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Pharmacogenomic Indicators Associated with ACE Inhibitor–Related Cough in a Diverse UAE Population

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ABSTRACT

ACE inhibitors (ACEIs) are a cornerstone in the treatment of hypertension and cardiovascular disorders, yet a notable side effect is dry cough, affecting roughly 5%–35% of patients and often resulting in treatment discontinuation. This study sought to uncover genetic variants that may predispose individuals to ACEI-related cough and to examine how these variants correlate with ACE enzyme levels in a multi-ethnic hypertensive cohort from the UAE. Participants were selected from the UAE-based EmHeart Study (n = 900), focusing on individuals receiving ACEI therapy. In this retrospective, multi-center analysis, 107 patients were included, comprising 35 individuals who developed a cough and 72 who did not. Genotyping targeted ACE rs1799752 I/D, BDKRB2 rs1799722 (C>T), and four KCNIP4 variants (rs7675300 C>A, rs1495509 T>C, rs7661530 T>C, and rs16870989 T>A). ACE plasma concentrations were measured using a sandwich ELISA to explore functional associations. Statistical analysis indicated that the ACE rs1799752 I/D genotype, evaluated under an over-dominant model, was significantly associated with cough in patients on ACEIs ($p = 0.046$), after controlling for sex. Similarly, individuals homozygous for the T allele at KCNIP4 rs7661530 showed a higher likelihood of developing cough compared with carriers of C/T or C/C genotypes ($p = 0.035$). No meaningful associations were observed for BDKRB2 rs1799722 or the other KCNIP4 variants. Plasma ACE levels were notably lower in the cough group than in non-cough patients ($p = 0.0014$), and subgroup analysis revealed that this difference was significant within the I/D genotype ($p = 0.0061$) but not among D/D or I/I genotypes. These findings provide evidence that ACEI-induced cough is linked to the ACE rs1799752 I/D genotype and reduced ACE plasma concentrations. This study is the first in the UAE and broader Middle East to analyze these variants collectively in relation to ACEI-induced cough. Although constrained by a limited cohort size, the results offer valuable insight into genetic susceptibility to ACEI-related adverse effects among hypertensive patients.

Keywords: KCNIP4, Hypertension, Cough, ACE inhibitors, UAE, Pharmacogenomics and personalized medicine, BDKRB2, ACE I/D polymorphism

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Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) are a cornerstone therapy for hypertension and other cardiovascular conditions, acting primarily by inhibiting the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. They also reduce aldosterone secretion, promoting sodium and water excretion, which contributes to their blood pressure–lowering effects [1, 2]. Despite their clinical efficacy, ACEIs can induce adverse effects, the most notable being a dry cough, reported in 5%–35% of users [3, 4]. Certain populations, including females, older adults, and patients with pre-existing respiratory conditions such as asthma, appear to be at higher risk [3, 5]. This cough is typically dry, accompanied by a tickling or scratchy sensation in the throat, and may emerge shortly after initiation or gradually over weeks to months. While generally mild to moderate, in some cases the cough necessitates ACEI discontinuation and may persist for weeks even after stopping the medication [6].

The underlying mechanism for ACEI-induced cough is not fully understood, though bradykinin (BK) accumulation is thought to play a central role. BK, a vasodilator, lowers blood pressure via BDKRB2 receptor

binding and can provoke bronchoconstriction through the stimulation of inflammatory mediators, including prostaglandins, histamine, and leukotrienes. Normally, ACE degrades BK, but ACEI therapy blocks this pathway, leading to BK accumulation in the respiratory tract and subsequent receptor-mediated bronchospasm and cough [1, 7].

Given the unpredictable occurrence of ACEI-induced cough, genetic predisposition has been proposed as a contributing factor [8]. Several variants have been implicated in previous studies, including ACE rs1799752 (I/D), BDKRB2 rs1799722 (C>T), and multiple intronic variants within KCNIP4 (rs145489027, rs7675300, rs1495509, rs7661530, rs16870989, and rs6838116) [9-11]. The ACE rs1799752 variant consists of an insertion (I) or deletion (D) of a 287-base-pair Alu sequence in intron 16 and is known to influence ACE serum levels. Individuals with the D/D genotype generally have higher ACE levels, whereas I/D and I/I carriers exhibit intermediate and lower levels, respectively, predisposing them to BK accumulation and higher cough risk [10, 12]. Similarly, the BDKRB2 rs1799722 T/T genotype has been associated with increased cough susceptibility [11], and genome-wide studies have linked KCNIP4 intron 4 SNPs to ACEI-induced cough [9].

Although ACEI-induced cough is usually not life-threatening, it can result in therapy discontinuation, which may negatively impact blood pressure control and increase the risk of cardiovascular events such as heart failure, stroke, or renal disease [8, 13]. Despite pharmacogenomic research in cardiovascular therapy within the UAE [14 -17], no studies have investigated the genetic basis of ACEI-induced cough in Middle Eastern populations.

The present study therefore aimed to examine the association between ACEI-induced cough and specific genetic variants previously identified in other populations, namely ACE rs1799752 I/D, BDKRB2 rs1799722 (C>T), and KCNIP4 rs7675300 (C>A), rs1495509 (T>C), rs7661530 (T>C), and rs16870989 (T>A), among hypertensive adults in the UAE. We additionally evaluated the relationship between ACE plasma levels and cough, and analyzed variant distribution across ethnicities, linkage disequilibrium patterns, haplotypes, and potential gene-gene interactions. This is the first study in the UAE and Middle East to simultaneously assess all these variants in relation to ACEI-induced cough.

Materials and Methods

Study design and participants

This retrospective, multi-center study was conducted between October 2022 and October 2023 at four sites in the UAE: Tawam Hospital, The Heart Medical Center, Mediclinic Al-Ain Hospital, and Burjeel Day Surgery Center. The study adhered to the Declaration of Helsinki and received approval from the Department of Health–Abu Dhabi (DOH/CVDC/2020/1187, DOH/CVDC/2021/1519, DOH/CVDC/2022/1458, DOH/CVDC/2023/1952) and relevant institutional review boards.

Participants were selected from the EmHeart Study, the UAE's first pharmacogenomic initiative integrating genetic data into cardiovascular drug prescribing. From the original 900-patient cohort, we identified adults (≥18 years) with hypertension who had been treated with ACEIs for at least one year or had discontinued therapy due to ACEI-induced cough. Exclusion criteria included patients not receiving ACEIs, those who stopped ACEIs for non-cough side effects, patients on ACEIs for less than one year, individuals with chronic cough–associated diseases (e.g., severe asthma, COPD, GERD), secondary hypertension, or refusal to provide blood samples.

