FREQUENCY OF THE SINGLE NUCLEOTIDE POLYMORPHISM RS743572 VARIANT OF CYP17A1 GENE AND ITS ASSOCIATION WITH ACNE SEVERITY IN VIETNAMESE PATIENTS

Le Nguyen Thuy Vy[1,2], Chau Van Tro[1,2], Nguyen Huu Ngoc Tuan[1,2*]

ABSTRACT

Objectives: To determine the frequency of the rs743572 variant of the CYP17A1 gene and its association with clinical characteristics in patients diagnosed with acne.

Materials and methods: A cross-sectional study was conducted on Vietnamese patients diagnosed with acne from March 2023 to July 2023 at Ho Chi Minh City Hospital of Dermatology and Venereology. The variant was identified using Sanger sequencing.

Results: A total of 95 Vietnamese patients were diagnosed with acne. The majority were aged 12 - 25 (84.2%), with a median age of 21 years (ranging from 12 to 43 years), and 60.0% were female. The allele frequencies were 43.2% for allele A and 56.8% for allele G. The genotype distribution was 16.8% AA, 52.6% AG, and 30.6% GG. A statistically significant association was found between the presence of the variant and the clinical severity of the disease.

Conclusions: This is the first study to determine the rate of the rs743572 variant in a Vietnamese acne population, initially noting a statistically significant association between the variant and disease severity.

Keywords: *Acne, CYP17A1, rs743572, Vietnamese.*

1. INTRODUCTION

Acne vulgaris is an inflammatory disorder of the pilosebaceous unit, primarily affecting adolescents and young adults, especially those aged 16 - 20[1]. The prevalence of acne vulgaris is estimated to be as high as 90% worldwide [2]. Although often self-limiting and with minimal impact on general health, acne can profoundly affect a patient's quality of life and psychological well-being.

The pathogenesis of acne results from a complex interplay between environmental and genetic factors. Following studies identifying *Cutibacterium acnes* bacteria as the main cause, genetic factors related to immune response have gained interest[2]. Human DNA sequences are

[1]Department of Dermatology - Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam
[2]Biomedical Research Center - Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam
**Correspondence: Email: nhntuan@pnt.edu.vn*
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99.9% identical on average, with the remaining 0.1% differences largely due to single nucleotide polymorphisms (SNPs), where one nucleotide in the DNA sequence is replaced by another. SNPs, occurring in more than 1% of the population, can influence disease risk, clinical progression, severity, and treatment response. SNPs are the most common form of genetic variation studied across various diseases, with significant implications for patient healthcare[3]. However, research on the role of SNPs in acne remains limited[4].

CYP17A1 is one of the genes influencing sebaceous gland function and activity, with potential risk variants affecting acne presentation and severity. It plays a crucial role in androgen metabolic pathways, encoding the enzyme 17-α-hydroxylase/17 - 20 lyase, which catalyzes the conversion of pregnenolone to 17-hydroxyprogesterone and progesterone to 17 - hydroxyprogesterone, a rate-limiting step in androgen biosynthesis[5]. *CYP17A1*, located on the 5'untranslated region, influences the transcription recognition complex, initiating and stabilizing the transcription process, thereby potentially affecting acne clinical manifestations[6].

The *rs743572* polymorphism in *CYP17A1* is the most studied variant[5]. Research in Chinese, Singaporean, Iranian, and Uzbek populations has shown a correlation between *rs743572* and acne onset and severity, while no significant correlation was found in Polish study[7,8]. Determining the allele and genotype ratios of *rs743572* in the Vietnamese population, as well as its relationship with epidemiological and clinical characteristics such as gender, age of onset, severity, and scarring, can help clarify pathophysiological mechanisms and inform individualized therapy.

2. MATERIALS AND METHOD

2.1. Subjects

The research group included 95 acne patients examined at the Ho Chi Minh City Hospital of Dermatology and Venereology from March to July 2023. Inclusion criteria consisted a clinical acne diagnosis, Vietnamese nationality with three generations living in Vietnam, and agreement to participate. Exclusion criteria were non-Vietnamese ancestry (e.g., Chinese) within three generations, insufficient information per the research protocol, and unsuitable DNA samples for testing.

