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ORIGINAL ARTICLE

Interleukin-17A gene single nucleotide polymorphism and its relation to fungal growth in psoriatic patients: A preliminary study

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Abstract

Background: Although dysbiosis and the role of the microbiome in the pathogenesis of inflammatory skin diseases have been intensively investigated, fungal colonization or infection has received minimal attention.

Aims: To isolate and identify different fungal species namely *Candida*, *Dermatophytes*, *Malassezia*, and *Aspergillus* from plaque psoriasis patients, evaluate the association of IL-17A gene single nucleotide polymorphisms (SNPs) with psoriasis, and to reveal the relation between IL-17A gene SNPs and the fungal presence within the psoriatic plaques.

Patients/Methods: Fifty plaque psoriasis patients and fifty healthy age and sex volunteers as controls were enrolled in this study. From psoriatic plaques, mycological isolation was done by direct microscopic examination (10% KOH mount), culture onto the three sets of media then species identification by phenotypic procedures. Genomic DNA extraction and genotyping for IL-17A (rs10484879) SNPs using polymerase chain reaction and restriction fragment length polymorphism were also done.

Results: Psoriasis cases showed higher frequency of fungal growth 86% vs. 14% in controls; ($p < 0.001$). The frequency of IL-17A GA, AA, and total polymorphism (GA+AA) genotypes in psoriasis cases was significantly higher than in controls. There was non-significant association between different IL-17A genotypes and fungal growth except *Aspergillus flavus*, which decreased gradually with GG, GA, and AA (37.5%, 20.8%, and 0%, respectively).

Conclusions: Psoriasis cases are significantly associated with fungal growth, which may be a contributing factor in its pathogenesis. SNPs of IL-17A (rs10484879) G/A gene led to increased susceptibility toward pathogenesis of psoriasis. Fungal growth and IL-17A GA+AA genotypes are suggested to be independent predictors of psoriasis susceptibility.

KEYWORDS
culture, fungal infections, IL-17A, psoriasis, single nucleotide polymorphism

1 | INTRODUCTION

Although psoriasis is one of the most studied dermatological conditions, the pathogenesis of this disease is still not completely elucidated due to the complex interactions between different cell types and cytokines.[1] Psoriasis has been considered as a T helper(Th)-1/Th-17 mediated, chronic inflammatory dermatosis and now, Th-17 cell subset is regarded as a key player in psoriasis.[2]

Interleukin (IL)-17 is a pleiotropic novel pro-inflammatory cytokine family containing 6 distinct isoforms (IL-17A to IL-17F). This family has been the focus of intensive research because of its crucial role in the pathogenesis of psoriasis. This family also has a very important role in regulating the response of the immune system to infectious, inflammatory, autoimmune, and neoplastic disorders.[3]

Recently, it is proposed that psoriasis is an IL-17A-driven disease.[2] IL-17A is a key mediator of the inflammatory pathway, and its role in the pathogenesis of psoriasis had been attributed to the disruption of the immune responses. It improves T-cell priming and promotes the release of multiple pro-inflammatory mediators by epithelial, endothelial, and fibroblastic cells as IL-1, IL-6, TNF-α, and chemokines. In addition, IL-17A is important for maintenance and recruitment of neutrophils.[1,4]

Genetic variations in inflammation-related genes, especially cytokines and their receptors, may lead to an increase in expression of IL-17. In this regard, it is reasonable to hypothesize that genetic variation in IL-17A may affect the expression or activity of this gene which in turn may influence the susceptibility and severity of psoriasis.[5]

The skin microbiome exerts an active role in immune regulation and pathogen defense. The association between the microbiome and inflammatory skin diseases has been increasingly recognized due to an aberrant immune activation triggered by them.[6] Microbial dysbiosis of the skin and mucosa is thought to cause an exaggerated immune response in a susceptible host, resulting in a persistent inflammatory process associated with autoimmune disorders.[7] Dysregulated skin microbiomes have been found to be associated with psoriasis, atopic dermatitis, and acne vulgaris.[8]

Various microorganisms like *Malassezia* (*M*) species, *Candida albicans*, Streptococcus pyogenes, and Staphylococcus aureus have been incriminated either in provocation or in exacerbation of psoriasis.[9]

The aim of the present study was to isolate and identify different species of fungal infection namely *Candida*, *Dermatophytes*, *Malassezia*, and *Aspergillus* from patients with plaque psoriasis, evaluate the association of IL-17A gene single nucleotide polymorphisms (SNPs) with psoriasis in comparison with the control group, correlate the presence of gene SNPs of IL-17A with the severity of psoriasis, and to reveal the relation between gene SNPs of IL-17A and the possibility of the fungal presence within the psoriatic plaques.

