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Original Article

Association of IL-17A rs2275913 Polymorphism and Gene Expression in Cutaneous Leishmaniasis

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Abstract

Background: Leishmaniasis is a protozoan infectious disease in which host genetic polymorphisms may influence susceptibility and disease severity. We aimed to evaluate the IL-17A rs2275913 polymorphism and IL-17 expression in patients with cutaneous leishmaniasis compared with healthy controls in Ilam Province, western Iran.

Methods: Blood samples were obtained from 45 patients with cutaneous leishmaniasis and 45 healthy controls. Cutaneous leishmaniasis was diagnosed microscopically using Giemsa-stained lesion smears, without species-level identification. The IL-17A (197A>G) rs2275913 polymorphism was genotyped using ARMS-PCR, and IL-17 mRNA expression in peripheral blood was quantified by real-time PCR.

Results: Of the 45 patients with cutaneous leishmaniasis, 28.9% were female and 71.1% were male. Most patients had one to two lesions, mainly located on the hands and feet. There was no significant difference in the distribution of IL-17A rs2275913 genotypes and alleles between patients and controls ($P>0.05$). In contrast, IL-17 expression was significantly elevated in patients, showing a 4.6-fold increase compared with controls ($P<0.001$).

Conclusion: The rs2275913 polymorphism does not appear to be associated with susceptibility to cutaneous leishmaniasis. Although the sample size was relatively small, the marked upregulation of IL-17 expression highlights the active involvement of the IL-17 pathway in host immune responses and the inflammatory milieu of cutaneous leishmaniasis, likely reflecting immune modulation rather than direct pathogenesis.

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Introduction

Leishmaniasis is an endemic vector-borne disease in many tropical and subtropical regions and is considered one of the major neglected tropical diseases by the WHO because of its substantial public-health burden (1). The disease is caused by obligate intracellular protozoan parasites of the genus *Leishmania* (order Kinetoplastida, family *Trypanosomatidae*) and is transmitted to humans through the bite of infected female sand flies. These parasites alternate between two main developmental forms: the promastigote stage in the sand fly vector and the intracellular amastigote stage within mammalian macrophages (2, 3).

The immune response to cutaneous leishmaniasis (CL) involves a complex interplay of innate and adaptive mechanisms. Innate immune cells, including macrophages, neutrophils, and NK cells, participate in early parasite control, while $CD4^+$ T lymphocytes orchestrate subsequent adaptive responses (4). A balanced interaction between Th1, Th2, and Th17 subsets is critical for disease outcome. Th1 cytokines such as IFN-γ, TNF-α, and IL-12 promote macrophage activation and parasite clearance, whereas Th2 cytokines, including IL-4, IL-5, and IL-13, contribute to parasite persistence (5). Th17 cells and their signature cytokine interleukin-17 (IL-17) play an increasingly recognized role in CL pathogenesis. IL-17 amplifies inflammation by inducing chemokine expression, recruiting neutrophils, and enhancing tissue inflammatory responses. The IL-17A gene contains several functional polymorphisms that may alter cytokine expression. Among them, the promoter variant rs2275913 (197A>G) has been widely studied because of its potential impact on transcriptional activity and has been associated with susceptibility to various infectious and inflammatory diseases (4, 6, 7). Although a few studies have examined the rs2275913 polymorphism in cutaneous leishmaniasis, available data remain limited and mainly originate from regions where CL is caused by species such as *L. braziliensis* (5). To date, no published data exist on this polymorphism in Iran, an endemic region where *L. major* and *L. tropica* are the primary causative agents of CL. Given the high prevalence of CL in Ilam Province, western Iran, and the importance of cytokine-mediated immune mechanisms in disease outcomes, investigating host genetic variants with potential functional relevance is essential.

Therefore, we aimed to evaluate the IL-17A rs2275913 (197A>G) polymorphism and IL-17 gene expression levels in patients with cutaneous leishmaniasis compared with healthy individuals in Ilam Province.