A total of 107 participants provided informed consent and were categorized into two groups: 72 patients without ACEI-induced cough who had received ACEIs for ≥1 year, and 35 patients who developed cough during ACEI therapy.

Data collection

Demographic data (age, sex, ethnicity), health behaviors (e.g., smoking), and concomitant medications were extracted from medical records. ACEI use and associated cough were confirmed through detailed EMR review and direct patient interviews using a structured questionnaire. This captured ACEI type, duration of therapy, cough onset and severity, timing patterns (day vs night), and reasons for ACEI discontinuation. **Figure 1** illustrates the participant recruitment and selection workflow.

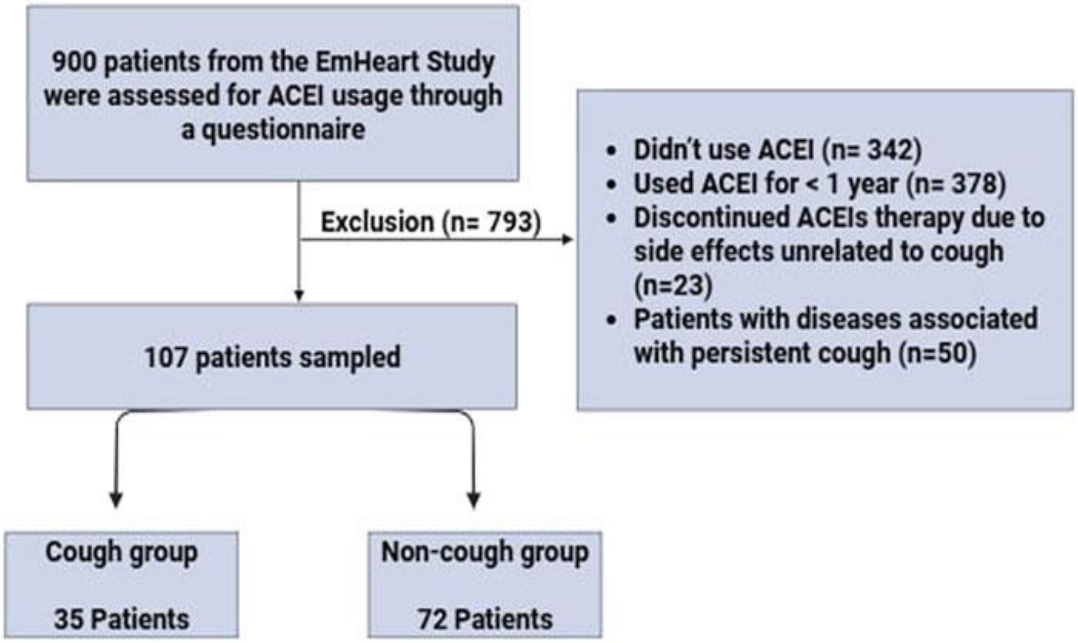


Figure 1. The flow of patient recruitment and the selection process within the study.

Blood collection and DNA preparation

Venous blood was drawn from participants into 3 mL EDTA tubes (BD Inc.) and processed for genomic DNA extraction using the QIAamp® DNA kit (Qiagen, Germany) according to the manufacturer's protocol. The concentration and purity of isolated DNA were evaluated using a Nanodrop One spectrophotometer (Thermo Fisher Scientific, USA). To obtain plasma, 500 µL of whole blood was centrifuged at 2,500 rpm for 10 minutes at room temperature, and the separated plasma was stored at −80 °C for subsequent analyses.

Genotyping of ACE, BDKRB2, and KCNIP4 variants

Target regions within ACE, BDKRB2, and KCNIP4 were amplified using primers designed via Primer3 (https://primer3.ut.ee/), with sequences provided in **Table 1**. PCR reactions were prepared in a final volume of 25 µL, containing 13.5 µL of nuclease-free water, 1× 10× PCR buffer, 1× 5× Q-Solution, 200 µM dNTP mix, 1.5 U of Taq polymerase, 100–200 pmol of each primer, and 296–350 ng of template DNA. Amplification was performed on a SimpliAmp thermal cycler (Thermo Fisher Scientific, Waltham, MA, USA) over 32 cycles, with the following program: initial denaturation at 95 °C for 5 min, denaturation at 95 °C for 45 s, annealing at 57 °C or 60 °C for 45 s, extension at 72 °C for 45 s, and a final elongation at 72 °C for 7 min. PCR products were resolved on a 1.5% agarose gel containing ethidium bromide and visualized using UV illumination.

Table 1. List of variants and their PCR oligonucleotide primers.

Gene and Target	Forward primer	Reverse primer	Ann. Temp (°C)	Product size (bp)
ACE rs1799752 (g.63488543_63488544ins-11TGAGACGGAGTCTCGCTCTGTCGCCCATACAGTCACTTTT)	5′-CTGGAGACCACTCCCATCCTTTCT-3′	5′-GATGTGGCCATCACATTCGTCAGAT-3′	60	190 (D), 490 (I)
BDKRB2 rs1799722 (g.96204802C>T)	5′- GGGCTACGCAAACATGGAAA-3′	5′- AGTTTGTCCTCCCAGCAGAG-3′	57	399
KCNIP4 rs7675300 (g.21383914C>A)	5′- TTTGCATGGAGGGGATCACT-3′	5′- GGCTGTGAGGTAGGACTGAG-3′	57	456
KCNIP4 rs1495509 (g.21391993T>C)	5′-TCCCCTGCAATCACATTCCT-3′	5′- TGCCAGAGTTCCCTTCCATT-3′	60	371
KCNIP4 rs7661530 (g.21349637T>C)	5′-ATGTGTCATTCAGCAGCGTC-3′	5′- GAGAATGCTAGCCCTTGTGC-3′	60	380

KCNIP4 rs16870989 (g.21385141T>A)	5′-GGGCGCTTTGTC TCTTTTCT-3′	5′- TTTATCCCACCT CCTGCTGG-3′	60	375

Ann. Temp: Annealing Temperature, bp: base pairs, ACE: angiotensin converting enzyme, BDKRB2: Bradykinin Receptor B2, KCNIP4: Potassium Voltage-Gated Channel Interacting Protein 4, D: deletion, I: insertion.

Detection of genetic variants

Genotyping of the ACE rs1799752 I/D polymorphism was performed by analyzing PCR products on an agarose gel **(Figure 2).** The presence of the D allele was indicated by a 190 bp fragment, while the I allele corresponded to a 490 bp fragment; samples carrying both alleles exhibited both bands, indicating heterozygosity. For BDKRB2 rs1799722 (C>T) and KCNIP4 variants (rs7675300 C>A, rs1495509 T>C, rs7661530 T>C, and rs16870989 T>A), genotypes were determined using Sanger sequencing. Sequencing reactions were carried out with the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Waltham, MA, USA), and the resulting data were read on a 3130xl Genetic Analyzer (Applied Biosystems, Waltham, MA, USA). Sequence traces were inspected and interpreted using Chromas software (Technelysium, Australia).

