

# Genetic Variants Associated with Acne Vulgaris

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**Abstract:** Acne vulgaris (AV) ranks among the common chronic inflammatory disorders that impact the sebaceous components of hair follicles. Acne vulgaris is characterised by cardinal manifestations such as the presence of pimples, nodules, pustules, and cysts, which have the potential to lead to the development of acne scarring and pigmentation. The phenomenon is influenced by polygenic inheritance or can be ascribed to the interplay between multiple genes and environmental factors. In recent years, some researchers have found that some genes (such as IL, TNF, RETN, CYP family, MMPs and TIMPs genes et al) are associated with acne vulgaris and may affect the progression and prognosis of the disease. The number of reviews addressing acne-associated genetic variants, however, is limited. In that case, we have compiled a list of prevalent genes associated with acne in recent times. This helps us understand acne's genetic basis and lets us step in early for people prone to severe acne, lowering the chance of acne scars.

**Keywords:** acne vulgaris, susceptible genes, genetic variants, genetics

## Introduction

Acne vulgaris is a prevalent chronic inflammatory condition affecting the hair follicles and sebaceous glands. It is characterised by the presence of various manifestations such as acne, inflammatory papules, cysts, nodules, pustules, and the potential for scar formation. During the period of adolescence, a considerable number of skin lesions manifest on the cheeks, forehead, and various other regions, thereby impacting the individual's aesthetic appeal. These lesions can result in pigmentation or the development of scars and may even have implications for both physical and psychological well-being.<sup>1,2</sup> The etiology of acne is multifaceted and encompasses various elements, such as the intricate interplay among androgen-mediated sebum synthesis, follicular keratinization, inflammatory responses, and the colonisation of pilosebaceous follicles by *Cutibacterium acnes*. In the early 20th century, Herman Werner Siemens was the first to establish a correlation between genetic inheritance and the occurrence of acne.<sup>3,4</sup> Following this, Bataille et al<sup>5</sup> conducted a study involving a sample size of 458 pairs of monozygotic female twins and 1099 pairs of dizygotic female twins. The findings of the study indicated that a significant proportion of the disease's variability, specifically 81%, could be attributed to genetic factors, with the remaining portion being influenced by environmental factors. To effectively identify, manage, and mitigate acne at an early stage, it is imperative to investigate the genetic factors that contribute to an individual's susceptibility to this condition. Additionally, a comprehensive examination of contemporary scientific studies elucidating the role of genetics in the etiology of acne holds significant scholarly merit.

## Interleukins (IL) Gene

There is a correlation between specific genes and the manifestation and severity of acne, as these genes are associated with immune and inflammatory responses. The interleukins (IL) serve as a notable illustration, with recent research primarily concentrating on IL-1 $\alpha$ , IL-1 $\beta$ , IL-4, IL-6, IL-8, IL-10, and others.

Acne vulgaris is a skin condition characterized by the development of lesions due to the abnormal secretion of epithelial cells and sebum. This pathological process is primarily attributed to the excessive keratinization of hair follicles, resulting in the narrowing and obstruction of sebum ducts. Interleukin-1 alpha (IL-1 $\alpha$ ) is a member of the interleukin-1 (IL-1) cytokine family. Research findings indicate that the activation of keratinocytes by *Propionibacterium*

acnes (*P. acnes*) can induce the production of IL- $\alpha$ , which subsequently triggers the hyperkeratinization of the infundibular segments of follicles. This process is considered the initial event in the development of comedogenesis.<sup>6</sup> According to reports, there is a correlation between the presence of -889 C>T (rs1800587) polymorphic variants in the IL-1 $\alpha$  gene and -251 T>A (rs4073) in the IL-8 gene, and increased transcription activity, heightened cytokine synthesis, and the onset of inflammatory disorders.<sup>7,8</sup> Sobjanek et al<sup>9</sup> conducted a survey among individuals of Polish descent, wherein they observed that the TT genotype of IL-1 $\alpha$  (rs1800587) exhibited a significant association with an elevated susceptibility to disease development (OR=3.77,  $P = 0.044$ ). No statistically significant differences were observed in the genotype and allele frequencies of IL-8 (rs4073) between patients with acne and the control group ( $P > 0.05$ ). Another study conducted on individuals of Greek descent also discovered that the TT genotype of IL-1 $\alpha$  poses a risk, while the CT genotype provides a protective effect.<sup>10</sup> In their initial findings, the authors proposed that there may be a potential link between IL-1 $\alpha$ -889 C>T(rs1800587) variants and the vulnerability of specific individuals with acne vulgaris to dietary factors. Research conducted in Pakistan revealed a significantly higher prevalence of the IL-6-572 G>C (rs1800796) and IL-1 $\alpha$ -889 C>T (rs1800587) variant allele haplotypes among individuals with acne.<sup>11</sup> The data presented in the study suggests a potential association between the occurrence of acne in Pakistan and the presence of IL-6-572C and IL-1 $\alpha$ -889T alleles. Two studies have reported a lower prevalence of the CT genotype of IL-1 $\alpha$ -889 C>T(rs1800587) variants among individuals affected by acne.<sup>9,10</sup> This discovery implies that this particular genotype may play a preventive role in the development of acne vulgaris. Contrarily, this assertion does not hold true for individuals of Pakistani origin.<sup>11</sup> According to the research conducted by Szabó et al<sup>12</sup> it was determined that there is a positive correlation between the minor T allele of the IL-1 $\alpha$  +4845 G>T (rs17561) single nucleotide polymorphism (SNP) and the occurrence of acne. The researchers reported a positive correlation between the severity of symptoms associated with inflammatory acne and the proportion of individuals who possessed the homozygous T/T genotype. However, the SNP IL-1 $\alpha$  + 4845 G>T exhibited a correlation exclusively among individuals of Caucasian descent in Hungary and Romania,<sup>12</sup> but not among individuals in the United States.<sup>13</sup> The following is Table 1. Interleukin 1 $\beta$  (IL-1 $\beta$ ), an additional pivotal proinflammatory cytokine, is primarily secreted by activated T lymphocytes and macrophages.<sup>14</sup> Polymorphic variants of IL-1 $\beta$ -511 have been identified in individuals diagnosed with brain abscess, chronic periodontitis, and major recurrent depression.<sup>14–16</sup> Recent research has elucidated the role of IL-1 $\beta$  pathways in the pathogenesis of acne, specifically their activation by *P. acnes*. The measurement of inflammatory acne lesions revealed a notable increase in the accumulation of Interleukin 1 $\beta$  mRNA and activated processed IL-1 $\beta$ . The activation of the NLRP3 inflammasome and the processing and secretion of IL-1 $\beta$  are believed to be induced by *P. acnes*.<sup>17,18</sup> In order to assess the correlation between IL-1 $\beta$ -511 (rs16944) gene polymorphisms and susceptibility to acne, as well as the severity of acne and the likelihood of postacne scarring, Akoglu et al<sup>19</sup> conducted a study in which they obtained peripheral venous blood samples from 90 individuals diagnosed with acne vulgaris and 30 healthy controls in Turkey. These samples were then subjected to real-time PCR analysis to detect genotypic variants of IL-1 $\beta$ -511 (rs16944). Nevertheless, the researchers discovered that there is no association between IL-1 $\beta$  polymorphic variants and acne, susceptibility to post-acne scarring, or the severity of acne, as indicated in Table 2. In their study, ElAttar et al<sup>20</sup> conducted skin biopsies on both patients and controls, followed by routine histopathology tests. The results revealed a significant positive association between the expression of IL-1 $\beta$  and the clinical severity of acne vulgaris ( $p = 0.022$ ), as well as the severity of histopathological inflammation ( $p = 0.011$ ). Nevertheless, the genetic correlation between IL-1 $\beta$  and AV was not examined in their analysis. Moreover, it is imperative to conduct larger-scale studies in order to validate this conclusion and gain a more comprehensive understanding of the involvement of IL-1 $\beta$  in the pathogenesis of AV.

