medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

1 # A GWAS of ACE Inhibitor-Induced Angioedema in a South African Population.

2 Jacquiline W. Mugo, PhD[1*], Cascia Day, Cert Allergy (Phys)[1,2*], Ananyo Choudhury, PhD[3],
3 Maria Deetlefs, Dip Allergy (SA)[1], Robert Freercks, MPhil[4], Sian Geraty, MMed[4], Angelica
4 Panieri, MBChB[4], Christian Cotchbos, MBChB[4], Melissa Ribeiro, MBChB[2], Adelein
5 Engelbrecht, MMed(FamMed), FCFP(SA)[5], Lisa K. Micklesfield, PhD[6], Michèle Ramsay, PhD[3],
6 Sarah Pedretti, PhD[2±] and Jonny Peter, PhD[1,2±].

7 [1]Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Health
8 Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town, 7625, Western
9 Cape, South Africa.
10 [2]Allergy and Immunology Unit, University of Cape Town Lung Institute (Pty) Ltd, George
11 Street, Mowbray, Cape Town, 7700, Western Cape, South Africa.
12 [3] Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of
13 the Witwatersrand, 1 Jan Smuts Avenue, Braamfontein, Johannesburg, 2000, South Africa.
14 [4]Faculty of Health Sciences, Department of Medicine, Nelson Mandela University, Gqeberha,
15 South Africa.
16 [5]Western Cape Department of Health, District 6 Day Hospital, 50 Caledon Street,
17 Zonnebloem, Cape Town, Western Cape, South Africa.
18 [6]South African Medical Research Council/Wits Developmental Pathways for Health Research
19 Unit (DPHRU), Department of Paediatrics, Faculty of Health Sciences, University of the
20 Witwatersrand, Johannesburg, South Africa.
21

22 *,± These two authors contributed equally to this work.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

23 **Corresponding Author**: Jonny Peter, Division of Allergy and Clinical Immunology,
24 Department of Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road,
25 Observatory, Cape Town, 7625, Western Cape, South Africa.
26 Telephone: +27 21 406-6889/7; Facsimile: +27 21 406-6888; Email: Jonny.Peter@uct.ac.za

27 **Word count**: 5982/6000

28

29 ## Abstract

30 **Background:** Angiotensin-converting enzyme inhibitor-induced angioedema (AE-ACEI) is a
31 life-threatening adverse event and, globally, the commonest cause of emergency
32 presentations with angioedema. Several large genome-wide association studies (GWAS)
33 have found genomic associations with AE-ACEI. However, despite African Americans having
34 a 5-fold increased risk of AE-ACEI, there are no published GWAS from Africa. The aim of this
35 study was to conduct a case-control GWAS of AE-ACEI in a South African population and
36 perform a meta-analysis with an African American and European American population.
37 **Methods:** The GWAS included 202 South African adults with a history of AE-ACEI and 513
38 controls without angioedema following angiotensin-converting enzyme inhibitor (ACEI)
39 treatment for at least 2 years. A meta-analysis was conducted with GWAS summary
40 statistics from an African American and European American cohort (from
41 Vanderbilt/Marshfield with 174 cases and 489 controls).
42 **Results:** No SNPs attained genome-wide significance. However, 26 SNPs in the post-
43 imputation standard GWAS of the South African cohort and 37 SNPs in the meta-analysis
44 were associated to AE-ACEI with suggestive threshold(p-value<5.0×10^{-06}). Some of these
45 SNPs were found to be located close to the genes *PRKCQ* and *RIMS1,* previously linked with

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

46 drug-induced angioedema, and also close to the *CSMD1* gene linked to ACEI cough,
47 providing replication at the gene level, but with novel lead SNPs.
48 **Conclusions:** Our results highlight the importance of African populations to detect novel
49 variants in replication studies. Further increased sampling across the continent and matched
50 functional work are needed to confirm the importance of genetic variation in understanding
51 the biology of AE-ACEI.
52 **Keywords:** Angioedema, Genome-wide association studies, Angiotensin-converting Enzyme
53 Inhibitor.
54

55 **Non-standard Abbreviations and Acronyms:**
56 AE-ACEI: Angiotensin-converting Enzyme Inhibitor-Induced Angioedema
57 ACE: Angiotensin converting enzyme
58 ACEI: Angiotensin converting enzyme inhibitors
59 ARBs: Angiotensin receptor blockers
60 AGR: African Genome Resource
61 AWI-Gen: Africa Wits INDEPTH Partnership for Genomic Research
62 CREOLE: Comparison of three combination therapies in lowering blood pressure in Black
63 Africans
64 GCTA: Genome-wide complex trait analysis
65 GWAS: Genome-wide association studies
66 H3Africa: Human heredity and health in Africa
67 LMICs: Low-middle income countries
68 MAGMA: Multimarker analysis of genomic annotation
69 MLMA: Mixed linear model's association

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

70 QQ: Quantile-quantile

71 RAAS: Renin angiotensin-aldosterone system (RAAS)

72 SSA: Sub-Saharan Africa (SSA)

73 TOPMed: Trans-Omics for Precision Medicine

74

75 **1. Introduction**

76 Cardiovascular disease is an exploding epidemic facing low-middle-income countries (LMICs)
77 in Africa, and hypertension is the leading cause of death globally, with the greatest burden
78 of disease in LMICs [1]. ACEI are a class of drugs that inhibit the renin-angiotensin-
79 aldosterone system (RAAS), with a proven reduction in mortality from hypertension,
80 diabetes mellitus, and cardiac failure [2]. They are widely available and affordable, making
81 them critical for use in LMICs [3]. ACEI use is limited by two major adverse events: ACEI-
82 angioedema (AE-ACEI) and cough (ACEI-cough) [4]. AE-ACEI typically involves the face,
83 tongue, or larynx and can be life-threatening in ~16% of cases [5]. AE-ACEI incidence ranges
84 from 0.2-0.7% in retrospective studies to 6% in prospective clinical trials [4-6]; in the only
85 large multicentre African study (CREOLE), the incidence was 0.7% [7]. AE-ACEI is the most
86 common angioedema presentation to emergency rooms across the world, including South
87 Africa [4, 8]. African Americans have a 5-fold increased risk of AE-ACEI compared to
88 European populations [4], and this has led several international hypertension guideline
89 groups to favour angiotensin receptor blockers (ARBs) over ACEI in African populations. We
90 have recently argued that these recommendations are potentially flawed with dire
91 consequences given the near-complete absence of studies of AE-ACEI across diverse African
92 populations [6]. This work aims to address this important gap.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

