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Association of insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme gene *(ACE)* with ST segment elevation myocardial infarction and factors risk in Western Algeria: case-control study

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SOUHRN

Kontext: Kardiovaskulární onemocnění jsou celosvětově hlavní příčinou mortality. Akutní koronární syndrom (AKS) je multifaktoriální onemocnění, které je výsledkem interakce mezi environmentálními a genetickými faktory. Polymorfismus I/D genu pro ACE byl již zmíněn v souvislosti s rizikem rozvoje AKS. Cílem naší studie případů a kontrol byl zhodnotit zkoumat možnou souvislost mezi polymorfismem inzerce/delece (I/D) genu pro angiotenzin konvertující enzym (*ACE*) a infarktem myokardu s elevacemi úseku ST (STEMI) ve vzorku pacientů ze západního Alžírska.
Metody: Provedli jsme studii případů a kontrol zahrnující 169 jedinců, zdravých osob a 99 pacientů po STEMI. ACE I/D polymorfismus byl zjišťován metodou polymerázové řetězové reakce se specifickými primery.
Výsledky: Prevalence genotypů DD, ID a II v naší skupině pacientů byla 48,48 %, 43,43 % a 8,08 % ve srovnání s 2,85 %, resp. 35,75 % a 61,42 % v kontrolní skupině. Tyto výsledky prokázaly, že frekvence genotypu DD a alely D je statisticky významně vyšší v případech s AKS než u kontrol ($\chi^2 = 67,63$; $p = 0,0001$) ($p < 0,05$; OR = 9,03; 95% CI 5,41–15,01). Rovněž jsme nezjistili žádnou statisticky významnou souvislost mezi ACE I/D polymorfismem a tradičními rizikovým faktory spojenými se STEMI, jako jsou věk, pohlaví, diabetes, hypertenze a kouření.
Závěr: Závěrem lze konstatovat, že uvedené výsledky naznačují statisticky významnou souvislost mezi I/D polymorfismem genu pro ACE a rizikem rozvoje AKS ve zkoumaném vzorku.

Keywords:
Acute coronary syndrome (ACS)
Case-control study
I/D *ACE* gene polymorphism
PCR
Western Algerian population

ABSTRACT

Background: Cardiovascular diseases are the leading cause of mortality worldwide. Acute coronary syndrome (ACS) is a multifactorial disease resulting from the interaction of environmental and genetic factors. The I/D polymorphism of the *ACE* gene has been associated with the risk of developing acute coronary syndrome (ACS). Our case-control study aimed to access the potential association of insertion/deletion (I/D) *ACE* (angiotensin converting enzyme) gene polymorphism and ST segment elevation myocardial infarction (STEMI) among a sample of Algerian patients from Western Algeria.
Methods: We conducted a case-control study comprising 169 individuals including 70 healthy subjects and 99 STEMI patients. *ACE* I/D polymorphism was detected by polymerase chain reaction with specific primers.
Results: The prevalence of DD, ID, and II genotypes in our patients group were 48.48%, 43.43%, and 8.08%respectively vs 2.85%, 35.75% and 61.42% in the control group. These results showed that the frequency of the DD genotype and the D allele was significantly higher in cases with ACS compared to controls ($\chi^2 = 67.63$; P = 0.0001) (P < 0.05, OR = 9.03, 95% CI: 5.41-15.01). We also noticed that there was no significant association between *ACE* I/D polymorphisms and STEMI-relevant traditional risk factors like age, gender, diabetes mellitus, hypertension, smoking.
Conclusion: In conclusion, these results suggest a statistically significant association between the I/D polymorphism of the *ACE* gene and the risk of developing ACS in the studied sample.

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Introduction

Acute myocardial infarction (AMI) remains a major cause of morbidity and mortality worldwide and in Algeria specifically.[1,2] The ST segment elevation myocardial infarction (STEMI) is one of the most severe types of acute AMI. It primarily occurs due to the rupture of atherosclerotic plaques. The pathogenesis of MI involves a complex interplay between genetic and environmental factors with an estimated heritability ranging from 50 to 60%.[1] Among the genetic factors, the angiotensin-converting enzyme (*ACE*) gene has attracted considerable attention due to its role in the renin-angiotensin-aldosterone system (RAAS) and its involvement in cardiovascular diseases.