Methods

This case–control study included 45 patients with microscopically confirmed cutaneous leishmaniasis referred to healthcare centers across Ilam Province, western Iran. The control group consisted of 45 healthy individuals with no history or clinical signs of cutaneous leishmaniasis. Controls were frequency-matched to the patient group at the cohort level by age, sex, and place of residence and had no history of chronic inflammatory or autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, or systemic lupus erythematosus.

Sampling and ethical approval

After providing a complete explanation of the study objectives, written informed consent was obtained from all participants. Demographic data were collected using a structured questionnaire.

For diagnostic confirmation, lesion smears were prepared, fixed with methanol, stained with Giemsa, and examined microscopically for the presence of *Leishmania* amastigotes. No

species-specific molecular assay, culture, or sequencing was performed; therefore, parasite species identification was not available for the study participants. Approximately 5 mL of peripheral venous blood was collected from each participant. Samples intended for DNA extraction were stored at −20 °C, while RNA extraction was performed immediately after sample collection. Simultaneously, 45 healthy individuals with no history or clinical signs of cutaneous leishmaniasis were recruited as the control group.

DNA extraction and genotyping

Genomic DNA was extracted from buffy coat samples using the AnaCell DNA extraction kit (Iran) according to the manufacturer's instructions. Genotyping of the IL-17A rs2275913 (197A>G) polymorphism was performed using the amplification refractory mutation system polymerase chain reaction (ARMS-PCR). Allele-specific primers were designed using Oligo software (version 7) and are listed in Table 1. Genotyping of the IL-17A rs2275913 polymorphism was performed using a tetra-primer ARMS-PCR assay. The reaction produced a common internal control amplicon of 722 bp to verify successful amplification, a 578 bp amplicon specific for the wild-type A allele, and a 199 bp amplicon specific for the mutant G allele. The PCR products were separated on a 2% agarose gel alongside a 100-bp DNA ladder and visualized under UV illumination using a gel documentation system. Genotypes were assigned as follows: AA (bands at 722 bp and 578 bp), AG (bands at 722 bp, 578 bp, and 199 bp), and GG (bands at 722 bp and 199 bp).

Table 1: Nucleotide sequences of primers for the rs2275913 polymorphism

Polymorphism		Primer	Alleles
rs2275913 IL17A	Forward inner primer	TTCCCATTTTCCTTCAGACGG	G
	Reverse inner primer	CCCCAATGAGGTCATAGAAGAATCTATT	A
	Forward outer primer	AATGGAAAATCAAGGTACATGACACC	
	Reverse outer primer	GATGGATGAGTTTGTGCCTGCT	

ARMS-PCR amplification was carried out with an initial denaturation at 95 °C for 5 min, followed by 35 cycles of denaturation at 95 °C for 30 sec, annealing at 60 °C for 45 sec, and extension at 72 °C for 1 min, with a final extension step at 72 °C for 10 min (8, 9)

Gel electrophoresis

PCR products were separated on a 2% agarose gel prepared in 1× TBE buffer and run at 90 V. A 100-bp DNA ladder (Sinagen, Iran) was used as a molecular size marker. Gels were visualized and documented using a SYNGENE gel documentation system.

RNA extraction and cDNA synthesis

Total RNA was extracted from buffy coat samples using RNX-PLUS reagent (Sinaclon, Iran) according to the manufacturer's protocol. RNA concentration and purity were assessed using a NanoDrop spectrophotometer (Thermo Scientific), and samples with acceptable A260/A280 ratios were selected for further analysis. Complementary DNA (cDNA) was synthesized using a commercial cDNA synthesis kit (AddBio, South Korea).

