Association of interleukin 4 (-590 T/C) and interleukin 4 receptor (Q551R A/G) gene polymorphisms with acne vulgaris

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BACKGROUND AND OBJECTIVES: Acne vulgaris is a common skin disorder. The complete etiology of this disease remains to be identified; however, it seems that aberrant expression of cytokine genes might be a contributing factor. This study aimed to investigate the association of genetic polymorphisms related to interleukin 4 (IL-4) promotor and receptor (IL-4R) genes as inflammatory modulators with acne vulgaris.
DESIGN AND SETTING: A case-control study 95 acne patients recruited from outpatient dermatology clinics affiliated with Qassim University, Qassim, Saudi Arabia.
PATIENTS AND METHODS: Acne patient data were compared with 87 normal healthy unrelated controls from the same locality. The genomic DNA was extracted and processed using the real-time polymerase chain reaction amplification for characterization of polymorphisms related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) genes.
RESULTS: Acne patients compared to controls showed no significant difference in the frequencies of IL-4 (-590 T/C) polymorphic genotypes (P=.8), yet had a highly significant difference in IL-4R (Q551R A/G) genotypes (P<.001). The frequencies of the mutant genotype IL-4R GG as well as the allele IL-4R G were significantly higher in cases of acne than in controls. Furthermore, acne cases showed higher frequencies of combined genotypes IL-4R_GG with IL-4_CC, CT, or TT. However, no significant difference was noted on comparing subgroups related to disease severity or response to treatment (P>.05).
CONCLUSIONS: This study provides evidence for a significant association of IL-4R (Q551R A/G) genetic polymorphisms with the susceptibility rather than the severity of acne vulgaris.

Acne vulgaris is a relatively common skin disorder for which millions of patients seek dermatological care. It often leads to significant psychologic and physical morbidity. The pathogenesis is multifactorial and so far incompletely understood, taking into consideration that inflammation is a key component in its pathogenesis.[1-3] Although many cytokines have been implicated in the development and persistence of inflammatory immune responses, it is unknown if any of these are important in inflammatory acne. There has previously been some evidence that acne is a genetically determined disease, and could be inherited.[4,5] The detailed mode of inheritance remains unproven; however, it is most likely by a polygenic interaction mechanism with bacterial infection, like *Propionibacterium acne*, and with other products of inflammation probably under certain environmental conditions.[6] Candidate genes have been studied as those of human cytochrome P450 1A1, steroid 21-hydroxylase, epithelial mucin, androgen receptor, tumor necrosis factor alpha, tumor necrosis factor receptor 2, toll-like receptor 2, and CYP17.[7-14]

Interleukin 4 (IL-4) was originally discovered as a low molecular weight T cell–derived polypeptide of 129 amino acids, which is encoded by the IL-4 gene on chromosome 5q23.31. It is critical for immunoglobulin G subclass 1 (lgGl) production from mitogen-activated B cells. It is secreted by CD4 T cells, helper T cells type 2 (TH2) lymphocytes, and natural killer T cells, and by cells of the innate immune system, including mast cells, basophils, and eosinophils.[15-19] Now, it is clear that IL-4 regulates proliferation, apoptosis, gene expression, and

differentiation in many hematopoietic cells; in particular, it directs the Ig class switch to IgG1 and IgE, and down-regulates the production of THl cells.[18,20-25]

The receptor for IL-4 is encoded by the interleukin 4 receptor (IL-4R) gene on chromosome 16p12. The human *IL-4R* gene spans about 51 kb and includes 12 exons.[26] The protein product of the membrane-bound form of IL-4R contains a signal peptide (exon 3), an extracellular domain (exons 3-7), a transmembrane domain (exon 9), and an intracellular domain (exons 10-12). Previously, 14 single nucleotide polymorphisms (SNPs) were identified in the coding region of the *IL-4R* gene.[27-30] Among the 8 replacement polymorphisms, 1 intracellular polymorphism (Gln551Arg) was proven to affect cell signaling in in vitro assays.[28,29,31] Several studies showed the variations in the *IL-4R* gene that have been associated with different diseases. IL-4R is a component of not only the IL-4, but also the IL-13 receptor and is essential for both the IL-4 and IL-13 signaling.

