

A GWAS of angiotensin-converting enzyme inhibitor-induced angioedema in a South African population



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Background: Angiotensin-converting enzyme inhibitor-induced angioedema (AE-ACEI) is a life-threatening adverse event; globally, it is the most common cause of emergency presentations with angioedema. Several genome-wide association studies (GWASs) have found genomic associations with AE-ACEI. However, despite African Americans having a 5-fold increased risk of AE-ACEI, there are no published GWASs from Africa. **Objective:** The aim of this study was to conduct a GWAS of AE-ACEI in a South African population and perform a meta-analysis with an African American and European American population.

Methods: The GWAS included 202 South African adults with a history of AE-ACEI and 513 controls without angioedema following angiotensin-converting enzyme inhibitor (ACEI) treatment for at least 2 years. A meta-analysis was conducted with GWAS summary statistics from an African American and European American cohort (from the Vanderbilt-Marshfield cohort, which consisted of 174 case patients and 489 controls). **Results:** No single-nucleotide polymorphisms (SNPs) attained genome-wide significance; however, 26 SNPs in the postimputation standard GWAS of the South African cohort and 73 SNPs in the meta-analysis attained suggestive thresholds ($P < 5.0 \times 10^{-6}$). Some of these SNPs were found to be located close to the genes *PRKCQ* (protein kinase C theta), *RAD51B* (RAD51 Paralog B), and *RIMS1* (regulating synaptic membrane

exocytosis 1), which were previously linked with drug-induced angioedema, and also close to the *CSMD1* (CUB and sushi multiple domains 1) gene, which has been linked to ACEI cough, providing replication at the gene level but with novel lead SNPs. The study also replicated SNP rs500766 on chromosome 10, which was previously found to be associated with AE-ACEI. **Conclusions:** Our results highlight the importance of African populations for detection of novel variants in replication studies. Further increased sampling across the continent and matched functional work are needed to confirm the importance of genetic variation in understanding the biology of AE-ACEI. (J Allergy Clin Immunol Global 2025;4:100464.)

Key words: Angioedema, genome-wide association studies, angiotensin-converting enzyme inhibitor

Cardiovascular disease is an exploding epidemic facing low- and middle-income countries (LMICs) in Africa, and hypertension is the leading cause of death globally, with the greatest burden of disease in LMICs.¹ Angiotensin-converting enzyme inhibitors (ACEIs) are a class of drugs that inhibit the renin-angiotensin-aldosterone system, with a proven reduction in mortality due to hypertension, diabetes mellitus, and cardiac failure.² ACEIs are widely available and affordable, making them critical for use in LMICs.³ Their use is limited by 2 major adverse events: ACEI-angioedema (AE-ACEI) and ACEI cough.⁴ AE-ACEI typically involves the face, tongue, or larynx; it can be life-threatening in approximately 16% of cases.⁵ AE-ACEI incidence ranges from 0.2% to 0.7% in retrospective studies to 6% in prospective clinical trials⁴⁻⁶; in the only large multicenter African study (Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans [CREOLE]), the incidence was 0.7%.⁷ AE-ACEI is the most common angioedema presentation in emergency rooms across the world, including in South Africa.^{4,8} African Americans have a 5-fold increased risk of AE-ACEI compared with European populations,⁴ and this has led several international hypertension guideline groups to favor angiotensin receptor blockers over ACEIs in African populations. We have recently argued that these recommendations are potentially flawed, with dire consequences given the near-complete absence of studies of AE-ACEI across diverse African populations.⁶ This work aims to address this important gap.

Several genome-wide association studies (GWASs) and candidate gene studies have been conducted for AE-ACEI,^{9,10} with the largest meta-analysis of 8 of these cohorts recently published and identifying 3 single-nucleotide polymorphisms

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Abbreviations used

ACE:	Angiotensin-converting enzyme
ACEI:	Angiotensin-converting enzyme inhibitors
AE-ACEI:	Angiotensin-converting enzyme inhibitor–induced angioedema
AWI-Gen:	Africa Wits INDEPTH Partnership for Genomic Research
DILI:	Drug-induced liver injury
GC:	Genomic control
GCTA:	Genome-wide complex trait analysis
GWAS:	Genome-wide association study
H3Africa:	Human Heredity and Health in Africa
LMIC:	Low- or middle-income country
MAF:	Minor allele frequency
MAGMA:	Multi-marker Analysis of GenoMic Annotation
MLMA:	Mixed linear model's association
NSAID:	Nonsteroidal anti-inflammatory drug
PC:	Principal component
PCA:	Principal component analysis
QC:	Quality control
QQ:	Quantile-quantile
SNP:	Single-nucleotide polymorphism

(SNPs) at genome-wide significance (rs6687813, rs35136400, and rs6060237 on chromosomes 1, 14, and 21, respectively). Further mapping and gene-based tests suggest that regulatory effects on the bradykinin receptor B2 and B1 (*BDKRB2* and *BDKRB1*) genes are the most likely underlying mechanisms for the association on chromosome 14. The genes most likely associated with 20 SNPs on chromosome 1 are *F5* (coagulation factor 5) and *PROCR*, encoding endothelial protein C receptor.¹¹ Other candidate genes with reported associations have been linked with the activities of alternative bradykinin-metabolizing enzymes (*XPNPEP2* [rs3788853], *MME* [rs989692], immune regulatory pathways (*PRKCQ* [rs500766], and *ETV6* [rs2724635]). Few of these polymorphisms have been confirmed functionally or replicated across diverse populations.