2 | PATIENTS AND METHODS

2.1 | Patients

This case-control study was carried out on a total of 100 individuals attending the Outpatient Clinic of Dermatology and Andrology Department of Benha University Hospitals, from April 2019 to December 2020. They were divided into:

2.1.1 | Patient group

This group included 50 patients having plaque psoriasis. The diagnosis of psoriasis was based on the clinical findings, and if necessary, being confirmed by histopathological studies.

2.1.2 | Control group

This group included 50 healthy volunteers who were age and sex matched with the patient group.

An informed consent approved by the local ethics committee of research of Benha Faculty of Medicine was taken from all individuals before being enrolled in this study.

The clinically diagnosed patients with plaque psoriasis involving both genders with different ages were included in this study. The newly diagnosed psoriatic patients (prior to treatment) and those who had stopped topical treatment for at least 2 weeks, systemic and phototherapy for at least 4 weeks were enrolled in this study.

Patients with any of the following conditions were excluded from this study; guttate, erythrodermic, or pustular psoriasis, psoriatic arthritis, concurrent significant medical conditions such as diabetes mellitus, hepatic, renal or cardiovascular diseases, acute or chronic cutaneous or systemic infections, any other coexistent autoimmune or allergic disorders or malignancies, any sort of immunosuppression, history of intake of topical or systemic antifungal drugs for one month prior to the study and treatment with any systemic antipsoriatic therapy or phototherapy within three months or application of topical antipsoriatic therapy within 2 weeks prior to sample collection.

2.2 | Methods

All patients were subjected to detailed medical history taking, general clinical examination, local dermatological examination of the psoriasis plaques, and grading of psoriasis severity using the Psoriasis Area and Severity Index (PASI) score.[10]

2.2.1 | Mycological isolation and identification

Specimen collection

From all individuals enrolled in this study, the area of skin to be sampled was first swabbed with 70% ethyl alcohol prior to sampling to remove surface bacterial contaminants.[11]

From patient group. Scales were collected from the most scaly site in the lesional area by gentle scraping using sterile scalpel blade then were placed in a clean sterile filter paper, which was folded to form a flat packet then enclosed by adhesive tape.[11] The filter paper was labeled with the patient's name, number, and date of collection and then sent without delay to the Medical Microbiology and Immunology Department, Benha University, where further investigations were done.

From control group. From the normal skin (matched site with lesions in patients) of healthy individuals, samples were collected by a standard swab method. Three swabs were taken from normal areas and spread on different culture media. A sterile cotton swab soaked with sterile saline was used to rub against the skin surface, with continuous rotation of the swab and over at least 15 s, and immediately streaked evenly onto already prepared media.[12]

Sample processing

All the collected specimens were divided into two portions: The first one was examined microscopically using 10% potassium hydroxide (KOH) according to Lindsay et al.[13] The second portion was cultured onto the three sets of media included in this study: Sabouraud's Dextrose Agar (SDA) (Oxoid, England), Sabouraud's Cycloheximide Chloramphenicol Agar (HIMEDIA), and Dixon's agar (Twin Pack) medium (HIMEDIA). Any fungal growth was identified according to Deorukhkar and Saini[14]; Ashbee[11]; Lindsay et al.[13]; Saunte et al.[15]

Interpretation of the fungal growth seen on SDA. Within incubation period of 24–72 h, *Candida* produces colonies which are cream colored, smooth, pasty, and convex.[14] *Aspergillus fumigatus* produces a fluffy to granular, white to blue-green growth. *A. flavus* produces a yellow-green colony, while *Aspergillus niger* Growth begins initially as a yellow colony that soon develops a black and dotted surface, later the colony becomes jet black and powdery.[13]

Interpretation of the fungal growth seen on Sabouraud's Cycloheximide chloramphenicol Agar

This medium inhibits fungi like *Aspergillus* and certain *Candida* species but allows the *dermatophytes* to grow well with its different colonies characteristics.[11] Plates for *dermatophytes* were incubated for 4 weeks and examined every alternative day for any growth. Dermatophyte growth was identified both by culture and by microscopic characters.