93 Several GWAS and candidate gene studies have been conducted for AE-ACEI [9, 10], with
94 the largest meta-analysis of eight of these cohorts recently published and identifying three
95 SNPs at genome-wide significance (*rs*6687813, *rs*35136400, and *rs*6060237 on
96 chromosomes 1, 14, and 21, respectively). Further mapping and gene-based tests suggest
97 that regulatory effects on *the BDKBR2* and *BDKRB1* genes are the most likely underlying
98 mechanisms for the association on chromosome 14. The genes most likely associated with
99 20 SNPs on chromosome 1 are *F5* and *PROCR*, encoding endothelial protein C receptor [11].
100 Other candidate genes with reported associations have been linked with the activities of
101 alternative bradykinin metabolising enzymes (*XPNPEP2* (*rs*3788853), *MME* (*rs*989692),
102 immune regulatory pathways (*PRKCQ* (*rs*500766) and *ETV6* (*rs*2724635)). Few of these
103 polymorphisms have been confirmed functionally or replicated across diverse populations.
104 At present, there have been only two candidate gene association studies (with less than 50
105 AE-ACEI cases and <250 hypertensive patients on ACEI) from Southern Africa that have
106 studied AE-ACEI and ACEI-responsiveness genomics in Sub-Saharan Africa (SSA)[12, 13].
107 These studies associated SNPs *rs*1042714 in the *ADRB2* gene, *rs*1799722 in the *BDKRB2*
108 gene, and the B_2 receptor -9 allele in the *BDKRB2* gene with AE-ACEI [12, 13]. Furthermore,
109 two lines of evidence support the hypothesis that ACE biology and genomics may vary
110 substantially across the African continent. First, carboxypeptidases, including ACE, are
111 important in shaping the immunopeptidomes of class-I HLA [14], and *Choudhury et al*. [15]
112 found the HLA region to be highly differentiated across African genomic regions. Thus, with
113 epistatic association between HLA and ACE, ACE genomics may vary substantially across SSA
114 populations. Second, polymorphisms in ABO blood group genes have been associated with
115 ACEI-cough, and it is hypothesized that oligosaccharide moieties, acted on by ABO-encoded
116 glycosyltransferases, impact ACE solubility and protease degradation [16]. *ABO* genes have

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

117 been under substantial selection pressure in Africa due to links with malaria susceptibility
118 [17], and therefore this may be another important mechanism for regional differences in
119 ACE across Africa. This preliminary GWAS from a South African population was aimed at
120 addressing this current research gap.
121

122 2. Materials and Methods

123 2.1 Ethics Statement

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

129 2.2 ACEI-Angioedema Cohort Description

130 A total of 207 adult patients who had experienced AE-ACEI were recruited retrospectively in
131 the Western (Cape Town area) and Eastern (Mthatha and Gqeberha areas) Cape provinces
132 of South Africa. Patients were defined as having AE-ACEI if they had angioedema while
133 taking an ACEI, with no preceding episodes of angioedema in the absence of ACEI use, and
134 no recurrence of angioedema after removal of the offending ACEI. All cases were reviewed
135 and adjudicated by a clinical expert in allergology. Samples were also obtained from 460
136 controls who had taken an ACEI for at least two years without signs or symptoms of AE.
137 Participants provided saliva collected in an OG-600 kit (DNA Genotek) that was stored at
138 room temperature until DNA extraction. The data collected included demographics and
139 clinical history. All samples were anonymised and labelled with random study identifiers,
140 and the collected data was de-identified for analysis. Seven cases and 92 controls from the

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

141 Soweto site (Gauteng province) of the Africa Wits-INDEPTH Partnership for Genomic
142 Research (AWI-Gen) study cohort in the Gauteng province were added to this cohort [18,
143 19].

144 **2.3 Genotyping and Quality Control**

145 Participants from the Western/Eastern Cape cohort provided saliva collected in an OG-600
146 kit (DNA Genotek) that was stored at room temperature until DNA extraction. DNA was
147 extracted from saliva using prepIT°L2P according to manufacturer instructions (DNA
148 Genotek, cat#PT-L2P). All cases and controls were genotyped on the Infinium™ H3Africa v2
149 array on an Illumina iScan instrument (Illumina, CA, USA) (https://chipinfo.h3abionet.org)
150 that has a total of 2,225,121 autosomal SNPs. We used GenomeStudio v2, a software
151 provided by Illumina, to assign genotypes to the raw data and evaluate the Infinium assay
152 controls. H3Africa cluster file v2, generated by Illumina, was used to cluster the genotypes.
153 The PLINK [20] plugin provided by Illumina and supported by GenomeStudio was used to
154 convert the genotype data into PLINK data format to allow for further quality controls using
155 PLINK.

156 A sex discrepancy check was conducted by calculating the X-chromosome homozygosity
157 rate. Any self-identified male that had a homozygosity estimate of $F > 0.8$ and any self-
158 identified female that had an estimate of $F < 0.2$ were removed from the analysis. Genotype
159 and individual missingness in the genotype and samples, respectively, were then checked,
160 and all genotypes and samples that had < 0.02 missingness were removed from the dataset.
161 1,919,455 SNPs and 635 samples were retained after these quality control checks. All our
162 remaining samples were within ±3 standard deviations from the sample heterozygosity rate
163 mean and were all retained after the heterozygosity check. Hardy-Weinberg Equilibrium
164 (HWE) p-values were then calculated from the controls, and all the SNPs with a p-

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

165 value<1.0x10^{-06} were further removed, retaining 1,914,061 SNPs. The sample relatedness
166 was then checked from an independent set of SNPs that had been pruned for linkage
167 disequilibrium (LD) by calculating the proportion of identity by descent (IBD) relatedness, *pi-*
168 *hat*, for each pair of samples. The recommended cut-off in GWAS is to use a *pi-hat* threshold
169 of 0.1875 to exclude related samples [21]. However, most of the current GWAS methods are
170 designed to control for sample relatedness, particularly those that implement the mixed
171 linear model's association (MLMA) [22]. As GCTA-MLMA [23] was to be used for the GWAS
172 analysis, a lenient threshold was set, and one of the pairs of samples with a *pi-hat* > 0.5 was
173 excluded. This retained 616 samples (195 cases and 421 controls). Common SNPs were then
174 extracted from the dataset, and 1,333,573 SNPs that had a minor allele frequency (MAF) >
175 0.05 were retained. The AWI-Gen data was subjected to the same QC procedure. The
176 Western/Eastern Cape dataset was then merged with the AWI-Gen data. The final analysis
177 includes 944,944 common SNPs, 202 cases, and 513 controls. Samples were then clustered
178 based on both the self-reported race and ethnicity and also by the phenotype status of the
179 participants by principal component analysis (PCA) using GCTA and plotted using GENESIS
180 [24]. **Figures 1A** and **B** show the PCA plots, respectively, while **Table IS** *(supplementary*
181 *material)* is the demographic table of the study cohort.

