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Association of the CYP17 MSP AI (T-34C) and CYP19 codon 39 (Trp/Arg) polymorphisms with susceptibility to acne vulgaris

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Summary

The aim of this study was to detect the association of the cytochrome P450 (CYP) 17 T-34C and CYP19 T<C polymorphisms with the risk of acne vulgaris (AV). The study enrolled 198 patients with AV (mild, moderate and severe) and 195 unrelated age-matched healthy controls from western Iran who had Kurdish ethnic background. The presence of the CYP17 TC genotype significantly increased the risk of mild, moderate and severe AV by 2.68, 2.28 and 2.94 times, respectively, while the presence of the CYP19 TC genotype significantly elevated the risk of overall AV and mild AV by 2.1 and 3.2 times, respectively. There was a synergy between the CYP 17 TC and CYP19 TT genotypes, which increased the risk of AV by 2.45-fold ($P < 0.001$). To our knowledge, this is the first study showing that the CYP17 T-34C and CYP19 T<C variants and their synergy are associated with susceptibility to AV in an Iranian population.

Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous unit. It is one of the most common skin diseases, affecting a large percentage of the general population, and it is particularly common during adolescence.[1] The genetic background and some environmental factors such as lifestyle play important roles in its pathogenesis.[2]

The CYP17 enzyme is essential for androgen biosynthesis through its dual bioactivities of steroid 17α-hydroxylase and 17,20-lyase in the adrenal gland and ovary.[2] A single T>C nucleotide polymorphism (T-34 C, Msp AI polymorphism, rs743572) at nucleotide 27 in the 5′-untranslated region promoter of the *CYP17* gene has been reported.[3] The presence of the C allele (the A2 allele) was hypothesized to create an additional Sp1 binding site with enhanced promoter activity and increased gene expression,[3] but experimental studies did not confirm this finding. The CYP17 T-34C polymorphism was not associated with the risk of AV among Polish patients,[4] but the presence of this polymorphism was associated with increased risk of developing severe acne in Chinese men.[5]

The human enzyme CYP19 (cytochrome P450 aromatase, family 19), which is encoded by the *CYP19* gene, is associated with circulating oestrogen levels. The polymorphism T>C (Trp/Arg) in codon 39 (rs2236722) of the *CYP19* gene may alter aromatase activity and steroid hormone levels.[6]

We could not find any study in the literature examining an association between the CYP19 T>C polymorphism and the risk of AV. Therefore, the aim of the present study was to identify the role of the CYP17 T-34C and CYP19 T>C codon 39 (Trp/Arg) polymorphisms and their synergy in determining susceptibility to AV.

The study was approved by the ethics committee of Kermanshah University of Medical Sciences and conducted in accordance with the principles of the Declaration of Helsinki II. Signed informed consent was obtained from each individual before participation.

We enrolled 198 patients with AV who were referred to dermatology clinics (169 female, 29 male patients; mean ± SD age 22.1 ± 4.7 years, range

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Table 1 Frequency of the CYP17 MSP AI (T>C) and CYP19 T>C genotypes and alleles in patients with acne vulgaris and controls and classification by acne status