At present, there have been only 2 candidate gene association studies (with <50 cases of AE-ACEI and <250 hypertensive patients taking an ACEI) from Southern Africa that have studied AE-ACEI and ACEI-responsiveness genomics in Sub-Saharan Africa.^{12,13} These studies associated the SNPs rs1042714 in the adrenergic receptor beta 2 (*ADRB2*) gene, rs1799722 in the *BDKRB2* gene, and the B₂ receptor -9 allele in the *BDKRB2* gene with AE-ACEI.^{12,13} Furthermore, 2 lines of evidence support the hypothesis that angiotensin-converting enzyme (ACE) biology and genomics may vary substantially across the African continent. First, carboxypeptidases, including ACE, are important in shaping the immunopeptidomes of class-I HLA,¹⁴ and Choudhury et al¹⁵ found the HLA region to be highly differentiated across African genomic regions. Thus, with epistatic association between HLA and ACE, ACE genomics may vary substantially across Sub-Saharan populations. Second, polymorphisms in ABO blood group genes have been associated with ACEI cough, and it is hypothesized that oligosaccharide moieties, acted on by ABO-encoded glycosyltransferases, affect ACE solubility and protease degradation.¹⁶ ABO genes have been under substantial selection pressure in Africa owing to links with malaria susceptibility¹⁷; therefore, this may be another important mechanism for regional differences in ACE across

Africa. This preliminary GWAS from a South African population was aimed at addressing this current research gap.

METHODS**Ethics statement**

The research was carried out in accordance with the latest update of the Declaration of Helsinki. Written informed consent was obtained from all participants in the AE-ACEI and control cohorts. The study protocol was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC 057/2020) and the Human Research Ethics Committee (Medical) of the University of Witwatersrand (M2210108).

ACEI-angioedema cohort description

A total of 207 adult patients who had experienced AE-ACEI were recruited retrospectively in the Western (the Cape Town area) and Eastern (the Mthatha and Gqeberha areas) Cape provinces of South Africa. Patients were defined as having AE-ACEI if they had angioedema while taking an ACEI, with no preceding episodes of angioedema in the absence of ACEI use, and no recurrence of angioedema after removal of the offending ACEI. All cases were reviewed and adjudicated by a clinical expert in allergology. Samples were also obtained from 460 controls who had taken an ACEI for at least 2 years without signs or symptoms of AE. Participants provided saliva collected in an OG-600 kit (DNA Genotek, Stittsville, Ontario, Canada), which was stored at room temperature until DNA extraction. The data collected included demographics and clinical history. All samples were anonymized and labeled with random study identifiers, and the collected data were deidentified for analysis. Seven case patients and 92 controls from the Soweto site (Gauteng Province) of the Africa Wits-INDEPTH Partnership for Genomic Research (AWI-Gen) study cohort in Gauteng Province were added to this cohort.^{18,19}

Genotyping and quality control

Participants from the Western and Eastern Cape cohort provided saliva collected in an OG-600 kit (DNA Genotek), which was stored at room temperature until DNA extraction. DNA was extracted from the saliva by using prepIT[®]L2P according to the manufacturer's instructions (DNA Genotek; catalog no. PT-L2P). All case patients and controls were genotyped on the Infinium Human Heredity and Health in Africa (H3Africa), v2, array on an Illumina iScan instrument (Illumina, San Diego, Calif) (<https://chipinfo.h3abionet.org>), which has a total of 2,225,121 autosomal SNPs. We used GenomeStudio, v2, a software package provided by Illumina, to assign genotypes to the raw data and evaluate the Infinium assay controls. The H3Africa cluster file, v2, generated by Illumina was used to cluster the genotypes. The PLINK²⁰ plugin provided by Illumina and supported by GenomeStudio was used to convert the genotype data into PLINK data format to allow for further quality controls using PLINK.

A sex discrepancy check was conducted by calculating the X chromosome homozygosity rate. Any self-identified male who had a homozygosity estimate of F greater than 0.8 and any self-identified female who had an estimate of F less than 0.2 were removed from the analysis. Genotype and individual missingness in the genotype and samples, respectively, were then checked, and all genotypes and samples with less than 0.02 missingness were

removed from the data set. A total of 1,919,455 SNPs and 635 samples were retained after these quality control (QC) checks. All of our remaining samples were within plus or minus 3 SDs from the mean sample heterozygosity rate, and they were all retained after the heterozygosity check. Hardy-Weinberg equilibrium P values were then calculated from the controls, and all of the SNPs with a P value less than 1.0×10^{-6} were further removed, as a result of which 1,914,061 SNPs were retained. The sample relatedness was then checked from an independent set of SNPs that had been pruned for linkage disequilibrium by calculating the proportion of identity by descent relatedness, π -hat, for each pair of samples. The recommended cutoff in GWASs is to use a π -hat threshold of 0.1875 to exclude related samples.²¹ However, most of the current GWAS methods, particularly those that implement the mixed linear model's association (MLMA), are designed to control for sample relatedness.²² As genome-wide complex trait analysis (GCTA)-MLMA²³ was to be used for the GWAS analysis, a lenient threshold was set, and 1 of the pairs of samples with a π -hat greater than 0.5 was excluded. This resulted in retention of 616 samples (from 195 case patients and 421 controls). Common SNPs were then extracted from the data set, and 1,333,573 SNPs with a minor allele frequency (MAF) less than 0.05 were retained. The AWI-Gen data were subjected to the same QC procedure. The Western and Eastern Cape data set was then merged with the AWI-Gen data. The final analysis included 944,944 common SNPs, 202 case patients, and 513 controls. Samples were then clustered on the basis of self-reported race and ethnicity and also by the phenotype status of the participants by principal component analysis (PCA) using GCTA and plotted using GENESIS.²⁴ Fig 1, A and B shows the respective PCA plots, whereas Table E1 (available in the Online Repository at www.jaci-global.org) presents the demographics of the study cohort.

Imputation and GWAS analysis

The South African cohort was imputed by using the African Genome Resource panel in the Sanger Imputation Server.²⁵ This was based on the results of a study of 11,000 Sub-Saharan Africans, with more than 90% of the samples genotyped by using the H3Africa Array, which showed that the African Genome Resource and Trans-Omics for Precision Medicine (TOPMed) panels performed best in this population.²⁶ Further QC was performed on the imputed data set, in which only the SNPs and samples that had less than 0.02 missingness on the genotype and samples, respectively, and common SNPs with a MAF greater than 0.05 were retained. The imputed data set after QC had 7,482,056 SNPs and 715 samples. The imputed data were also clustered on the basis of self-identified ancestry background, and the PCA plot shown in Fig E1 (available in the Online Repository at www.jaci-global.org) was generated. A standard GWAS was then conducted on the imputed data set by using GCTA-MLMA while controlling for age, sex, and global ancestry (using 5 principal components [PCs]). The number of PCs used was determined by obtaining a scree plot for the proportion of variance explained by the first 100 PCs, with 5 PCs selected by using the elbow method (see Fig E2 in the Online Repository at www.jaci-global.org). We also controlled for hypercholesterolemia, HIV, previous tuberculosis, and asthma comorbidities in the analysis, as these were found to be significantly different between the case patients and controls (see Table E1), and we compared the results with those of a GWAS that excluded these comorbidities.