**Table 1** IL-1 $\alpha$  +4845 (rs17561) Acne Presentation

Study	Allele	Acne		Controls		OR(95%CI)	P
		TG+TT(%)	GG(%)	TG+TT(%)	GG(%)		
Szabó et al, 2010 (Hungary and Romania) <sup>12</sup>		128(59.0)	89(41)	60(47.2)	67(52.8)	1.61(1.03;2.5)	0.03

**Note:**  $P < 0.05$  is statistically significant.

**Table 2** Frequencies of IL-1 $\beta$ -511 (rs16944) Genetic Variants in Acne Patients and Controls

	Total n	CC n(%)	CT n(%)	TT n(%)	P
Subject					
Patients	90	28(31.1)	46(51.1)	16(17.8)	0.466
Controls	30	13(43.3)	13(43.3)	4(13.4)	
Acne severity					
Mild	26	8(30.8)	15(57.7)	3(11.5)	0.509
Moderate	27	11(40.8)	10(37.0)	6(22.2)	
Severe	37	9(24.3)	21(56.8)	7(18.9)	
Controls	30	13(43.3)	13(43.3)	4(13.4)	
Presence of scar					
Nonscarring acne (NSA)	54	18 (33.3)	26 (48.2)	10 (18.5)	0.734
Scarring acne (SA)	36	10 (27.8)	20 (55.5)	6 (16.7)	
Controls	30	13 (43.3)	13 (43.3)	4 (13.4)	

**Note:** P < 0.05 is statistically significant.

IL-6, a multifunctional signaling molecule secreted by various cell types, assumes a critical role in orchestrating the body's defence mechanisms, governing immune responses, hematopoiesis, and the inflammatory process.<sup>21</sup> The investigation of IL-6 polymorphisms has been conducted in various inflammatory conditions, including systemic lupus erythematosus and rheumatoid arthritis.<sup>22,23</sup> P. acnes elicits the activation of various pathways, ultimately resulting in the activation of the transcription factor known as nuclear factor (NF)-KB. The aforementioned process elicits the secretion of diverse inflammatory mediators, including IL-6, IL-8, IL-10, and tumour necrosis factor. IL-6 and various inflammatory cytokines serve to activate the T helper (Th)17 axis of adaptive immune responses. This elicits an inflammatory reaction in the context of acne.<sup>24</sup>

The IL-6 gene is situated on the chromosomal locus 7p21, and specific SNPs within this region have been previously examined in relation to their potential association with susceptibility to diverse diseases. The previous examples include the nucleotide substitutions 572 G>C (rs1800796), 174 G>C (rs1800795), and 597 G>A (rs1800797).<sup>25</sup> Concurrently, additional surveys were undertaken to ascertain the correlation between IL-6 polymorphism and acne.

The study revealed a high prevalence of variant genotypes (GC+CC) at position -572 (rs1800796) of the IL-6 gene among acne patients in Pakistan and Egypt.<sup>11,26</sup> Nevertheless, a notable disparity remained. The Egyptian population exhibited a significantly higher prevalence of CC polymorphisms compared to healthy controls (HCs), whereas the Pakistani population demonstrated a strong association between GC polymorphisms and AV. The observed disparity may be attributed to the diverse ethnic backgrounds present in the two studies. In a recent study conducted by Chen et al<sup>27</sup> a significantly higher prevalence of the IL-6-572 G>C (rs1800796) variant genotype was observed in individuals with acne compared to the control group. This finding suggests a potential association between the presence of this genotype and an elevated risk of developing acne. The researchers also established a correlation between the IL-6-572 G>C (rs1800796) variant and the severity of acne, as well as the presence of a family history of acne. They observed that the frequency of the CC genotype increased with the severity of the disease (p < 0.001). In the same way, it was observed that the prevalence of the CC genotype was significantly greater among individuals with a familial predisposition to acne in comparison to those without such a predisposition (p < 0.001). In addition, it has been observed that the presence of the C allele is associated with the onset of acne in individuals of Egyptian, Chinese, and Pakistani descent. Additionally, it was discovered that the presence of RETN-420 C>G (rs1862513) alleles was associated with an elevated susceptibility to the development of acne. In contrast to prior investigations, the present study did not observe a noteworthy disparity in the IL-1 $\alpha$ -889 C>T variant between individuals without any health issues and those afflicted with acne. This discrepancy could potentially be attributed to racial disparities and the limited size of the sample population, as indicated in Table 3. The results of their study present the initial evidence suggesting that the RETN-420 C>G and IL-6-572 G>C polymorphisms play a significant role in the development of acne within the Chinese population, as indicated in Table 4.