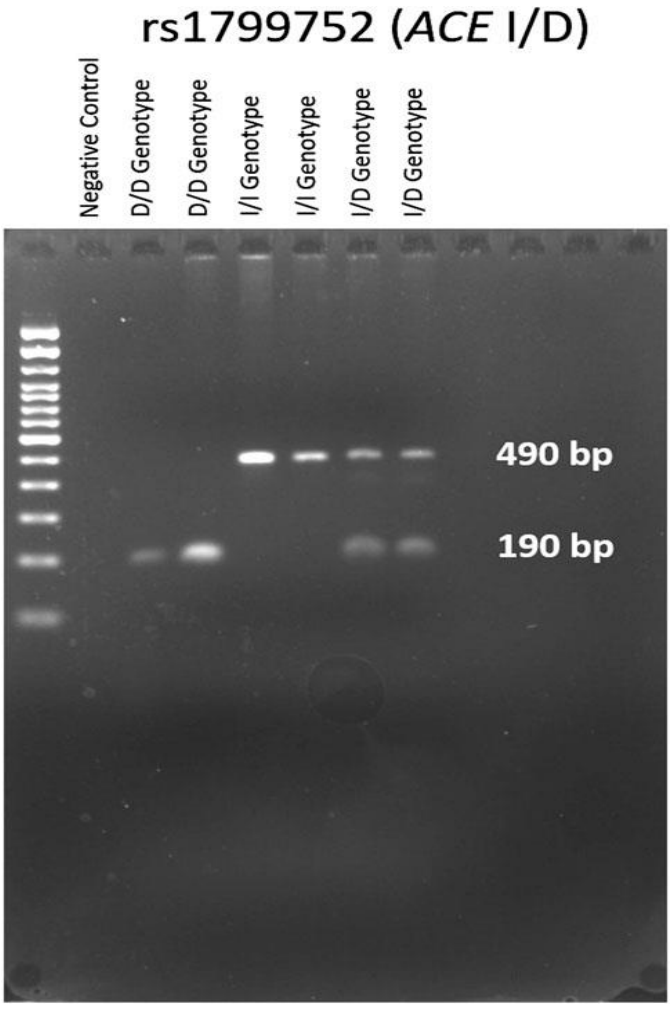


Figure 2. Representative agarose gel depicting ACE rs1799752 (I/D) genotypes: D/D, I/I, and I/D.

Measurement of ACE plasma levels

Plasma ACE concentrations were quantified using a sandwich ELISA approach with the Human ACE ELISA Kit (ab263889; Abcam, Cambridge, UK), strictly adhering to the manufacturer's instructions. To prevent interference from ACE inhibitor therapy, assays were conducted only on samples from patients who were either not currently taking ACEIs or had discontinued the medication at least five days prior to blood collection. Each plasma sample was measured in quadruplicate to improve reliability and reduce experimental variability.

Distribution of variants across ethnic groups

To examine potential ethnicity-specific patterns, genotype frequencies were stratified according to the main ethnic groups represented in the cohort. Ethnicity data were initially obtained from medical records and verified directly with participants to ensure accuracy.

Linkage Disequilibrium (LD) analysis

LD analysis was conducted among the four KCNIP4 variants (rs7675300 C>A, rs1495509 T>C, rs7661530 T>C, and rs16870989 T>A) to assess non-random associations between alleles at different loci.

Haplotype analysis

Haplotype construction was performed for the KCNIP4 variants to evaluate the combined influence of these alleles on the risk of ACEI-induced cough.

Variant interaction analysis

To investigate potential synergistic or interactive effects among genetic loci, variant interaction analysis was carried out incorporating ACE rs1799752 (I/D), BDKRB2 rs1799722 (C>T), and KCNIP4 rs7675300 (C>A).

Statistical analysis

All statistical analyses were performed using SNPStats and SPSS version 29.0.2.0 (SPSS Inc., USA) [18], while ELISA data were analyzed using GraphPad Prism version 10.2.2 (GraphPad Software, Boston, MA, USA). Categorical variables and Hardy-Weinberg equilibrium (HWE) were evaluated via the Chi-square (χ^2) test. Continuous variables were expressed as mean ± standard deviation. Associations between genetic variants and ACEI-induced cough were calculated as odds ratios (OR) with 95% confidence intervals (CI), considering $p < 0.05$ as statistically significant. For plasma ACE levels, the Mann-Whitney test was used to compare values between cough and non-cough groups, as well as within groups stratified by ACE rs1799752 I/D genotype, while the Kruskal–Wallis test was applied to assess differences across all three ACE I/D genotypes. Chi-square tests also evaluated the distribution of variants across ethnic groups, with adjusted residuals exceeding +2 or below −2 highlighting specific genotype-ethnicity associations. LD among KCNIP4 variants was quantified using D′ values on the SHEsisPlus platform [19]. Haplotype frequencies were derived using SNPStats, and logistic regression calculated ORs and 95% CIs relative to reference haplotypes. Variant interaction analysis examined combined genetic effects on the likelihood of developing ACEI-induced cough.

Results and Discussion

Baseline demographics and clinical characteristics

A total of 107 hypertensive adults from the EmHeart cohort who were receiving ACEIs were included in this study. The overall prevalence of ACEI-induced cough was 32.7% (35 patients). **Table 2** summarizes the demographic characteristics, comorbidities, and types of ACEIs administered. The majority of participants were male (73.8%), with no significant difference in sex distribution between cough and non-cough groups (P = 0.18). The mean age across all patients was 53.79 ± 11.13 years. Participants were ethnically diverse, classified into five groups: Arabs, East Asians, Indians, Africans, and others. Coronary heart disease affected 48.6% of the cohort evenly across both groups. Diabetes was slightly more prevalent among patients who experienced cough (54.3%) compared to those who did not (50%). Chronic kidney disease was the least common comorbidity, present in 5.6% of participants, with similar proportions in both groups.

Table 2. Patient baseline characteristics of ACEI-induced cough and non-cough groups.