The standard GWAS significance threshold of 5.0×10^{-8} was applied to determine significance SNPs, whereas SNPs with a P value less than 5.0×10^{-6} were considered suggestive.

Meta-analysis

A meta-analysis was performed with the South African and American cohort GWAS summary statistics. The data on the Vanderbilt-Marshfield cohort are publicly available by request on dbGAP under study accession no. *phs000438.v1.p1*. The data set consisted of 546,556 autosomal SNPs that had been genotyped using the 610Quadv1.B BeadChip (Illumina). A build liftover from hg18 to hg19 was first conducted using the liftOver script, which is publicly provided by the Center for Statistical Genetics at the University of Michigan. This cohort was imputed by using the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) reference panel on the Michigan Imputation Server.²⁷ The panel consists of samples from 883 African American individuals. After a quality check on the data, in which genotypes and samples that had a missingness quality less than 0.02 and rare SNPs with a MAF less than 0.05 were excluded, 5,222,201 SNPs and the 663 samples were retained. A standard GWAS of this cohort was then conducted by using GCTA-MLMA with sex and 2 PCs as covariates, and genomic control (GC) was performed on the P values. The total sample for the meta-analysis thus consisted of 376 case patients with AE-ACEI and 1002 matched controls. In all, 4,589,885 SNPs that were shared in common in the South African and Vanderbilt-Marshfield cohorts were selected. To account for possible heterogeneity, the variation observed in individual study effect sizes owing to differences in design of the study or risk of bias, participants, interventions, or outcomes,²⁸ METASOFT's Han and Eskin random effects model (RE2) using the Markov chain Monte Carlo (MCMC) method²⁹ was implemented to run the meta-analysis while correcting for population structure using genomic control for the mean effect and the heterogeneity part. A comparison of the RE2 model with the METASOFT fixed effect (FE) model was also performed to determine the extent of the effect of heterogeneity in the meta-analysis. Thresholds similar to those in the standard GWAS were applied to determine significant and suggestive SNPs.

Functional annotation and gene-based tests

Functional annotation of the SNPs and prioritization of genes were performed using FUMA (v1.5.2),³⁰ whereas Multi-marker Analysis of GenoMic Annotation (MAGMA), implemented in FUMA, was used in the gene-based tests. All of the SNPs from the GWAS of the South African cohort and the meta-analysis were annotated. The 1000 Genomes Phase 3 African population reference panel linkage disequilibrium backgrounds were used, and a P value threshold of 1.0×10^{-5} was set for the lead SNPs in FUMA.

Replication of reported variants

A number of AE-ACEI association studies of angioedema predominantly in European populations have been conducted to date.^{9,31-34} In particular, Liau et al³¹ have identified more than 10 GWASs examining AE-ACEI. Additional variants linked to AE-ACEI have also been reported on the GWAS catalog. Cumulatively, these studies have highlighted a total of 75 SNPs that

