of top SNP results, we conducted a meta-analysis that included only cohorts with >50 cases.

Replication

We sought replication in non-Hispanic EA (78%) and AA (22%) MVP participants (Supplementary Section 1).[10,11] Participants with estimated glomerular filtration rate ≥ 60 ml/min/1.73 m^2 were included. Total numbers of samples across ethnicities included 16,833 cases (11,762 EAs and 5,071 AAs) and 53,931 controls (42,850 EAs and 11,081 AAs). Cases were defined using the same definition as the discovery analysis. Controls were patients who achieved BP control (<140/90 mm Hg) on 1 or 2 medication classes. Case–control status was regressed onto additively coded genotypes imputed to 1000 Genomes phase 3 version 5, adjusting for age, age^2, sex, body mass index, and 10 principal components within ethnicity using SNPTEST v2.54. Genotyping, quality control, and imputation procedures have been described.[10]

RESULTS

Overall EA and AA cases were older than controls and more likely male (Supplementary Table 4a and 4b). The average number of AHT medication classes for EA cases ranged from 3.2 to 3.8 and from 3.3 to 3.9 for AAs. Across the individual cohort genome-wide association study (GWAS) analyses, there was not excessive evidence for the deviation of *P*-values from their expected values (Supplementary Table 5). Manhattan plots and QQ plots for each discovery meta-analysis are presented in Supplementary Figures 1a–d and 2a–d for the comparison of AA cases to AA normotensive controls, EA cases to EA normotensive controls, AA cases to AA treatment-responsive controls, and EA cases to EA treatment-responsive controls, respectively. Meta-analysis corrected inflation that existed in the cohort-specific analyses.

The top 5 results for each case–control model are presented in Table 1. When comparing aTRH cases to normotensive controls, the top finding for AAs was rs76967376 intronic to myosin-Vb (*MYO5B*). At that SNP, the direction of effect was consistent across each of the 5 cohorts and the odds of being a case were 2.65 (95% confidence interval: 1.9–3.8) times higher among those with the A allele vs. the C allele. Among EAs, the top findings for the normotensive control comparison were intronic to castor zinc finger 1 (*CASZ1*). In the race-combined analysis, *CASZ1* rs12046278 T carriers were less likely to be a case ($P = 1.5 \times 10^{-9}$, odds ratio = 0.71 (95% confidence interval 0.63–0.80)). Another SNP within 3,500 bp to DNA (cytosine-5-)-methyltransferase 3 alpha (*DNMT3A*) was associated with aTRH ($P = 4.9 \times 10^{-8}$) in the race-combined analysis using normotensive controls. Regional plots (Supplementary Figures 3–5) for rs76967376 (*MYO5B*), rs12046278 (*CASZ1*), and rs11674660 (near *DNMT3A*) display linkage disequilibrium support for these top findings. Results of the race-combined analysis are presented in Supplementary Table 6 and Supplementary Figure 6.

When comparing aTRH cases to treatment-responsive controls no SNP was statistically significant after correcting for multiple testing in either racial stratum. Race-combined analysis did not increase the significance of top hits. In the sensitivity analysis limiting contributing cohorts to those with >50 cases results were generally consistent with the main findings in Table 1 (Supplementary Table 7).

The MVP cases in the replication study were older (63 ± 9 vs. 62 ± 10 years for EAs and 58 ± 9 vs. 56 ± 10 years for AAs) and had slightly higher body mass index compared with the treatment-responsive controls. Results for AAs as well as the EAs for the treatment-responsive control group were not replicated in the MVP. However, results from the EA discovery for the normotensive control group were robustly replicated with the same direction of effect for SNPs in *CASZ1* ($P < 5 \times 10^{-8}$) and the direction of association for rs11674660 intergenic to *DNMT3A, DTNB* was consistent in direction but not statistically significant ($P = 0.09$) (Supplementary Table 8).

DISCUSSION

Although the genetics of BP and essential HTN have been extensively investigated, few genetic studies have explored genes associated with less common and more severe aTRH. Using data available from observational epidemiological cohort studies, the current meta-GWAS study examined SNPs associated with aTRH in EA and AA cases with respect to 2 different control sets. Our study confirmed the known BP locus, *CASZ1*, as being robustly associated with aTRH in the discovery and replication data set. Other notable findings, *MYO5B* and *DMNT3A/DTNB*, warrant additional replication efforts.