The type 1 IL-4 receptor is composed of two subunits, an α subunit (IL-4Rα), which binds IL-4 and transduces its growth-promoting and transcription-activating functions, and a γ c subunit, common to several cytokine receptors, that amplifies signaling of IL-4Rα.[32] IL-4 and IL-13 are cytokines that share immunoregulatory functions and a common IL-4RA chain on their receptors. They both play a central role in allergy by inducing IgE synthesis and both can inhibit inflammatory cytokines.[33,34] Interestingly, IL-4 and IL-13 showed a strong antitumor activity in mice; and, induced inhibition of proliferation of tumor cell lines.[35,36] Genetic alterations in the IL-13/IL-4R signaling pathway regulate TH1 or TH2 cytokine-driven inflammatory mechanisms.[37] Ueta et al suggested that IL-4R might be linked to innate immunity that constitutes a link between the environment and the adaptive immune system.[38] Hence, the speculation is that it affects immunological processes and disease susceptibility.[39]

The aim of this study was to investigate the association of SNP in the regulatory region (promoter) of IL-4 (-590 T/C), and with the receptor IL-4R (Q551R A/G) genes, in acne patients with the susceptibility and severity of disease in acne cases.

PATIENTS AND METHODS

This was a case-control study involving acne vulgaris patients (n=96, male=60, female=12, with a mean standard deviation [SD] age of 20.4 [3.5] years). They were recruited from the outpatient dermatology clinics affiliated with Qassim University. Acne vulgaris was unambiguously diagnosed by a consultant dermatologist. On the basis of severity of acne, patients were divided into three subgroups: mild, patients who exhibited mild-inflammatory acne; moderate, patients with inflammatory acne (acne papulopustulosa); and severe, patients with severe forms like the nodulocystic acne. Furthermore, the cases were also subgrouped as follows on the basis of response to treatment: with no response, with moderate response, or excellent response. Results obtained from the study subjects were compared with a control group of healthy unrelated subjects from the same locality (n=87, male=77, female=10, mean [SD] age: 20.1 [3.3] years). Conventional treatment was in the form of topical anti-acne agents including tretinoin creams and benzyl peroxide 5% in addition to systemic doxycycline. Patients were seen biweekly to evaluate the response and side effects of medications. To determine the efficacy of treatment on acne severity, we used both the total lesion count, which was calculated as papules + pustules + comedones + nodules, and the acne severity index, which was calculated as papules + (2 × pustules) + (comedones/4). Informed consent was obtained from all participants in addition to an ethical approval from the scientific and ethical committees of Qassim University. Peripheral blood samples were collected from all participants.

The isolation of DNA was done on a MagNA Pure LC instrument (Roche Molecular Biochemicals, Mannheim, Germany) using an LC DNA Isolation Kit LV (standard protocol; Roche Molecular Biochemicals). The LightCycler capillaries (Roche Diagnostics, Germany) and the reaction vessels, including the master mix, were placed into the postelution area. As soon as the postelution protocol started, the MagNA Pure LC automatically pipetted out 15 μL of the master mix and 5 μL of the processed sample into each of the LightCycler capillaries. Oligonucleotide primers and fluorescence-labeled hybridization probes were designed for amplification and sequence-specific detection of both IL-4 and IL-4R gene polymorphism. The primers and probes were obtained from TIB MolBiol (Berlin, Germany) as a premade lightmix standardized SNiP kit. The master mixture contained 2 μL of a 10 × mixture of LightCycler FastStart DNA master hybridization probes (Tib Mol Bol, Berlin, Germany), 5mM magnesium chloride ($MgCl_2$) (final concentration), 1μM final concentration of IL-4 and IL-4R-a primers, 0.075 μM final concentration of specific primers, and 0.2 μM final concentration of hybridization probes. The polymerase chain reaction (PCR) amplification and detection of the polymorphisms related to IL-4 (-590 T/C) (rs2243250) at the IL4 promoter region and the IL-4R (Q551R A/G) (rs1801275) at