**Table 3** IL-1 $\alpha$ -889 (rs1800587) Acne Presentation

Study \ Allele	Acne		Controls		OR(95% CI)	P
	T(%)	C(%)	T(%)	C(%)		
Sobjanek et al, 2011 (Poland) <sup>9</sup>	74(32.2)	156(67.8)	51(25.5)	149(74.5)	1.39(-)	–
Ibrahim et al, 2019 (Greece) <sup>10</sup>	89(44.5)	111(55.5)	64(32)	136(68)	1.70(1.13;2.56)	<0.01
Younis & Javed, 2015 (Pakistan) <sup>11</sup>	291(34)	569(66)	154(20)	606(80)	2.01(1.60;2.52)	<0.0001
Chen et al, 2022 (China) <sup>27</sup>	87(14.2)	525(85.8)	77(12.6)	535(87.4)	1.15(0.83;1.60)	0.402

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, T vs C. P < 0.05 is statistically significant. - means that there is no data in the original paper; numbers with percentages are in parentheses.

**Table 4** IL-6 rs1800796 Acne Presentation

Study \ Allele	Acne		Controls		OR(95% CI)	P
	C(%)	G(%)	C(%)	G(%)		
Younis & Javed, 2015 (Pakistan) <sup>11</sup>	326(38)	534(62)	177(23)	583(77)	2.01(1.61;2.45)	<0.0001
Ragab et al, 2019 (Egypt) <sup>26</sup>	42(70)	18(30)	12(30)	28(70)	5.44(2.27;13.04)	<0.001
Chen et al, 2022 (China) <sup>27</sup>	388(63.4)	224(36.6)	283(46.2)	329(53.8)	2.01(1.60;2.53)	<0.001

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, C vs G. P < 0.01 is statistically significant.

A research investigation conducted in Pakistan revealed a significant association between IL-8-251 T>A (rs4073) and both the presence of acne and its severity.<sup>28</sup> However, this association was not observed in the Polish population.<sup>9</sup> The data presented in Table 5 illustrates the relevant information pertaining to the subject matter under investigation.

## Tumor Necrosis Factor (TNF) Gene

Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) is widely recognised as the primary pro-inflammatory cytokine, exerting a crucial influence in the initiation and regulation of the cytokine cascade within the context of the inflammatory response. The gene encoding tumour necrosis factor alpha (TNF- $\alpha$ ) is situated on chromosome 6 (6p21.3) within the major histocompatibility complex III region, specifically positioned between the HLA-B and DR genes. Various genetic variations have been identified within the promoter region of the TNF- $\alpha$  gene across diverse populations.<sup>29</sup> These genetic variations contribute to the regulation of gene expression for certain alleles that may have protective effects in the development of inflammation, infectious diseases, or certain types of cancer. The development of acne lesions may be influenced by genetic factors that control the expression of TNF- $\alpha$ .

A study conducted by Tian et al<sup>30</sup> demonstrated a significantly higher likelihood of acne vulgaris in Han Chinese individuals with TNF receptor polymorphism. This finding provides additional evidence for the involvement of inflammatory cytokines in the development of acne vulgaris. Baz et al<sup>31</sup> conducted a study on the Turkish population and observed a statistically significant elevation in the prevalence of the TNF- $\alpha$  308 G>A (rs1800629) genotype among individuals with acne in comparison to their healthy counterparts. Nevertheless, no significant associations were identified between acne and either gender or acne severity. A separate investigation conducted in Turkey revealed that there is no significant association between the TNF  $\alpha$ -308 polymorphic variants (rs1800629) and the occurrence of acne,

**Table 5** IL-8 rs4073 Acne Presentation

Study \ Allele	Acne		Controls		OR(95% CI)	P
	A(%)	T(%)	A(%)	T(%)		
Sobjanek et al, 2011 (Poland) <sup>9</sup>	126(54.8)	104(45.2)	106(53.0)	94(47.0)	1.07(-)	>0.05
Hussain et al, 2015 (Pakistan) <sup>28</sup>	128(24.2)	400(75.8)	88(16.7)	440(83.3)	1.60(1.16;2.19)	0.003

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, A vs T. P < 0.05 is statistically significant.

post-acne scarring, or the severity of acne.<sup>19</sup> In a study conducted by Al-shobaili et al<sup>32</sup> notable disparities were observed in the frequencies of genotypic variants of the TNF- $\alpha$  polymorphism between individuals diagnosed with acne and the control group in Saudi Arabia. Additional examination indicated that gender could potentially explain the observed disparities. The presence of the TNF- $\alpha$  308 GG gene variant in females and the AA variant in males may potentially enhance the vulnerability to acne without any discernible correlation to the severity of the condition. The findings of a meta-analysis revealed that the TNF- $\alpha$  308 G>A (rs1800629) polymorphism exhibits distinct implications in terms of acne susceptibility among female and male individuals with acne. The solitary presence of the A allele did not exert any significant influence on the susceptibility to acne.<sup>29</sup> The presence of the AA genotype at a high frequency may contribute to an increased susceptibility to severe acne. Research conducted on various ethnic regions, including Saudi Arabia and Pakistan, as well as three meta-analyses involving participants from China and Greece, has consistently identified the TNF gene polymorphism –308 G>A (rs1800629) as a significant factor contributing to the risk of developing acne.<sup>29,33,34</sup> A research investigation conducted in Pakistan revealed a significant correlation between the TNF- $\alpha$  308 G>A (rs1800629) and TNF- $\alpha$  238 G>A SNPs (rs361525) and the occurrence and severity of acne. The presence of AA genotypes at both –308 and –238 loci was found to be associated with a higher incidence of AV.<sup>35</sup> However, a distinct investigation revealed that there was no substantial association between promoter polymorphisms at positions –308 and –238 of the TNF- $\alpha$  gene and the prevalence of acne vulgaris in patients originating from Poland.<sup>36</sup> The study conducted by Szabó et al<sup>37</sup> revealed a higher prevalence of the minor TNF- $\alpha$  308 A allele among female patients with acne. Concurrently, the researchers identified the protective function of the minor T allele of TNF- $\alpha$  857 (rs1799724). Nevertheless, when comparing the control group to the acne group for the –1031 (1799964), –863 (1800630), and –238 (rs361525) single nucleotide polymorphisms (SNPs), the researchers were unable to find any significant differences in genotype or allele frequencies. Prior research has indicated a potential higher prevalence of the TNF- $\alpha$  308 genotype among individuals with acne, and its correlation with sex has been observed. However, it is necessary to verify these findings in a diverse ethnic population, as indicated in Tables 6–9.

