


The Relationship Between Angiotensin-Converting Enzyme Gene I/D Polymorphism and Psoriasis, Including Psoriasis with Comorbid Hypertension and Diabetes

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Objective: The relationship between angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism and psoriasis remains unclear. This study aims to analyze the association between ACE gene I/D polymorphism and the risk of psoriasis vulgaris in the Chinese Han population and to examine the correlation between ACE gene I/D polymorphism and psoriasis with comorbid hypertension and diabetes.

Methods: A total of 358 patients with psoriasis vulgaris and 347 age- and sex-matched healthy volunteers from the Chinese Han population were selected. Clinical data, including blood pressure and fasting blood glucose, were collected from the patients. The ACE gene I/D polymorphism was analyzed using polymerase chain reaction (PCR). The association between ACE gene I/D polymorphism and psoriasis vulgaris, as well as comorbid hypertension and diabetes, was analyzed using the Pearson χ^2 -test.

Results: The frequency of the ACE II genotype (OR = 1.84, 95% CI = 1.30, 2.61; $P < 0.01$) and the I allele (OR = 1.51, 95% CI = 1.22, 1.86; $P < 0.01$) was significantly higher in psoriasis patients compared to the control group. Conversely, the frequency of the ACE DD genotype (OR = 0.62, 95% CI = 0.44, 0.87; $P < 0.01$) and the D allele (OR = 0.66, 95% CI = 0.54, 0.82; $P < 0.01$) was significantly lower in psoriasis patients compared to the control group. No statistically significant differences were observed when stratified by blood pressure and blood glucose abnormalities ($P > 0.05$).

Conclusion: The ACE II genotype and I allele are risk factors for psoriasis vulgaris in the Northern Chinese Han population.

Keywords: psoriasis vulgaris, angiotensin-converting enzyme, insertion/deletion mutation, gene polymorphism, Chinese Han ethnic group

Introduction

Psoriasis, characterized by hyperproliferative keratinocytes and immune dysregulation with a genetic predisposition, manifests as scaly erythematous plaques often accompanied by wax drops, thin film phenomena, and Auspitz's sign. These lesions predominantly affect areas such as the scalp, trunk, limbs, and genital regions. The prevalence of psoriasis is about 2–4% worldwide.¹ Remarkably, psoriasis incidence displays regional disparities, with lower rates observed in China and Japan compared to Europe, and its absence noted among indigenous populations in the Andes region of South America.² Moreover, individuals with psoriasis face heightened risks of comorbidities like hypertension and diabetes,^{3,4} profoundly impacting their well-being, recovery, and long-term prognosis. This multifaceted condition is influenced by a confluence of factors, including ethnicity, genetic makeup, environmental triggers, and aberrant immune responses.

At the molecular level, angiotensin-converting enzyme (ACE) assumes a pivotal role in the renin-angiotensin-aldosterone system (RAAS), exerting its effects across various tissues, including the skin, vascular endothelium, lungs, kidneys, and

heart.^{5,6} ACE catalyzes the conversion of biologically inert angiotensin I (Ang I) into the potent vasoconstrictor angiotensin II (Ang II). Genetically, the ACE gene, situated on chromosome 17q23,⁷ encompasses 26 exons and 25 introns, harboring a 287 bp insertion (I)/deletion (D) polymorphism within its 16th intron. This ACE I/D polymorphism dictates functional variations in ACE expression levels, with homozygotes for insertion/insertion (I/I) genotype exhibiting the lowest ACE levels, homozygotes for deletion/deletion (D/D) displaying the highest levels, and heterozygotes (I/D) manifesting intermediate levels.^{8,9} Prior investigations have uncovered elevated serum ACE activity in nearly half of psoriasis patients,¹⁰ suggesting a potential interplay between ACE I/D polymorphism and psoriasis pathogenesis.

Despite these insights, the precise role of ACE I/D polymorphism in psoriasis remains enigmatic, particularly concerning the Chinese Han population, where research is scarce. Hence, exploring the association between ACE gene I/D polymorphism and the risk of psoriasis vulgaris in the Chinese Han population is crucial for several reasons. Firstly, psoriasis has a multifactorial etiology, and understanding genetic predispositions within specific populations can help tailor prevention and treatment strategies. Secondly, the prevalence of comorbidities such as hypertension and diabetes among psoriasis patients suggests a complex interplay between genetic factors and these conditions, which may influence disease severity and management. Investigating this relationship can enhance our understanding of the pathophysiological mechanisms underlying psoriasis and its associated comorbidities, ultimately guiding more effective therapeutic approaches tailored to the genetic and environmental context of the Chinese Han population.