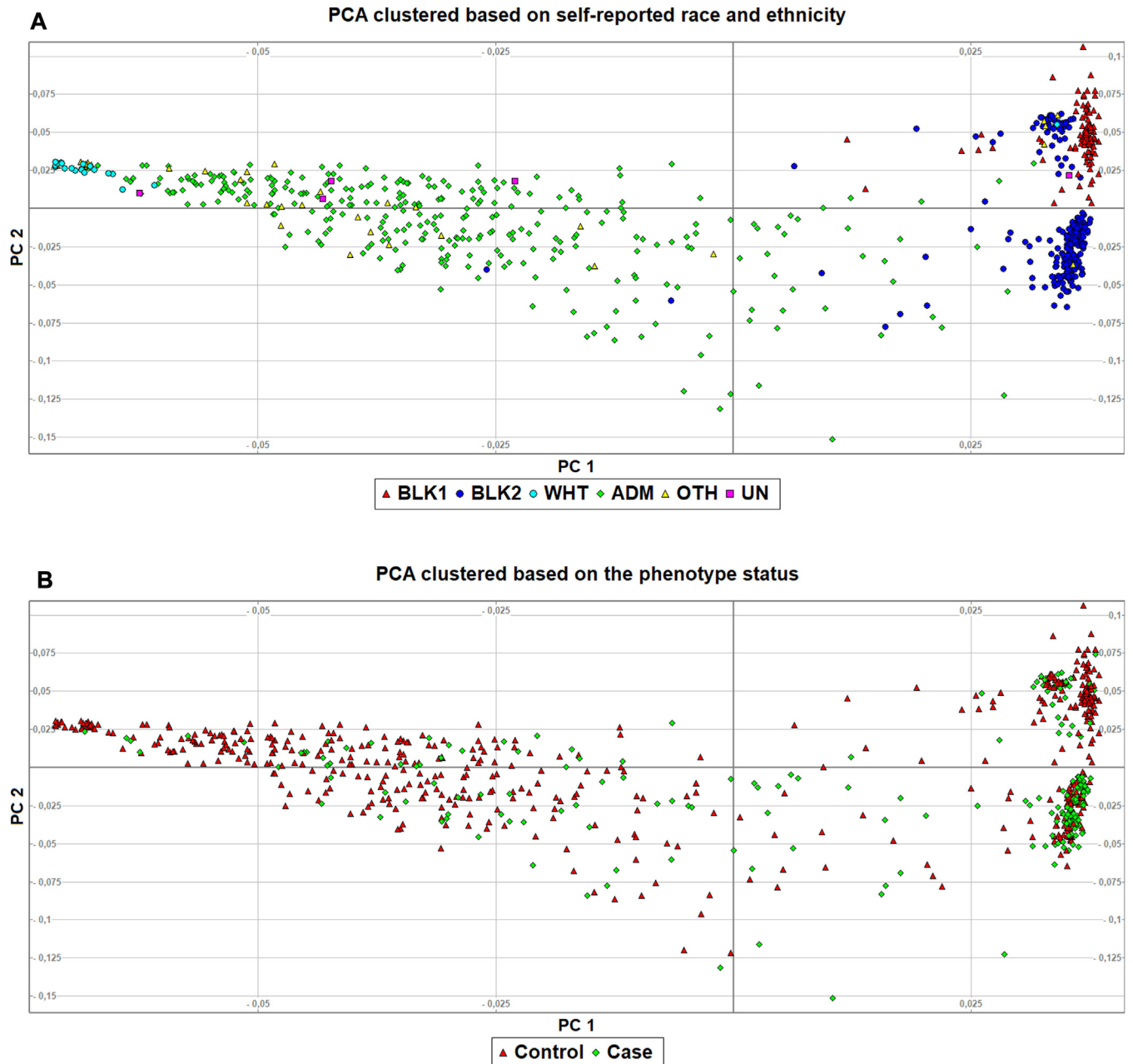


FIG 1. PCA plot of the South African cohort clustered on the basis of self-identified race and ethnicity (Black population from Western and Eastern Cape [BLK1], Black population from Soweto [BLK2], White [WHT], mixed ancestry [ADM], other [OTH], and unreported [UN]) (A) and AE-ACEI status (B). The genomic diversity and distribution of the case patients and controls in study cohort are highlighted.

have been found to be associated with angioedema. We sought to replicate some of the SNPs detected in both the standard GWAS and the meta-analysis.

RESULTS

The case patients with AE-ACEI ($n = 202$) and controls ($n = 513$) used in the standard GWAS and meta-analysis were similar in terms of age (55.5 ± 17.8 years vs 59 ± 18.0 years, respectively [$P = .16$]), predominance of female sex (63% [128 of 202] vs male sex (52% [269 of 513]), respectively [$P = .008$]), and comorbid illness. The set of case patients with AE-ACEI included

significantly more patients who self-reported as Black (58.6% [116 of 202]) than did the set of ACEI-tolerant controls (43.3% [224 of 513]) ($P < .00$; see [Table E1](#)).

GWAS association and functional annotation of the South African cohort

The respective Manhattan and QQ plots of the postimputation South African GWAS are shown in [Fig 2, A and B](#). In this analysis, 26 SNPs ([Table I](#)) were detected at a suggestive threshold ($P < 5.0 \times 10^{-6}$). Additionally, no inflated P values

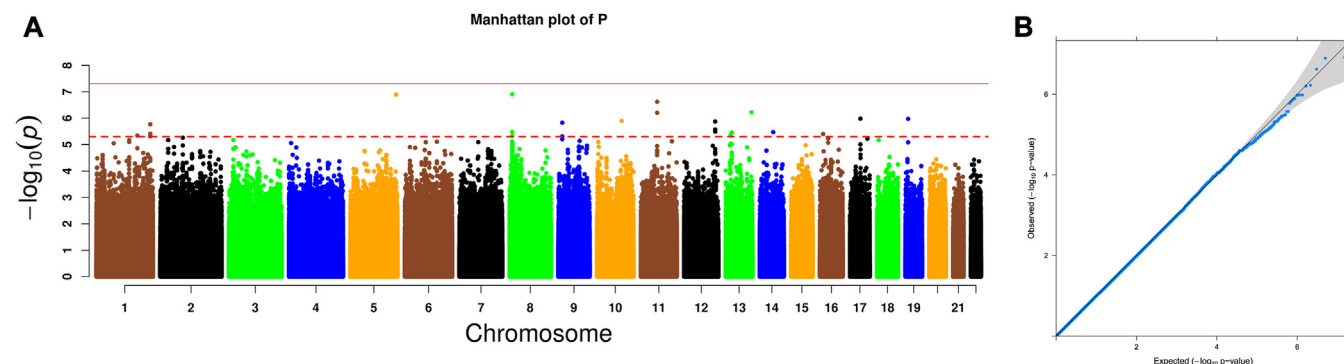


FIG 2. **A**, Manhattan plot of the standard GWAS of the South African cohort. Dashed red line corresponds to a P value of 5.0×10^{-6} ; solid line is the GWAS significance threshold P value of 5.0×10^{-8} . **B**, Corresponding QQ plot of the P values of the standard GWAS ($\lambda = 0.99$).

TABLE I. The 26 SNPs obtained at a suggestive threshold ($P < 5.0 \times 10^{-6}$) in the postimputation standard GWAS, along with the corresponding list of genes found close to them by positional mapping, their function, and whether the SNP was genotyped or imputed