182 **2.4 Imputation and GWAS Analysis**

183 The South African cohort was imputed using the African Genome Resource (AGR) panel in
184 the Sanger Imputation Server [25]. This was based on the results of a study of 11,000 sub-
185 Saharan Africans, where >90% of the samples were genotyped using the H3Africa Array,
186 which showed the AGR and Trans-Omics for Precision Medicine (TOPMed) panels performed
187 best in this population [26]. Further quality control was performed on the imputed dataset,
188 where only the SNPs and samples that had <0.02 missingness on the genotype and samples,

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

189 respectively, and common SNPs with MAF>0.05 were retained. The imputed dataset after
190 quality control had 7,482,056 SNPs and 715 samples. The imputed data was also clustered
191 based on the self-identified ancestry background, and the PCA plot shown in **Figure 1S**
192 (*supplementary material*) was generated. Standard GWAS was then conducted on the
193 imputed dataset using GCTA-MLMA while controlling for age, sex, global ancestry (using 5
194 principal components (PCs)), and whether or not the samples had hypercholesterolemia,
195 HIV, previous tuberculosis, or asthma, as these were found to be significantly different
196 between the cases and controls (**Table IS**, *supplementary material*). The number of PCs used
197 was determined by obtaining a scree plot for the proportion of variance explained by the
198 first 100 PCs, where 5 PCs were selected using the elbow method (**Figure 2S**, *supplementary*
199 *material*).

200 **2.5 Meta-Analysis**

201 A meta-analysis was performed with the South African and American cohort GWAS
202 summary statistics. The data from the Vanderbilt/Marshfield cohort is publicly available by
203 request on dbGAP under study accession number *phs000438.v1. p1*. It consisted of 546,556
204 autosomal SNPs that had been genotyped using the 610Quadv1.B BeadChip (Illumina, San
205 Diego, California, USA). A build liftover from hg18 to hg19 was first conducted using the
206 liftOver script that is publicly provided by the Centre for Statistical Genetics at the University
207 of Michigan. This cohort was imputed using the Consortium on Asthma among African-
208 ancestry Populations in the Americas (CAAPA) reference panel on the Michigan Imputation
209 Server [27]. The panel consists of 883 African American individuals. After a quality check on
210 the data, where genotypes and samples that had a missingness quality of < 0.02 and rare
211 SNPs with MAF < 0.05 were excluded, 5,222,201 SNPs and the 663 samples were retained. A
212 standard GWAS of this cohort was then conducted using GCTA-MLMA with sex and two PCs

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

213 as covariates, and genomic control (GC) was performed on the p-values. The total sample
214 size for the meta-analysis was thus 376 AE-ACEI cases and 1002 controls. 4,589,885 SNPs
215 that were in common in the South African and Vanderbilt/Marshfield cohorts were selected.
216 METASOFT [28] was first implemented to estimate the heterogeneity of the study, which
217 was found to be 0, and thus a fixed effect model in METASOFT was used for the meta-
218 analysis.

219 **2.6 Functional Annotation and Gene-Based Tests**

220 Functional annotation of the SNPs and prioritization of genes were performed using FUMA
221 (v1.5.2) [29], while MAGMA (Multi-marker Analysis of GenoMic Annotation), implemented
222 in FUMA, was used in the gene-based tests. All the SNPs from the GWAS of the South
223 African cohort and the meta-analysis were annotated. The 1000 genomes Phase3 African
224 population reference panel LD backgrounds were used, and a p-value threshold of 1.0×10^{-05}
225 was set for the lead SNPs in FUMA.

226 **2.7 Replication**

227 A number of AE-ACEI association studies on angioedema have been conducted to date [9,
228 30-33]. In particular, *Liau et al.* [30] have identified more than 10 GWAS for AE-ACEI.
229 Cumulatively, these studies have highlighted a total of 75 SNPs that have been found to be
230 associated with angioedema. We sought to replicate some of the SNPs detected in both the
231 standard GWAS and the meta-analysis.
232

233 **3. Results**

234 The AE-ACEI cases (n=202) and controls (n=513) used in the standard GWAS and meta-
235 analysis were similar in terms of age (55.5±17.8 years vs. 59±18.0 years, respectively, p-
236 value=0.16), predominantly female sex (63% [128/202] vs. 52% [269/513] respectively, p-

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

237 value=0.008), and co-morbid illness. The AE-ACEI cases had significantly more patients who
238 self-reported as black at 58.6% (116/202), than the ACEI-tolerant controls at 43.3%
239 (224/513) (p-value<0.001) (**Table IS**, *supplementary material*).

240 **3.1 GWAS Association and Functional Annotation of the South African Cohort**

241 The Manhattan and QQ plots of the post-imputation South African GWAS are shown in
242 **Figures 2A** and **B**, respectively. In this analysis, 26 SNPs (**Table I**) were detected at a
243 suggestive threshold (p-values<$5.0\text{x}10^{-06}$). Additionally, no inflated p-values were observed
244 in the post-imputation GWAS analysis (λ=0.99). As is common in GWAS, most of the 26 SNPs
245 detected at a suggestive threshold were found to be either intergenic or intronic variants
246 and included both imputed and genotyped variants (**Table I**). These were also found to be
247 close to 14 genes by positional mapping. The CUB and Sushi multiple domains 1 gene,
248 *CSMD1*, reported by *Hallberg et al.* [34] in the GWAS catalog, has been linked to ACEI-
249 induced cough. None of the other variants have previously been linked to angioedema.

250 **3.2 Meta-analysis and Functional Annotation**

251 The Manhattan and QQ plots of the standard GWAS of the Vanderbilt/Marshfield cohort
252 post-imputation are shown in **Figures 3S A** and **B** (*supplementary material*). To correct for
253 the effect of population structure, the p-values were GC-corrected, and the inflation factor
254 improved from λ=0.56 to λ_{GC}=1.0. Similar to a previous GWAS on this cohort by *Pare et al.*
255 [35], none of the SNPs studied were observed to be significant; however, 25 SNPs with a p-
256 value<$5.0\text{x}10^{-06}$ were detected. Using a pre-imputed dataset of this cohort, *Pare et al. [35]*
257 performed the association study using conditional logistic regression stratified by ancestry
258 and obtained 41 SNPs that had a p-value<$1.0\text{x}10^{-04}$. They highlighted two of the SNPs,
259 *rs*500766 on chromosome 10 and *rs*2724635 on chromosome 12, which they linked to the
260 *PRKCQ* and *ETV6* genes, respectively. We observed *rs*500766 at p-value=$2.14\text{x}10^{-05}$ and

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

261 *rs*2724635 at p-value=1.71x10^{-03} in our post-imputation standard GWAS analysis of the
262 cohort. The fixed-effect meta-analysis of the South African and Vanderbilt/Marshfield
263 cohorts resulted in the Manhattan and QQ plots in **Figures 3A** and **B**. No p-value inflation of
264 p-values was observed in the analysis (λ=0.99). The meta-analysis detected 37 SNPs with a
265 p-value<5.0x10^{-06} and were observed to be mainly intergenic or intronic by positional
266 mapping; see **Table II**.
267 In addition to detecting SNP *rs*7815832 (p-value=8.26x10^{-07}) located near gene *CSMD1* as
268 was observed in the standard GWAS, the meta-analysis detected SNP *rs*4750617 (p-
269 value=2.92x10^{-06}) about 56 kb upstream of SNP *rs*500766 located in the *PRKCQ* (protein
270 kinase C theta) gene on chromosome 10 that was linked to AE-ACEI by *Pare et al* [35]. The
271 meta-analysis also detected 9 SNPs at a suggestive threshold on chromosome 6 that were
272 located close to *RIMS1*, the regulating synaptic membrane exocytosis 1 gene, which has
273 previously been linked to angioedema in a Spanish population [36].