Baseline characteristics	Total patients (n = 107)	Cough (n = 35)	Non-cough (n = 72)	P value
Age (years)				
	53.79 ± 11.13	53.37 ± 12.34	54 ± 10.57	0.78
Gender				
Male	79 (73.8%)	23 (65.7%)	56 (77.8%)	0.18

Female	28 (26.2%)	12 (34.3%)	16 (22.2%)	
Smoking				
	37 (34.6%)	11 (31.4%)	26 (36.1%)	0.633
Blood Pressure Reading				
Systolic pressure (mmHg)	129.98 ± 16.13	127.37 ± 16.82	131.25 ± 15.74	0.24
Diastolic pressure (mmHg)	78.51 ± 12	75.41 ± 12.3	79.97 ± 11.74	0.069
Ethnicity				
Arab	53 (49.5%)	17 (48.6%)	36 (50%)	0.89
East Asian	13 (12.1%)	3 (8.5%)	10 (13.9%)	0.53
Indians	38 (35.5%)	15 (42.9%)	23 (31.9%)	0.26
African	2 (1.87)	0	2 (2.8%)	1
Others	1 (0.93%)	0	1 (1.4%)	1
Comorbidities				
Hypertension	107 (100%)	35 (100%)	72 (100%)	NA
Coronary heart disease	52 (48.6%)	17 (48.6%)	35 (48.6%)	0.99
Chronic kidney disease	6 (5.6%)	2 (5.7%)	4 (5.6%)	1
Diabetes Mellitus	55 (51.4%)	19 (54.3%)	36 (50%)	0.67
ACEIs type				
Perindopril	52 (48.5%)	17 (48.6%)	35 (48.6%)	0.99
Lisinopril	46 (43%)	17 (48.6%)	29 (40.3%)	0.25
Ramipril	7 (6.5%)	0	7 (9.7%)	0.09
Enalapril	1 (1%)	1 (2.8%)	0	0.32
Captopril	1 (1%)	0	1 (1.4%)	1

ap < 0.05 was considered significant. ACEIs: Angiotensin Converting Enzyme Inhibitors.

Within the cohort, perindopril emerged as the predominant ACE inhibitor, prescribed to 48.5% of participants, with nearly identical usage among those who experienced cough (48.6%) and those who did not (48.6%). Lisinopril was the second most common, representing 43% of all prescriptions, slightly more frequent in the cough group (48.6%) than the non-cough group (40.3%). Ramipril was administered to 6.5% of patients, exclusively in the non-cough group. The least prescribed agents were enalapril and captopril, each accounting for just 1% of usage, with enalapril limited to the cough group and captopril to the non-cough group. Overall, no significant differences were observed in ACEI type distribution between the two groups.

Among patients who developed ACEI-induced cough, therapy duration, timing of symptom onset, and discontinuation patterns are summarized in **Table 3**. Treatment length varied, most commonly ranging from 2–6 months (25.7%) or 1–7 weeks (22.8%), with fewer patients receiving ACEIs for longer periods. Cough onset was heterogeneous: 28.5% reported symptoms within the first week of therapy, while 25.7% experienced onset between 1–7 weeks or 2–6 months. Nocturnal coughing was predominant, affecting 60% of cases. The majority (94.3%) stopped ACEI therapy due to the cough, which was generally tolerable, and in all instances, symptoms resolved within seven days of discontinuation.

Table 3. Cough group ACEIs usage information.

Characteristics	Cough (n = 35)
Duration of ACEIs use	
1–7 weeks	8 (22.8%)
2–6 months	9 (25.7%)
7–11 months	7 (20%)
1–5 years	7 (20%)
>5 years	4 (11.4%)
Time from start of ACEIs to occurrence of cough	
<1 week	10 (28.5%)
1–7 weeks	9 (25.7%)
2–6 months	9 (25.7%)
7–11 months	4 (11.4%)
1–5 years	3 (8.5%)
Time of cough	

All the day	14 (40%)
Night	21 (60%)
ACEIs discontinuation	
Discontinued	33 (94.3%)
Continued	2 (5.7%)
Drug discontinuation decision (n = 33)	
Patient's self-own	5 (15.1%)
Under Physicians supervision	28 (84.8%)
Cough disappearance after ACEIs discontinuation (n = 33)	
<1 week	33 (100%)

ACEIs: Angiotensin Converting Enzyme Inhibitors.

Association between ACE, BDKRB2, and KCNIP4 Variants and ACEI-Induced Cough

The observed genotype distributions for ACE rs1799752 (I/D), BDKRB2 rs1799722 (C>T), and KCNIP4 variants (rs7675300 C>A, rs1495509 T>C, rs7661530 T>C, and rs16870989 C>A) conformed to Hardy-Weinberg equilibrium in both the cough and non-cough groups ($p > 0.05$)**. Tables 4–9** display the unadjusted analyses alongside results adjusted for gender as a potential confounding factor. Associations were examined under multiple inheritance models, including codominant, dominant, recessive, and over-dominant frameworks.

Table 4. Association between *ACE* rs1799752 I/D variant and ACEI-induced cough.

Model	Genotype	Total (n = 107)	Cough (n = 35)	Non-cough (n = 72)	OR (95% CI)[a]	P-value[a]	OR (95% CI)[b]	P-value[b]
Codominant	D/D	44 (41%)	11 (31.4%)	33 (45.8%)	1.00	0.15	1.00	0.13
	I/D	41 (38%)	18 (51.4%)	23 (31.9%)	2.35 (0.94–5.89)		2.52 (0.99–6.45)	
	I/I	22 (21%)	6 (17.1%)	16 (22.2%)	1.12 (0.35–3.59)		1.25 (0.38–4.06)	
Dominant	D/D	44 (41%)	11 (31.4%)	33 (45.8%)	1.00	0.15	1.00	0.11
	I/D + I/I	63 (59%)	24 (68.6%)	39 (54.2%)	1.85 (0.79–4.32)		2.01 (0.84–4.81)	
Recessive	D/D + I/D	85 (79%)	29 (82.9%)	56 (77.8%)	1.00	0.54	1.00	0.62
	I/I	22 (21%)	6 (17.1%)	16 (22.2%)	0.72 (0.26–2.05)		0.77 (0.27–2.19)	
Over-dominant	D/D + I/I	66 (62%)	17 (48.6%)	49 (68.1%)	1.00	0.053	1.00	0.046
	I/D	41 (38%)	18 (51.4%)	23 (31.9%)	2.26 (0.99–5.16)		2.34 (1.01–5.41)	
Allele frequency	D	129 (0.6)	40 (0.57)	89 (0.62)	1.21 (0.68–2.17)	0.61	---	---
	I*	85 (0.4)	30 (0.43)	55 (0.38)				

OR: odds ratio; CI: confidence interval; *: Risk allele.

acrude analysis; bAdjusted for gender analysis. $p < 0.05$ was considered significant. Significant values are indicated by Bold font.

Table 5. Association between *BDKRB2* rs1799752 (C>T) variant and ACEI-induced cough.