To our knowledge our top finding in the AA stratum (rs76967376 in *MYO5B* involved in cell trafficking and plasma membrane recycling) has been associated with lipid levels in previous GWAS, but has not been associated with HTN. The nearest published BP locus (rs745821) is in the MAK4 gene (~505 kb in distance) and is not in linkage disequilibrium with our finding ($r^2 < 0.01$).[12] At least one animal model has reported *MYO5B* may regulate an atrial voltage-gated potassium channel (Kv1.5) important for cardiac excitability.[13] This result was not replicated in the MVP aTRH case–control data set. Future studies may still be warranted given the differences in the replication data set that used treatment-responsive controls with estimated glomerular filtration rate ≥ 60 ml/min/1.73 m^2. The top finding among EAs was the known HTN locus *CASZ1*, a zinc finger transcription factor which plays a key role in cardiac development and postnatal adaptation.[14] The gene has been previously associated with BP and HTN in Asian ancestry and EA populations.[15–17] The biological role of *CASZ1* in aTRH needs additional investigation but may be related to expression changes in genes that regulate BP or AHT response.[18] Taken together the significant results from the discovery and

Table 1. Top hits for genome-wide case–control association analysis of apparent treatment-resistant hypertension

rs#	CHR	A1/A2	EAF	OR	95% CI	*P*-value	Direction*	Location	Gene(s)
228 AA cases									
2,490 normotensive*									
rs76967376	18	A/C	0.11	2.65	1.87, 3.78	5.75E-08	+++++	Intronic	*MYO5B*
rs185169399	5	A/G	0.94	11.96	4.53, 31.55	5.27E-07	+++?+	Intergenic	*CDH18*
rs114349263	5	A/C	0.06	0.08	0.03, 0.22	5.52E-07	---?-	Intergenic	*CDH18*
rs12665245	6	T/C	0.86	0.36	0.24, 0.54	1.34E-06	----?	Intronic	*ENPP3*
rs143255889	10	C/G	0.07	3.10	1.95, 4.92	1.80E-06	+++++	Intergenic	*LINC01519*
1,817 hypertensive*									
rs138399316	6	T/C	0.15	5.85	3.00, 11.37	1.89E-07	++?+?	Intronic	*BPHL*
rs146183009	1	A/G	0.11	2.49	1.75, 3.54	4.41E-07	+++++	Intronic	*ICMT*
rs111285947	17	A/G	0.06	3.89	2.21, 6.83	2.16E-06	+?++?	Downstream	*LINC00670*
rs1651805	19	C/G	0.26	1.84	1.43, 2.36	2.17E-06	+++++	Intergenic	*LSM14A,KIAA0355*
rs114511751	1	T/C	0.10	2.44	1.68, 3.53	2.20E-06	+++++	Intronic	*TMCC2*
931 EA cases									
14,201 normotensive*									
rs12046278	1	T/C	0.63	0.71	0.63, 0.80	1.11E-08	----------?	Intronic	*CASZ1*
rs34071855	1	C/G	0.64	0.72	0.64, 0.81	4.87E-08	----------+	Intronic	*CASZ1*
rs11674660	2	T/C	0.15	1.53	1.31, 1.80	7.63E-08	+++-+++-+++-+	Intergenic	*DNMT3A,DTNB*
rs17035646	1	A/G	0.35	1.36	1.26,1.59	7.90E-08	++++++++++++-	Intronic	*CASZ1*
rs880315	1	T/C	0.65	0.74	0.66, 0.83	1.19E-07	----------+	Intronic	*CASZ1*
5,266 hypertensive*									
rs74725390	7	T/C	0.07	1.70	1.38, 2.09	5.36E-07	+++-+-+++-+?	Intergenic	*COBL,POM121L12*
rs12050053	13	T/G	0.06	2.43	1.71, 3.47	8.39E-07	++???+?++???	Intergenic	*EEF1DP3,FRY-AS1*
rs4844662	1	C/G	0.47	1.31	1.18, 1.47	9.01E-07	+++-++++-+++	Intronic	*PLXNA2*
rs111281682	7	A/G	0.83	0.72	0.63, 0.82	1.63E-06	+----++-----	Intergenic	*MYL10,CUX1*
rs77270397	13	A/G	0.07	2.09	1.54, 2.82	1.75E-06	++???+-+++??	Intergenic	*EEF1DP3,FRY-AS1*