274 **3.3 Replication Analysis**

275 In this analysis, a Bonferroni-corrected significance threshold of 6.67x10^{-04} (0.05/75) was
276 used. Though SNP *rs*34485356 previously mapped to *BDKRB2* was observed in the standard
277 GWAS with a p-value of 0.004 and SNP *rs*500766 located in gene *PRKCQ* was observed at a
278 p-value of 0.009 in the meta-analysis, none of the SNPs in both studies were replicated at a
279 significant threshold.

280 **3.4 Gene-based Test**

281 In total, all the input SNPs in FUMA for the standard GWAS and meta-analysis were mapped
282 to 18,853 and 18,093 protein-coding genes, respectively. The gene-based test using
283 MAGMA for the standard GWAS thus considered a Bonferroni-corrected significance
284 threshold of 2.65x10^{-06} and 2.76x10^{-06} for the two tests, respectively. None of the genes

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

285 considered were found to be significant. **Tables IIS** and **IIIS** (*supplementary material*) list the
286 top 10 genes highlighted by MAGMA in each analysis, respectively, while **Figures 4S** and **5S**
287 (*supplementary material*) are the corresponding Manhattan plots.
288

289 4. Discussion

290 Our results highlight the importance of African populations to detect novel variants and
291 potentially replicate preliminary signals from other populations. To our knowledge, this is
292 the largest GWAS to investigate AE-ACEI in a diverse African cohort on the continent. The
293 underrepresentation of continental African populations in GWAS is concerning [37]. This
294 may lead to healthcare disparities once GWAS results are translated into clinical relevance,
295 as well as limit our understanding of the still-missing heritability that continues to plague
296 GWAS and impact the accuracy of predicting drug responses in diverse populations [38]. In
297 the context of ACEI use, we have highlighted the influence that early epidemiological
298 evidence from African American studies has had on international hypertension guidelines
299 and have warned against the potential pitfalls of extrapolating this very limited data to all
300 continental African populations [6].
301 In this study, we have performed both a standard GWAS analysis in the South African
302 population and meta-analysed our study with an African American and European American
303 cohort from Vanderbilt (Nashville, Tennessee) and Marshfield (Wisconsin). We have further
304 implemented FUMA to annotate all the SNPs and conducted a gene-based test for the
305 protein-coding genes that were found close to these SNPs. Our standard GWAS of the South
306 African cohort and the meta-analysis detected 26 SNPs and 37 SNPs at suggestive thresholds
307 (p-value<5.0×10^{-06}), respectively, which were located close to 23 genes by positional
308 mapping in FUMA. Among them, the *RIMS1* gene has been associated with non-steroidal

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

309 anti-inflammatory drug (NSAID)-induced angioedema [36]. *RIMS1* modulates G-proteins, in
310 particular those linked to the opening of calcium channels, and this has been best studied in
311 relation to the release of neurotransmitters and insulin [39]. *BDKRB1* and *BDKRB2* are both
312 G-protein coupled receptors, and therefore *RIMS1* may play a role in modulating bradykinin
313 receptor-2 sensitivity in susceptible individuals [40]. In addition, in a GWAS study of smoking
314 patterns and meta-analysis of smoking status, *Xu et al.* [41] found a significant variant
315 *rs*1334346 (p-value=8.22×10^{-09}) close to *RIMS1* that was associated with smoking behaviour
316 over time. The *CSMD1* gene, which is a complement regulatory protein linked to kallikrein in
317 pathway analyses, was also found close to the SNPs detected at a suggestive threshold and
318 has been reported by *Hallberg et al.* [34] and *Saunders et al. [42]* on the GWAS catalog.
319 *CSMD1* is linked to cough in response to ACEI drugs and to age at initiation of smoking,
320 respectively. Smoking has been epidemiologically identified as a risk factor for AE-ACEI [50],
321 but we did not capture smoking status in our clinical data. The *PRKCQ* gene on chromosome
322 10, which is associated with T-cell activation [43], was a signal highlighted in the original
323 Vanderbilt/Marshfield cohort analysis [35] to be linked to AE-ACEI. As noted in the recent
324 meta-analysis of AE-ACEI in European participants, there is now an urgent need for
325 functional data to confirm the biological role of some of these associated genes, particularly
326 those impacting bradykinin receptor sensitivity and signalling channels.

327 The main limitation of our study is the small sample size and, thus, the low power to attain
328 genome-wide significance for novel SNP associations. However, these findings highlight the
329 importance of the inclusion of African GWAS in replication and meta-analysis. The large
330 number of SNPs obtained at a suggestive threshold in both the post-imputation standard
331 GWAS and the meta-analysis further highlights the need for increased sampling on the
332 continent if African GWAS is to catch up with European GWAS.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

333 In conclusion, this study presents the largest GWAS of AE-ACEI from a continental African
334 population, with several SNPs detected at a suggestive threshold in both the post-
335 imputation GWAS and meta-analysis, including SNPs near genes with biological plausibility
336 and prior associations with drug-induced angioedema. Further work is now required to
337 increase sampling across diverse African regions to improve study power and further
338 illuminate the heritability of AE-ACEI.
339

340 **Perspectives**

341 We performed a GWAS of a South African cohort and a meta-analysis with summary
342 statistics of an African American and European American cohort. We located SNPs
343 associated with AE-ACEI at a suggestive threshold (p-value<5.0×10^{-06}) close to the *CSMD1*
344 gene, previously linked to ACEI cough, as well as the *RIMS1* and *PRKCQ* genes linked to drug-
345 induced angioedema. The study highlights the importance of African populations in meta-
346 analysis and replication studies and the need for increased sampling on the continent of
347 Africa.
348

349 **Novelty and Relevance**

350 **What is new?**

351 To our knowledge, this is the largest GWAS and meta-analysis study on AE-ACEI in a South
352 African cohort that has replicated genes linked to drug-induced angioedema.