CHR	rsID	Position	A1	A2	MAF	P value	Nearest gene	Function	Genotyped or imputed
1	rs6666273	191428753	A	G	0.23	4.58×10^{-6}	<i>RP11-309H21.2</i>	Intergenic	Imputed
1	rs4660011	241039771	C	A	0.44	1.72×10^{-6}	<i>RGS7</i>	Intronic	Imputed
1	rs12239109	241042754	C	T	0.37	4.59×10^{-6}	<i>RGS7</i>	Intronic	Genotyped
1	rs10926374	241047316	C	T	0.38	4.94×10^{-6}	<i>RGS7</i>	Intronic	Imputed
1	rs7544945	241048562	T	C	0.38	4.92×10^{-6}	<i>RGS7</i>	Intronic	Imputed
1	rs12127148	241049298	G	T	0.37	3.9×10^{-6}	<i>RGS7</i>	Intronic	Imputed
5	rs28630061	176204086	T	C	0.16	1.27×10^{-7}	<i>RP11-375B1.3</i>	Intergenic	Imputed
8	rs62488207	4808991	T	G	0.34	4.79×10^{-6}	<i>CSMD1</i>	Intronic	Imputed
8	rs12544185	4812064	A	T	0.33	3.32×10^{-6}	<i>CSMD1</i>	Intronic	Imputed
8	rs7815832	4812436	A	C	0.35	1.24×10^{-7}	<i>CSMD1</i>	Intronic	Genotyped
9	rs142454594	10278823	A	G	0.07	1.50×10^{-6}	<i>PTPRD</i>	Intronic	Imputed
9	rs79552273	10279110	T	C	0.07	4.91×10^{-6}	<i>PTPRD</i>	Intronic	Genotyped
11	rs12287265	60237028	A	T	0.20	2.41×10^{-7}	<i>MS4A1</i>	UTR3	Imputed
11	rs75124932	60250467	C	G	0.20	6.28×10^{-7}	<i>MS4A12</i>	Intergenic	Imputed
12	rs73409491	124545501	A	G	0.13	3.22×10^{-6}	<i>FAM101A</i>	Intronic	Genotyped
12	rs58371925	124550518	C	T	0.14	2.69×10^{-6}	<i>FAM101A</i>	Intronic	Imputed
12	rs58449918	124551080	G	T	0.13	2.69×10^{-6}	<i>FAM101A</i>	Intronic	Imputed
12	rs112593781	124559622	G	A	0.14	1.34×10^{-6}	<i>FAM101A</i>	Intronic	Imputed
13	rs116365021	34778472	G	A	0.06	4.19×10^{-6}	<i>SNORA25</i>	Intergenic	Imputed
13	rs28810452	38841040	A	G	0.19	3.53×10^{-6}	<i>UFM1</i>	Intergenic	Imputed
13	rs58482084	38845507	G	A	0.19	3.53×10^{-6}	<i>UFM1</i>	Intergenic	Imputed
13	rs59296363	112101252	T	G	0.12	6.00×10^{-7}	<i>TEX29</i>	Intergenic	Genotyped
14	rs2145156	69095279	A	G	0.08	3.39×10^{-6}	<i>RAD51B</i>	Intronic	Imputed
17	rs73321625	45977502	T	A	0.16	1.05×10^{-6}	<i>SP2:AC003665.1</i>	ncRNA exonic	Imputed
17	rs73321628	45977632	G	A	0.16	1.05×10^{-6}	<i>SP2:AC003665.1</i>	ncRNA exonic	Genotyped
19	rs12610494	8407470	C	G	0.09	1.07×10^{-6}	<i>KANK3</i>	Intronic	Imputed

A, Adenine; A1, minor allele, A2, reference allele; C, cytosine; CHR, chromosome; G, guanine; ncRNA, noncoding RNA; rsID, reference SNP identifier; T, thymine.

were observed in the postimputation GWAS analysis ($\lambda = 0.99$), whereas minimal confounding by the 4 comorbidities was observed, as the GWAS not accounting for the comorbidities (see Fig E3, A and B in the Online Repository at www.jaci-global.org) had results very similar to those presented in Fig 2, A and B. As is common in GWASs, most of the 26 SNPs detected at a suggestive threshold were found to be either intergenic or intronic variants, and they included both imputed and genotyped variants (Table I). These were also found to be close to 14 genes by positional mapping. The CUB and Sushi multiple domains 1

gene, *CSMD1*, reported by Hallberg et al³⁵ in the GWAS catalog, has been linked to ACEI-induced cough, whereas *RAD51B* has been linked to nonsteroidal anti-inflammatory drug (NSAID)-induced angioedema, acute urticaria, and drug-induced liver injury (DILI).^{36,37} None of the other variants and associated genes have previously been linked to angioedema. Table E2 (available in the Online Repository at www.jaci-global.org) lists some of the genes with their corresponding functions that could be investigated further for possible links to AE-ACEI.

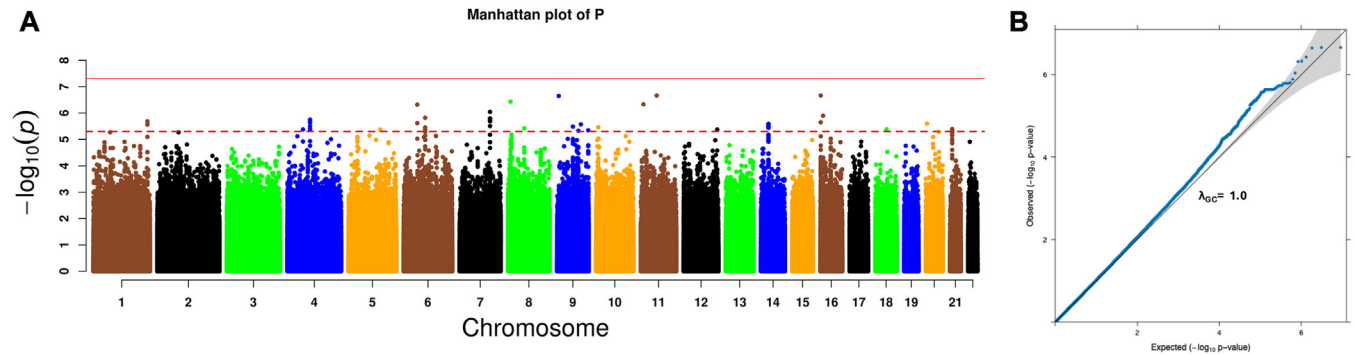


FIG 3. **A**, Manhattan plot of the meta-analysis of the South African and Vanderbilt-Marshfield cohort summary statistics. Dashed red line corresponds to a P value of 5.0×10^{-6} , whereas the solid red line is the GWAS significance threshold ($P = 5.0 \times 10^{-8}$). SNP rs1228726 (in red), on chromosome 11, was detected as significant. **B**, Corresponding QQ plot of the P values of the standard GWAS.