Interpretation of the fungal growth seen on Dixon's Agar

Only *Malassezia* can grow onto this medium. The colonies are cream to yellowish, smooth or lightly wrinkled, moist and glistening or dull.[15]

Extraction of genomic DNA and genotyping for IL-17A (rs10484879) SNPs

This was done using polymerase chain reaction (PCR) and restriction fragment length polymorphism (PCR-RFLP) according to Du et al.[16]; Lee et al.[17]

2.3 | Statistical analysis

Statistical analysis of the data was performed using Statistical Package for Social Sciences (SPSS, trial version 16.0) developed by IBM corporation on Java platform. The observed genotype distributions were compared with those expected from Hardy-Weinberg equilibrium using a standard chi-square test. Adjusted odds ratio (OR) for the genotypes was calculated after correction for psoriasis risk factors with binary logistic regression. The power of the study was calculated using CaTS-Power Calculator software.[18] Calculated power was 98%, using disease allele frequency of 0.52 and odds ratio of 2.26 and level of significance of 0.05. All quantitative statistical analysis was carried out at 5 percent value of significance.

3 | RESULTS

3.1 | Demographic and clinical data

The current study included 50 psoriasis cases; their mean age was 41.2 ± 11.6 years. They were 30 males (60%) and 20 females (40%). Control group was selected to be matched in age and gender ($p > 0.05$ for each). Their mean age was 41.1 ± 12.5 years; they were 30 males (60%) and 20 females (40%). Psoriasis cases were significantly associated with higher frequency of positive family history (18% vs. 4% in control group) ($p = 0.025$) and smoking (44% vs. 10% in control group) ($p < 0.001$).

Most of psoriasis cases had gradual onset (96%), while only 4% had acute onset, 68% had remission and exacerbation course and 32% were progressive. Most of them had generalized form (96%), and only 5% had localized psoriasis. On determination of PASI score in psoriasis cases, the mean PASI score was 9.4 (SD ± 3.1), the PASI score was found to be mild in 68%, moderate in 26%, and severe in 6%.

3.2 | Determination of different IL-17A genotypes using Rsa 1 restriction profiles of the 197G/A polymorphic sites of IL-17A gene in all recruited individuals

On viewing gel electrophoresis of psoriasis cases, the GG genotype (Lane 3) represents the homozygous alleles normal pattern, while gene polymorphisms were demonstrated in the AG genotype and the AA genotype. Polymorphism of a single gene allele was observed in the AG genotype (heterozygous pattern) (Lane 2), while both gene

alleles showed polymorphisms in the AA genotype (homozygous pattern) (Figure 1A).

In controls, the gel showed two different alleles expressions: the homozygous normal GG genotype and the heterozygous AG genotype with polymorphism of one of its two alleles (Figure 1B).

3.3 | Assessment of IL-17 genotypes and alleles in psoriasis

Regarding the frequency of IL-17A GA, AA, and total polymorphism (GA+AA) genotypes in psoriasis cases, it was found to be significantly higher than that in the control group ($p = 0.015$, 0.012, 0.004, respectively). A allele had higher frequency in psoriasis cases when compared to the control group ($p < 0.001$). This indicated higher risk to develop psoriasis (OR = 1.584, 1.688, 1.625, 5.922, respectively) (Table 1).

3.4 | Association of clinical and demographic data with different IL-17A genotypes in psoriasis cases

There was non-significant relation between all demographic and clinical data of patients and different IL-17A genotypes except for PASI score which increased gradually with GG, GA, and AA (mean ± SD = 6 ± 1.9, 8.7 ± 1.2, 11.8 ± 3.9, respectively; $p < 0.001$). Frequency of mild PASI decreased gradually with GG, GA, and AA (100%, 91.7%, 22.2%, respectively; $p < 0.001$), while frequency of moderate PASI increased gradually with GG, GA, and AA (0%, 8.3, 61.1%, respectively; $p < 0.001$). The results of this study also showed that the frequency of progressive course increased gradually with GG, GA, and AA (12.5%, 20.8%, 55.6%, respectively; $p = 0.031$) (Table 2).