Model	Genotype	Total (n = 107)	Cough (n = 35)	Non-cough (n = 72)	OR (95% CI)[a]	P-value[a]	OR (95% CI)[b]	P-value[b]
Codominant	C/C	37 (35%)	9 (25.7%)	28 (38.9%)	1.00	0.29	1.00	0.37
	C/T	53 (49%)	21 (60%)	32 (44.4%)	2.04 (0.80–5.18)		1.92 (0.75–4.91)	
	T/T	17 (16%)	5 (14.3%)	12 (16.7%)	1.30 (0.36–4.69)		1.27 (0.35–4.61)	
Dominant	C/C	37 (35%)	9 (25.7%)	28 (38.9%)	1.00	0.17	1.00	0.22
	C/T + T/T	70 (65%)	26 (74.3%)	44 (61.1%)	1.84 (0.75–4.49)		1.74 (0.70–4.29)	
Recessive	C/C + C/T	90 (84%)	30 (85.7%)	60 (83.3%)	1.00	0.75	1.00	0.77
	T/T	17 (16%)	5 (14.3%)	12 (16.7%)	0.83 (0.27–2.58)		0.85 (0.27–2.65)	
	C/C + T/T	54 (51%)	14 (40%)	40 (55.6%)	1.00	0.13	1.00	0.17

Over-dominant	C/T	53 (49%)	21 (60%)	32 (44.4%)	1.87 (0.83–4.26)		1.77 (0.77–4.06)	
Allele frequency	C	127 (0.59)	39 (0.56)	88 (0.61)	1.25 (0.7–2.23)	0.54	---	---
	T*	87 (0.41)	31 (0.44)	56 (0.39)				

OR: odds ratio; CI: confidence interval; *: Risk allele.

acrude analysis; bAdjusted for gender analysis. p < 0.05 was considered significant.

Table 6. Association between *KCNIP4* rs7675300 (C>A) variant and ACEI-induced cough.

Model	**Genotype**	**Total (n = 107)**	**Cough (n = 35)**	**Non-cough (n = 72)**	**OR (95% CI)[a]**	**P-value[a]**	**OR (95% CI)[b]**	**P-value[b]**
Codominant	C/C	50 (47%)	13 (37.1%)	37 (51.4%)	1.00	0.23	1.00	0.16
	C/A	43 (40%)	15 (42.9%)	28 (38.9%)	1.52 (0.63–3.71)		1.75 (0.69–4.39)	
	A/A	14 (13%)	7 (20%)	7 (9.7%)	2.85 (0.84–9.67)		3.23 (0.92–11.34)	
Dominant	C/C	50 (47%)	13 (37.1%)	37 (51.4%)	1.00	0.16	1.00	0.097
	C/A + A/A	57 (53%)	22 (62.9%)	35 (48.6%)	1.79 (0.78–4.09)		2.05 (0.87–4.84)	
Recessive	C/C + C/A	93 (87%)	28 (80%)	65 (90.3%)	1.00	0.15	1.00	0.13
	A/A	14 (13%)	7 (20%)	7 (9.7%)	2.32 (0.74–7.24)		2.45 (0.77–7.74)	
Over-dominant	C/C + A/A	64 (60%)	20 (57.1%)	44 (61.1%)	1.00	0.7	1.00	0.55
	C/A	43 (40%)	15 (42.9%)	28 (38.9%)	1.18 (0.52–2.68)		1.29 (0.56–2.98)	
Allele frequency	C	143 (0.67)	41 (0.59)	102 (0.71)	1.72 (0.95–3.12)	0.1	---	---
	A*	71 (0.33)	29 (0.41)	42 (0.29)				

OR: odds ratio; CI: confidence interval; *: Risk allele.

acrude analysis; bAdjusted for gender analysis. p < 0.05 was considered significant.

Table 7. Association between *KCNIP4* rs1495509 (T>C) variant and ACEI-induced cough.

Model	Genotype	Total (n = 107)	Cough (n = 35)	Non-cough (n = 72)	OR (95% CI)[a]	P-value[a]	OR (95% CI)[b]	P-value[b]
Codominant	T/T	52 (49%)	15 (42.9%)	37 (51.4%)	1.00	0.5	1.00	0.38
	T/C	42 (39%)	14 (40%)	28 (38.9%)	1.23 (0.51–2.97)		1.35 (0.55–3.31)	
	C/C	13 (12%)	6 (17.1%)	7 (9.7%)	2.11 (0.61–7.34)		2.44 (0.68–8.74)	
Dominant	T/T	52 (49%)	15 (42.9%)	37 (51.4%)	1.00	0.41	1.00	0.3
	T/C + C/C	55 (51%)	20 (57.1%)	35 (48.6%)	1.41 (0.62–3.18)		1.56 (0.67–3.59)	
Recessive	T/T + T/C	94 (88%)	29 (82.9%)	65 (90.3%)	1.00	0.28	1.00	0.22
	C/C	13 (12%)	6 (17.1%)	7 (9.7%)	1.92 (0.59–6.22)		2.12 (0.64–6.99)	
Over-dominant	T/T + C/C	65 (61%)	21 (60%)	44 (61.1%)	1.00	0.91	1.00	0.82
	T/C	42 (39%)	14 (40%)	28 (38.9%)	1.05 (0.46–2.39)		1.10 (0.48–2.55)	
Allele frequency	T	146 (0.68)	44 (0.63)	102 (0.71)	1.44 (0.78–2.62)	0.3	---	---
	C*	68 (0.32)	26 (0.37)	42 (0.29)				

OR: odds ratio; CI: confidence interval; *: Risk allele.

acrude analysis; bAdjusted for gender analysis. p < 0.05 was considered significant.

Table 8. Association between *KCNIP4* rs7661530 (T>C) variant and ACEI-induced cough.

Model	Genotype	Total (n = 107)	Cough (n = 35)	Non-cough (n = 72)	OR (95% CI)[a]	P-value[a]	OR (95% CI)[b]	P-value[b]
Codominant	C/C	56 (52%)	16 (45.7%)	40 (55.6%)	1.00	0.11	1.00	0.082
	T/C	35 (33%)	10 (28.6%)	25 (34.7%)	1.00 (0.39–2.55)		1.02 (0.40–2.63)	

	T/T	16 (15%)	9 (25.7%)	7 (9.7%)	3.21 (1.02–10.10)		3.55 (1.10–11.40)	
Dominant	C/C	56 (52%)	16 (45.7%)	40 (55.6%)	1.00	0.34	1.00	0.3
	T/C + T/T	51 (48%)	19 (54.3%)	32 (44.4%)	1.48 (0.66–3.34)		1.55 (0.68–3.52)	
Recessive	C/C + T/C	91 (85%)	26 (74.3%)	65 (90.3%)	1.00	0.035	1.00	0.025
	T/T	16 (15%)	9 (25.7%)	7 (9.7%)	3.21 (1.08–9.54)		3.52 (1.16–10.65)	
Over-dominant	C/C + T/T	72 (67%)	25 (71.4%)	47 (65.3%)	1.00	0.52	1.00	0.52
	T/C	35 (33%)	10 (28.6%)	25 (34.7%)	0.75 (0.31–1.81)		0.75 (0.31–1.82)	
Allele frequency	T*	67 (0.31)	28 (0.40)	39 (0.23)	1.79 (0.98–3.28)	0.07	---	---
	C	147 (0.69)	42 (0.60)	105 (0.73)				

OR: odds ratio; CI: confidence interval; *: Risk allele.

acrude analysis; bAdjusted for gender analysis. p < 0.05 was considered significant. Significant values are indicated by Bold font.