Quantitative real-time PCR

Quantitative real-time PCR (qPCR) was performed using a SYBR Green master mix (Yekta Tajhiz, Iran) in a final reaction volume of 20 µL. All reactions were conducted under

RNase-free conditions. The human RNase P gene was used as the internal reference due to its stable expression in peripheral blood leukocytes. Negative controls (no-template controls) were systematically included in all ARMS-PCR and real-time RT-PCR runs to monitor for contamination.

Gene expression analysis

Relative expression levels of IL-17 were calculated using the $2^{-\Delta\Delta Ct}$ method. The ΔCt value was determined by subtracting the Ct value of the reference gene (RNase P) from that of the target gene (IL-17). The ΔΔCt value was calculated by comparing the ΔCt of each sample to the mean ΔCt of the control group. Fold changes in gene expression were calculated as $2^{-\Delta\Delta Ct}$.

Statistical analysis

Statistical analyses were performed using SPSS software (ver. 22.0; IBM Corp., Armonk, NY, USA). Because a frequency-matched design was employed, independent comparative tests were conducted. Differences in genotype frequencies under the codominant model (AA vs. AG vs. GG) and allele frequencies under the allelic model (A vs. G) between patients and controls were analyzed using Fisher's exact test and Pearson's chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between the IL-17A rs2275913 polymorphism and susceptibility to cutaneous leishmaniasis. Conformity of genotype distributions with Hardy–Weinberg equilibrium (HWE) was assessed in both groups using the chi-square goodness-of-fit test. Differences in *IL-17A* expression levels between groups and across genotypes were evaluated by comparing normalized ΔCt values using the non-parametric Mann–Whitney U test, while relative fold changes were calculated using the$2^{-\Delta\Delta Ct}$. A *P*-value<0.05 was considered statistically significant.

Ethical Considerations

All procedures conducted in this study were reviewed and approved by the Ethics Committee of Hamadan University of Medical Sciences under the approval code IR.UMSHA.REC.1401.408. Written informed consent was obtained from all participants prior to sample collection. Confidentiality of participant information was strictly maintained throughout all stages of the research, and all data were analyzed and reported in aggregate form to ensure participant anonymity.

Results

Among the 45 confirmed patients with cutaneous leishmaniasis, 13 (28.9%) were female and 32 (71.1%) were male. The mean age of the patients and controls was 44.29 ± 15.77 and 42.62 ± 7.47 yr, respectively. Most lesions were located on the hands (48.9%), and overall, 82.2% of the lesions were observed on the hands and feet. The number of lesions ranged from one to more than seven; however, the majority of patients (62.2%) presented with one to two lesions. The mean number of lesions was 2.51 ± 1.78, and the mean duration of the disease was 6.60 ± 4.7 months (Table 2). The ARMS-PCR results showed that the majority of samples in both groups exhibited a 578 bp band corresponding to the wild-type homozygous genotype. This genotype was observed in 24 patients (53.3%) and 25 controls (55.6%) (Fig. 1). The frequencies of the AA and AG genotypes were higher in the control group than in the patient group, whereas the GG genotype was more frequent among patients.

The distribution of IL-17A rs2275913 genotypes in the patient and control groups is summarized in Table 3. According to Fisher's exact test, no statistically significant association was observed between this polymorphism and susceptibility to cutaneous leishmaniasis ($P>0.05$). Assessment of Hardy–Weinberg equilibrium revealed a significant deviation from expected proportions in both the control and patient groups ($P<0.001$), mainly due to the low frequency of the heterozygous AG genotype.