353 **What is Relevant?**

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

354 The study identifies SNPs with suggestive significance thresholds that are associated with
355 AE-ACEI. It also highlights the need for increased sampling on the African continent to
356 ensure novel results and thus equitable healthcare when GWAS hits are translated to clinical
357 relevance.

358 **Clinical/Pathophysiological Implications?**

359 Identification of risk variants associated with AE-ACEI in African populations will better
360 inform hypertension treatment guidelines for this population.

361

362 **Acknowledgements**

363 We are grateful to the National Integrated Cyber Infrastructure System (NICIS) for their
364 Centre for High Performance Computing in South Africa (CHPC) and the University of Cape
365 Town's High-Performance Computing (HPC) facilities for providing the computing platform
366 for this study.

367 **Funding**

368 Research reported in this manuscript was supported by the South African Medical Research
369 Council with funds received from the South African Department of Science and Innovation.
370 JWM received training in research supported by the Fogarty International Center of the NIH
371 under Award Number D43 TW010559. The content is solely the responsibility of the authors
372 and does not necessarily represent the official views of the NIH.

373 **Disclosures**

374 None.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

375 **Supplementary data**

376 Supplementary Figures (**1S**-**5S**) and Tables (**IS**-**IIIS**) are available.

377 **References**

378 1. *Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479*
379 *population-based measurement studies with 19·1 million participants.* Lancet, 2017.
380 **389**(10064): p. 37-55.
381 2. van Vark, L.C., et al., *Angiotensin-converting enzyme inhibitors reduce mortality in*
382 *hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-*
383 *aldosterone system inhibitors involving 158,998 patients.* Eur Heart J, 2012. **33**(16): p.
384 2088-97.
385 3. Husain, M.J., et al., *Access to Cardiovascular Disease and Hypertension Medicines in*
386 *Developing Countries: An Analysis of Essential Medicine Lists, Price, Availability, and*
387 *Affordability.* J Am Heart Assoc, 2020. **9**(9): p. e015302.
388 4. Banerji, A., et al., *Multicenter study of patients with angiotensin-converting enzyme*
389 *inhibitor-induced angioedema who present to the emergency department.* Ann
390 Allergy Asthma Immunol, 2008. **100**(4): p. 327-32.
391 5. Stone, C., Jr. and N.J. Brown, *Angiotensin-converting Enzyme Inhibitor and Other*
392 *Drug-associated Angioedema.* Immunol Allergy Clin North Am, 2017. **37**(3): p. 483-
393 495.
394 6. Peter, J.G., N.A.B. Ntusi, and M. Ntsekhe, *Are Recommendations That Favor Other*
395 *Agents Over Angiotensin-Converting Enzyme Inhibitors in Africans With Hypertension*
396 *Justified?* Circulation, 2024. **149**(11): p. 804-806.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

397 7. Castellano, J.M., et al., *Polypill Strategy in Secondary Cardiovascular Prevention.* N
398 Engl J Med, 2022. **387**(11): p. 967-977.
399 8. Day, C., et al., *Acute angioedema in Cape Town emergency centres and a suggested*
400 *algorithm to simplify and improve management.* S Afr Med J, 2023. **113**(8): p. 51-57.
401 9. Mathey, C.M., et al., *Meta-analysis of ACE inhibitor-induced angioedema identifies*
402 *novel risk locus.* J Allergy Clin Immunol, 2024. **153**(4): p. 1073-1082.
403 10. Mu, G., et al., *Association between genetic polymorphisms and angiotensin-*
404 *converting enzyme inhibitor-induced cough: a systematic review and meta-analysis.*
405 Pharmacogenomics, 2019. **20**(3): p. 189-212.
406 11. Lee, C.J., et al., *Genetic Variants Associated with Adverse Events after Angiotensin-*
407 *Converting Enzyme Inhibitor Use: Replication after GWAS-Based Discovery.* Yonsei
408 Med J, 2022. **63**(4): p. 342-348.
409 12. Masilela, C., et al., *Cross-sectional study of the association of 5 single nucleotide*
410 *polymorphisms with enalapril treatment response among South African adults with*
411 *hypertension.* Medicine (Baltimore), 2021. **100**(46): p. e27836.
412 13. Moholisa, R.R., et al., *Association of B2 receptor polymorphisms and ACE activity with*
413 *ACE inhibitor-induced angioedema in black and mixed-race South Africans.* J Clin
414 Hypertens (Greenwich), 2013. **15**(6): p. 413-9.
415 14. Kubiniok, P., et al., *Understanding the constitutive presentation of MHC class I*
416 *immunopeptidomes in primary tissues.* iScience, 2022. **25**(2): p. 103768.
417 15. Choudhury, A., et al., *High-depth African genomes inform human migration and*
418 *health.* Nature, 2020. **586**(7831): p. 741-748.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

419 16. Flaten, H.K. and A.A. Monte, *The Pharmacogenomic and Metabolomic Predictors of*
420 *ACE Inhibitor and Angiotensin II Receptor Blocker Effectiveness and Safety.*
421 Cardiovasc Drugs Ther, 2017. **31**(4): p. 471-482.
422 17. Jajosky, R.P., et al., *ABO blood group antigens and differential glycan expression:*
423 *Perspective on the evolution of common human enzyme deficiencies.* iScience, 2023.
424 **26**(1): p. 105798.
425 18. Ali, S.A., et al., *Genomic and environmental risk factors for cardiometabolic diseases*
426 *in Africa: methods used for Phase 1 of the AWI-Gen population cross-sectional study.*
427 Glob Health Action, 2018. **11**(sup2): p. 1507133.
428 19. Ramsay, M., et al., *H3Africa AWI-Gen Collaborative Centre: a resource to study the*
429 *interplay between genomic and environmental risk factors for cardiometabolic*
430 *diseases in four sub-Saharan African countries.* Glob Health Epidemiol Genom, 2016.
431 **1**: p. e20.
432 20. Purcell, S., et al., *PLINK: a tool set for whole-genome association and population-*
433 *based linkage analyses.* Am J Hum Genet, 2007. **81**(3): p. 559-75.
434 21. Weale, M.E., *Quality control for genome-wide association studies.* Methods Mol Biol,
435 2010. **628**: p. 341-72.
436 22. Kang, H.M., et al., *Variance component model to account for sample structure in*
437 *genome-wide association studies.* Nat Genet, 2010. **42**(4): p. 348-54.
438 23. Yang, J., et al., *GCTA: a tool for genome-wide complex trait analysis.* Am J Hum
439 Genet, 2011. **88**(1): p. 76-82.
440 24. Buchmann, R. and S. Hazelhurst, *Genesis manual, University of Witwatersrand,*
441 *Johannesburg.* http://www.bioinf.wits.ac.za/software/genesis/Genesis.pdf, 2014.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