Table 9. Association between *KCNIP4* rs16870989 (T>A) variant and ACEI-induced cough.

Model	Genotype	Total (n = 107)	Cough (n = 35)	Non-cough (n = 72)	OR (95% CI)[a]	P-value[a]	OR (95% CI)[b]	P-value[b]
Codominant	T/T	50 (47%)	13 (37.1%)	37 (51.4%)	1.00	0.31	1.00	0.2
	T/A	44 (41%)	16 (45.7%)	28 (38.9%)	1.63 (0.67–3.93)		1.84 (0.74–4.59)	
	A/A	13 (12%)	6 (17.1%)	7 (9.7%)	2.44 (0.69–8.60)		2.91 (0.79–10.66)	
Dominant	T/T	50 (47%)	13 (37.1%)	37 (51.4%)	1.00	0.16	1.00	0.097
	T/A + A/A	57 (53%)	22 (62.9%)	35 (48.6%)	1.79 (0.78–4.09)		2.05 (0.87–4.84)	
Recessive	T/T + T/A	94 (88%)	29 (82.9%)	65 (90.3%)	1.00	0.28	1.00	0.22
	A/A	13 (12%)	6 (17.1%)	7 (9.7%)	1.92 (0.59–6.22)		2.12 (0.64–6.99)	
Over-dominant	T/T + A/A	63 (59%)	19 (54.3%)	44 (61.1%)	1.00	0.5	1.00	0.41
	T/A	44 (41%)	16 (45.7%)	28 (38.9%)	1.32 (0.58–2.99)		1.42 (0.62–3.27)	
Allele frequency	T	144 (0.67)	42 (0.60)	102 (0.71)	1.62 (0.89–2.94)	0.15	---	---
	A*	70 (0.33)	28 (0.40)	42 (0.29)				

OR: odds ratio; CI: confidence interval; *: Risk allele.

acrude analysis; bAdjusted for gender analysis. p < 0.05 was considered significant.

ACE rs1799752 (I/D) variant

Analysis of the ACE rs1799752 (I/D) variant **(Table 4)** revealed that, within the cough group, 31.4% of patients carried the D/D genotype, 51.4% were heterozygous I/D, and 17.2% were homozygous I/I. In contrast, among participants without cough, 46% were D/D, 32% I/D, and 22% I/I. The I allele frequency was 0.43 in cough patients and 0.38 in the non-cough group. Although the I/I genotype (p = 0.15) and I allele (p = 0.61) did not individually show significant association with cough, adjusting for gender in an over-dominant model demonstrated that heterozygous I/D individuals had a markedly higher risk of ACEI-induced cough than the combined homozygotes (OR = 2.34; p = 0.046).

BDKRB2 rs1799722 (C>T) variant

For the BDKRB2 rs1799722 (C>T) variant **(Table 5)**, genotype distributions in the cough group were 26% C/C, 60% C/T, and 14% T/T, while in the non-cough group, they were 39%, 44%, and 17%, respectively. The T allele occurred at a frequency of 0.44 in the cough group versus 0.39 in those without cough. Neither crude nor gender-adjusted analyses demonstrated a statistically meaningful association with ACEI-induced cough (allele: p = 0.54; T/T genotype: crude p = 0.29, adjusted p = 0.37).

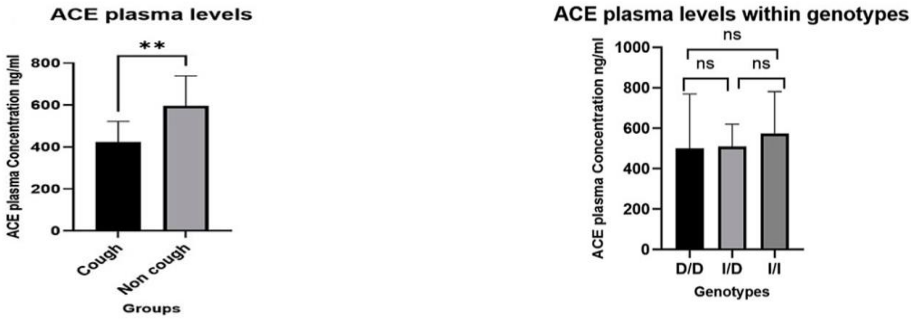
KCNIP4 variants

- rs7675300 (C>A): Among cough patients, genotypes were 37% C/C, 43% C/A, and 20% A/A; non-coughers showed 51%, 39%, and 10% respectively **(Table 6)**. The A allele was more frequent in cough patients (0.41 vs 0.29), but neither the allele nor homozygous A/A genotype reached significance (allele: p = 0.10; A/A: crude p = 0.23, adjusted p = 0.16).

- rs1495509 (T>C): In the cough group, 43% were T/T, 40% T/C, and 17% C/C; among non-coughers, 51%, 39%, and 10% respectively **(Table 7).** The C allele frequency was 0.37 versus 0.29, yet associations remained non-significant in both crude and gender-adjusted analyses.
- rs7661530 (T>C): Cough patients had 26% T/T, 29% T/C, and 45% C/C; non-coughers were 10%, 35%, and 55%, respectively **(Table 8).** The T allele was enriched in cough patients (0.40 vs 0.23), indicating elevated risk. While codominant analysis did not reach significance (p = 0.11), the recessive model demonstrated that T/T carriers had a significantly higher likelihood of developing ACEI-induced cough compared to C/C and T/C combined (crude OR = 3.21, p = 0.035; adjusted OR = 3.52, p = 0.025).
- rs16870989 (T>A): In cough patients, 37% were T/T, 46% T/A, and 17% A/A; non-coughers showed 51%, 39%, and 10% **(Table 9).** The A allele frequency was 0.40 vs 0.29, but no significant associations were detected (allele: p = 0.15; A/A: crude p = 0.31, adjusted p = 0.20).