**Table 6** TNF- $\alpha$  308 G>A (rs1800629) Acne Presentation

Study	Allele	Acne		Controls		OR (95% CI)	P
		A(%)	G(%)	A(%)	G(%)		
Akoglu et al, 2019 (Turkey) <sup>19</sup>		32(17.8)	148(82.2)	17(28.3)	43(71.7)	0.55(0.28;1.08)	–
Baz et al, 2008 (Turkey) <sup>31</sup>		51(22.6)	175(77.4)	15(6.6)	213(93.4)	4.14(2.25;7.61)	–
Al-Shobailiet et al, 2012 (Saudi Arabia) <sup>32</sup>		63(19.2)	265(80.8)	166(21.3)	614(78.7)	0.88(0.64;1.22)	–
Grech et al, 2014 (Greece) <sup>33</sup>		31(8.4)	339(91.6)	17(5.2)	313(94.8)	1.68(0.91;3.1)	–
Aisha et al, 2016 (Pakistan) <sup>35</sup>		105(37.5)	175(62.5)	90(28.1)	230(71.9)	1.53(1.07;2.19)	<0.02
Sobjanek et al, 2009 (Poland) <sup>36</sup>		20(11.9)	148(88.1)	27(18)	123(82)	0.62(0.33;1.15)	–
Szabó et al, 2011 (Hungary and Romania) <sup>37</sup>		80(17.5)	378(82.5)	32(12.6)	220(87.4)	1.46(0.94;2.27)	–

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, A vs G. P < 0.05 is statistically significant. – means that there is no data in the original paper; numbers with percentages are in parentheses.

**Table 7** TNF- $\alpha$  308 G>A (rs1800629) Acne Severity

Study	Ethnicity	Cases			Total	Controls
		Mild(%)	Moderate(%)	Severe(%)		
Akoglu et al, 2019 (Turkey) <sup>19</sup>	Asian	26(28.9)	27(30)	37(41.1)	90	30
Baz et al, 2008 (Turkey) <sup>31</sup>	Asian	32(28.3)	51(45.1)	30(26.6)	113	114
Al-Shobailiet et al, 2012 (Saudi Arabia) <sup>32</sup>	Asian	44(26.8)	72(43.9)	48(29.3)	164	390
Aisha et al, 2016 (Pakistan) <sup>35</sup>	Asian	69(49.3)	37(26.4)	34(24.3)	140	160
Szabó et al, 2011 (Hungary and Romania) <sup>37</sup>	Caucasian	29(12.7)	156(68.1)	44(19.2)	229	126

**Table 8** The Association Between the TNF rs1800629 Polymorphism and the Degree of Severity of Acne Patients

(A)										
Subject	Mild n (%)			Moderate n (%)			Severe n (%)			P
	GG	GA	AA	GG	GA	AA	GG	GA	AA	
Akoglu et al, 2019 (Turkey) <sup>19</sup>	19(73.1)	5(19.2)	2(7.7)	21(77.8)	2(7.4)	4(14.8)	28(75.7)	5(13.5)	4(10.8)	0.568
Baz et al, 2008 (Turkey) <sup>31</sup>	16(50.0)	15(46.8)	1(3.2)	34(66.7)	16(31.4)	1(1.9)	16(53.3)	12(40.0)	2(6.7)	0.463
Al-Shobailiet et al, 2012 (Saud Arabia) <sup>32</sup>	33(75.0)	9(20.5)	2(4.5)	48(66.7)	19(26.4)	5(6.9)	30(62.5)	15(31.3)	3(6.2)	0.77
(B)										
Subject				GG			GA+AA			P
				Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	
Aisha et al, 2016 (Pakistan) <sup>35</sup>				46(76.7)	11(18.3)	3 (5.0)	23(28.8)	26(32.4)	31(38.8)	<0.001
Szabó et al, 2011 (Hungary and Romania) <sup>37</sup>				20(13.0)	104 (68.0)	29(19.0)	9(11.9)	52(68.4)	15(19.7)	0.101

Note: P < 0.05 is statistically significant.

**Table 9** TNF-α 238 G>A (rs361525) Acne Presentation

Study	Allele	Acne		Controls		OR(95% CI)	P
		A(%)	G(%)	A(%)	G(%)		
Grech et al, 2014 (Greece) <sup>33</sup>		3(0.8)	367(99.2)	6(1.8)	324(98.1)	0.44(-)	–
Aisha et al, 2016 (Pakistan) <sup>35</sup>		69(24.6)	211(75.4)	54(16.9)	266(83.1)	1.61(1.06;2.44)	<0.03
Sobjanek et al, 2009 (poland) <sup>36</sup>		9(5.4)	159(94.6)	6(4.0)	144(96.0)	1.36(0.47;3.91)	–
Szabó et al, 2011 (Hungary and Romania) <sup>37</sup>		22(4.8)	436(95.2)	9(3.6)	239(96.3)	1.34(0.61;2.96)	–

Notes: The analysis was performed using the allele model (minor allele vs major allele), that is, A vs G. P < 0.05 is statistically significant. – means that there is no data in the original paper; numbers with percentages are in parentheses.