Methods

Study Population

This hospital-based case-control study included 358 psoriasis patients and 347 healthy volunteers, all from Northern China and of Han ethnicity. The sample size of 358 psoriasis patients and 347 healthy controls was determined based on the available patient data from hospital records at the time of the study. Although a formal sample size calculation was not performed, we aimed to include as many patients as possible to ensure statistical power in detecting significant associations between the ACE gene polymorphism and psoriasis. The final number was determined by the available eligible patients and controls who met the inclusion criteria. All participants were between the ages of 18 and 70. Inclusion Criteria: Participants were included if they were diagnosed with psoriasis vulgaris based on clinical and/or histopathological examination, were of Han ethnicity, and aged between 18 and 70 years. All participants provided informed consent. Clinical data, including age, gender, blood pressure (calibrated mercury sphygmomanometer) and fasting blood glucose (isolated serum from native venous blood samples collected after overnight fasting), were collected from patient medical records and through interviews. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current antihypertensive treatment. Elevated fasting blood glucose was defined as ≥ 6.1 mmol/L or a diagnosis of type 2 diabetes under treatment. The control group consisted of age- and sex-matched healthy volunteers. Exclusion Criteria: Individuals were excluded from the study if they refused to participate, were younger than 18 or older than 70 years, had erythrodermic or pustular psoriasis, drug-induced psoriasis, other chronic skin diseases, severe liver or kidney diseases, malignancies, bleeding disorders, or a history of organ transplantation or hematopoietic stem cell transplantation. Additionally, individuals with a family history of psoriasis or genetic diseases were also excluded. Although this study primarily focused on the genetic association of the ACE gene polymorphism with psoriasis, lifestyle factors such as smoking and alcohol consumption were not included in the analysis. These factors, while relevant, were beyond the scope of the current investigation and should be considered in future research to better understand their potential confounding effects.

The study protocol was approved by the Clinical Ethics Committee of the Affiliated Hospital of Shandong Second Medical University (No. wyfy-2023-ky-192). The study adhered to the ethical principles of the World Medical Association Declaration of Helsinki, and all participants provided informed consent. There were no conflicts of interest in the study.

Genotype Analysis

Under sterile conditions, 2 mL of venous blood was collected and anticoagulated with disodium EDTA (EDTA·2Na). Genomic DNA was extracted using a whole blood genomic DNA extraction kit (Sangon Biotech, Shanghai, catalog number: B518253-0100) following the manufacturer's instructions. The A260/A280 ratio, measured using a UV spectrophotometer,

was between 1.7 and 1.8. PCR amplification of the ACE gene (Sangon Biotech, Shanghai, catalog number: B532061-0005) was performed with the following conditions: initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30s, annealing at 55°C for 30s, and extension at 72°C for 40s, with a final extension at 72°C for 5 min. Primers were synthesized by Sangon Biotech with the following sequences: forward - 5'-CTGGAGACCACTCCCATCCTTTCT-3', reverse - 5'-GATGTGGCCATCACATTCGT-CAGAT-3'. PCR products were subjected to 2% agarose gel electrophoresis, stained with ethidium bromide, and analyzed under UV light. A 490 bp product indicated the II genotype, a 190 bp product indicated the DD genotype, and both 190 bp and 490 bp products indicated the ID genotype.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA). Differences between continuous variables were assessed using the Student's *t*-test, and differences between categorical variables were assessed using Pearson's chi-square test. Differences in allele and genotype frequencies between groups were also assessed using Pearson's chi-square test. Logistic regression analysis was employed to determine odds ratios (OR) and 95% confidence intervals (CI). A *P*-value < 0.05 was considered statistically significant.

Results

A total of 358 psoriasis patients (244 males and 114 females; mean age 45.3 ± 13.3 years) and 347 healthy volunteers (232 males and 115 females; mean age 44.5 ± 14.3 years) were included in the study. The age, gender, and characteristics of psoriasis patients regarding blood pressure and blood glucose abnormalities are shown in Table 1. There were no significant differences in age and gender between the psoriasis and control groups (*P* > 0.05).

The distribution of genotypes and allele frequencies of the ACE I/D polymorphism in the psoriasis and control groups is presented in Table 2. All observed genotype frequencies in the control group were consistent with Hardy-Weinberg equilibrium (HWE). The frequency of the ACE II genotype was significantly higher in psoriasis patients compared to the control group (OR = 1.84, 95% CI = 1.30, 2.61; *P* < 0.01). Similarly, the I allele was more prevalent among psoriasis patients (OR = 1.51, 95% CI = 1.22, 1.86; *P* < 0.01). Conversely, the frequency of the ACE DD genotype was significantly lower in psoriasis patients (OR = 0.62, 95% CI = 0.44, 0.87; *P* < 0.01), as was the D allele (OR = 0.66, 95% CI = 0.54, 0.82; *P* < 0.01).

A stratified analysis based on the presence of blood pressure and blood glucose abnormalities revealed no statistically significant differences in the frequencies of ACE genotypes and alleles between patients with and without these comorbidities (*P* > 0.05), as shown in Table 3.