The renin-angiotensin-aldosterone system (RAAS) is a crucial regulator of blood pressure and exerts a significant influence on the development and progression of coronary artery disease (CAD). Serving as one of the primary regulatory systems in cardiovascular physiology, the RAAS plays a pivotal role in various aspects, including cardiovascular remodeling, maintenance of vascular tone, and sodium homeostasis.[3]

Different studies have suggested that polymorphisms occurring in the components of RAAS play a crucial role in the development and progression of coronary artery disease (CAD) in certain individuals.[4] Among these components, the angiotensin-converting enzyme (ACE) has garnered significant attention, leading to frequent investigations into the potential association between *ACE* insertion/deletion (I/D) polymorphisms and cardiovascular disease like hypertension[5] and CAD.[6,7]

The *ACE* gene, located on chromosome 17q23, encodes the angiotensin-converting enzyme responsible for the conversion of angiotensin I to angiotensin II. This enzyme is also involved in the inactivation of bradykinin, a vasodilator peptide. The *ACE* gene contains a common insertion/deletion (I/D) polymorphism in intron 16, characterized by the presence or absence of a 287 base pair Alu repeat sequence. The D allele is associated with higher *ACE* activity and increased levels of angiotensin II, which promotes vasoconstriction, inflammation, oxidative stress, and vascular remodeling.[8] Angiotensin II is also known to be an essential regulator of proliferation, migration, and hypertrophy of vascular smooth muscle cells, increasing thus its association with CAD and MI risk of occurrence.[9]

The association between the *ACE* I/D polymorphism and the risk of MI has been extensively investigated in various populations. Indeed, it was reported in many studies that the DD genotype is associated with various cardiovascular diseases, including myocardial infarction.[10,11] However, results from other association studies between *ACE* I/D polymorphism and MI revealed conflicting results[11,12,13] and did not consider the relationship between the *ACE* I/D polymorphism and MI.

Thus, we aim in this study to investigate the association between the *ACE* I/D polymorphism and the risk of MI in Algerian patients from the city of Oran.

Methods

Population study

We have enrolled a case-control study from 2021 until 2022 where we have included 169 Algerian subjects. All the implicated subjects have already given their written consent to participate in this study which was conducted according to the declaration of Helsinki Principles and approved by the local ethics committee.

The study covered all the files of patients hospitalized for ACS with ST segment elevation myocardial infarction (STEMI) at the Cardiology Service of the University Hospital Center of the Oran city. We included all patients of both sexes and of all ages in the study. We excluded all incomplete records or patients who presented with traumatic or non-ischemic chest pain from this study. Data is collected using pre-established forms. All patients had undergone an electrocardiogram (ECG), a cardiac ultrasound and a biological assessment (blood count, creatinine, glycemia, troponin, cholesterol, triglyceride, prothrombin level, activated partial thromboplastin time). The control group was selected from healthy blood donors.

Diagnosis of STEMI

The diagnosis of ACS was done according to the American College of Cardiology/ American Heart Association (ACC/AHA) definitions.[14–16] We classified ACS patients according to the electrocardiographic results as having ST-segment elevations in the case of the presence of clinical symptoms of myocardial infarction lasting ≥30 min with ECG changes of either ST elevation of at least 0.1 mv in two contiguous precordial leads or two limb leads, or the presence of a new left bundle branch block (LBBB). Moreover, troponin I levels and the myocardial band (MB) fraction of total creatinine phosphokinase (CPK) were measured in order to confirm myocardial cell death. We excluded from this study all incomplete records or patients who presented with traumatic or non-ischemic chest pain.