In their study, Younis et al<sup>38</sup> investigated the correlation between TNF-α polymorphisms at three specific loci (–857 rs1799724, –863 1800630, and –1031 1799964), serum TNF-α levels, lipid profiles, and the occurrence of acne vulgaris (AV) in a substantial patient cohort from Pakistan. Based on their research, the TNF-α 863 polymorphism exhibits a significant correlation with the occurrence of acne across the entire population. This observation holds true for both patient groups categorised by sex and those categorised by severity. Furthermore, the presence of a significant proportion of the –857 T allele among the control group suggests a potential protective effect against the development of acne. However, no association was observed between the polymorphism at –1031 and acne development.

## Resistin Gene (RETN)

Resistin is a peptide hormone generated by adipocytes. Resistin is a protein hormone that is produced by adipocytes and is encoded by the RETN gene located on chromosome 19p13.2. It has a molecular weight of approximately 12.5 kilodaltons (kDa). In the case of humans, the length of the entity in question is comprised of 108 amino acids. Resistin is observed to be present in the sebaceous glands and interfollicular epidermis of individuals afflicted with diverse dermatological conditions, including acne, melanoma, and psoriasis. The expression of human resistin (RETN) is observed in various immune cell types, including macrophages, monocytes, and neutrophils.<sup>39</sup> Resistin elicits pro-inflammatory responses via distinct signalling pathways, which are contingent upon the specific target tissue.<sup>40</sup> Immune cells are activated to secrete resistin when pro-inflammatory cytokines such C-Reactive Protein (CRP), Interleukin-6 (IL-6), Interleukin-1 (IL-1), Interleukin-12 (IL-12), and Tumour Necrosis Factor-alpha (TNF-alpha) are present.<sup>41</sup>



The study conducted by Younis et al<sup>42</sup> examined the involvement of resistin polymorphisms, specifically RETN+299 G>A (rs3745367) and -420 C>G (rs1862513), in the pathogenesis of acne vulgaris. The study demonstrated a robust correlation between acne vulgaris, the severity of acne symptoms, and polymorphisms of the RETN gene. In the female population, there was a significantly higher occurrence of variant alleles for both single nucleotide polymorphisms (SNPs) in patients compared to controls. However, this was not the case for males. Significantly, HDL-C levels exhibited a substantial decrease in individuals with the RETN variant genotype. According to the findings of the study, resistin has emerged as a potentially promising therapeutic target. This is due to the observed association between RETN polymorphisms and an elevated risk of developing acne, as well as their ability to enhance the expression of resistin. However, a study conducted in the Iraqi population revealed that there was no statistically significant disparity in the prevalence of genotypic variants of the RETN-420 C>G (rs1862513) gene between individuals diagnosed with acne vulgaris and the control group.<sup>43</sup> The observed disparities in outcomes can potentially be attributed to variations in the methodologies employed and the sizes of the samples utilised in the respective studies.

Hussain et al<sup>44</sup> were the first to demonstrate a noteworthy correlation between the RETN-420 C>G (rs1862513) functional polymorphism and familial acne vulgaris. A noteworthy correlation was observed between the minor allele G at RETN-420 and the occurrence of acne ( $P=0.002$ ). The RETN-420 C>G polymorphism exhibited a statistically significant association with both acne vulgaris ( $P=0.014$ ) and the severity of acne symptoms ( $P=0.0097$ ). In a comparable manner, the association between the RETN rs1862513 GG and G alleles and the onset and severity of acne vulgaris was observed in a representative sample of the Egyptian population.<sup>45</sup> Patients who possessed the G allele exhibited elevated levels of resistin. The initial investigation on the correlation between AV risk and the polymorphism of the resistin gene (-420 C>G) in the Turkish population was conducted and reported by Akcilar et al.<sup>46</sup> The frequency of CC and GG genotypes was significantly higher in AV patients when compared to the control group. The CG genotype exhibited a significant association with decreased susceptibility to AV. The findings indicate that individuals with the CG genotype may exhibit a potential protective effect against AV, as evidenced by an odds ratio (OR) of 0.08, a 95% confidence interval (CI) ranging from 0.01 to 0.64, and a p-value of 0.002. This diverges from the examination of populations in Pakistan and Egypt.<sup>40,41</sup> Furthermore, the researchers conducted measurements to investigate the potential correlation between the genotypic frequencies of the resistin gene (-420 C>G) and the clinicopathological characteristics of individuals affected by atherosclerotic vascular disease (AV). The findings indicated a lack of a clear correlation between the two variables.

Chen et al<sup>27</sup> identified the potential impact of the RETN-420 C>G (rs1862513) polymorphism (Table 10 and Table 11) on AV susceptibility within the Chinese population. However, no significant associations, including disease grade, were observed based on clinical parameters. It was demonstrated for the first time that RETN-420 polymorphisms are associated with the pathogenesis of acne in the Chinese population. Numerous prior investigations have established a correlation between the RETN-420 gene and acne. Nevertheless, the association between the RETN-420 gene and the degree of severity has exhibited variability across diverse populations. Hence, it is imperative to employ a more extensive sample size in order to investigate the occurrence of acne across diverse populations. Most previous studies linked resistin polymorphisms to acne

**Table 10** RETN-420 C>G (rs1862513) Acne Presentation

Study \ Allele	Acne		Controls		OR(95% CI)	P
	G(%)	C(%)	G(%)	C(%)		
Chen et al, 2022 (China) <sup>27</sup>	413(67.5)	199(32.5)	287(46.9)	325(53.1)	2.35(1.86;2.96)	<0.001
Younis et al, 2016 (Pakistan) <sup>42</sup>	592(56)	468(44)	556(51.0)	544(49.0)	1.24(1.05;1.47)	0.013
Al-Hilali et al, 2016 (Iraq) <sup>43</sup>	85(86.7)	13(13.3)	40(80.0)	10(20.0)	1.63(-)	-
Hussain et al, 2015 (Pakistan) <sup>44</sup>	75(20.9)	285(79.1)	44(12.2)	316(87.8)	1.89(1.23;2.89)	0.002
Shehata et al, 2021 (Egypt) <sup>45</sup>	29(36.3)	51(63.7)	11(13.7)	69(86.3)	3.57(1.63;7.80)	0.001
Akcilar et al, 2022 (Turkey) <sup>46</sup>	99(52.7)	89(47.3)	100(53.2)	88(46.8)	0.98(-)	-

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, G vs C.  $P < 0.05$  is statistically significant. - means that there is no data in the original paper; numbers with percentages are in parentheses.