Table 1 Characteristics of Patients with Psoriasis and Controls

	Psoriasis	Controls	P value
Total number	358	347	
Age, mean±SD (years)	45.3±13.3	44.5±14.3	0.47
Gender (%)			0.71
Male	244 (68.2%)	232 (66.9%)	
Female	114 (31.8%)	115 (33.1%)	
HT			
Yes	126 (35.2%)		
No	232 (64.8%)		
EFBG			
Yes	104 (29.1%)		
No	254 (70.9%)		

Abbreviations: HT, high blood pressure or treatment; EFBG, elevated fasting blood glucose or treatment; SD, standard deviation.

Table 2 Genotype Distribution and Allele Frequencies of ACE I/D Polymorphism Between Psoriasis Patients (Cases) and Controls

	Psoriasis (%)	Control (%)	OR (95% CI)	P value
Genotype				
II	111 (31.0%)	68 (19.6%)	1.84 (1.30–2.61)	<0.01
ID	174 (48.6%)	177 (51.0%)	0.91 (0.68–1.22)	0.52
DD	73 (20.4%)	102 (29.4%)	0.62 (0.44–0.87)	<0.01
Allele				
I	396 (55.3%)	313 (45.1%)	1.51 (1.22–1.86)	<0.01
D	320 (44.7%)	381 (54.9%)	0.66 (0.54–0.82)	<0.01

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3 Genotype Frequencies of the Insertion/deletion (I/D) Polymorphism of the Angiotensin-converting Enzyme (ACE) Gene with Elevated Fasting Blood Glucose and High Blood Pressure in the Psoriasis Group

Variable	n (%)	ACE Genotypes			OR (95% CI, P)		
		II	ID	DD	II	ID	DD
HT							
Yes	124 (34.6%)	37	65	22	0.92 (0.57–1.48, 0.73)	1.26 (0.82–1.95, 0.29)	0.77 (0.44–1.35, 0.37)
No	234 (65.4%)	74	109	51	I (Ref.)	I (Ref.)	I (Ref.)
EFBG							
Yes	104 (29.1%)	30	53	21	0.87 (0.53–1.43, 0.57)	1.14 (0.72–1.80, 0.57)	0.98 (0.56–1.73, 0.95)
No	254 (70.9%)	81	121	52	I (Ref.)	I (Ref.)	I (Ref.)

Abbreviations: EFBG, elevated fasting blood glucose or treatment; HT, high blood pressure or treatment; OR, odds ratio; CI, confidence interval.

Discussion

The relationship between psoriasis and the angiotensin-converting enzyme (ACE) gene I/D polymorphism has been extensively studied across diverse populations worldwide, as shown in Table 4, yet achieving a definitive consensus

Table 4 The Main Previous Studies in the World

Author	Year	Ethnicity	Psoriasis			Control			Comments
			II	ID	DD	II	ID	DD	
Ozkur ¹¹	2004	Caucasian (Turkish)	12	40	34	28	69	57	The presence of the I allele may confer susceptibility to development of psoriasis in individuals from psoriatic families
Al-Awadhi ¹²	2007	Caucasian (Arab)	7	19	25	14	45	41	No difference was found between the distribution of the ACE genotype in PsA patients and the general population in Kuwait
Weger ¹³	2007	Caucasian (European)	61	92	54	35	93	54	Homozygosity for the ACE I allele may affect susceptibility to early-onset psoriasis
Coto-Segura ¹⁴	2009	Caucasian (European)	38	124	106	34	145	93	The ACE polymorphism is not likely to be associated with either psoriasis or psoriatic arthritis
Agha ¹⁵	2018	Caucasian (Pakistani)	72	87	74	90	122	51	The DD genotype was found to be significantly different among psoriasis subjects and healthy controls, when calculated under the recessive model
Chang ¹⁶	2007	Asian (Taiwan, China)	172	108	32	287	265	63	The presence of the I allele may confer susceptibility to development of psoriasis among ethnically Chinese Taiwanese individuals.
Yang ¹⁷	2014	Asian (China)	350	269	49	304	299	65	ACE II genotype and I allele might confer susceptibility to psoriasis in a Chinese population.
Huang ¹⁸	2017	Asian (China)	55	71	35	119	111	26	The DD frequency of ACE I/D polymorphism among cases was significantly different from controls.

remains a challenge. Initial investigations by Ozkur et al suggested a potential association between ACE I/D gene polymorphism and psoriasis risk in the Turkish population, highlighting the I allele as a potential risk factor.¹¹ However, subsequent studies conducted in various countries, including Austria, Kuwait, Spain, and China, have yielded conflicting results, underscoring the complexity and variability of this genetic relationship.^{12–18} Meta-analyses performed by Song et al and Ramezani et al further underscore the discrepancies observed, with Song et al suggesting a negative correlation between certain genotypes and psoriasis risk,¹⁹ while Ramezani et al found no significant association particularly in East Asian populations.²⁰ This heterogeneity underscores the importance of considering population-specific factors such as ethnicity and geographic region in understanding the genetic underpinnings of psoriasis susceptibility.