Risk factors assessment

We used a standardized questionnaire to record data as socio-demographic characteristics. Risk factors of each patient were identified. The identification of dyslipidemia was based on whether patient is taking lipid lowering drugs or biochemically indicated by total cholesterol > 240 mg/dL, triglycerides >150 mg/dL, low density lipoproteins (LDL) >130 mg/dL and high-density lipoproteins (HDL) <50 mg/dL, <40 mg/dL for females and males respectively. Diabetes mellitus was defined as either the patient is under medication or presenting clinical symptoms and having plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) or fasting blood sugar ≥126 mg/dL (7.0 mmol/L)]. Hypertension was also defined as having systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or being on antihypertensive treatment. Moreover, other risk factors like smoking and hormonal status for women were assessed.

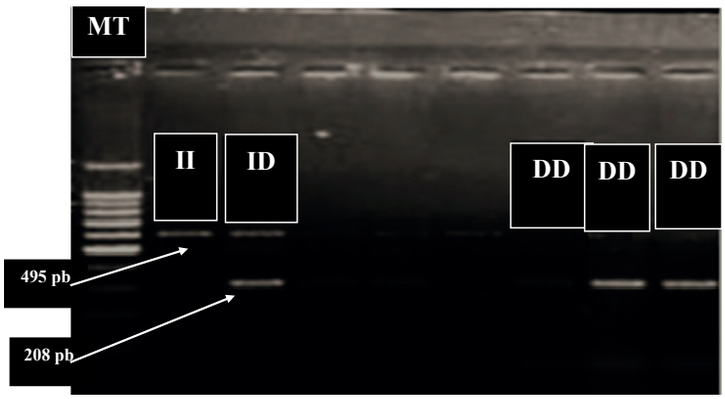

Fig. 1 – Representative gel picture of ACE I/D polymorphism in 2% agarose gel.

Genotyping methods

Genomic DNA was extracted using five milliliters of blood samples using Salting-out method as previously described by Miller et al.[17] and quantified following spectrophotometric analysis. We used polymerase chain reaction (PCR) to genotype DNA samples for the I/D *ACE* polymorphism, as previously described Chou et al.[18] using primers flanking the polymorphic region of intron 16 with the following primer sequences: 5' TGGAGACCACTCCCATCCTTTCT-3' and 5'-CAGGTCTTCATATTTCCGATGTGG-3'. Reactions were carried out in 25-µL volumes containing 50 ng of genomic DNA, 0,4 µM of each primer, 200 mM dNTP, 1X Taq polymerase buffer and 1U Taq DNA polymerase (Wiragen, Algeria). The cycling conditions for I/D were set as follows: an initial denaturation at 94 °C for 4 minutes, 35 cycles at 94 °C for 30 seconds, 58 °C for 30 seconds, and 72 °C for 60 seconds, and a final extension at 72 °C for 10 minutes. Electrophoresis of the amplified products in 2% agarose gel allowed detection of a 495-base pair (bp) fragment (insertion) and a 208-bp fragment (deletion) (**Fig. 1**).

Statistical analysis

Data analysis was done with the help of an (SPSS Inc., Chicago, Illinois, USA) version 26.0. Clinical characteristics of all the subjects are expressed as means ± SD. Descriptive statistics were used to analyze all studied variables such as the socio-demographic characteristics, anthropometric measurements, biological parameters. A two-tailed Student's *t*-test was used to compare continuous variables between the two groups. Allele frequencies were calculated from genotype frequencies and they were compared between the two groups using chi-squared (χ^2) statistics. Odds ratio (OR) were calculated to estimate the association between genotypes and MI risk with a confidence interval (CI) of 95%. Hardy–Weinberg's equilibrium was checked by a χ^2 test. *P*-value <0.05 was considered statistically significant.

Results

Allelic and genotypic distribution of I/D ACE gene polymorphism in cases and controls

Table 1 presents the distribution of alleles and genotypes of the *ACE* I/D polymorphism among cases and controls. Among cases, the frequencies of the *ACE* genotypes II, ID, and DD were 8.08%, 43.4%, and 48.4%, respectively. In contrast, the control group exhibited genotype frequencies of 61.42% for II, 35.71% for ID, and 2.85% for DD.

A statistically significant difference was observed in the genotype distribution between cases and controls (χ^2 = 67.63, p = 0.0001).