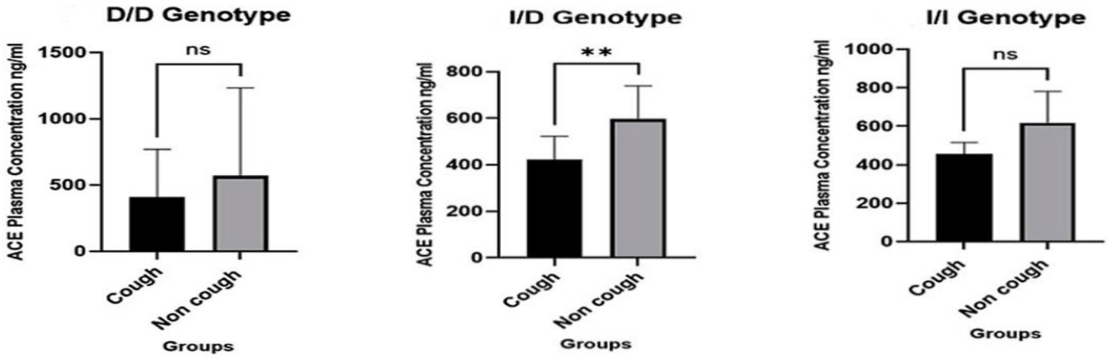
ACE plasma levels

ACE concentrations were measured in 28 plasma samples (14 per group). Median ACE levels were substantially lower in patients experiencing cough (423 ng/mL) compared to those without cough (595.8 ng/mL; p = 0.0014, **Figure 3a**), suggesting that reduced ACE may contribute to cough susceptibility. When stratified by genotype, median plasma levels were 499.9 ng/mL (D/D), 510.4 ng/mL (I/D), and 574.8 ng/mL (I/I), with no statistically significant differences among genotypes overall (p = 0.43, **Figure 3b**). Comparing plasma levels between cough and non-cough groups by genotype revealed that only the I/D genotype exhibited a significant reduction in the cough group (437.8 ng/mL vs 593.6 ng/mL; p = 0.0061, **Figure 4b**). No significant differences were observed for D/D (408.1 vs 569.8 ng/mL; p = 0.54, **Figure 4a**) or I/I genotypes (455.4 vs 616.8 ng/mL; p = 0.19, **Figure 4c**).



a) b)

Figure 3. (a) ACE plasma levels in patients with and without ACEI-induced cough. (b) ACE plasma concentrations stratified by ACE rs1799752 I/D genotypes (D/D, I/D, I/I). ** denotes a statistically significant difference (p < 0.05); ns indicates no significant difference.



a) b) c)

Figure 4. ACE plasma levels compared across ACE rs1799752 I/D genotypes between patients with and without ACEI-induced cough. (a) D/D genotype, (b) I/D genotype, (c) I/I genotype. ** indicates statistically significant differences (p < 0.05); ns denotes no significance.

Distribution of variants across ethnic groups

The study cohort of 107 patients represented diverse ethnicities: Arabs (n = 53), Indians (n = 38), East Asians (n = 13), Africans (n = 2), and others (n = 1).

For ACE rs1799752 (I/D), a significant difference was observed among ethnic groups ($p < 0.01$), with Arabs displaying a higher-than-expected D/D genotype frequency (adjusted residual = +4.4) and Indians a lower-than-expected frequency (adjusted residual = -4.4). BDKRB2 rs1799722 (C>T) showed no significant ethnic variation ($p = 0.15$).

Among KCNIP4 variants, rs7675300 (C>A) exhibited significant ethnic differences ($p = 0.04$), with Arabs having more C/C genotypes than expected (adjusted residual = +3.2), Indians fewer (adjusted residual = -2.7), and East Asians a higher A/A frequency (adjusted residual = +3). For rs1495509 (T>C), genotype distribution differed significantly ($p = 0.04$), with Arabs enriched for T/T (adjusted residual = +2.8) and Indians for T/C (adjusted residual = +2.5). The rs7661530 (T>C) variant did not show significant ethnic differences ($p = 0.23$), whereas rs16870989 (T>A) did ($p = 0.04$), with Arabs showing a higher T/T frequency (adjusted residual = +3.2) and Indians a higher T/A frequency (adjusted residual = +2.2).

Linkage disequilibrium analysis

LD assessment among the four KCNIP4 variants (rs7675300, rs1495509, rs7661530, rs16870989) demonstrated strong non-random associations, indicating frequent co-inheritance. Notably, rs7675300 and rs16870989 were in complete LD ($D' = 1$), and rs7675300 and rs1495509 showed very strong LD ($D' = 0.97$). High linkage was also observed between rs1495509 and rs16870989, suggesting these alleles are commonly inherited together in the cohort **(Figure 5).**

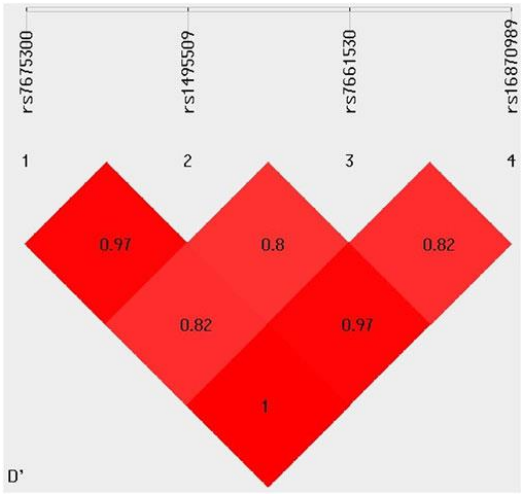


Figure 5. Linkage disequilibrium analysis of *KCNIP4* variants.

Haplotype association with ACEI-Induced cough

Haplotypes were derived from the LD patterns observed among the KCNIP4 variants. The most common haplotype, CTCT, occurred at a frequency of 0.6241 and was used as the reference for analysis. While certain haplotypes showed elevated odds ratios suggesting a possible increased risk of ACEI-induced cough, none reached statistical significance. The overall haplotype association test also indicated no significant relationship, with a global p-value of 0.38. Detailed findings are provided in **Table 10.**

Table 10. KCNIP4 haplotype frequencies and their association with ACEI-induced cough.

Haplotype	rs7675300 (C>A)	rs1495509 (T>C)	rs7661530 (T>C)	rs16870989 (T>A)	Frequency	OR (95% CI)	P-value
1	C	T	C	T	0.6241	1.00	---
2	A	C	T	A	0.2698	1.58 (0.86–2.91)	0.14
3	A	C	C	A	0.0432	1.52 (0.33–6.94)	0.59
4	C	T	T	T	0.0394	2.61 (0.60–11.43)	0.21
5	A	T	C	A	0.0102	3.55 (0.22–58.09)	0.38
Rare	*	*	*	*	0.0133	5.12 (0.40–66.05)	0.21

Global haplotype association p-value: 0.38

OR: odds ratio; CI: confidence interval.