Table 2: Demographic and clinical characteristics of patients with cutaneous leishmaniasis (n = 45)

Variable	Category/Value	N (%) Mean ±SD
Sex	**Male**	32 (71.1)
	Female	13 (28.9)
Age (yr)	**Mean±SD**	44.29±15.77
Number of lesions	**1-2**	28 (62.2)
	3-4	10 (22.2)
	5-6	4 (8.9)
	≥7	3 (6.7)
Duration of disease (months)	**Mean±SD**	6.6±4.7
Location of lesions	**Hand**	22 (48.9)
	Foot	15 (33.3)
	Face	3 (6.7)
	Trunk	5 (11.1)
Educational level	**Illiterate/Primary**	14 (31.1)
	Diploma	22 (48.9)
	University	9 (20)
Occupation	**Self employed**	18 (40)
	Employee	12 (26.7)
	Farmer /Animal husbandry	4 (8.9)
	Unemployed	11 (24.4)

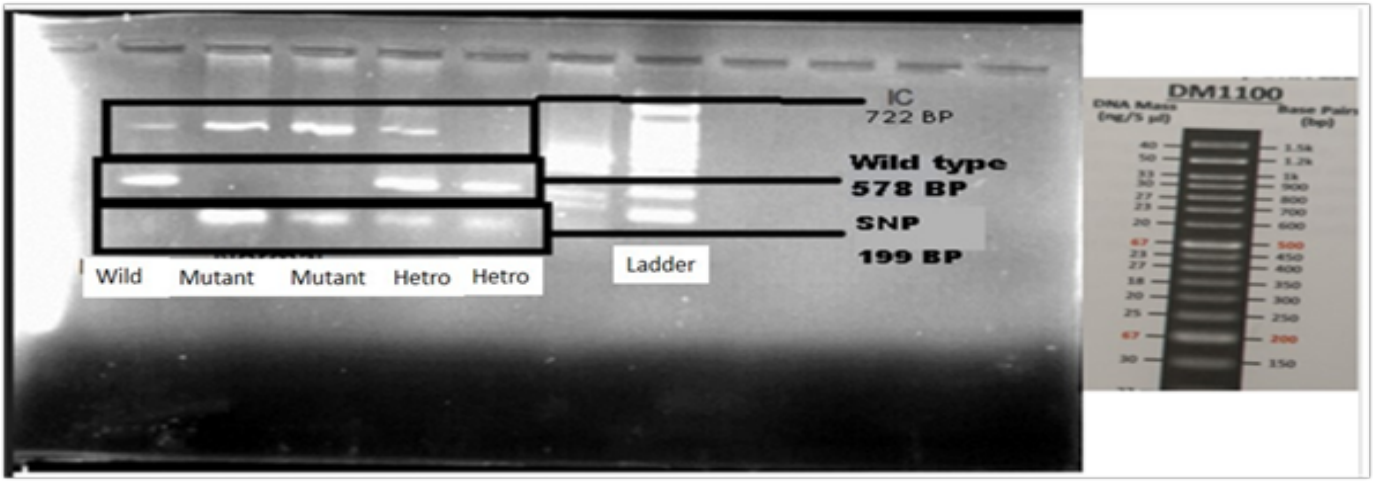


Fig. 1: Agarose gel electrophoresis (2%) of tetra-primer ARMS-PCR products for *IL-17A* rs2275913 genotyping.
Lanes 1 (Wild / AA): Homozygous wild-type genotype showing the 722-bp internal control (IC) band and the 578-bp allele-specific band.
Lanes 2 & 3 (Mutant / GG): Homozygous mutant genotype showing the 722-bp IC band and the 199-bp allele-specific band.
Lanes 4 & 5 (Hetro / AG): Heterozygous genotype showing all three amplicons (722-bp IC, 578-bp wild-type allele, and 199-bp mutant allele).
Lane Ladder: DNA molecular weight marker (DM1100, 100–1500 bp)

Distribution of IL-17A rs2275913 genotype and allele frequencies in patients with cutaneous leishmaniasis and healthy controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using AA genotype and A allele as the reference categories. No significant association was observed between IL-17A rs2275913 polymorphism and susceptibility to cutaneous leishmaniasis. Hardy–Weinberg equilibrium: patients (P<0.001), controls (P<0.001).

Table 3: Distribution of IL-17A rs2275913 genotype and allele frequencies in patients with cutaneous leishmaniasis and healthy controls.