Additionally, the frequency of the D allele was significantly higher among cases (70%) compared to controls (29%) (p < 0.05, OR = 9.03, 95% CI: 5.41–15.01). These findings suggest a strong association between the D allele and acute coronary syndrome.

Association between *ACE* genotypes and traditional risk factors

Age distribution

No significant association was identified between age categories and *ACE* genotypes (p = 0.847). The DD genotype was more prevalent in the oldest age group (>68 years, 58.33%), but the overall distribution of genotypes across age groups was balanced, indicating no clear relationship between *ACE* polymorphism and age in this cohort (**Table 2**).

Gender distribution

Gender differences did not significantly correlate with *ACE* genotypes (p = 0.546). Males were more represented in the ID (48.38%) and DD (41.93%) genotypes, whereas females were slightly more prevalent in the DD genotype

Table 1 – Allelic and genotypic distribution of I/D *ACE* polymorphism among cases and controls

Variables	Patients N (%) N = 99	Controls N (%) N = 70	χ^2	*p*-value	OR 95% CI
II	8 (8.08%)	43 (61.42%)	67.63	0.0001*	
ID	43 (43.43%)	25 (35.75%)			
DD	48 (48.48%)	02 (2.85%)			
I allele	59 (29.79%)	111 (79.28%)	80,34	0.0001*	9.08 (5.41–15.01)
D allele	139 (70.20%)	29 (20.71%)			

Table 2 – Traditional risk factors according to *ACE* genotypes distribution among STEMI cases

	STEMI cases (N = 99)			
	II n (%)	ID n (%)	DD n (%)	*p*-value
Age (years)				
<45	1 (4.54%)	10 (45.45%)	11 (50%)	
46–56 57–67 >68	1 (3.22%) 4 (11.76%) 1 (8.33%)	15 (48.38%) 14 (41.17%) 4 (33.33%)	15 (48.38%) 16 (47.05%) 7 (58.33%)	0.847
Gender Male Female	 3 (9.67%) 4 (5.88%)	 15 (48.38%) 28 (41.17%)	 13 (41.93%) 36 (52.94%)	0.546
Hypertension Yes No	 3 (4.54%) 4 (12.12%)	 27 (40.9%) 16 (48.48%)	 36 (54.54%) 13 (39.39%)	0.213
Diabetes Yes No	 0 (0%) 7 (11,11%)	 18 (50%) 25 (39.68%)	 18 (50%) 31 (49.2%)	0.102
Dyslipidemia Yes No	 2 (4.44%) 5 (9.25%)	 26 (57.77%) 17 (31.48%)	 17 (37.77%) 32 (59.25%)	0.03*
Smoking Yes No	 3 (13.04%) 4 (5.26%)	 11 (47.82%) 32 (42.1%)	 9 (39.13%) 40 (52.63%)	0.317

(52.94%). These results suggest that gender does not significantly influence the distribution of *ACE* genotypes among STEMI patients.

Hypertension

Hypertension prevalence was highest in the DD genotype group (54.54%), followed by ID (40.90%) and II (4.54%). Despite this trend, no significant association was observed between hypertension and *ACE* genotypes ($p = 0.213$). This aligns with prior studies indicating a potential, but non-conclusive, link between the DD genotype and hypertension.

Diabetes mellitus

No significant association was detected between diabetes and *ACE* genotypes ($p = 0.102$). Notably, no diabetes cases were observed in the II genotype group (0%), whereas diabetes was evenly distributed among ID and DD genotypes (50% each). These findings may suggest population-specific variability regarding the impact of *ACE* polymorphism on diabetes risk.

Dyslipidemia

A statistically significant association was identified between dyslipidemia and *ACE* genotypes ($p = 0.03$). The ID genotype exhibited the highest prevalence of dyslipidemia (57.77%), followed by DD (37.77%) and II (4.44%). Conversely, non-dyslipidemic individuals were more likely to belong to the DD group (59.25%). These results suggest a potential role of the ID genotype in lipid metabolism disturbances and its contribution to STEMI development.