**Table 11** The Association Between the RETN-420 C>G (rs1862513) Polymorphism and the Degree of Severity of Acne Patients

Subject	Mild n (%)			Moderate n (%)			Severe n (%)			P
	CC	CG	GG	CC	CG	GG	CC	CG	GG	
Chen et al, 2022 (China) <sup>27</sup>	13(11.9)	51(46.8)	45(41.3)	10(8.3)	62(51.2)	49(40.5)	8(10.5)	32(42.1)	36(47.4)	0.702
Younis et al, 2016 (Pakistan) <sup>42</sup>	35(20.0)	98(56.0)	42(24.0)	48(21.0)	107(48.0)	69(31.0)	14(11.0)	69(52.0)	48(37.0)	0.027
Al-Hilali et al, 2016 (Iraq) <sup>43</sup>	1(5.3)	4(21.0)	14(73.6)	2(7.1)	3(10.7)	23(82.2)	0(0.0)	0(0.0)	2(100.0)	0.74
Shehata et al, 2021 (Egypt) <sup>45</sup>	10(76.9)	3(23.1)	0(0.0)	7(43.8)	9(56.2)	0(0.0)	0(0.0)	5(45.5)	6(54.5)	0.001

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is. A vs G. P < 0.05 is statistically significant.

and acne severity, and the RETN variant genotype may also be associated with HDL-C levels. Further validation in larger samples is needed, and the association of variant genotypes with the level of protein transcription warrants further exploration.

## CYP Family Gene

The investigated CYP genes comprised CYP17, CYP19A1, and CYP17A1. The CYP17 gene is situated on the chromosomal locus 10q24.3. This genetic sequence represents the cytochrome P450c17 $\alpha$  enzyme. This enzyme plays a crucial role in the biosynthesis of androgens, serving as a mediator for both steroid 17 $\alpha$ -hydroxylase and 17,20-lyase activities.<sup>47</sup> In their study, He et al<sup>48</sup> observed that the CYP17-34 T/C SNP was associated with variations in acne severity, specifically among males. However, the relationship between this SNP and acne severity differed when considering the overall population and specifically among females. These findings imply the existence of sex-specific disparities in the genetic predisposition to acne severity. The authors hypothesised that the development of acne vulgaris (AV) may be attributed to an elevation in androgen levels, which subsequently leads to an augmentation in sebum production and follicular keratosis. The CYP17-34C (rs743572) allele was initially discovered as a genetic predisposing factor for the development of severe acne in males. A separate investigation conducted on individuals belonging to the Han population residing in Hunan Province revealed that the occurrence of a base substitution within the androgen-related CYP17 gene at -34 bp (T>C) amplified the susceptibility to post-adolescent acne among female participants exhibiting elevated androgen levels.<sup>49</sup> Chamaie-Nejad et al<sup>50</sup> conducted a study examining the relationship between CYP17A1 (rs743572) and acne, finding a statistically significant correlation with both the presence and severity of acne. In contrast, Zhang et al<sup>13</sup> did not observe a similar association, as indicated in Table 12. Based on a comprehensive meta-analysis examining the association between single nucleotide polymorphisms (SNPs) and the incidence of acne, it was found that this particular SNP did not exhibit a significant correlation with the occurrence of acne.<sup>51</sup> Furthermore, Chamaie-Nejad et al discovered a significant association between the single nucleotide polymorphisms (SNPs) of the CYP19A1 gene, specifically rs2236722, and the manifestation and intensity of acne.<sup>50</sup> The presence of a synergistic effect was observed between the CYP 17 TC and CYP19 TT genotypes, resulting in a 2.45-fold increase in the risk of AV (P < 0.001). The potential involvement of the CYP17 T-34C and CYP19 T>C polymorphisms in the pathogenesis of AV could be attributed to their influence on androgen levels.

CYP19A1 is situated in the endoplasmic reticulum and facilitates the production of estrogen through the process of aromatization, specifically targeting the A ring of androgenic steroid substrates. Variations in this particular gene have the potential to augment or diminish aromatase activity, levels of sex hormones (specifically estrogen), bone mineral density

**Table 12** CYP17A1 rs743572 Acne Presentation

Study	Allele	Acne		Controls		OR(95% CI)	P
		T(%)	C(%)	T(%)	C(%)		
He et al, 2006 (China) <sup>48</sup>		190(46.1)	222(53.9)	217(54.3)	183(45.7)	0.72(0.55;0.95)	–
Chamaie-Nejad F et al, 2018 (Iran) <sup>50</sup>		330(83.3)	66(16.7)	359(92.1)	31(7.9)	0.43(-)	–

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, T vs C. - means that there is no data in the original paper; numbers with percentages are in parentheses.



and the occurrence of fractures.<sup>52</sup> The CYP19 polymorphism, specifically identified as rs700518, refers to an unidentified genetic variation occurring in exon 3, resulting in a valine-to-valine substitution at position 80. Post-transcriptional processing can exert an influence on various biological processes, including alterations in gene expression, levels of aromatase, and the consequent production of estrogen.<sup>53</sup> According to the findings of Ebrahimi et al,<sup>54</sup> there is evidence to suggest that the presence of the GG genotype of the CYP19 rs700518 polymorphism is associated with an increased risk and severity of AV. Conversely, diminished levels of estradiol in females were also deemed crucial.