Genotype/Allele	Patients n (%)	Controls n (%)	OR (95 % CI)	*P*-value
AA	24 (53.3)	25 (55.6)	Reference	-
AG	2 (4.4)	3 (6.7)	0.69 (0.11-4.37)	0.71
GG	19 (42.2)	17 (37.8)	1.16 (0.52-2.59)	0.71
A allele	50 (55.6)	53 (58.9)	Reference	-
G allele	40 (44.4)	37 (41.1)	1.15 (0.63-2.11)	0.63

Relative gene expression was calculated using the Ct values of the reference and target genes, and the fold change in IL-17 expression was determined using the $2^{-}\Delta\Delta Ct$ method with REST software. The mean IL-17 expression level in the patient group showed a 4.6-fold increase compared with the control group. Fig. 2 presents the amplification, melting-curve, and standard-curve analyses for IL-17A and the reference gene RNase P. The amplification and melting profiles were used to verify successful amplification and product specificity, while the standard curves were used to assess assay performance.

Before group comparison, data normality was assessed using the Kolmogorov–Smirnov test. Because the data were not normally distributed (P<0.001), comparisons were performed using the non-parametric Mann–Whitney U test. Relative IL-17A expression, calculated using the $2^{-}\Delta\Delta Ct$ method, was significantly higher in patients with cutaneous leishmaniasis than in controls (4.6 ± 3.49 vs. 1.00 ± 1.53, respectively; P<0.001). The patient group showed a markedly higher mean relative IL-17A expression, although inter-individual variability was observed within both groups (Fig. 3)

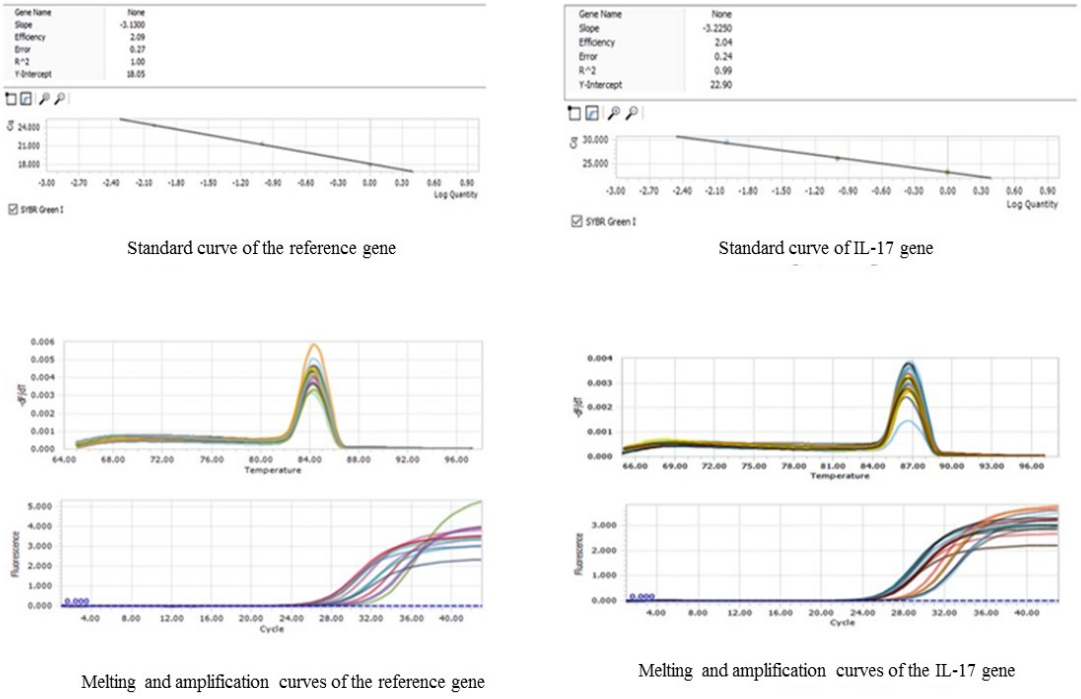


Fig. 2: Standard curves, amplification plots, and melting-curve profiles of *IL-17A* and *RNase P* genes. The single melting peak confirms amplification specificity