Smoking

No significant association was found between smoking status and *ACE* genotypes ($p = 0.317$). However, smokers were more prevalent in the II genotype group (13.04%) compared to the ID (47.82%) and DD (39.13%) genotypes. Non-smokers predominated across all genotypes, particularly in the DD group (52.63%). This suggests that *ACE* polymorphism does not significantly influence smoking behavior in this cohort.

Discussion

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide, accounting for 31% of total global mortality.[18] Coronary heart disease is a polygenic and multifactorial disease characterized by the formation of atherosclerotic plaque in the coronary vessels.[3]

Many studies reported the contribution of genetic variations in the pathogenesis of cardiac disorders including hypertension[5] and myocardial infarction.[6] Angiotensin I-converting enzyme *(ACE*) gene insertion/deletion (I/D) polymorphism, characterized by an insertion/deletion of a 287 bp nucleotide sequence at intron 16, has been extensively studied and several studies reported its eventual association with MI by modifying *ACE* activity and contributing to enhanced plaque vulnerability, ulceration and thrombosis.[20–22] However, the contribution of *ACE* gene polymorphism as a risk factor of CAD remains controversial with conflicting results.[22,23]

In our study, we found that the percentage of DD genotype was higher in cases compared to controls (OR

= 9, 03, 95% CI: 5.41–15.01) which was confirmed in different studies of African and Western populations.[6,24–27] However, other Asian studies reported the lowest percentage of the DD genotype compared to the II and ID genotypes.[28–31]

Similarly, Dai et al.[32] reported in a case-control study that the ACE DD genotype is an independent risk factor for STEMI. This result was also confirmed in many studies of different populations.[33,34] Furthermore, we noticed no significant association between conventional risk factors of CAD like advanced age, diabetes mellitus, hypertension, smoking, and *ACE* genotypes. Indeed, Moorthy et al.[35] did not find any association between these risk factors and *ACE* genotypes in an Indian cohort of 934 STEMI patients. Nevertheless, other studies reported a significant association between *ACE* genotypes and hypertension,[5,36–38] diabetes mellitus and its complications.[39–42] However, we have found a significant association between dyslipidemia and *ACE* genotypes in STEMI patients. This result has been already confirmed in many studies.[39]

It should be noted that the increased risk of ACS in DD subjects could be the consequence of chronic coronary vasoconstriction or a predisposition to spasm linked to the action of *ACE* on the vasoactive peptides that it metabolizes. In the presence of coronary vasoconstriction, a myocardial infarction could occur in an atherosclerotic lesion of smaller size than in the absence of vasoconstriction.

These conflicting results underscore the intricate nature of association studies in complex diseases like acute coronary syndrome (ACS). Several factors have been proposed to explain these inconsistencies, such as differing selection criteria for control and disease groups, uncontrollable environmental influences within populations, variations in genetic and ethnic backgrounds, and age disparities among the subjects. Additionally, emerging evidence suggests that epigenetic mechanisms, particularly DNA methylation, may play a key role in the etiology of coronary artery disease (CAD). Alterations in DNA methylation patterns can affect gene expression, potentially contributing to the development of CAD by modulating pathways linked to inflammation, lipid metabolism, and vascular function.[43]

Conclusion

The *ACE* DD genotype was observed to correlate with the severity of CAD compared to the II or ID genotypes in Algerian patients. This research marks the first study in Algeria exploring the association between a genetic polymorphism and coronary artery lesion severity, thus adding valuable insights to the role of *ACE* I/D polymorphism in AMI pathophysiology within Algerian populations. Consequently, considering *ACE* I/D status could enhance the comprehensive assessment and aggressive management of AMI patients.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical statement

The study was conducted in accordance with Helsinki declaration.

Informed consent

The patients signed the informed consent.