Interaction analysis of genetic variants

Owing to the strong linkage disequilibrium among the four KCNIP4 SNPs, rs7675300 (C>A) was selected as the representative for interaction testing. Analysis results, presented in **Table 11**, revealed no significant effects: the combination of ACE rs1799752 (I/D) with BDKRB2 rs1799722 (C>T) showed a p-value of 0.870, ACE rs1799752 (I/D) with KCNIP4 rs7675300 (C>A) had a p-value of 0.841, and the three-way interaction of ACE rs1799752 (I/D), BDKRB2 rs1799722 (C>T), and KCNIP4 rs7675300 (C>A) yielded a p-value of 0.965. These findings indicate that these variants do not exhibit any statistically meaningful synergistic influence on ACEI-induced cough susceptibility.

Table 11. Variant interaction analysis between *ACE*, *BDKRB2*, and *KCNIP4* variants.

Variants interaction	B	p-value	OR (95% CI)
rs1799752 and rs1799722	−0.157	0.870	0.855 (0.131–5.580)
rs1799752 and rs7675300	−0.178	0.841	0.837 (0.147–4.755)
rs1799752, rs1799722 and rs7675300	0.034	0.965	1.034 (0.232–4.605)

B; regression coefficient, OR; odds ratio, CI; confidence interval.

This study sheds light on the genetic factors contributing to ACEI-induced cough in a multi-ethnic population, validating previously suggested variants and exploring their impact on patients who developed this adverse effect. We also assessed the influence of a common ACE gene variant on circulating ACE levels.

ACE inhibitors are widely used to manage hypertension and cardiovascular conditions, yet a persistent dry cough affects up to 35% of users. This adverse effect is unpredictable, dose-independent, and can occur anytime from one week to a year after therapy initiation. While often mild to moderate, in some cases the cough is severe enough to necessitate discontinuation of ACEIs and switching to alternatives like angiotensin receptor blockers (ARBs) [8, 20, 21].

Diagnosing ACEI-induced cough remains challenging due to the lack of specific biomarkers, and its underlying mechanism is not fully elucidated. Bradykinin (BK) and substance P are thought to play central roles: ACE normally degrades BK, but ACEIs lead to its accumulation in the respiratory tract, where it binds BDKRB2 receptors, triggering histamine release, bronchospasm, and cough. The selective occurrence of cough in some patients suggests a genetic predisposition, potentially involving ACE I/D, BDKRB2, and KCNIP4 variants, indicating a multifactorial rather than a single-gene mechanism [9, 21-23].

Previous studies on these variants have shown inconsistent results. A meta-analysis reported a significant link between the ACE rs1799752 I/I genotype and ACEI-induced cough in East Asian populations [24], whereas studies in African and Caucasian cohorts found no such association [13, 25]. Regarding BDKRB2 rs1799722 (C>T), Japanese studies indicated that the T/T genotype and T allele were associated with cough in females [11, 26], yet no associations were observed in Korean and South African populations [25, 27]. GWAS have linked KCNIP4 variants rs7675300, rs1495509, rs7661530, and rs16870989 with ACEI-induced cough [9], but other studies, such as one in a Swedish cohort, found no significant associations [3].

Given these discrepancies and the lack of data from Middle Eastern populations, we examined the relationships between these variants and ACEI-induced cough in the UAE population, alongside assessing ACE plasma levels and the effect of ACE rs1799752 genotypes on these levels. This is the first study to evaluate all six variants in a single analysis within this population. Our results indicate that BDKRB2 rs1799722 and KCNIP4 variants rs7675300, rs1495509, and rs16870989 showed no significant association with cough. Conversely, the ACE rs1799752 I/D genotype was significantly associated with an increased cough risk in the over-dominant model after adjusting for gender, and the KCNIP4 rs7661530 T/T genotype was associated with higher cough risk under codominant and recessive models, both before and after gender adjustment.

Analysis of ACE plasma levels revealed lower levels in patients with cough compared to those without ($p < 0.01$), suggesting that reduced ACE activity may contribute to cough development. Notably, within the rs1799752 I/D genotype, patients without cough had significantly higher ACE levels than those with cough ($p < 0.01$), whereas

no significant differences were seen for D/D or I/I genotypes. This pattern highlights the I/D genotype as a potential determinant of ACE plasma levels and susceptibility to ACEI-induced cough.

Ethnicity-stratified analyses showed significant variation in genotype distributions. Arab participants had higher frequencies of the ACE D/D genotype and KCNIP4 C/C and T/T genotypes, while East Asian and Indian participants displayed alternative genotype distributions. These findings underscore the importance of considering ethnic background in pharmacogenomic research and highlight the need for population-specific studies to interpret genetic associations with ACEI-induced cough.

Linkage analysis demonstrated strong LD among the four KCNIP4 variants, forming haplotype blocks; however, haplotype-based association analysis showed no significant relationship with cough (global $p = 0.38$). Likewise, interaction analysis between ACE, BDKRB2, and KCNIP4 variants did not reveal any synergistic effects on cough risk.

Limitations include the small sample size, which restricted adjustment for additional covariates such as age, smoking, comorbidities, and ACEI type, and the absence of multiple testing correction. These factors warrant cautious interpretation of the findings.

In conclusion, this study represents the first assessment of these six variants in relation to ACEI-induced cough in an Arab and Middle Eastern population. Our findings suggest that the ACE rs1799752 I/D and KCNIP4 rs7661530 T/T genotypes may influence susceptibility, and ACE plasma levels are lower in patients with cough, particularly in those with the I/D genotype. Replication in larger, ethnically diverse cohorts is needed, alongside functional studies to clarify the mechanistic role of these variants and support personalized therapeutic strategies.

Conclusion

This study sheds light on the genetic contribution to ACEI-induced cough, focusing on variants in ACE, BDKRB2, and KCNIP4. Among the investigated variants, the ACE rs1799752 I/D and KCNIP4 rs7661530 T/T genotypes were linked to a higher likelihood of developing cough, suggesting that inherited genetic differences play a significant role in patient susceptibility. In addition, individuals without cough exhibited higher ACE plasma concentrations, particularly those with the I/D genotype, pointing to a potential influence of enzyme levels on symptom manifestation. These findings highlight the interplay between genetic makeup and ACE activity in determining the risk of ACEI-induced cough and may support more personalized approaches to ACEI therapy.

Limitations

Several factors may affect the interpretation of these results. The modest sample size limits the statistical power and generalizability, and replication in larger cohorts is needed. Moreover, the analysis was largely restricted to patients taking perindopril and lisinopril, which may limit extrapolation to other ACE inhibitors such as enalapril or ramipril due to their lower representation in the study population.

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