A standard questionnaire survey on acne was conducted by Yang et al.<sup>55</sup> To investigate the associations between severe acne and existing genetic variations, a total of 22 single nucleotide polymorphisms (SNPs) were analysed using the SNaPshot assay. The research conducted in this study revealed a significant association between specific alleles and genotypes of rs6474 and rs6465, respectively, and the prevalence of Pillsbury III–IV severe acne vulgaris in males. Furthermore, it was observed that haplotypes of the CYP21A2 gene were also linked to this particular condition. In addition, it was observed that the presence of the GT genotype of rs8023263 and the CT genotype of rs2470152 within the CYP19A1 gene exhibited an association with the manifestation of Pillsbury III–IV severe acne vulgaris. The GT genotype of rs8023263 provided limited protective effects in male individuals diagnosed with severe acne vulgaris, whereas the heterozygous CT genotype of rs2470152 was associated with a substantial risk for male patients with severe acne vulgaris. Nevertheless, there was no observed association between CYP21A2 and CYP19A1 and the occurrence of severe acne vulgaris in women. Darmani et al<sup>56</sup> discovered a disproportionate prevalence of the m1 allele of CYP1A1. The presence of the m1 allele in the CYP1A1 polymorphism gene is associated with alterations in the regulatory regions, resulting in an accelerated metabolism of endogenous retinoids, leading to their conversion into an inactive state. The occurrence of acne can be attributed to a reduction in the levels of endogenous retinoids. Therefore, the presence of CYP1A1 polymorphisms with the m1 allele may potentially elevate the susceptibility to acne vulgaris. However, in their study, Heng et al<sup>51</sup> concluded that there is no significant association between CYP1A1 single nucleotide polymorphisms (SNPs) and the occurrence of acne.

In contemporary research, the prevailing consensus among scholars is that there is an association between CYP and acne, with a particular emphasis on males. However, it is important to note that further investigation is required to confirm these findings in a more extensive sample size and across diverse ethnic populations.

## MMPs and TIMPs Gene

Inflammation plays a significant role in the development and progression of acne. The impact of matrix metalloproteinase (MMP) family members on inflammation has been demonstrated through various mechanisms.<sup>57</sup> Matrix metalloproteinases (MMPs) are a group of endoproteases that rely on zinc for their enzymatic activity. They play diverse roles in the process of tissue remodelling and are involved in the degradation of various proteins within the extracellular matrix (ECM). Matrix metalloproteinases (MMPs) are subject to regulation at various levels, encompassing the control of mRNA expression, the conversion of the proenzyme into its active form, and the counterbalancing of the effects exerted by endogenous tissue inhibitors of metalloproteinases (TIMPs).<sup>58</sup> The equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) governs the process of extracellular matrix (ECM) remodelling. The occurrence of acne and other inflammatory diseases may arise when there is an imbalance between the two factors. Keratinocytes play a significant role in the production of matrix metalloproteinases (MMPs) in acne. *P. acnes* has the ability to stimulate the expression of various MMPs, such as MMP-1, -2, -3, -9, and -13.<sup>59</sup>

MMP-2, a significant constituent of the MMP family, is an endoproteinase that relies on  $Zn^{+2}$  for its enzymatic activity. The primary endogenous inhibitor of this substance is tissue inhibitor of metalloproteinase-2 (TIMP-2). The MMP-2 gene is situated on the genomic region 16q21 of the human chromosome. The presence of polymorphisms in the MMP-2 (–1306 C/T) and TIMP-2 (–418 G/C) genes, specifically located within the SP1 binding site of the promoter region, can potentially lead to the down-regulation of MMP-2 and TIMP-2 genes. This down-regulation is attributed to the substitution of cytosine (C) with thymine (T) in the MMP-2 gene and guanine (G) with cytosine (C) in the TIMP-2 gene, which ultimately results in the elimination of the SP1 binding site.<sup>60</sup>

Cytokines, including IL-1 $\beta$ , Pro-IL-1 $\beta$ , TGF- $\beta$ , latent TNF- $\alpha$ , and increased levels of triglycerides, may be produced due to decreased MMP-2 activity. The aforementioned substances are essential modulators in the onset and development of acne.<sup>61,62</sup>

In a research investigation conducted on the Turkish population, it was observed that the TIMP-2-418CC genotype exhibited a twofold higher expression in the acne group. However, no significant associations were identified between the MMP-2-1306C/T (rs243865) and TIMP-2-418G/C (rs8179090) polymorphisms and the occurrence of acne vulgaris.<sup>63</sup> The presence of the TIMP-2-418CC genotype has the potential to disrupt the equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), thereby potentially promoting the development and progression of acne. The findings of a study conducted on the Chinese Han population revealed a significant association between the MMP-2-1306C/T polymorphism and acne vulgaris ( $P < 0.001$ ). While no significant correlation was observed between the TIMP-2-41/C polymorphism and acne vulgaris, it was found that individuals carrying the MMP-2 CT/TIMP-2 GG or GC alleles exhibited a heightened susceptibility to developing acne. Concurrently, there was a notable distinction in the severity of acne vulgaris between patients with and without a familial predisposition ( $P < 0.001$ ).<sup>64</sup> According to a prospective, analytical, and observational study conducted on a population in India, the presence of nucleotide polymorphisms in MMP-2 (rs243865) and TIMP-2 (rs8179090) did not demonstrate an elevated risk for the development of acne or atrophic post-acne scarring. Nevertheless, it has been observed that individuals who exhibit hypertrophic post-acne scarring often possess the CC genotype of MMP-2-1306C/T. Hence, individuals exhibiting the aforementioned genotype may be identified as being at a higher risk of developing these aesthetically distasteful consequences associated with acne.<sup>65</sup> The primary focus of this study was on the topic of acne scarring in a broad sense. In order to enhance future analysis of the observed phenomena, it would be beneficial to include a larger sample size of patients exhibiting hypertrophic scarring (as indicated in Table 13 and Table 14).