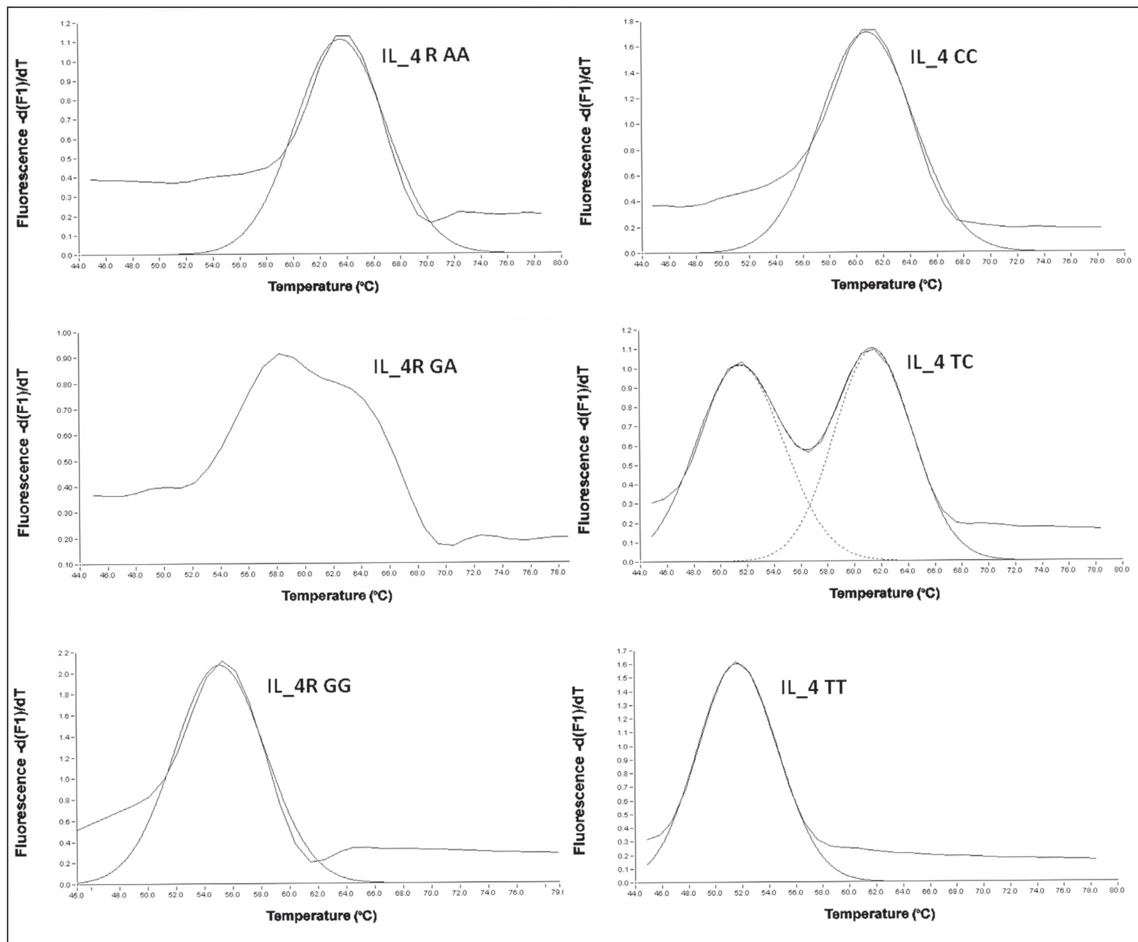

Figure 1. Real time polymerase chain reaction (RT PCR) tracing showing the melting curves corresponding to genetic polymorphisms of interleukin 4 [IL-4 (-590 T/C)] and interleukin 4 receptor [IL-4R (Q551R A/G)] genes.

the IL4 receptor gene using real-time PCR was done using LightCycler instrument (Roche Diagnostics, Mannheim, Germany). Fluorescence curves were analyzed at wavelengths of 640 and 705 nm (dual-color option). Each run contained a positive control for the wild type, and mutant and heterozygous standards in addition to a negative control of blank reagent and water. Each result was confirmed by the specific peak in the corresponding melting curve (**Figure 1**).

The statistical analysis was performed using the statistical software program Statistical Package for the Social Sciences (SPSS) version 13 (IBM Corp, Armonk, NY, United States). Comparisons between cases, control genotype, and allele frequencies were done using the chi-square test considering a *P* level of <.05 to be significant. In addition, the difference between the observed to that of the expected genotypes was tested using the Hardy Weinberg law of genetic equilibrium, and confirmed to be nonsignificant (*P*>.05).