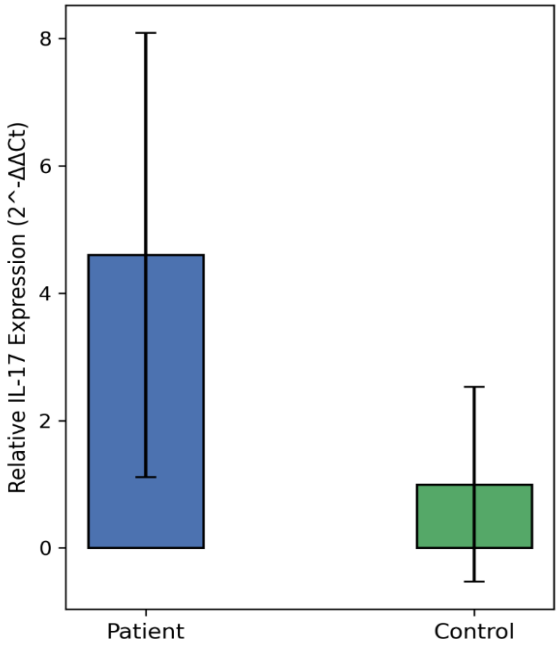


Fig. 3: Relative IL-17A mRNA expression in patients with cutaneous leishmaniasis and healthy controls, calculated using the $2^{-}\Delta\Delta Ct$ method. Data are presented as mean ± SD. IL-17A expression was significantly higher in patients than in controls (Mann–Whitney U test, $P<0.001$)

Discussion

The findings of the present study demonstrated that the IL-17A rs2275913 polymorphism was not significantly associated with susceptibility to cutaneous leishmaniasis. Nevertheless, IL-17 gene expression was markedly upregulated in patients, showing a 4.6-fold increase compared with healthy controls. These findings suggest that enhanced transcriptional activity of IL-17, rather than genetic variation at the rs2275913 locus, may contribute more substantially to the immunopathogenesis of cutaneous leishmaniasis.

The role of IL-17 in leishmaniasis was first highlighted in Sudan, that reported *L. donovani* strongly induces the production of IL-17 and IL-22. Subsequent studies have shown that *Leishmania* infection promotes the expansion of Th17 cells, leading to increased levels of these cytokines. Th17 cells are known to modulate monocyte and neutrophil activity and facilitate the recruitment of Th1 cells to granulomatous lesions, thereby contributing to the regulation of the inflammatory response. In addition, IL-17 and IL-22 participate in epithelial barrier maintenance and tissue repair, which may further enhance host defense mechanisms. Taken together, these findings highlight the complex immunological role of IL-17 in leishmaniasis and support the possibility that increased IL-17 expression in patients may occur independently of rs2275913 polymorphic variation (10).

The rs2275913 polymorphism is a promoter variant located at position −197 of the human IL-17A gene and involves an A-to-G substitution (11). Variations at this locus may influence the transcriptional activity of the IL-17A gene and consequently alter cytokine production levels. Such genetic differences in the host immune system can affect inflammatory responses and may contribute to variations in susceptibility or clinical outcomes in infectious diseases, including cutaneous leishmaniasis (12). Therefore, investigating this polymorphism may provide insights into host genetic factors that modulate immune responses against *Leishmania* infection.