In a study conducted by Wen et al,<sup>66</sup> a promoter single nucleotide polymorphism (SNP) known as TIMP2 (rs4789932) was found to have an association with the risk of acne scarring (OR [95% CI] = 1.23 [1.10–1.37]). Additionally, the clinical severity of acne scarring in patients from a Chinese Han population was also found to be significantly associated with this SNP ( $p < 2.2 \times 10^{-16}$ ). The gene encoding TIMP-1 is situated on the X chromosome at the chromosomal region Xp11.23–11.4.<sup>67</sup> This implies that males possess either the C or T alleles exclusively, while females exhibit genotypes consisting of CC, CT, or TT. In order to extend the applicability of prior research findings to different populations, it is imperative to conduct additional studies. In a study conducted by Mohammed et al<sup>68</sup> it was

**Table 13** MMP-2 rs243865 Acne Presentation

Study \ Allele	Acne		Controls		OR(95% CI)	P
	C(%)	T(%)	C(%)	T(%)		
Yaykasli et al, 2013 (Turkey) <sup>63</sup>	65(75.6)	21(24.4)	60(71.4)	24(28.6)	1.24(-)	-
Gao et al, 2019 (China) <sup>64</sup>	418(83.3)	84(16.7)	228(94.2)	14(5.8)	0.31(0.17;0.55)	-
Gupta et al, 2020 (India) <sup>65</sup>	883(86.2)	141(13.8)	273(84.8)	49(15.2)	1.12(-)	-

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, C vs T. - means that there is no data in the original paper; numbers with percentages are in parentheses.

**Table 14** TIMP-2 rs8179090 Acne Presentation

Study \ Allele	Acne		Controls		OR(95% CI)	P
	C(%)	G(%)	C(%)	G(%)		
Yaykasli et al, 2013 (Turkey) <sup>63</sup>	17(19.8)	69(80.2)	18(21.4)	66(78.6)	0.90(0.43;1.90)	-
Gao et al, 2019 (China) <sup>64</sup>	92(18.3)	410(81.7)	35(14.5)	207(85.5)	1.33(0.87;2.03)	0.19
Gupta et al, 2020 (India) <sup>65</sup>	93(9.1)	931(90.9)	30(9.3)	292(90.7)	0.97(-)	-

**Notes:** The analysis was performed using the allele model (minor allele vs major allele), that is, C vs G. - means that there is no data in the original paper; numbers with percentages are in parentheses.  $P < 0.05$  is statistically significant.

observed that the TT genotype and T allele of the TIMP-1 (372C/T) (rs4898) gene were found to be significantly more prevalent among female individuals with acne compared to the control group. On the other hand, the distinctions among male participants were not readily discernible. A significant proportion, specifically 77.5%, of female patients who possessed the TIMP-1 (372C/T) CT and TT genotypes, which are considered polymorphic genotypes, exhibited symptoms of back affliction. It is noteworthy that all of these individuals experienced the presence of severe acne and the subsequent formation of scars resulting from acne. This observation indicates that individuals with TIMP-1 (372C/T) polymorphisms who have acne are at a higher risk of developing severe, extensive acne vulgaris and are more prone to the formation of postacne scars.

The relationship between MMP-1 and TIMP-1 polymorphisms and acne vulgaris exhibits interindividual variability. In order to enhance the accuracy of predicting the incidence of acne and elucidating the association between gene polymorphisms and acne scarring, future investigations necessitate the utilisation of expanded sample sizes and advanced biomolecular methodologies to thoroughly investigate the interplay among diverse genes. Furthermore, it is of great significance to investigate the correlation between the expression of MMP-2 and TIMP-2 in various biological contexts, including tissue, serum, and genes.

## Other Genes

Acne or the severity of acne is linked to a wide range of genes and polymorphisms. The involvement of insulin-like growth factor-1 (IGF-1) is significant in the development and progression of acne.<sup>69</sup> Prior research has indicated that there exists a potential association between IGF-1 polymorphisms and various factors such as plasma IGF-1 levels,<sup>70,71</sup> acne susceptibility and severity,<sup>72</sup> patient age,<sup>73</sup> and sex.<sup>74</sup> The study conducted by Abdelaal et al<sup>75</sup> revealed a notable disparity in the prevalence of the Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)-3928C/T polymorphism between individuals diagnosed with acne and those who were deemed healthy controls. Previous research conducted on TLR4 has yielded inconclusive findings regarding its potential correlation with susceptibility to acne. Nevertheless, a comprehensive analysis revealed a significant correlation between Toll-like receptor 4 (TLR4) and the manifestation of acne.<sup>51</sup> In addition, it was observed that TLR2 variants +2258 G/A had a significant influence on the occurrence and severity of acne in individuals of Han Chinese descent.<sup>30</sup> In their study, Petridis et al<sup>76</sup> conducted a genome-wide association study (GWAS) on a cohort of 3823 individuals with severe acne. The researchers investigated the relationship between the TGFB2 (transforming growth factor beta 2) rs1256580 variant and susceptibility to acne. Calprotectin has been identified by researchers as a potentially reliable indicator of the severity of acne and its effectiveness in assessing treatment outcomes.<sup>77–79</sup> According to a study, calprotectin could be connected to the onset of illness by influencing both gene expression and serum levels.<sup>80</sup> For the androgen receptor (AR), a Chinese study observed a strong connection between CAG (Gln) repeat VNTR (variable number tandem repeats) and acne risk,<sup>81</sup> whereas other studies have shown that it correlates with sex. In addition to the aforementioned genes, there are other genes associated with acne, such as NLRP3 (NLR family pyrin domain containing 3), angiotensin-converting enzyme (ACE) I/D VNTR gene, MAPK11 (mitogen-activated protein kinase 11) gene, SEMA4B (semaphorin4B) gene, selectin L (SELL), TRAF3IP2 (TRAF3 Interacting Protein 2) gene, TYK2 (tyrosine kinase 2), peroxisome proliferator activated receptor gamma (PPARG), and DDB2 (damage-specific D-binding protein 2).

## Conclusions and Perspectives

Acne vulgaris is a disease caused by multiple factors and aberrant gene expression. In the pathogenesis of acne vulgaris, both genetics and the environment play a significant role. Currently, only a handful of genes are associated with genetic predispositions in the pathogenesis of acne, and they are influenced by the origin of cases, environmental factors, and ethnic differences. In recent years, we have summarized and analysed the common genes related to acne (such as IL, TNF, RETN, CYP family, MMPs and TIMPs genes, etc.) and found that the majority of these genes are involved in sebaceous gland function and activity as well as inflammatory response.

Our understanding of the pathogenesis of acne, a prevalent skin disease, will be improved by further investigation into the genetic susceptibility to the condition, evaluating the risk of acne at the gene level, judging the prognosis, and preventing and screening drug targets for gene therapy.

## Disclosure

The authors report no conflicts of interest in this work.

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