RESULTS

When acne patients were compared with controls (**Table 1**) for the IL-4 (-590 T/C) genotype polymorphism, nonsignificant differences were noted with nearly equal frequencies i (TT vs TC-CC, *P*=.77). However, cases showed a significantly higher frequency of the IL-4R (Q551R A/G) homozygous mutant polymorphism GG than in controls (42.7% vs 8%, respectively) with a lower frequency of the wild type genotype AA in cases than in controls (55.2% vs 63.2%, respectively, *P*= <.001). The odds ratio (95% CI) of the frequency of GG genotype vs the GA and AA genotypes in cases compared to controls was 8.5 (3.6-20.4), which is relatively high. The allele frequency assessment confirmed the significant higher frequency of the IL-4R G allele (43.8% vs 22.4%) and lower frequency of the A allele (56.2 % vs 72.6%) in patients compared with controls (P<.001), with no significant difference related to the IL-4 allele frequencies (*P*>.05; **Table 2**). The odds ratio

Table 1. Genotypes related to interleukin 4 [IL-4 (-590 T/C)] and interleukin 4 receptor (IL-4R) (Q551R A/G) polymorphisms among cases compared to controls.

	Case n (%)	Control n (%)	χ^2	*P*
IL-4 (-590 T/C)				
CC	56 (58.9)	50 (53.8)		
CT	30 (31.6)	33 (35.5)	0.514	.773
TT	9 (9.5)	10 (10.8)		
IL-4R (Q551R A/G)				
GG	41 (42.7)	7 (8.0)		
GA	2 (2.1)	25 (28.7)	43.375	<.001
AA	53 (55.2)	55 (63.2)		

L-4. Interleukin 4; IL-4R. interleukin 4 receptor.

Table 3. Genotypes related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms among case-subgroups as regard severity of acne.

	Severity of acne			χ^2	*P*
	Mild n (%)	Moderate n (%)	Severe n (%)		
IL-4 (-590 T/C)					
CC	19 (57.6)	29 (58.0)	8 (66.7)		
CT	8 (24.2)	19 (38.0)	3 (25.0)	5.758	.22
TT	6 (18.2)	2 (4.0)	1 (8.3)		
IL-4R (Q551R A/G)					
GG	14 (41.2)	23 (46.0)	4 (33.3)		
GA	2 (5.9)	0 (.0)	0 (.0)	4.370	.40
AA	18 (52.9)	27 (54.0)	8 (66.7)		

IL-4. Interleukin 4; IL-4R. interleukin 4 receptor.

Table 4. Genotypes related to IL-4 and IL-4R polymorphisms among case-subgroups as regard response to treatment of acne.

	Response to treatment			χ^2	*P*
	No N (%)	Moderate N (%)	Excellent N (%)		
IL-4 (-590 T/C)					
CC	46 (59.0)	9 (64.3)	1 (33.3)		
CT	25 (32.1)	3 (21.4)	2 (66.7)	2.680	.613
TT	7 (9.0)	2 (14.3)	0 (.0)		
IL-4R (Q551R A/G)					
GG	32 (40.5)	6 (42.9)	3 (100.0)		
GA	2 (2.5)	0 (.0)	0 (.0)	4.536	.338
AA	45 (57.0)	8 (57.1)	0 (.0)		

IL-4. Interleukin 4; IL-4R. interleukin 4 receptor.

Table 2. Allele frequencies related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms among cases compared to controls.

	Cases n (%)	Controls n (%)	χ^2	*P*
IL-4 (-590 T/C)	**n=190**	**n=186**		
C	142 (74.7)	133 (71.5)	0.5	.5
T	48 (25.3)	53 (28.5)		
IL-4R (Q551R A/G)	**n=192**	**n=174**		
G	84 (43.8)	39 (22.4)	18.6	<.001
A	108 (56.2)	135 (72.6)		

IL-4. Interleukin 4; IL-4R. interleukin 4 receptor.

(95% confidence interval) of the frequency of the G allele vs the A allele in cases compared to controls was 2.7 (1.7-4.2). When compared case subgroups with different disease severity (**Table 3**) and response to treatment (**Table 4**) regarding the genotype frequencies of their IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms, insignificant difference (*P*>.05) were observed.