AA order: ARIC, HyperGEN, JHS, PHG, MESA. EA order: normotensive, AFTER-EU, AGES, ARIC, HyperGEN, NEO, CHS, HVH1 cases, HVH1 controls, HVH2 cases, HVH2 controls, PROSPER, FHS, MESA. EA order: treatment responsive, AFTER-EU, AGES, ARIC, HyperGEN, NEO, CHS, HVH1 cases, HVH1 controls, HVH2 cases, HVH1 controls, PROSPER, MESA. Significant *P*-value after correction for multiple testing $<5 \times 10^{-8}$. Abbreviations: AA, African American, EA, European American, EAF, effect allele frequency; OR, odds ratio; CI, confidence interval; A1, allele 1, effect allele; A2, allele 2.

*Controls.

replication analysis suggest *CASZ1* is an aTRH locus among EAs. The result for the top SNP was consistent but marginally significant for AAs in CHARGE (odds ratio = 0.69 (95% confidence interval: 0.48–0.99); $P = 0.04$ for the T allele). Rs880315 in *CASZ1* from Table 1 was marginally significant in MVP AAs (odds ratio = 1.09 (95% confidence interval: 1.03–1.15); $P = 0.008$ for the C allele). Loci near *DMNT3A/DTNB* on chromosome 2 have been identified in a recent BP GWAS study (~300 kb downstream of *ADCY3*) though rs11674660 from our study and previously published *ADCY3* rs55701159 are not in linkage disequilibrium ($r^2 < 0.01$).[12] *DMNT3A* is causal for clonal hematopoiesis of indeterminate potential (CHIP), and mutations in *DMNT3A* have been associated with coronary heart disease.[19] The isoprenylcysteine carboxyl methyltransferase (*ICMT*) locus was the only gene near a previously identified HTN gene (~15 kb downstream of *RNF207 rs709209*)[20] that we report on for the treatment-responsive control group. The SNP rs11674660 near *DMNT3A/DTNB* and rs146183009 in *ICMT* were not replicated in the MVP.

We also compared our results with published GWAS studies.[5,6] In the electronic MEdical Records & GEnomics study among 3,006 cases and 876 treatment-responsive controls, there were no statistically significant findings. In the INternational VErapamil SR Trandolapril STudy GENEtic Substudy, an SNP (rs12817819) in ATPase Plasma Membrane Ca^{2+} Transporting 1 (*ATP2B1*) was associated with aTRH in EAs and Hispanics. In our data, SNPs in *ATP2B1* were most strongly associated with aTRH when cases were compared with normotensive controls (AAs rs58302337 ($P = 0.001$), rs12580678 ($P = 0.004$); EAs rs1401982 ($P = 0.006$)) vs. treatment responsive controls (AAs rs152754 ($P = 0.01$); EAs

rs34205054 ($P = 0.006$)). Differences between these studies and our own include the use of clinical rather than observational populations and the consideration of only controlled hypertensive patients as controls.

Strengths of the present study include collaboration among well-characterized cardiovascular disease cohorts for which BP measurement and the recording of AHT information was a focus. Furthermore, we replicated our findings in a large data set with comparable ethnic groups. However, aTRH is complex and our study had several weaknesses including lack of information on white coat HTN, adherence information, and medication dosage data, which may contribute to phenotypic misclassification which could dilute our results. We were unable to distinguish AHT use for conditions other than HTN such as glaucoma. Other limitations included heterogeneity among study populations regarding phenotypic focus (e.g., obesity, cardiovascular disease) and different methods for the measurement of BP. Finally, the case–control group available for the replication analysis was not identical to our discovery data set.