Expanding upon this foundation, our study delved into the Han Chinese population residing in northern China, aiming to elucidate the precise role of ACE gene polymorphism in the pathogenesis of psoriasis. Consistent with previous findings by Yang et al, our results corroborate a significant association between the ACE II genotype, I allele, and heightened psoriasis risk. The findings of this study provide significant insights into the association between ACE gene polymorphism and psoriasis risk among the Han Chinese population. Our results indicate a higher prevalence of the ACE II genotype and I allele in psoriasis patients compared to healthy controls, aligning with our objective to investigate the genetic factors influencing psoriasis susceptibility. Furthermore, these findings contribute to the broader understanding of the genetic basis of psoriasis, highlighting the need for further exploration of genetic variations across diverse populations. This relevance underscores the importance of considering genetic factors in the management and treatment of psoriasis, particularly in populations with distinct ethnic backgrounds.

Mechanistic Insights into ACE-Mediated Pathways

Despite significant strides, the molecular mechanisms linking ACE I/D polymorphism to psoriasis susceptibility remain inadequately understood. Emerging evidence suggests that ACE inhibitors, commonly utilized in hypertension management, may exhibit paradoxical effects on psoriasis, potentially exacerbating the condition.²¹ This underscores the intricate interplay between ACE and skin immunity, wherein ACE modulates the degradation of inflammatory mediators like bradykinin and substance P.^{22,23} Our study provides further support to these hypotheses by demonstrating a higher prevalence of the II and ID genotypes, associated with diminished ACE levels, among psoriasis patients, hinting at potential dysregulation within inflammatory pathways.

Moreover, recent investigations have begun to explore the role of ACE in mediating broader immunological responses beyond the classical renin-angiotensin-aldosterone system (RAAS). ACE has been implicated in modulating cytokine networks and leukocyte trafficking,²⁴ suggesting broader implications for its role in immune-mediated disorders like psoriasis. Future mechanistic studies should aim to unravel these intricate pathways, shedding light on novel therapeutic targets for psoriasis management.

Implications for Comorbidities and Therapeutic Strategies

Psoriasis commonly co-occurs with hypertension and diabetes, posing significant challenges for patient management. While our study found no direct correlation between ACE I/D gene polymorphism and the presence of these comorbidities in psoriasis patients, the broader literature exhibits substantial heterogeneity in this regard.^{25–28} Studies investigating the association between ACE I/D polymorphism and hypertension or diabetes risk have yielded conflicting results across different populations, emphasizing the need for nuanced investigations into population-specific genetic determinants of comorbidities in psoriasis.

These findings have profound implications for therapeutic strategies targeting ACE-mediated pathways in psoriasis management. Given the potential dual roles of ACE inhibitors in modulating psoriasis severity, future clinical trials should carefully evaluate their efficacy and safety profiles in psoriasis patients, considering genetic predispositions and comorbidities. Additionally, exploring novel therapeutic avenues targeting ACE-related pathways may offer promising avenues for personalized treatment approaches tailored to individual patient profiles.

Limitations and Future Directions

While our study offers valuable insights, several limitations should be acknowledged. First, the exclusive focus on the Han Chinese population from northern China limits the generalizability of our findings to other ethnic groups and geographic regions. Additionally, the absence of detailed analyses of serum ACE concentrations and enzymatic activity restricts our ability to fully understand the role of ACE in the pathogenesis of psoriasis. Future research should address these limitations by including more diverse patient populations and conducting mechanistic studies to clarify the functional impact of ACE gene polymorphisms in psoriasis development. Moreover, while we employed Chi-square and Logistic regression analyses to examine the association between ACE gene polymorphism and psoriasis risk, more sophisticated approaches—such as adjusting for confounding variables, performing sensitivity analyses, and exploring subgroup differences—may provide further insights. Incorporating these advanced statistical techniques in future studies will enhance the robustness and depth of the findings.

Conclusion

In conclusion, our study underscores the significance of ACE gene polymorphism in psoriasis susceptibility among the Han Chinese population residing in northern China. While further mechanistic insights into ACE-mediated pathways are warranted, our findings emphasize the need for personalized therapeutic approaches targeting ACE-related pathways in psoriasis management. Collaborative efforts across diverse populations are imperative to unravel the intricate genetic underpinnings of psoriasis and its associated comorbidities, paving the way for precision medicine approaches and improved patient outcomes.

Data Sharing Statement

All data used and analyzed to support the findings of this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare no competing financial interests.

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