2.2. Research methods

Cross-sectional study investigating all cases of Vietnamese patients diagnosed with acne from March 2023 to July 2023 at the Ho Chi Minh City Hospital of Dermatology and Venereology.

The examination to determine acne cases was based on clinical criteria. Selected cases were directly interviewed to collect information such as age, gender, personal and family history, and age of onset, following a data collection form. Clinical features recorded included primary lesions (closed comedones, open comedones, papules, pustules, nodules, cysts), distribution of lesions, and disease severity according to the Global Acne Grading System (GAGS). Severity was graded as mild (1 - 18 points), moderate (19 - 30 points), severe (31 - 38 points), and very severe (> 38 points)[9].

Patients were photographed, with images of typical lesions recorded under sufficient light conditions. They also provided 2 mL of venous blood, which was collected in specialized tubes containing 1.5 mg/mL EDTA anticoagulant, stored at 4°C. The *rs743572* variant of the *CYP17A1* gene

was examined at the Biomedical Research Center of Pham Ngoc Thach University of Medicine by Sanger sequencing method with the BigDye Terminator v3.1 Cycle Sequencing Kit from ThermoFisher (USA). The variant determination, faciliated by the Variant ReporterTM Software v2.0, was then finalized by comparing the results with the standard sequence (ENSG00000148795, Genome Reference Consortium Human Build 38 (GRCh38) version).

2.3. Statistical analysis

SPSS version 22.0 software was used to manage and analyze all data. Quantitative variables were presented as mean ± standard deviation ($\bar{X} \pm SD$) if they followed a standard normal distribution, or as median (interquartile range) [Me (IQR)] if they did not. Qualitative variables were shown as frequency and percentage. Possible associations between *CYP17A1* polymorphisms and certain clinical characteristics of patients diagnosed with acne were explored using the Chi-squared test (χ^2). Fisher's exact test was used instead if the expected value was less than 5. The significance level was set at $p < 0.05$ with a 95% confidence interval.

2.4. Research ethics

The study was granted the "Certificate of Approval of the Ethics Council in Biomedical Research of Pham Ngoc Thach University of Medicine" No. 2318/QD-TDHYKPNT, dated November 8, 2022, by Pham Ngoc Thach University of Medicine. All research subjects (1) were clearly informed about the study and signed a consent form if they agreed to participate, (2) had the right to refuse participation and withdraw from the study at any time, (3) had their personal information kept confidential through encryption, and (4) did not incur any costs for participating in the study.

3. RESULTS

3.1. Epidemiological characteristics of study subjects

The epidemiological characteristics of the studied sample are presented in Table 1. There were 95 patients who qualified for the study, with 84.2% being adolescents (aged 12 - 25). The median age was 21 years, with an interquartile range of 19 - 23 years, the youngest patient being 12 years old and the oldest 43 years old. In terms of gender, the prevalence of females (60.0%) was 1.5 times that of males (40.0%). Regarding residence, 67.4% of the patients lived in Ho Chi Minh City.

Table 1. Epidemiological characteristics of study subjects (N = 95)

Epidemiological characteristics	
Age, years	
Me (IQR)	21 (19 - 23)
X_{min} - X_{max}	12 - 43
Ratio (male : female)	2 : 3
Aged group, n (%)	
< 12 years old	0 (0)
12 - 25 years old	80 (84.2)

Epidemiological characteristics	
> 25 years old	15 (15.8)
Residence, n (%)	
Ho Chi Minh City	64 (67.4)
Other provinces	31 (32.6)

3.2. Clinical characteristics of study subjects

Table 2. Clinical characteristics of study subjects (N = 95)

Clinical characteristics	
Age of onset, n (%)	
≤ 25 years old	84 (88.4)
> 25 years old	11 (11.6)
Family history of acne, n (%)	
Not	62 (65.3)
Mom and Dad	7 (7.4)
Siblings	11 (11.6)
Both parents and siblings	15 (15.7)
Primary lesion, n (%)	
Open comedones	95 (100)
Closed comedones	88 (92.6)
Papule	85 (89.5)
Pustule	74 (77.9)
Nodules	25 (26.3)
Cyst	2 (2.1)
Distribution, n (%)	
On each area of the body	
Face	95 (100)
Chest	42 (44.2)
Back	45 (47.4)
On the face	
Forehead	78 (82.1)
Nose	94 (99)
Cheeks	85 (89.5)
Jaw	70 (73.7)
Chin	50 (52.6)