Sadighi et al. investigated the IL-17 rs2275913 polymorphism in 259 individuals, including 88 subjects with a history of visceral leishmaniasis and 171 healthy controls. Using the indirect fluorescent antibody (IFA) test, the control group was further subdivided into seropositive (n = 88) and seronegative (n = 83) individuals. In their study, the G allele was more frequent than the A allele across all groups; however, no significant differences were observed between patients and controls, and the distribution of the A allele was relatively similar among them. Among patients, the AG genotype (37%) was slightly more frequent than GG (35%) and AA (30%) (13). In contrast, our study demonstrated a different distribution pattern. Among patients with cutaneous leishmaniasis, the AA and GG genotypes were more frequent (53.3% and 42.2%, respectively), whereas in healthy controls the AA genotype was predominant (55.6%). Despite these differences in genotype distribution, no statistically significant association was observed between rs2275913 and susceptibility to cutaneous leishmaniasis in our population. These findings are consistent with those of Sadighi et al., who also reported no significant association between IL-17 polymorphisms and visceral leishmaniasis. Collectively, these results suggest that IL-17 rs2275913—and possibly other IL-17 variants—may not have a strong independent effect on susceptibility to leishmaniasis (13). The TT genotype of IL-17 rs8193036 was associated with a 4.7-fold increase in the risk of visceral leishmaniasis, suggesting a role for this specific variant in disease pathogenesis. However, regarding the rs2275913 polymorphism, they observed that while the A allele was associated with active

kala-azar, the overall genotype distributions did not differ significantly between the studied groups (14). In agreement with these observations, the present study also found no significant difference in the frequency of the rs2275913 A allele or genotypes between patients and healthy controls, further suggesting that this specific locus may not be a primary genetic determinant for leishmaniasis susceptibility across different populations.

Although protective role of IL-17 in visceral leishmaniasis has been well documented, its function in cutaneous leishmaniasis is less clear and remains the subject of ongoing research (15). Th17 cells contribute to the initiation and persistence of cutaneous infection as well as lesion development. While IL-17 is known to amplify inflammatory responses, its capacity to directly mediate parasite killing remains controversial. Current evidence suggests that IL-17 primarily promotes inflammation and tissue pathology rather than effective parasite clearance (15-17). Consequently, the precise contribution of IL-17 to parasite control and the development of symptomatic cutaneous leishmaniasis has yet to be fully elucidated (15).

Albuquerque et al. reported a weak association between the A allele of IL-17A rs2275913 and susceptibility to *L. braziliensis* infection; however, genotype frequencies did not differ significantly between patients and controls (5). Similarly, our results showed no significant association between this polymorphism and cutaneous leishmaniasis. The discrepancies between the two studies may be attributed to differences in parasite species, host genetic background, or local epidemiological factors. In both studies, a predominance of male patients was observed, which is more likely related to increased exposure to sand fly bites rather than sex-related differences in immunity. Furthermore, functional evidence suggests that IL-17 genetic variants may still influence cytokine production levels, even in the absence of significant differences in genotype distribution (5). Beyond occupational and behavioral exposure, sex-based immunological differences driven by sex hormones may also modulate Th17 responses and cytokine production. While the high proportion of male patients might have influenced overall IL-17 expression patterns, the small sample size precluded stratified subgroup analyses by sex (18).

Interestingly, a protective role of IL-17 has also been reported in *T. cruzi* infection, another member of the *Kinetoplastida* order. In Chagas disease, IL-17 has been linked both to parasite control and to the development of severe cardiomyopathy, and the A allele of rs2275913 has shown a significant association with Chagas cardiomyopathy in Latin American populations (19, 20). In Brazil, rs2275913 was strongly associated with protection against tuberculosis, where the A allele was linked to higher IL-17 expression and the G allele to increased disease susceptibility (21). In contrast, our findings showed no association between rs2275913 and susceptibility to cutaneous leishmaniasis, which may reflect differences in pathogen type, dominant immune responses, and host genetic background. These SNPs have also been implicated in viral infections. For example, rs2275913 has been associated with chronic hepatitis B and an increased risk of hepatocellular carcinoma, with the GG genotype correlating with higher IL 17 production. In contrast, rs8193036 has been reported to contribute to resistance against hepatitis B virus infection (22).