442 25. McCarthy, S., et al., *A reference panel of 64,976 haplotypes for genotype imputation.*
443 Nat Genet, 2016. **48**(10): p. 1279-83.
444 26. Sengupta, D., et al., *Performance and accuracy evaluation of reference panels for*
445 *genotype imputation in sub-Saharan African populations.* Cell Genom, 2023. **3**(6): p.
446 100332.
447 27. Das, S., et al., *Next-generation genotype imputation service and methods.* Nat Genet,
448 2016. **48**(10): p. 1284-1287.
449 28. Han, B. and E. Eskin, *Random-effects model aimed at discovering associations in*
450 *meta-analysis of genome-wide association studies.* Am J Hum Genet, 2011. **88**(5): p.
451 586-98.
452 29. Watanabe, K., et al., *Functional mapping and annotation of genetic associations with*
453 *FUMA.* Nat Commun, 2017. **8**(1): p. 1826.
454 30. Liau, Y., et al., *Pharmacogenetics of angiotensin-converting enzyme inhibitor-induced*
455 *angioedema.* Clin Exp Allergy, 2019. **49**(2): p. 142-154.
456 31. Ghouse, J., et al., *Association of Variants Near the Bradykinin Receptor B(2) Gene*
457 *With Angioedema in Patients Taking ACE Inhibitors.* J Am Coll Cardiol, 2021. **78**(7): p.
458 696-709.
459 32. Maroteau, C., et al., *Exome Sequencing Reveals Common and Rare Variants in F5*
460 *Associated With ACE Inhibitor and Angiotensin Receptor Blocker-Induced*
461 *Angioedema.* Clin Pharmacol Ther, 2020. **108**(6): p. 1195-1202.
462 33. Rasmussen, E.R., et al., *Genome-wide association study of angioedema induced by*
463 *angiotensin-converting enzyme inhibitor and angiotensin receptor blocker treatment.*
464 Pharmacogenomics J, 2020. **20**(6): p. 770-783.

medRxiv preprint doi: https://doi.org/10.1101/2024.09.13.24313664; this version posted September 15, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

465 34. Hallberg, P., et al., *Genetic variants associated with angiotensin-converting enzyme*
466 *inhibitor-induced cough: a genome-wide association study in a Swedish population.*
467 Pharmacogenomics, 2017. **18**(3): p. 201-213.
468 35. Pare, G., et al., *Genetic variants associated with angiotensin-converting enzyme*
469 *inhibitor-associated angioedema.* Pharmacogenet Genomics, 2013. **23**(9): p. 470-8.
470 36. Cornejo-García, J.A., et al., *Genome-wide association study in NSAID-induced acute*
471 *urticaria/angioedema in Spanish and Han Chinese populations.* Pharmacogenomics,
472 2013. **14**(15): p. 1857-69.
473 37. Abdellaoui, A., et al., *15 years of GWAS discovery: Realizing the promise.* Am J Hum
474 Genet, 2023. **110**(2): p. 179-194.
475 38. Hassan, R., et al., *Drug response in association with pharmacogenomics and*
476 *pharmacomicrobiomics: towards a better personalized medicine.* Brief Bioinform,
477 2021. **22**(4).
478 39. Weiss, N., et al., *Rim1 modulates direct G-protein regulation of Ca(v)2.2 channels.*
479 Pflugers Arch, 2011. **461**(4): p. 447-59.
480 40. Shen, J.K. and H.T. Zhang, *Function and structure of bradykinin receptor 2 for drug*
481 *discovery.* Acta Pharmacol Sin, 2023. **44**(3): p. 489-498.
482 41. Xu, K., et al., *Genome-wide association study of smoking trajectory and meta-*
483 *analysis of smoking status in 842,000 individuals.* Nat Commun, 2020. **11**(1): p. 5302.
484 42. Saunders, G.R.B., et al., *Genetic diversity fuels gene discovery for tobacco and alcohol*
485 *use.* Nature, 2022. **612**(7941): p. 720-724.
486 43. Salek-Ardakani, S., et al., *Differential regulation of Th2 and Th1 lung inflammatory*
487 *responses by protein kinase C theta.* J Immunol, 2004. **173**(10): p. 6440-7.

488

Table I: List of 26 SNPs that were obtained at a suggestive threshold (p-value < 5.0 x 10^{-06}) in the post-imputation standard GWAS, the corresponding list of genes they were found close to the SNPs by positional mapping, their function, and whether the SNP was genotyped or imputed.

CHR	rsID	Position	A1	A2	MAF	Pvalue	Nearest Gene	Function	Genotyped/Imputed
1	*rs*6666273	191428753	A	G	0.23	4.58×10^{-06}	*RP11-309H21.2*	intergenic	Imputed
1	*rs*4660011	241039771	C	A	0.44	1.72×10^{-06}	*RGS7*	intronic	Imputed
1	*rs*12239109	241042754	C	T	0.37	4.59×10^{-06}	*RGS7*	intronic	Genotyped
1	*rs*10926374	241047316	C	T	0.38	4.94×10^{-06}	*RGS7*	intronic	Imputed
1	*rs*7544945	241048562	T	C	0.38	4.92×10^{-06}	*RGS7*	intronic	Imputed
1	*rs*12127148	241049298	G	T	0.37	3.9×10^{-06}	*RGS7*	intronic	Imputed
5	*rs*28630061	176204086	T	C	0.16	1.27×10^{-07}	*RP11-375B1.3*	intergenic	Imputed
8	*rs*62488207	4808991	T	G	0.34	4.79×10^{-06}	***CSMD1***	intronic	Imputed
8	*rs*12544185	4812064	A	T	0.33	3.32×10^{-06}	***CSMD1***	intronic	Imputed
8	*rs*7815832	4812436	A	C	0.35	1.24×10^{-07}	***CSMD1***	intronic	Genotyped
9	*rs*142454594	10278823	A	G	0.07	1.50×10^{-06}	*PTPRD*	intronic	Imputed
9	*rs*79552273	10279110	T	C	0.07	4.91×10^{-06}	*PTPRD*	intronic	Genotyped
11	*rs*12287265	60237028	A	T	0.20	2.41×10^{-07}	*MS4A1*	UTR3	Imputed