3.5 | Fungal growth in psoriasis cases vs. healthy controls

In patients with psoriasis, out of the 50 cases, fungal growth was identified in 43 of them. Also, fungal growth was identified in 7 out of the 50 healthy controls, psoriasis cases were significantly associated with higher frequency of fungal growth (86% vs. 14%, $p < 0.001$) than that found in controls (Table 3).

Aspergillus mold was found in 56% of cases (28 out of 50) and in 8% of controls (4 out of 50) denoting a significant difference ($p < 0.001$) between the 2 groups. *Candida* was found in 18% of cases (9 out of 50) and 4% of controls (2 out of 50) denoting a significant difference ($p = 0.025$) between the 2 groups. *Malassezia* was found in 22% of cases (11 out of 50) and 2% of controls (1 out of 50). These results were considered significant ($p = 0.002$). *Dermatophytes* were found in only one case (2%) (Table 3).

All the isolated *Candida* yeast were *C. albicans* (Figure 2C, D). From *Malassezia* yeast, *M. furfur* and *M. restricta* were identified, *M. furfur* was significantly associated with psoriasis cases compared to the control group (18%; 9 out of 50 vs. 2%; 1 out of 50, respectively). These results denoting a significant difference ($p = 0.008$) (Figure 2F), *M. restricta* did not differ significantly between both groups ($p = 0.495$) (Table 3). T. mentagrophytes was the only *dermatophytes* species identified (Figure 2H).

From the isolated *Aspergillus* mold, *A. fumigatus* was identified in 20% of psoriasis cases (10 out of 50) and in 2% of controls (1 out of 50) (Figure 3B, G). *A. niger* was identified in 28% of psoriasis cases (14 out of 50) and in 2% of controls (1 out of 50) (Figure 3E, F). *A. flavus* was identified in 16% of psoriasis cases (8 out of 50) and in 4% of controls (2 out of 50) (Figure 3C, D, H). *A. fumigatus*, *A. niger*, and *A. flavus* were significantly associated with psoriasis cases compared to the control group ($p = 0.004$, <0.001, 0.046, respectively).

3.6 | Association of fungal growth with other data in psoriasis patients

In psoriasis cases, non-significant association was found between all demographic and clinical data with fungal growth except psoriasis severity as fungal growth was significantly associated with higher PASI score ($p = 0.042$)(mean PASI was 9.75 ± 3.1 in patients with fungal growth versus 7 ± 2.3 in patients without fungal growth.

There was non-significant association between the different IL-17A genotypes and the fungal growth in psoriasis cases, except for the frequency of *Aspergillus flavus* which decreased gradually with

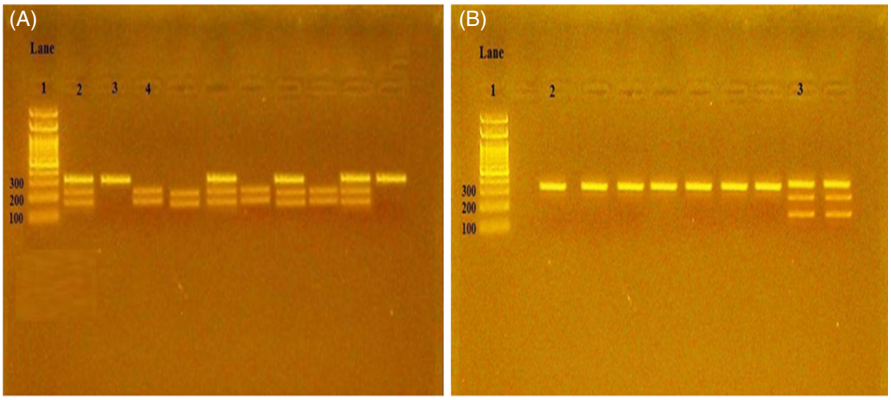

FIGURE 1 (A) The Rsa 1 restriction profiles of the 197G/A polymorphic sites of IL-17A gene in patients with plaque psoriasis. (B) The Rsa 1 restriction profiles of the 197G/A polymorphic sites of IL-17A gene in controls

TABLE 1 Association of IL-17 (genotypes and alleles) in psoriasis patients and healthy controls