Meta-analysis and functional annotation

The Manhattan and QQ plots of the standard GWAS of the Vanderbilt-Marshfield cohort after imputation are shown in Fig E4, A and B (available in the Online Repository at www.jaci-global.org). To correct for the effect of population structure, the P values were GC-corrected, and the inflation factor improved from $\lambda = 0.56$ to $\lambda_{GC} = 1.0$. Similar to the findings of Pare et al³⁸ in a previous GWAS examining this cohort, none of the SNPs studied were observed to be significant; however, 25 SNPs with a P value less than 5.0×10^{-6} were detected. Using a preimputed set of data regarding this cohort, Pare et al³⁸ performed the association study using conditional logistic regression stratified by ancestry; they obtained 41 SNPs with a P value less than 1.0×10^{-4} . Pare et al³⁸ highlighted 2 of the SNPs, rs500766 on chromosome 10 and rs2724635 on chromosome 12, which they linked to the *PRKCQ* and *ETV6* genes, respectively. In our postimputation standard GWAS analysis of the cohort, we observed rs500766 at a P value of 2.14×10^{-5} and rs2724635 at a P value of 1.71×10^{-3} . The RE2 meta-analysis of the South African and Vanderbilt-Marshfield cohorts resulted in the Manhattan and QQ plots in Fig 3, A and B. Genomic control was applied to correct for P value inflation in the RE2 model ($\lambda_{GC} = 1.0$). In all, with use of the RE2 model, 73 SNPs were detected at a suggestive threshold ($P < 5.0 \times 10^{-6}$) and observed by positional mapping to be mainly intergenic or intronic (see Table II).

A number of SNPs that were detected at a suggestive threshold in the standard GWAS were found at lower P values in the meta-analysis. These include SNPs on chromosome 1 and 11. In addition to detection of SNP rs7815832 on chromosome 8 located near gene *CSMD1* ($P = 3.71 \times 10^{-7}$) in the meta-analysis, SNP rs4750617 (located about 56 kb upstream of SNP rs500766 located in the *PRKCQ* [protein kinase C theta] gene on chromosome 10 linked to AE-ACEI by Pare et al³⁸), was detected at a suggestive threshold ($P = 3.49 \times 10^{-6}$). The meta-analysis also detected 5 SNPs at a suggestive threshold on chromosome 6 (they were located close to *RIMS1*, the regulating synaptic membrane exocytosis 1 gene, which has previously been linked to angioedema in a Spanish population).³⁶

The FE model detected 37 SNPs at suggestive thresholds (see Fig E5, A and B and Table E3 in the Online Repository at www.jaci-global.org). In addition to the regions detected via the FE model, the RE2 model detected additional regions on

chromosomes 1, 4, 9, 12, 14, and 16 at suggestive thresholds (Table II). This highlights the increase in power of the RE2 to detect SNPs in the presence of heterogeneity compared with that of the FE model.

Replication analysis

In this analysis, a Bonferroni-corrected significance threshold of 6.67×10^{-4} (0.05 divided by 75) was used. SNP rs500766 on chromosome 10 located in gene *PRKCQ*, which was reported by Pare et al³⁸ to be associated with AE-ACEI, was replicated in the meta-analysis at a P value of 9.63×10^{-5} .

Gene-based test

In total, all of the input SNPs in FUMA for the standard GWAS and meta-analysis were mapped to 18,853 and 18,093 protein-coding genes, respectively. The gene-based test using MAGMA for the standard GWAS thus considered a Bonferroni-corrected significance threshold of 2.65×10^{-6} and 2.76×10^{-6} for the 2 tests, respectively. None of the genes considered were found to be significant. Tables E4 and E5 (available in the Online Repository at www.jaci-global.org) list the top 10 genes highlighted by MAGMA in each analysis, respectively, whereas Figs E6 and E7 (available in the Online Repository at www.jaci-global.org) present the corresponding Manhattan plots.

DISCUSSION

Our results highlight the importance of African populations for detection of novel variants and potential replication of preliminary signals from other populations. To our knowledge, this is the largest GWAS to investigate AE-ACEI in a diverse African cohort on the continent. The underrepresentation of continental African populations in GWASs is concerning.³⁹ This may lead to health care disparities once GWAS results are translated into clinical relevance, and it may also limit our understanding of the still-missing heritability that continues to plague GWASs and affect the accuracy of predicting drug responses in diverse populations.⁴⁰ In the context of ACEI use, we have highlighted the influence that early epidemiologic evidence from African American studies has had on international hypertension guidelines and

TABLE II. The 73 SNPs obtained at a suggestive threshold ($P < 5.0 \times 10^{-6}$) in the meta-analysis, the corresponding list of genes found close to them by positional mapping, their function, and whether the SNP was genotyped or imputed