The analysis of combined genotypes related to IL-4 (-590 T/C) and IL-4R (Q551R A/G) polymorphisms among cases and controls (**Table 5**) showed a significant increase in the frequency of CC + GG, TT + GG, and CT + GG genotypes in acne cases (21.1%, 3.2%, and 17.9%, respectively) compared to controls (4.6%, 0.0%, and 3.4%, respectively) with a decrease in the frequencies of the genotypes CC + GA, CT + GA, TT + GA, and CT + AA among cases (1.1%, 0.0%, 1.1%, and 13.7%, respectively) compared to controls (16.1%, 9.2%, 3.4%, and 20.7%, respectively, *P*=<.001).

DISCUSSION

Despite the power of modern approaches and persisting investigative efforts in the field of genetic association polymorphisms, acne vulgaris remains an enigmatic disorder so that the agent(s) triggering this disorder remain(s) to be identified.[8-15] In this work, the contribution of inflammatory component of acne imposed by the TH2 type cytokines is investigated through testing its association with IL-4 and IL-4R gene polymorphisms. To our knowledge, this is the first study searching in that direction taking into consideration the complex mechanisms interacting in the evolution of acne as a skin disorder.

Although the IL-4 (-590 T/C) polymorphism has been proven to affect the rate of transcription of IL-4 gene,[40] the present study showed no significant difference between cases and controls. Similarly, also no significant difference was observed in the frequency of IL-4 (-590 T/C) polymorphisms between cases and subgroups in

terms of disease severity or treatment response. These results are similar to those described in a previous case-control study showing no effect of the mutant genotype IL-4 (-590) TT in a number of inflammatory diseases including multiple sclerosis in Iranian patients.[41] This finding probably indicates that the mechanism involved in the pathogenesis of acne is not controlled in particular by the IL-4 cytokine, but rather by other interactive genetic susceptibility factors.[8,10,12,42,43]

Interestingly, and in contrast to the aforementioned finding, this study showed an extremely significant difference between acne cases and controls in the distribution of polymorphic genotypes related to IL-4 receptor Gln551Arg gene. Acne cases showed a high significant increase in the mutant genotype with a high frequency of the mutant G allele, although there was also no significant difference in these genotypes between the acne cases subgroups related to disease severity or therapeutic response. In fact the A>G polymorphism of the *IL-4R* gene was reported to be involved in the enhancement of atopic and allergic conditions or other immune-mediated disorders through modified TH1- or TH2-driven inflammatory reactions[37] in addition to a probable role in the innate immunity of the skin.[38] In this respect, observing this extreme significant difference led us to speculate that the signaling of TH1 or TH2 inflammatory pathways may be also playing a role in acne pathogenesis through the control of IL-4 receptors and may represent a specific factor in the susceptibility of acne affliction. This is demonstrated more by the high frequencies of IL-4R GG genotype with all polymorphic genotypes of IL-4 (CC, CT, and TT). A further study is probably needed for estimation of cytokines, both in the serum and in the local acne lesions, and also culturing of skin cells may be required to learn whether TH1 and/or TH2 have a specific role in the pathogenesis of acne. We also recommend another wider scale study with more cases and controls to investigate all genetic and protein polymorphisms related to the TH2 inflammatory pathway. In conclusion, this study provides evidence for a significant association of IL-4 receptor Q551R (A/G) genetic polymorphism with the susceptibility, rather than the severity of acne vulgaris in affected subjects.

Table 5. Combined genotypes related to interleukin 4 [IL-4 (-590 T/C)] and interleukin 4 receptor [IL-4R (Q551R A/G)] polymorphisms among cases compared to controls.

IL-4/IL-4R	Case n=95 (%)	Control n=87 (%)	χ^2	P
CC/GG	20 (21.1)	4 (4.6)		
CC/GA	1 (1.1)	14 (16.1)		
CC/AA	35 (36.8)	31 (35.6)		
CT/GG	17 (17.9)	3 (3.4)		
CT/GA	0 (.0)	8 (9.2)	44.61	<.001
CT/AA	13 (13.7)	18 (20.7)		
TT/GG	3 (3.2)	0 (.0)		
TT/GA	1 (1.1)	3 (3.4)		
TT/AA	5 (5.3)	6 (6.9)		

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