11	*rs*75124932	60250467	C	G	0.20	6.28×10^{-07}	*MS4A12*	intergenic	Imputed
12	*rs*73409491	124545501	A	G	0.13	3.22×10^{-06}	*FAM101A*	intronic	Genotyped
12	*rs*58371925	124550518	C	T	0.14	2.69×10^{-06}	*FAM101A*	intronic	Imputed
12	*rs*58449918	124551080	G	T	0.13	2.69×10^{-06}	*FAM101A*	intronic	Imputed
12	*rs*112593781	124559622	G	A	0.14	1.34×10^{-06}	*FAM101A*	intronic	Imputed
13	*rs*116365021	34778472	G	A	0.06	4.19×10^{-06}	*SNORA25*	intergenic	Imputed
13	*rs*28810452	38841040	A	G	0.19	3.53×10^{-06}	*UFM1*	intergenic	Imputed
13	*rs*58482084	38845507	G	A	0.19	3.53×10^{-06}	*UFM1*	intergenic	Imputed
13	*rs*59296363	112101252	T	G	0.12	6.00×10^{-07}	*TEX29*	intergenic	Genotyped
14	*rs*2145156	69095279	A	G	0.08	3.39×10^{-06}	*RAD51B*	intronic	Imputed
17	*rs*73321625	45977502	T	A	0.16	1.05×10^{-06}	*SP2:AC003665.1*	ncRNA exonic	Imputed
17	*rs*73321628	45977632	G	A	0.16	1.05×10^{-06}	*SP2:AC003665.1*	ncRNA exonic	Genotyped
19	*rs*12610494	8407470	C	G	0.09	1.07×10^{-06}	*KANK3*	intronic	Imputed

***CHR-**chromosome, ***A1**–minor allele, ***A2**-reference alleles, ***MAF**-minor allele frequency

Table II: The list of 37 SNPs that were obtained at a suggestive threshold (p-value<5.0 x 10^{-06}) in the meta-analysis, the corresponding list of genes they were found close to 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/Imputed
2	*rs*6726307	72030471	G	A	0.2	$4.51{\times}10^{-06}$	*DYSF*	intergenic	Genotyped
5	*rs*3924097	120445067	T	A	0.4	$3.6{\times}10^{-06}$	*CTD-2613O8.1*	intergenic	Imputed
6	*rs*34388291	40580161	A	G	0.2	$4.31{\times}10^{-06}$	*LRFN2*	intergenic	Imputed
6	*rs*34207487	40582609	T	C	0.21	$7.23{\times}10^{-07}$	*LRFN2*	intergenic	Imputed
6	*rs*1192177	72572886	T	C	0.5	$3.01{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1192178	72573194	A	G	0.5	$3.01{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1192179	72573244	C	T	0.5	$3.01{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1763305	72576793	G	T	0.5	$4.28{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1612461	72576794	A	C	0.5	$4.28{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1147527	72579416	A	G	0.49	$3.59{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1147526	72579596	G	C	0.5	$4.28{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1192182	72581129	G	A	0.5	$4.28{\times}10^{-06}$	***RIMS1***	intergenic	Imputed
6	*rs*1147522	72583600	T	C	0.47	$1.28{\times}10^{-06}$	***RIMS1***	intergenic	Genotyped
7	*rs*6952303	119603778	T	C	0.46	$1.35{\times}10^{-06}$	*U1*	intergenic	Imputed

7	*rs*6953016	119604064	A	G	0.46	1.35×10^{-06}	*U1*	intergenic	Imputed
7	*rs*10281213	119605536	T	C	0.46	1.74×10^{-06}	*U1*	intergenic	Genotyped
7	*rs*7802501	119629586	G	A	0.46	1.35×10^{-06}	*U1*	intergenic	Genotyped
7	*rs*10236345	119631602	C	A	0.46	1.35×10^{-06}	*U1*	intergenic	Imputed
7	*rs*10257336	119635285	A	G	0.46	1.62×10^{-06}	*U1*	intergenic	Imputed
7	*rs*10247779	119639646	G	A	0.46	1.62×10^{-06}	*U1*	intergenic	Imputed
7	*rs*58094128	119651727	C	T	0.46	2.62×10^{-06}	*U1*	intergenic	Imputed
7	*rs*10245443	119656806	T	G	0.47	7.70×10^{-07}	*U1*	intergenic	Imputed
8	*rs*7815832	4812436	C	A	0.35	8.26×10^{-07}	***CSMD1***	intronic	Imputed
10	*rs*4750617	6606334	A	C	0.36	2.92×10^{-06}	***PRKCQ***	intronic	Imputed
11	*rs*12287265	60237028	A	T	0.2	1.70×10^{-07}	*MS4A1*	UTR3	Imputed
18	*rs*4553714	44298996	A	G	0.16	3.54×10^{-06}	*ST8SIA5*	intronic	Imputed
20	*rs*6021761	50776522	C	A	0.34	4.41×10^{-06}	*ZFP64*	intronic	Imputed
21	*rs*2826127	21666445	G	A	0.38	3.45×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*9981281	21666624	T	C	0.38	3.45×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1077650	21666756	A	G	0.38	4.27×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1077651	21666997	C	T	0.38	3.89×10^{-06}	*AP001171.1*	intergenic	Genotyped

21	*rs*1027063	21667752	G	C	0.38	3.89×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1027064	21667841	T	A	0.38	3.89×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1027065	21667851	C	T	0.38	4.62×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1027066	21667880	A	G	0.38	3.89×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1028981	21668483	A	G	0.38	4.27×10^{-06}	*AP001171.1*	intergenic	Imputed
21	*rs*1028982	21668534	A	G	0.38	4.09×10^{-06}	*AP001171.1*	intergenic	Imputed