		Control	Psoriasis			
		N = 50	*N* = 50			
IL-17A		***N* (%)**	***N* (%)**	***p***	**OR**	**95% CI**
Genotypes	GG	44 (88)	8 (16)	–	1	Reference
	GA	5 (10)	24 (48)	**0.015***	1.584	1.095–2.292
	AA	1 (2)	18 (36)	**0.012***	1.688	1.120–2.542
Dominant model	GA+AA	6 (12)	42 (84)	**0.004***	1.625	1.172–2.253
Alleles	G	93 (93)	40 (40)	–	1	Reference
	A	7 (7)	60 (60)	**<0.001***	5.922	3.731–9.401

Abbreviations: CI, confidence interval; OR, odds ratio; R, reference; regression analysis test was used.
*$p \leq 0.05$ (Significant).

TABLE 2 Association of clinical and demographic data with different IL-17A genotypes in psoriasis cases

		GG		GA		AA		
		N = 8		*N* = 24		*N* = 18		***p***
Age (years)	Mean ±SD	47.6 ±14.1		37.9 ±11.5		42.8 ±12.7		0.360
Males	N %	6 75%		11 45.8%		13 72.2%		0.165
Females	N %	2 25%		13 54.2%		5 27.8%		
Family history	Positive	2	25%	3	12.5	4	22.2	0.616
	Negative	6	75%	21	87.5	14	77.8	
Onset	Gradual	8	100%	23	95.8%	17	94.4%	0.799
	Acute	0	0%	1	4.2%	1	5.6%	
Course	Remission and exacerbation	7	87.5%	19	79.2%	8	44.4%	0.031*
	Progressive	1	12.5%	5	20.8%	10	55.6%	
Distribution	Generalized	7	87.5%	24	100%	17	94.4%	0.140
	Localized	1	12.5%	0	0%	1	5.6%	
PASI	Mild	8	100%	22	91.7%	4	22.2%	**<0.001***
	Moderate	0	0%	2	8.3%	11	61.1%	**<0.001***
		0	0%	0	0%	3	16.7%	0.104

Abbreviations: PASI, psoriasis area and severity index.
*$p \leq 0.05$ (Significant).

GG, GA, and AA (37.5%, 20.8%, and 0%, respectively) with significant differences ($p = 0.015$) (Table 4).

3.7 | Prediction of fungal infection susceptibility

Logistic regression analysis was conducted for prediction of fungal infection susceptibility in psoriasis patients using smoking, positive family history, psoriasis, PASI, and IL-17A dominant model as risk factors. Smoking, presence of psoriasis, and IL-17A GA+AA genotypes were significantly associated with fungal infection susceptibility in univariable analysis; however, taking significant covariates in univariable analysis into multivariable analysis revealed that only presence of psoriasis was suggested to be independent predictors of fungal infection susceptibility (Table 5).

4 | DISCUSSION

Because several studies reported that the IL-17 plays an important role in psoriasis pathogenesis and any variation in its genes was linked to the risk for developing psoriasis or had an effect on the disease severity,[4,5,19] it is reasonable to hypothesize that any genetic variation in IL-17A may affect the expression or the activity of these genes which in turn may influence the susceptibility and/or the severity of psoriasis. Therefore, one of the aims of this study was to identify the association between IL-17A

TABLE 3 Comparison of fungal growth between psoriasis patients and healthy controls

		Control	Psoriasis	
		N = 50	*N* = 50	
		N (%)	*N* (%)	*p*
Direct examination (KOH 10%)		7 (14)	43 (86)	**<0.001***
Fungal growth on the three different culture media	Any	7 (14)	43 (86)	**<0.001***
Identified fungal Genus	*Aspergillus*	4 (8)	28 (56)	**<0.001***
	Candida	2 (4)	9 (18)	**0.025***
	Malassezia	1 (2)	11 (22)	**0.002***
	Dermatophytes	0 (0)	1 (2)	1
Species identification	*Aspergillus fumigatus*	1 (2)	10 (20)	**0.004***
	Aspergillus niger	1 (2)	14 (28)	**<0.001***
	Aspergillus flavus	2 (4)	8 (16)	**0.046***
	Malassezia furfur	1 (2)	9 (18)	**0.008***
	Malassezia restricta	0 (0)	2 (4)	0.495
Single species		7 (14)	34 (68)	0.325
Combined growth		0 (0)	9 (18)	

*$p \leq 0.05$ (Significant).