CHR	rsID	Position	A1	A2	MAF	P value	Nearest gene	Function	Genotyped or imputed
1	rs12239109	241042754	C	T	0.37	2.08×10^{-6}	<i>RGS7</i>	Intronic	Imputed
1	rs10926374	241047316	C	T	0.38	2.75×10^{-6}	<i>RGS7</i>	Intronic	Imputed
1	rs7544945	241048562	T	C	0.38	2.69×10^{-6}	<i>RGS7</i>	Intronic	Imputed
1	rs12127148	241049298	G	T	0.37	2.7×10^{-6}	<i>RGS7</i>	Intronic	Imputed
4	rs4425441	56074276	A	G	0.16	4.24×10^{-6}	<i>RN7SL822P</i>	Intergenic	Imputed
4	rs74332970	79943086	G	A	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs77517799	79944357	A	G	0.24	3.21×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs56118735	79944905	A	G	0.26	4.05×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs6853917	79945449	T	C	0.24	2.22×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs56112016	79945526	G	A	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs74596027	79945885	A	C	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs17003575	79945925	T	C	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs17003576	79946127	A	G	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs7654451	79946527	A	G	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs286480	79946740	A	G	0.24	1.81×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs286479	79947170	T	C	0.24	1.81×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Genotyped
4	rs17003579	79947321	A	C	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs79293536	79947405	T	G	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs286478	79947664	A	G	0.24	1.81×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs286477	79948983	C	T	0.24	4.28×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs6827052	79949076	T	C	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs17003582	79949599	G	A	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Genotyped
4	rs7674874	79949863	C	G	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs1378384	79950607	T	C	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
4	rs1378383	79950885	A	G	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Genotyped
4	rs1378382	79951011	G	A	0.24	2.32×10^{-6}	<i>LINC01088</i>	ncRNA intronic	Imputed
5	rs3924097	120445067	T	A	0.4	4.30×10^{-6}	<i>CTD-261308.1</i>	Intergenic	Imputed
6	rs34388291	40580161	A	G	0.2	2.44×10^{-6}	<i>LRFN2</i>	Intergenic	Genotyped
6	rs34207487	40582609	T	C	0.21	4.82×10^{-7}	<i>LRFN2</i>	Intergenic	Imputed
6	rs1192177	72572886	T	C	0.5	3.59×10^{-6}	<i>RIMS1</i>	Intergenic	Imputed
6	rs1192178	72573194	A	G	0.5	3.59×10^{-6}	<i>RIMS1</i>	Intergenic	Imputed
6	rs1192179	72573244	C	T	0.5	3.59×10^{-6}	<i>RIMS1</i>	Intergenic	Imputed
6	rs1147527	72579416	A	G	0.49	4.29×10^{-6}	<i>RIMS1</i>	Intergenic	Imputed
6	rs1147522	72583600	T	C	0.47	1.53×10^{-6}	<i>RIMS1</i>	Intergenic	Genotyped
7	rs6952303	119603778	T	C	0.46	1.62×10^{-6}	<i>U1</i>	Intergenic	Imputed
7	rs6953016	119604064	A	G	0.46	1.62×10^{-6}	<i>U1</i>	Intergenic	Imputed
7	rs10281213	119605536	T	C	0.46	2.07×10^{-6}	<i>U1</i>	Intergenic	Genotyped
7	rs7802501	119629586	G	A	0.46	1.61×10^{-6}	<i>U1</i>	Intergenic	Genotyped
7	rs10236345	119631602	C	A	0.46	1.61×10^{-6}	<i>U1</i>	Intergenic	Imputed
7	rs10257336	119635285	A	G	0.46	1.93×10^{-6}	<i>U1</i>	Intergenic	Imputed
7	rs10247779	119639646	G	A	0.46	1.93×10^{-6}	<i>U1</i>	Intergenic	Imputed
7	rs58094128	119651727	C	T	0.46	3.13×10^{-6}	<i>U1</i>	Intergenic	Imputed
7	rs10245443	119656806	T	G	0.47	9.12×10^{-7}	<i>U1</i>	Intergenic	Imputed
8	rs7815832	4812436	C	A	0.35	3.71×10^{-7}	<i>CSMD1</i>	Intronic	Imputed
8	rs2220157	50879666	A	G	0.13	3.78×10^{-6}	<i>SNTG1</i>	Intronic	Imputed
9	rs622308	4026061	G	C	0.38	2.25×10^{-7}	<i>GLIS3</i>	Intronic	Imputed
9	rs67121370	80974449	G	A	0.17	3.29×10^{-6}	<i>PSAT1</i>	Intergenic	Genotyped
9	rs10760694	102413754	G	T	0.02	4.74×10^{-6}	<i>RP11-554F20.1</i>	ncRNA intronic	Imputed
9	rs669329	110954331	T	C	0.15	2.69×10^{-6}	<i>RP11-505C13.1</i>	Intergenic	Imputed
9	rs59342860	138509275	G	T	0.19	4.53×10^{-6}	<i>RP11-98L5.5</i>	Intergenic	Imputed
10	rs4750617	6606334	A	C	0.36	3.49×10^{-6}	<i>PRKCQ</i>	Intronic	Genotyped
11	rs2061036	8266559	T	C	0.24	4.71×10^{-7}	<i>LMO1</i>	Intronic	Genotyped
11	rs12287265	60237028	A	T	0.2	2.17×10^{-7}	<i>MS4A1</i>	UTR3	Imputed
12	rs78543588	129750628	G	T	0.11	4.26×10^{-6}	<i>TMEM132D</i>	Intronic	Imputed
12	rs78943182	129751502	G	A	0.11	4.35×10^{-6}	<i>TMEM132D</i>	Intronic	Imputed
14	rs72686653	46752781	C	T	0.19	3.09×10^{-6}	<i>LINC00871</i>	ncRNA intronic	Imputed
14	rs72686654	46752873	G	A	0.19	3.09×10^{-6}	<i>LINC00871</i>	ncRNA intronic	Imputed
14	rs58238734	46753607	A	G	0.19	2.59×10^{-6}	<i>LINC00871</i>	ncRNA intronic	Imputed
14	rs59028097	46753753	C	T	0.19	2.66×10^{-6}	<i>LINC00871</i>	ncRNA intronic	Imputed
14	rs111287977	46754088	G	A	0.19	2.66×10^{-6}	<i>LINC00871</i>	ncRNA intronic	Genotyped

(Continued)

TABLE II. (Continued)

CHR	rsID	Position	A1	A2	MAF	P value	Nearest gene	Function	Genotyped or imputed
14	rs76062551	46755037	T	C	0.19	3.66×10^{-06}	<i>LINC00871</i>	ncRNA intronic	Imputed
16	rs112690906	1853335	T	C	0.44	2.26×10^{-06}	<i>HAGH</i>	Intronic	Genotyped
16	rs78207788	1853375	C	T	0.43	2.16×10^{-07}	<i>HAGH</i>	Intronic	Imputed
18	rs4553714	44298996	A	G	0.16	4.22×10^{-06}	<i>ST8SIA5</i>	Intronic	Genotyped
20	rs1552323	3450811	A	G	0.45	2.54×10^{-06}	<i>ATRN</i>	Upstream	Genotyped
21	rs2826127	21666445	G	A	0.38	4.11×10^{-06}	<i>AP001171.1</i>	Intergenic	Imputed
21	rs9981281	21666624	T	C	0.38	4.11×10^{-06}	<i>AP001171.1</i>	Intergenic	Imputed
21	rs1077651	21666997	C	T	0.38	4.66×10^{-06}	<i>AP001171.1</i>	Intergenic	Genotyped
21	rs1027063	21667752	G	C	0.38	4.66×10^{-06}	<i>AP001171.1</i>	Intergenic	Imputed
21	rs1027064	21667841	T	A	0.38	4.66×10^{-06}	<i>AP001171.1</i>	Intergenic	Imputed
21	rs1027066	21667880	A	G	0.38	4.66×10^{-06}	<i>AP001171.1</i>	Intergenic	Imputed
21	rs1028982	21668534	A	G	0.38	4.90×10^{-06}	<i>AP001171.1</i>	Intergenic	Imputed

have warned against the potential pitfalls of extrapolating these very limited data to all continental African populations.⁶