Parameter	HCs (n = 195) n (%)	Patients with acne vulgaris			
		All patients (n = 198), n (%)	Mild acne (n = 89), n (%)	Moderate acne (n = 53), n (%)	Severe acne (n = 56), n (%)
CYP17 T>C					
Genotypes					
TT	164 (84.1)	132 (66.7)	59 (66.3)	37 (69.8)	36 (64.3)
TC	31 (15.9)	66 (33.3) χ^2 = 16; OR = 2.64; 95% CI 1.6–4.3; P < 0.001	30 (33.7) χ^2 = 11.5; OR = 2.68; 95% CI 1.5–4.8; P = 0.001	16 (30.2) χ^2 = 5.54; OR = 2.28; 95% CI 1.13–4.6; P = 0.02	20 (35.7) χ^2 = 10.55; OR = 2.94; 95% CI 1.5–5.74; P < 0.01
Alleles					
T	359 (92.1)	330 (83.3)	148 (83.1)	90 (84.9)	92 (82.1)
C	31 (7.9)	66 (16.7) χ^2 = 13.8; OR = 2.31; 95% CI 1.47–3.64; P < 0.001	30 (16.9) χ^2 = 10.1; OR = 2.35; 95% CI 1.37–4.0; P = 0.001	16 (15.1) χ^2 = 4.96; OR = 2.06; 95% CI 1.08–3.92; P < 0.03	20 (17.9) χ^2 = 9.4; OR = 2.52; 95% CI 1.37–4.63; P < 0.01
CYP19 T>C					
Genotypes					
TT	183 (93.8)	174 (87.9)	62 (82.7)	48 (90.6)	50 (89.3)
TC	12 (6.2)	24 (12.1) χ^2 = 4.2; OR = 2.1; 95% CI 1.02–4.3; P = 0.04	13 (17.3) χ^2 = 8.06; OR = 3.2; 95% CI 1.38–7.35; P < 0.01	5 (9.4) χ^2 = 0.7; P = 0.4	6 (10.7) χ^2 = 1.39; P = 0.24
Alleles					
T	378 (96.9)	372 (93.9)	137 (91.3)	101 (95.3)	106 (94.6)
C	12 (3.1)	24 (6.1) χ^2 = 4; OR = 2.03; 95% CI 1–4.12; P < 0.05	13 (8.7) χ^2 = 7.66; OR = 3.0; 95% CI 1.33–6.71; P < 0.01	5 (4.7) χ^2 = 0.7; P = 0.4	6 (5.4) χ^2 = 1.3; P = 0.25

HC, healthy control.

13–43). The healthy control (HC) group consisted of 195 unrelated age-matched individuals (143 female, 52 male controls; mean ± SD age 22.6 ± 4.2 years, range 13–33) without any systemic or dermatological disorders. There was no significant difference in age ($P = 0.33$) between patients and HCs. The ethnic background of all studied individuals was Kurdish. Exclusion criteria included pregnancy or breast-feeding; use of anti-inflammatory or anti-androgenic drugs, oral contraceptive pills, or isotretinoin within the 3 months prior to enrolment; use of anabolic androgens; or presence of systemic or autoimmune diseases.

The clinical grade of AV was determined according to the Consensus Conference on Acne Classification.[5] Acne grading area was defined according to the Global Acne Grading System, which divides the face, chest and upper back into six areas, and assigns a number to each area on the basis of surface area, distribution and density of pilosebaceous units.[7]

DNA was extracted from venous whole blood samples using standard phenol–chloroform procedure. The CYP17 T-34C (MSP AI) and the CYP19 T>C (Trp/Arg) polymorphisms were identified as previously described.[8,9] To evaluate the accuracy of MSP AI digestion, the PCR product of samples with known genotype (TC), along with unknown samples, was digested with the same restriction enzyme and was loaded onto the same gel.

SPSS software (v16; SPSS, Inc. Chicago, IL, USA) was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

There was no significant difference in body mass index (BMI) between patients (23.3 ± 6.3 kg/m^2) and HCs (22.5 ± 3.8 kg/m^2) ($P = 0.15$).

Distribution of the CYP17 T-34C genotypes was in Hardy–Weinberg equilibrium (HWE) in HCs ($\chi^2 = 1.45$, $P > 0.1$) and the distribution of the CYP19 T>C genotypes was in HWE in both patients ($\chi^2 = 0.82$, $P > 0.1$) and HCs ($\chi^2 = 0.2$, $P > 0.1$).

The comparison of the CYP17 T-34C genotypes and alleles in patients and HCs is shown in Table 1. The presence of the CYP17 TC genotype increased the risk of overall, mild, moderate and severe AV by 2.64 ($P < 0.001$), 2.68 ($P = 0.001$), 2.28 ($P = 0.02$) and 2.94 ($P < 0.01$) times, respectively (Table 1).