Clinical characteristics	
Severity, n (%)	
Mild	27 (28.4)
Moderate	50 (52.6)
Severe	16 (16.8)
Very severe	2 (2.2)
Scar, n (%)	
No	45 (47.4)
Yes	50 (52.6)

The onset of the disease in the age group ≤ 25 years old was predominant, accounting for 88.4% of cases. Additionally, 65.3% of patients had no family history of acne. Non-inflammatory lesions, including open comedones and closed comedones, were present in 100% and 92.6% of patients, respectively. Inflammatory lesions, such as papules and pustules, were found in more than three-quarters of the study samples, while nodules and cyst lesions comprised only a small proportion (26.3% - 2.1%). All patients had lesions in the facial area, and approximately 50% had lesions on the back and chest. On the face, the most common lesions were on the nose (99%) and cheeks (89.5%). According to the GAGS score, the rates of mild, moderate, severe, and very severe acne were 28.4%, 52.6%, 16.8%, and 2.2%, respectively. Furthermore, 52.6% of patients had acne scars (Table 2).

3.3. Allele and genotype distribution of variant rs743572

In the study population, the prevalence of individuals carrying allele G (considered a risk allele) was 56.8% . The proportion of these individuals was six times higher than those without the risk allele (79 : 16) (Figure 1-3).

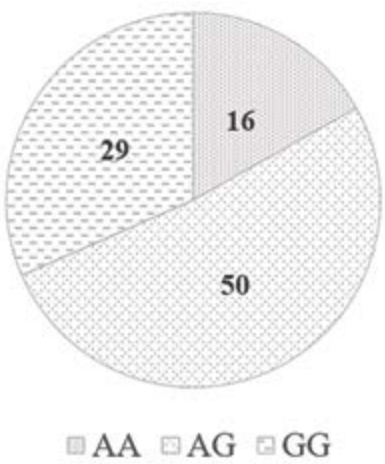

Figure 1. Genotype frequency distribution chart (n) of variant rs743572

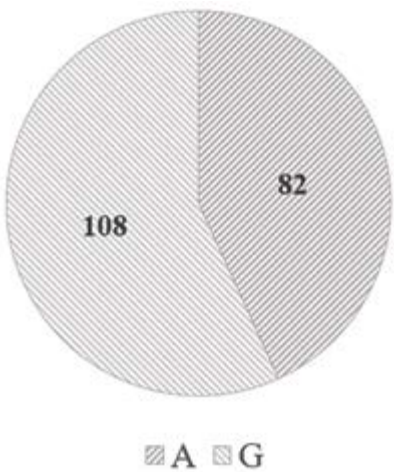

Figure 2. Allele frequency distribution chart (n) of variant rs743572

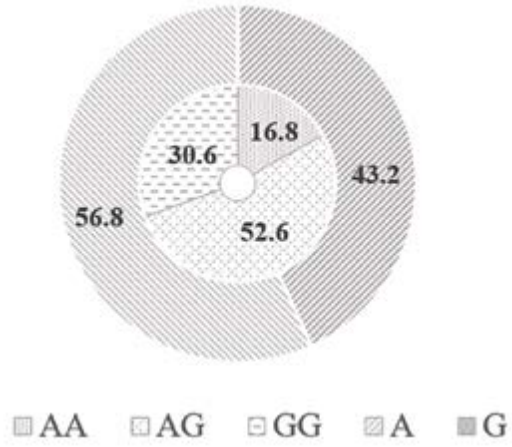

Figure 3. The prevelance of allele and genotype distribution (%) of variant rs743572

3.4. The association between genotype and characteristics of the study subjects

Table 3. The association between genotype and characteristics of the study subjects

Characteristics	Allele type		p
	In those with allele G	In those without allele G	
Gender			
Male	7 (43.8%)	31 (39.2%)	p = 0.737[a]
Female	9 (56.2%)	48 (60.8%)	
Age of onset			
≤ 25 years old	14 (87.5%)	69 (87.3%)	p = 1[b]
> 25 years old	2 (12.5%)	10 (12.7%)	
Family history			
No	10 (62.5%)	52 (65.8%)	p = 0.799[a]
Yes	6 (37.5%)	27 (34.2%)	
Severity			
Mild	9 (56.3%)	18 (22.8%)	**p = 0.016[b]**
Moderate	4 (25.0%)	46 (58.2%)	
Severe	2 (12.5%)	14 (17.7%)	
Very severe	1 (6.2%)	1 (1.3%)	
Scars			
No	8 (50.0%)	37 (46.8%)	p = 0.817[a]
Yes	8 (50.0%)	42 (53.2%)	

(a): Using Chi - Square test.