The A allele of rs2275913 markedly increases the binding affinity of nuclear factor of activated T cells (NFAT) to the IL-17A promoter, thereby enhancing IL-17 transcription and secretion. Accordingly, individuals carrying the AA or AG genotypes were suggested to produce higher IL-17 levels than those with the GG genotype (23). Consistent with this functional evidence, our results demonstrated an approximately

4.6-fold increase in IL-17 gene expression in patients compared with controls, supporting the regulatory effect attributed to the A allele. Studies of *L. braziliensis* infection have also indicated that the A allele may be associated with altered Th17 differentiation, while IL-17 levels in PBMC supernatants remain elevated in infected individuals. *Leishmania* infection strongly stimulates IL-17 production, and increased cytokine levels have frequently been reported in PBMC cultures derived from infected patients. However, the cellular heterogeneity of PBMC populations and the complexity of host immune responses may influence both Th17 differentiation and cytokine secretion. Consequently, infection-driven immune activation may partially modify or override the functional effects attributed to this SNP (24).

IL-17A is a central amplifier of pro-inflammatory immunity (25), and has been implicated in both parasite control and spontaneous healing in certain *Leishmania* infections (17). However, its principal role is the amplification of inflammation rather than direct parasite killing, which mainly depends on IFN-γ–activated macrophages (16). The reported positive correlation between IL-17 and IFN-γ expression in human samples further indicates that IL-17 may help sustain macrophage activation during subclinical infection (16). In line with these findings, the elevated IL-17 expression observed in our patients likely reflects its role in promoting cutaneous inflammation. Genetic variants within the IL-17 pathway have also been associated with a variety of diseases, including gastric cancer, inflammatory bowel disease—particularly involving the rs8193036 T allele (26), and tuberculosis, where the rs2275913 A allele has been implicated. In contrast, no association has been reported between IL-17 polymorphisms and susceptibility to brucellosis (27).

Limitations

Nevertheless, the present study has several limitations, including the relatively small sample size, evaluation of only a single SNP, and the absence of functional assays or detailed parasite species identification. A limitation of this study is the lack of molecular species identification. Diagnosis was established microscopically via Giemsa-stained smears; therefore, although the ulcerative lesions clinically suggested *Leishmania major* (the predominant species in Ilam Province), the presence of *L. tropica* cannot be definitively excluded. Future studies employing molecular assays are necessary to determine if IL-17 pathway dynamics are species-dependent. Future studies with larger cohorts, simultaneous analysis of multiple IL-17–related polymorphisms, and comprehensive characterization of parasite species and clinical phenotypes are therefore required to better clarify the role of IL-17 and its genetic variants in cutaneous leishmaniasis. Additionally, IL-17 was evaluated solely at the transcript (mRNA) level; because mRNA abundance does not always directly correlate with functional circulating protein levels, future studies measuring serum IL-17 concentrations alongside gene expression are recommended. Finally, control subjects were selected based on clinical history and physical examination (absence of active lesions or suggestive scars). While this clinical screening is standard practice in field-based case-control studies for cutaneous leishmaniasis, we acknowledge that it cannot definitively rule out subclinical *Leishmania* exposure, which represents a potential study limitation.

Conclusion

The IL-17A rs2275913 polymorphism is not independently associated with susceptibility to cutaneous leishmaniasis in the studied population. Given the cross-sectional nature of this study, the elevated IL-17 expression

observed in CL patients should be interpreted with caution. Rather than acting as a direct driver of immunopathology, this upregulation may reflect a downstream inflammatory reaction, a compensatory regulatory response to control localized tissue inflammation, or an attempt to modulate host defenses during active infection.

The heterogeneous results reported across different populations and infectious diseases suggest that the influence of this polymorphism may depend on multiple factors, including pathogen characteristics, host genetic background, and environmental context.

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Conflict of interest

The authors declare that there is no conflict of interests.

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