In this study, we have both performed a standard GWAS analysis in the South African population and meta-analyzed our study with an African American and European American cohort from Vanderbilt (Nashville, Tenn) and Marshfield (Wis). We have further implemented FUMA to annotate all of the SNPs and conducted a gene-based test for the protein-coding genes that were found close to these SNPs. Our standard GWAS of the South African cohort and the meta-analysis detected 26 SNPs and 73 SNPs, respectively. These SNPs, which were located close to 33 genes by positional mapping in FUMA, were detected at suggestive thresholds ($P < 5.0 \times 10^{-06}$). Among them, the *RIMS1* gene has been associated with NSAID-induced angioedema.³⁶ *RIMS1* modulates G proteins (in particular, those linked to the opening of calcium channels), and this has been best studied in relation to the release of neurotransmitters and insulin.⁴¹ *BDKRB1* and *BDKRB2* are both G protein-coupled receptors, and therefore, *RIMS1* may play a role in modulating bradykinin receptor-2 sensitivity in susceptible individuals.⁴² In addition, in a GWAS study of smoking patterns and meta-analysis of smoking status, Xu et al⁴³ found a significant variant, rs1334346 ($P = 8.22 \times 10^{-09}$), close to *RIMS1* that was associated with smoking behaviour over time. The gene *RAD51B* has been linked to NSAID-induced angioedema and acute urticaria by Cornejo-García et al³⁶ and NSAID-induced DILI by Nicoletti et al³⁷ on the GWAS catalog. The *CSMD1* gene, which is a complement regulatory protein linked to kallikrein in pathway analyses, was also found close to the SNPs detected at a suggestive threshold and has been reported by Hallberg et al³⁵ and Saunders et al⁴⁴ on the GWAS catalog. *CSMD1* is linked to cough in response to ACEIs and age at initiation of smoking, respectively. Smoking has been epidemiologically identified as a risk factor for development of AE-ACEI,⁴⁵ but we did not capture smoking status in our clinical data. The *PRKCQ* gene on chromosome 10, which is associated with T-cell activation,⁴⁶ was a signal highlighted in the original Vanderbilt-Marshfield cohort analysis³⁸ to be linked to AE-ACEI.

As noted in the recent meta-analysis of AE-ACEI in European participants, there is now an urgent need for functional data to confirm the biologic role of some of these associated genes (particularly those affecting bradykinin receptor sensitivity and signaling channels).

The main limitation of our study is its small sample size and, thus, its low power to attain genome-wide significance for novel SNP associations, as is common in GWASs and pharmacogenomics studies involving African populations.⁴⁷⁻⁴⁹ Given the 1% to 3% prevalence of ACE-AE in the African population, for 20% to 49% of the ACE-AE risk allele frequency (Table II), with an expected genotype relative risk ranging from 1.3 to 1.4, our study of 376 case patients and 1002 controls has a predictive power of 29% to identify candidate risk SNPs at $P < 5.0 \times 10^{-08}$. A sample size of more than 2000 combined case patients and controls will be required to achieve more than 80% power in the study, and this work serves as the starting point toward this larger definitive sampling (see Fig E8 [available in the Online Repository at www.jaci-global.org]). However, the increase in power to detect some of the SNPs in the meta-analysis and the replication of the SNP rs500766 that was detected in an AE-ACEI GWAS of the African American population highlight the importance of inclusion of African GWASs in replication and meta-analysis. In addition, the large number of SNPs obtained at a suggestive threshold in both the post-imputation standard GWAS and the meta-analysis further highlights the need for increased sampling on the continent if African GWASs are to catch up with European GWASs. The lack of smoking data and other environmental information that may interact with the genetic information limits our exploration of possible effects of gene-environment interaction. Furthermore, inclusion of local ancestry information in our association analysis could enhance the study with increased power to capture novel results, as demonstrated in previous GWASs of admixed populations.^{50,51} We highlight this as a promising avenue for future research.

In conclusion, this study presents the largest GWAS of AE-ACEI from a continental African population, with several SNPs detected at a suggestive threshold in both the postimputation GWAS and meta-analysis. The SNPs are located near the genes *RIMS1*, *CSMD1*, *RAD51B*, and *PRKCQ* with biologic plausibility and prior associations with drug-induced angioedema, DILI, and acute urticaria. Replication of the SNP rs500766 in the meta-analysis, which has previously been detected in an African American population, emphasizes the potential of including diverse African populations for discovery and validation. Further work is now required to increase sampling across diverse African regions and explore the potential of joint local ancestry and genotype association methods to improve study power and further illuminate the heritability of AE-ACEI.

Supplementary data

Figs E1 to E8 and Tables E1 to E5 are available in the Online Repository at www.jaci-global.org.

DISCLOSURE STATEMENT

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Key messages

- A GWAS analysis of a South African cohort located SNPs associated with AE-ACEI at a suggestive threshold ($P < 5.0 \times 10^{-6}$) close to the *CSMD1* gene, which was previously linked to ACEI cough.
- Meta-analysis with summary statistics of an African American and European American cohort also obtained SNPs associated with AE-ACEI at a suggestive threshold close to the *CSMD1* gene, as well as to the *RIMS1*, *RAD51B*, and *PRKCQ* genes, which have been linked to drug-induced angioedema. *RAD51B* has in addition been linked to DILI and acute urticaria.
- A replication study detected SNP rs500766, which was previously associated with AE-ACEI.
- The study highlights the importance of African populations in meta-analysis and replication studies and the need for increased sampling on the continent of Africa.

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