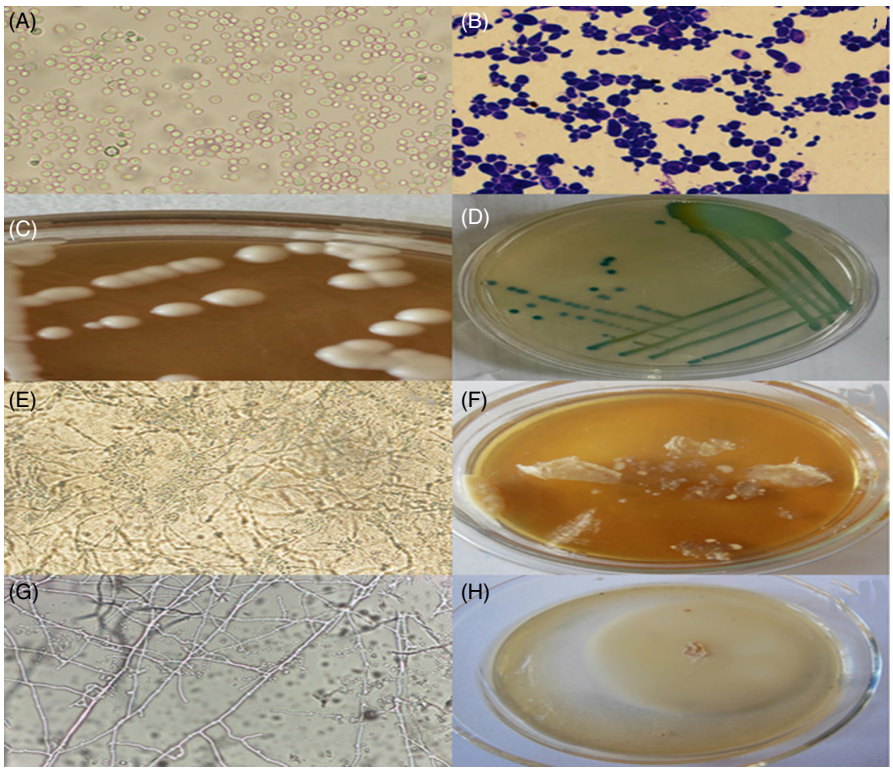

FIGURE 2 (A) KOH 10% showing oval, budding yeast and pseudohyphae of *C. albicans* (40×). (B) Gram stain smear showing Gram +ve oval, budding *C. albicans* (100×). (C) Culture of *C. albicans* on SDA. (D) Culture of *C. albicans* on CHROMagarCandida showing the blue-green colonies. (E) KOH 10% showing "spaghetti and meatball appearance" of *Malassezia* yeast (40×). (F) Creamy colonies of *Malassezia* on Dixon's agar. (G) KOH 10% showing microconidia of Trichophyton mentagrophytes arranged in loose grape like clusters. (H) Trichophyton mentagrophytes on Sabouraud's cycloheximide chloramphenicol agar

(rs10484879) G/A gene polymorphism and the susceptibility of developing psoriasis in patients attending Benha University Hospitals.

The results of our study showed that the SNPs of IL-17A (rs10484879) G/A gene led to increased susceptibility toward pathogenesis of psoriasis. This was evidenced by the decrease in the frequency of having the G allele in psoriasis patients compared to the healthy controls. These results suggested that G allele might play a protective role against psoriasis for IL-17A (rs10484879).

Further analysis of our results as regard the variation between the G/A allele at the IL-17 gene beside the association of A allele and the risk of psoriasis, revealed that the frequency of IL-17A GA, AA, and GA+AA genotypes was significantly higher in psoriasis cases than in the control group ($p = 0.015$, 0.012, and 0.004, respectively). A allele had higher frequency in psoriasis cases when compared to the control group ($p < 0.001$). A allele was significantly associated with the risk to develop psoriasis.