The comparison of the CYP19 T>C genotypes and alleles between patients and HCs is also shown in Table 1. The presence of the CYP19 TC genotype increased the risk of overall and mild AV by 2.1 ($P = 0.04$) and 3.2 ($P < 0.01$) times, respectively.

Synergy between the CYP17 TC and CYP19 TT genotypes was detected, which was associated with an increase in the risk of AV by 2.45-fold (95% CI 1.49–4.0; $P < 0.001$). In addition, the concomitant presence of both the CYP17 TC and the CYP19 TC genotypes was observed in 4% of patients ($P = 0.001$) compared with the absence of both genotypes in HCs.

In our study, the presence of the CYP17 TC genotype increased the risk of all types of AV, especially the severe type. One study reported an association between the CYP17 T>C polymorphism with severe AV in men,[5] but another study did not confirm this association.[4] The presence of this polymorphism enhances the promoter activity and increases the gene expression, with subsequent elevation of androgen production.[3]

In this study, we found that the TC genotype of the rare CYP19 T>C polymorphism increased the risk of overall and mild AV by 2.1 and 3.2 times, respectively, which is the first such report, to our knowledge. It has been suggested that the presence of CYP19 T>C might reduce enzyme activity and lower the production of oestrogens.[10]

We detected synergy between the CYP17 TC and CYP19 TT genotypes, which significantly increased the risk of AV. Further, a significantly higher percentage of patients had both the CYP17 TC and CYP19 TC genotypes compared with the HCs. It might be that by affecting androgen level, both the CYP17 T-34C and CYP19 T>C polymorphisms are involved in the pathogenesis of AV. An increase in androgen level through enhancement of sebum production and follicular keratosis is involved in AV development.[5]

In conclusion, the present study suggests that the CYP17 T-34C and CYP19 T>C polymorphisms and their synergism may be genetic markers for susceptibility to AV.

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References

1 Gollnick HP, Bettoli V, Lambert J *et al.* A consensus-based practical and daily guide for the treatment of acne patients. *J Eur Acad Dermatol Venereol* 2016; **30**: 1480–90.
2 SzabO K, Kemeny L. Studying the genetic predisposing factors in the pathogenesis of acne vulgaris. *Hum Immunol* 2011; **72**: 766–73.

3 Ambrosone CB, Moysich KB, Furberg H *et al.* CYP17 genetic polymorphism, breast cancer, and breast cancer risk factors. *Breast Cancer Res* 2003; **5**: R45–51.
4 Sobjanek M, Zabłotna M, Dobosz-Kawałko M *et al.* Polymorphisms in the cytochrome P-450 (CYP) 1A1 and 17 genes are not associated with acne vulgaris in the Polish population. *Postepy Dermatol Alergol* 2015; **32**: 323–6.
5 He L, Yang Z, Yu H *et al.* The relationship between CYP17 -34T/C polymorphism and acne in Chinese subjects revealed by sequencing. *Dermatology* 2006; **212**: 338–42.
6 Wang L, Lu X, Wang D *et al.* CYP19 gene variant confers susceptibility to endometriosis-associated infertility in Chinese women. *Exp Mol Med* 2014; **46**: e103.
7 Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. *Int J Dermatol* 1997; **36**: 416–8.
8 Hirose K, Matsuo K, Toyama T *et al.* The CYP19 gene codon 39 Trp/Arg polymorphism increases breast cancer risk in subsets of premenopausal Japanese. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1407–11.
9 Han QH, Shan ZJ, Hu JT *et al.* Relationship between gene polymorphisms and prostate cancer risk. *Asian Pac J Trop Med* 2015; **8**: 569–73.
10 Miyoshi Y, Iwao K, Ikeda N *et al.* Breast cancer risk associated with polymorphism in CYP19 in Japanese women. *Int J Cancer* 2000; **89**: 325–8.