***CHR-**chromosome, ***A1**–minor allele, ***A2**-reference alleles, ***MAF**-minor allele frequency.

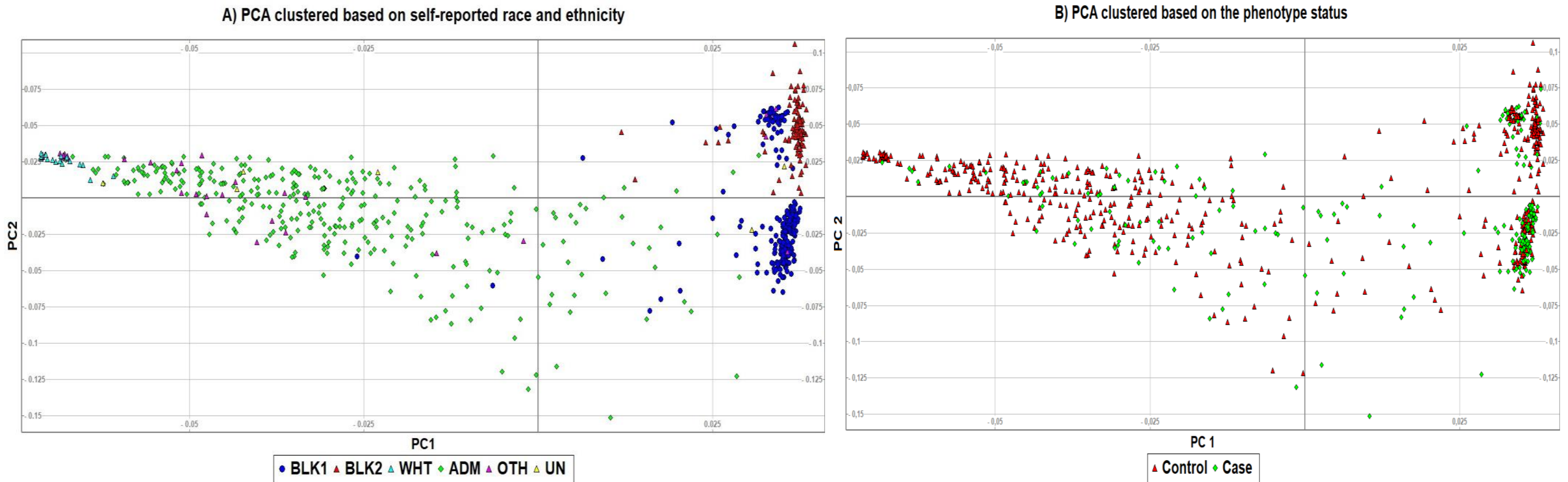

Figure 1: The PCA plot of the South African cohort clustered based on **A)** self-identified race and ethnicity: BLK1 – Black population from Western and Eastern Cape, BLK2 – Black population from Soweto, WHT – White, ADM – mixed ancestry, OTH- Other, UN – Unreported, and **B)** AE-ACEI status. This highlights the genomic diversity and the distribution of the cases and controls in study cohort.

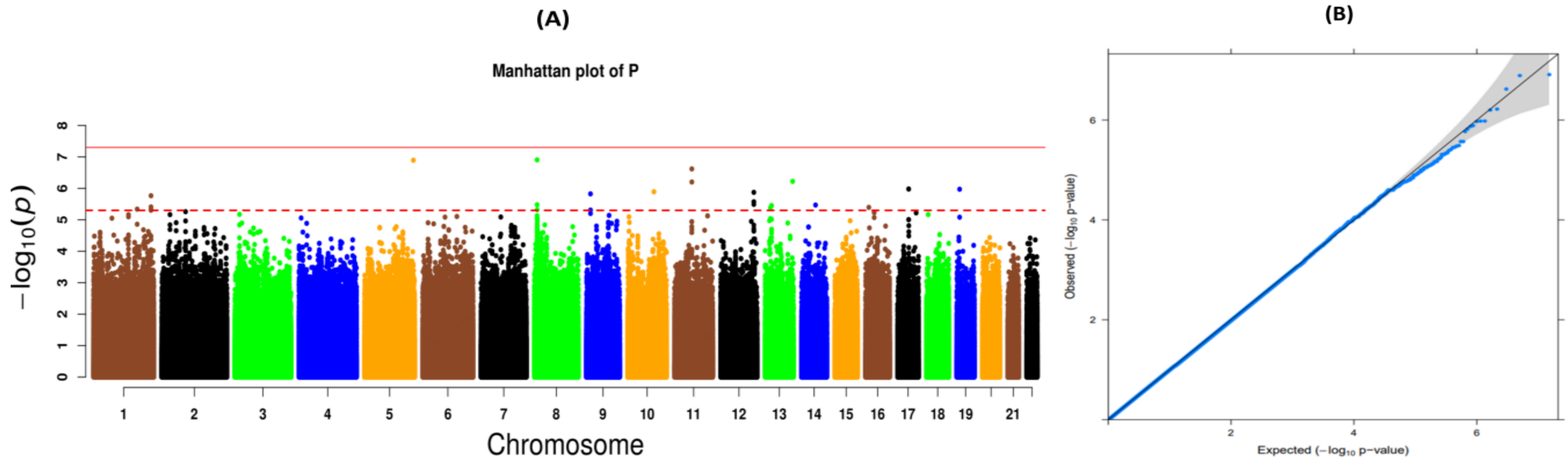

Figure 2: A) The Manhattan plot of the standard GWAS of the South African cohort. The dashed red line corresponds to p-value=5.0x10^{-06}, while the solid line is the GWAS significance threshold p-value=5.0x10^{-08}. **B)** The corresponding QQ plot of the p-values of the standard GWAS (λ=0.99).

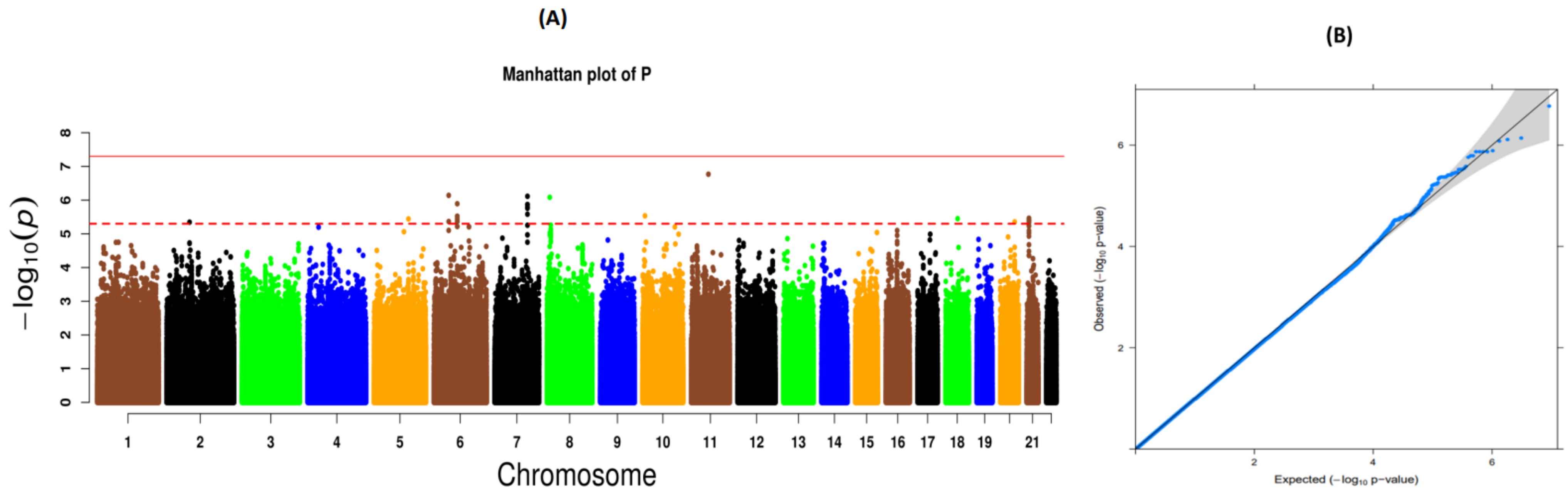

Figure 3: A) The Manhattan plot of the meta-analysis of the South African and Vanderbilt/Marshfield cohort summary statistics. The dashed red line corresponds to p-value=$5.0\text{x}10^{-06}$, while the solid line is the GWAS significance threshold p-value=$5.0\text{x}10^{-08}$. **B)** The corresponding QQ plot of the p-values of the standard GWAS (λ=0.99).