References

1. Dai X, Wiernek S, Evans JP, Runge MS. Genetics of coronary artery disease and myocardial infarction. World J Cardiol 2016;8:1–23.
2. Amrani-Midoun A LN, Djebaili T, et al. Gender differences in epidemiology and risk factors of acute coronary syndrome in Algerian patients of the Oran city: descriptive cross-sectional study. Cor Vasa 2023;65:496–500.
3. Das SR, Alexander KP, Chen AY, et al. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50,149 patients with ST-Segment elevation myocardial infarction results from the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol 2011;58:2642–2650.
4. Amrani A, Baba Hamed MB. Relationship between angiotensinogen gene T174 M polymorphism and essential hypertension in a sample of Algerian population: case control study. Journal of Medical Sciences 2014;14:168–173.
5. Amrani A, Baba Hamed MB, Mesli Talebbendiab F. Association study between some renin-angiotensin system gene variants and essential hypertension in a sample of Algerian population: case control study. Ann Biol Clin (Paris) 2015;73:557–563.
6. Cambien F, Poirier O, Lecerf L, et al. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. Nature 1992;359:641–644.
7. Lin C, Yang HY, Wu CC, et al. Angiotensin-converting enzyme insertion/deletion polymorphism contributes high risk for chronic kidney disease in Asian male with hypertension--a meta-regression analysis of 98 observational studies. PloS one 2014;9:e87604.
8. Sakhteh M, Poopak B, Amirizadeh N, et al. Polymorphism and synergism of angiotensin-converting enzyme (ACE) and plasminogen activator inhibitor-1 (PAI-1) genes in coronary artery disease. J Renin Angiotensin Aldosterone Syst 2015;16:1168–1174.
9. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol Rev 2000;52:639–672.
10. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043–1052.
11. Zintzaras E, Raman G, Kitsios G, Lau J. Angiotensin-converting enzyme insertion/deletion gene polymorphic variant as a marker of coronary artery disease: a meta-analysis. Arch Intern Med 2008;168:1077–1089.
12. Agerholm-Larsen B, Nordestgaard BG, Tybjaerg-Hansen A. ACE gene polymorphism in cardiovascular disease: meta-analyses of small and large studies in whites. Arterioscler Thromb Vasc Biol 2000;20:484–492.
13. Meroufel DN, Mediene-Benchekor S, Dumont J, et al. A study on the polymorphisms of the renin-angiotensin system pathway genes for their effect on blood pressure levels in males from Algeria. J Renin Angiotensin Aldosterone Syst 2014;15:1–6.
14. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration

with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2013;82:E1–E27.
15. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:2022–2060.
16. Jneid H, Addison D, Bhatt DL, et al. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circ Cardiovasc Qual Outcomes 2017;10:e000032.
17. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988;16:1215.
18. Chou HT, Tsai CH, Tsai FJ. Association between angiotensin I-converting enzyme gene insertion/deletion polymorphism and risk of rheumatic heart disease. Jpn Heart J 2004;45:949–957.
19. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation 2015;131:e29–e322.
20. Cambien F. The angiotensin-converting enzyme (ACE) genetic polymorphism: its relationship with plasma ACE level and myocardial infarction. Clin Genet 1994;46(1 Spec No):94–101.
21. Chen Y, Dong S, He M, et al. Angiotensin-converting enzyme insertion/deletion polymorphism and risk of myocardial infarction in an updated meta-analysis based on 34993 participants. Gene 2013;522:196–205.
22. Samani NJ, Thompson JR, O'Toole L, et al. A meta-analysis of the association of the deletion allele of the angiotensin-converting enzyme gene with myocardial infarction. Circulation 1996;94:708–712.
23. Palmer BR, Pilbrow AP, Yandle TG, et al. Angiotensin-converting enzyme gene polymorphism interacts with left ventricular ejection fraction and brain natriuretic peptide levels to predict mortality after myocardial infarction. J Am Coll Cardiol 2003;41:729–736.
24. Mehri S, Mahjoub S, Farhati A, et al. Angiotensinogen gene polymorphism in acute myocardial infarction patients. J Renin Angiotensin Aldosterone Syst 2011;12:42–47.
25. Martinez-Quintana E, Chirino R, Nieto-Lago V, et al. Prognostic value of ACE I/D, AT1R A1166C, PAI-I 4G/5G and GPIIIa a1/a2 polymorphisms in myocardial infarction. Cardiol J 2014;21:229–237.
26. Amara A, Mrad M, Sayeh A, et al. The Effect of ACE I/D Polymorphisms Alone and With Concomitant Risk Factors on Coronary Artery Disease. Clin Appl Thromb Hemost 2018;24:157–163.
27. Hmimech W, Idrissi HH, Diakite B, et al. Impact of I/D polymorphism of angiotensin-converting enzyme (ACE) gene on myocardial infarction susceptibility among young Moroccan patients. BMC Res Notes 2017;10:763.
28. Tran DC, Le LHG, Thai TT, et al. Association between ACE I/D genetic polymorphism and the severity of coronary artery disease in Vietnamese patients with acute myocardial infarction. Front Cardiovasc Med 2023:10:1091612.
29. Baruah S, Chaliha MS, Borah PK, et al. Insertion/Insertion Genotype of Angiotensin I-Converting-Enzyme Gene Predicts Risk of Myocardial Infarction in North East India. Biochem Genet 2016;54:134–146.
30. Yoshida M, Iwai N, Ohmichi N, et al. D allele of the angiotensin-converting enzyme gene is a risk factor for secondary cardiac events after myocardial infarction. Int J Cardiol 1999;70:119–125.
31. Zhao W, Ma ST, Cui LQ. Meta-analysis of angiotensin-converting enzyme insertion/deletion polymorphism and myocardial infarction in Han Chinese. Genet Mol Res 2015;14:8068–8076.
32. Dai S, Ding M, Liang N, et al. Associations of ACE I/D polymorphism with the levels of ACE, kallikrein, angiotensin II and interleukin-6 in STEMI patients. Sci Rep 2019;9:19719.
33. Vaisi-Raygani A, Ghaneialvar H, Rahimi Z, et al. The angiotensin converting enzyme D allele is an independent risk factor for early onset coronary artery disease. Clin Biochem 2010;43:1189–1194.
34. Parenica J, Goldbergova MP, Kala P, et al. ACE gene insertion/deletion polymorphism has a mild influence on the acute development of left ventricular dysfunction in patients with ST elevation myocardial infarction treated with primary PCI. BMC Cardiovasc Disord 2010:10:60.
35. Moorthy N, Saligrama Ramegowda K, et al. Role of Angiotensin-Converting Enzyme (ACE) gene polymorphism and ACE activity in predicting outcome after acute myocardial infarction. Int J Cardiol Heart Vasc 2021;32:100701.
36. Krishnan R, Sekar D, Karunanithy S, Subramanium S. Association of angiotensin converting enzyme gene insertion/deletion polymorphism with essential hypertension in south Indian population. Genes Dis 2016;3:159–163.
37. Siddharth KM, Kapur S, Ram CV. Angiotensin converting enzyme gene polymorphism and hypertension: no ace yet in the pack of cards. J Assoc Physicians India 2012;60:9–10.
38. Borah PK, Shankarishan P, Hazarika NC, Mahanta J. Hypertension subtypes and angiotensin converting enzyme (ACE) gene polymorphism in Indian population. J Assoc Physicians India 2012;60:11, 15–17.
39. Mahwish UN, Ponnaluri KC, Heera B, et al. Link between ACE I/D Gene Polymorphism and Dyslipidemia in Diabetic Nephropathy: A Case-control Study from Hyderabad, India. Indian J Nephrol 2020;30:77–84.
40. Ha SK. ACE insertion/deletion polymorphism and diabetic nephropathy: clinical implications of genetic information. J Diabetes Res 2014;2014:846068.
41. Schmidt S, Schone N, Ritz E. Association of ACE gene polymorphism and diabetic nephropathy? The Diabetic Nephropathy Study Group. Kidney Int 1995;47:1176–1181.
42. Wang Y, Peng W, Zhang X, et al. The association of ACE gene polymorphism with diabetic kidney disease and renoprotective efficacy of valsartan. J Renin Angiotensin Aldosterone Syst 2016;17:1470320316666749.
43. Amrani-Midoun A LN, Boukerche F. DNA methylation and coronary artery disease: Brief summary of the main findings. Cor Vasa 2023;65:843–847.