Despite being common among persons with HTN, little is known about the genetic etiology of aTRH. In this discovery and replication effort, the main finding included a transcription factor and known HTN locus involved in cardiac development (*CASZ1*). *MYO5B* and *DMNT3A/DTNB* were biologically interesting cardiovascular candidates that were not replicated but remain worthy of further investigation for this severe form of HTN.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

ACKNOWLEDGMENTS

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- White River Junction VA Medical Center (Brooks Robey)
- William S. Middleton Memorial Veterans Hospital (Robert Striker)

FUNDING

Age, Gene, Environment, Susceptibility—Reykjavik Study (AGES) has been funded by NIH contracts N01-AG-1-2100 and HHSN271201200022C, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee (VSN: 00-476 063). The researchers are indebted to the participants for their willingness to participate in the study.

The **Atherosclerosis Risk in Communities (ARIC)** study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, and HHSN268201700005I), R01HL087641, R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by grant number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

The **Cardiovascular Health Study (CHS)** was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, HHSN268200960009C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086, and NHLBI Grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, U01HL130114, and R01HL085251 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI Grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) Grant DK063491 to the Southern California Diabetes Endocrinology Research Center. J.S.F. was supported by K08HL116640.

The **Heart and Vascular Health Study** has been funded in part by NHLBI grants R01HL085251 and R01HL073410.

The **HyperGEN: Genetics of Left Ventricular Hypertrophy** is ancillary to the Family Blood Pressure Program, http://clinicaltrials.gov/ct/show/NCT00005267. Funding sources included National Heart, Lung, and Blood Institute grant R01HL055673 and cooperative agreements (U01) with the National Heart, Lung, and Blood Institute: U01HL054471, U01HL54515 (UT); U01HL054472, 471 U01HL054496 (MN); U01HL054473 (DCC); U01HL054495 (AL); U01HL054509 (NC).

The authors of the **Netherlands Epidemiology of Obesity (NEO)** study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank the NEO study group, Pat van Beelen, Petra Noordijk, and Ingeborg de Jonge for the coordination, lab, and data management of the NEO study. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze. The NEO study is supported by the participating Departments, the Division, and the Board of Directors of the Leiden University Medical Center and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. D.O.M.-K. is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023).

The **Jackson Heart Study (JHS)** is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I), and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I, and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI)

and the National Institute for Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS. L.M.R. is funded by T32 HL12998. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Multi-ethnic Study of Atherosclerosis (MESA) and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420. Funding for SHARe genotyping was provided by NHLBI contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, CA) and the Broad Institute of Harvard and MIT (Boston, MA) using the Affymetrix Genome-Wide Human SNP Array 6.0. Also supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

The **Prospective study of Pravastatin in the Elderly at Risk (PROSPER)** study was supported by an investigator-initiated grant obtained from Bristol-Myers Squibb. Prof. Dr. J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European Commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

The **AfterEU** study is the Danish part of the EURAGEDIC study, which was supported by the European Commission (contract QLG2-CT-2001–01669). The genotyping for this study was part of the Genetics of Diabetic Nephropathy (Gen DN) study, primarily funded by Juvenile Diabetes Research Foundation (JDRF) International Prime Award Number 17-2013-8. T.S.A. was also funded by the GenDN grant and acknowledges the same. Additionally, TSA was supported by internal funding from Steno Diabetes Center Copenhagen, Gentofte, Denmark and from the Novo Nordisk Foundation (Steno Collaborative 2018) Grant NNF18OC0052457 and acknowledged the same. No potential conflicts of interest relevant to this article were reported. The authors acknowledge the technical assistance of Tina R. Juhl, Anne G. Lundgaard, Berit R. Jensen, and Ulla M. Smidt. In addition, the authors thank Dr. Steve Rich, who was involved in genotyping from the University of Virginia, USA.

This research is based on data from the Million Veteran Program, Office of Research and Development, Veterans Health Administration and was supported by award I01BX003360 to A.M.H. This work was supported using resources and facilities of the VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457. J.N.H. and A.G. are supported by the Building Interdisciplinary Research Careers in Women's Health Career Development Program grant K12HD043483 (PI: K.E. Hartmann). T.L.E. was supported by NIH/NHLBI grant HL121429.

DISCLOSURE

The authors declared no conflict of interest.

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