(b): Using Fisher's exact test.

When comparing allele distribution with clinical characteristics such as gender, age of onset, family history, and acne scars, there was no statistically significant difference between the prevalence of individuals carrying the risk allele (AG and GG) and those without it (AA). However, there was a statistically significant difference in the clinical severity of the disease between individuals carrying allele G and those without it ($p = 0.016$) (Table 3).

4. DISCUSSION

Acne results from a complex interplay of multiple factors, including environmental and genetic influences. One of the primary mechanisms is excessive sebum production. Studies have shown that acne patients produce more sebum, and the amount of secretion correlates with the severity of acne, though the composition of sebum remains similar to that in individuals without acne. Triglycerides and lipoperoxides are two key components in acne development. These create a lipid-rich environment that allows C. acnes bacteria to flourish[10]. C. acnes bacteria break down triglycerides into free fatty acids, promoting bacterial growth and leading to inflammation. Lipoperoxides trigger proinflammatory cytokines and activate pathways that increase sebum production. The function of sebaceous glands is regulated by various factors, including hormones, cytokines, chemokines, and growth factors. Androgens particularly influence sebum production and the proliferation of follicular keratinocytes, both of which are crucial in acne pathogenesis[11]. Consequently, Cytochrome P450 (CYP) genes may play a role in the formation and development of acne[8].

In our study, the risk allele (allele G) constituted 56.8%, while genotypes containing the risk allele (AG and GG) accounted for 83.1% (Figure 3). This research marks the first investigation into the frequency of the *rs743572* variants of the *CYP17A1* gene in Vietnamese acne patients. When comparing the frequency of allele G in the general population across different racial groups, it was observed that the frequency in this study was somewhat similar to the general Asian data (51%) from the National Center for Biotechnology Information (NCBI) database. This frequency is among the highest globally, surpassing East Asia (52.7%) and South Asia (30%). It is also higher than other regions, such as Uzbekistan (43.3%)[7], China (53.9%)[10] and Iran (16.7%)[11]. These findings suggest that Asian ethnic groups, particularly Vietnamese, have a higher susceptibility to acne due to the presence of the *CYP17A1* gene's risk allele compared to other races worldwide. Therefore, clinical severity prognosis requires greater attention.

When grading acne severity using the GAGS scale (mild, moderate, severe, and very severe), we found a statistically significant difference between groups with the risk alleles (G allele, AG, and GG genotypes) and those without risk alleles (allele A, AA genotype) in terms of clinical severity ($p = 0.016$). This result aligns with studies conducted in Uzbekistan[7], Iran[11] and China [12]. However, it differs from the research findings in Poland [8].

Currently, the only study on single nucleotide polymorphisms of the *CYP17* gene in Chinese acne patients has recorded a correlation between homozygous allele C carriers and severe acne cases in male patients. The hypothesis is that this variant may influence the regulation of the *CYP17* gene by creating an SP1 binding site on the promoter region, although in vitro experiments have not

yet confirmed this assumption. Several studies have shown correlations between this variant and various endocrine diseases, suggesting that the role of single nucleotide polymorphisms in the *CYP17* gene remains controversial[12].

Our study did not show statistically significant differences when comparing the distribution of allele G with allele A across various clinical characteristics, such as gender, age of onset, family history of acne, and presence of acne scars. However, due to limited resources, our study had significant drawbacks in terms of sample selection methodology. To confirm these findings, future studies need to be designed appropriately for each scientific question and adhere to more rigorous standards.

5. CONCLUSIONS

This study was the first to describe the prevalence of *rs743572* variants of the *CYP17A1* gene in Vietnamese acne patients. The risk allele G accounted for 56.8%, while genotypes containing the risk allele (AG and GG) made up 83.1%. The research also demonstrated a statistically significant association between the presence of the risk allele and the clinical severity of the disease ($p = 0.016$).

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