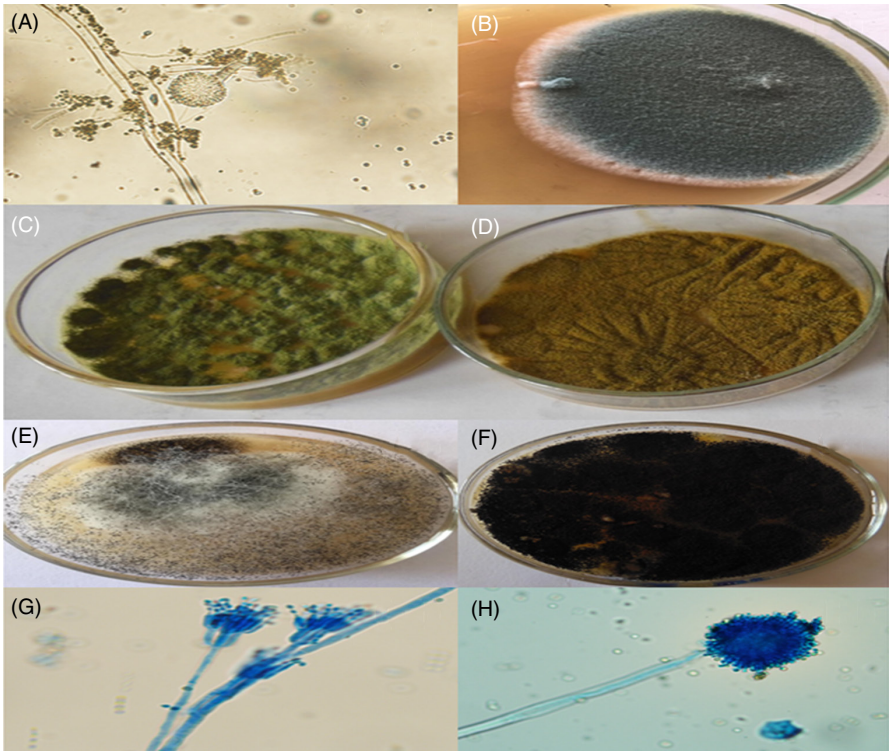

FIGURE 3 (A) KOH 10% showing *Aspergillus* elements (hyphae, spores and head (40×) (B) Blue-green colonies of *A. fumigatus* on SDA. (C) Yellow-green colonies of *A. flavus* on SDA. (D) yellow-brown colonies of *A. flavus* on SDA. (E) Young white colonies of *A. niger* on SDA showing hyphae carrying black spores. (F) Jet black mature colonies of *A. niger* on SDA. (G) *A. fumigatus* head stained by lacto phenol cotton blue stain (40x). (H) *A. flavus* head stained by lacto phenol cotton blue stain (40×)

TABLE 4 Association of fungal growth with different IL-17A genotypes in psoriasis cases

		GG		GA		AA		
		N = 8		*N* = 24		*N* = 18		*p*
Fungal growth on the three different culture media	Any	6	75%	22	91.7%	15	83.3%	0.431
Identified fungal genus	*Aspergillus*	5	62.5%	15	62.5%	8	44.4%	0.482
	Candida	1	12.5%	6	25%	2	11.1%	0.458
	Malassezia	1	12.5%	5	20.8%	5	27.8%	0.732
	Dermatophytes	0	0%	1	4.2%	0	0%	1
Species identification	*Aspergillus fumigatus*	2	25%	2	8.3%	6	33.3%	0.129
	Aspergillus niger	2	25%	10	41.7%	2	11.1%	0.096
	Aspergillus flavus	3	37.5%	5	20.8%	0	0%	**0.015***
	Malassezia furfur	1	12.5%	3	12.5%	5	27.8%	0.481
	Malassezia restricta	0	0%	0	0%	2	11.1%	0.265
Single species		3	37.5%	18	75.0%	13	72.2%	0.257
Combined growth		3	37.5%	4	16.7%	2	11.1%	

*$p \leq 0.05$ (Significant).

Our results were in line with that reported by Białecka et al.[19] who studied another type of polymorphism within the IL-17A gene and reported an association between the IL-17A (rs2275913) polymorphisms and psoriasis susceptibility in Polish subjects. Also, our results agreed with Kaur et al.[5] who studied the same locus but with another type of restriction enzyme in north Indian population and reported that the IL-17A (rs10484879) G/T gene polymorphisms may lead to an increased susceptibility of psoriasis. They explained their results as follows: With SNPs of IL-17A, the increased susceptibility of psoriasis may be a result of increased expression of IL-17, which causes the activation of NF-κB pathway. In addition, IL-17A upregulates the expression of various other inflammation-related genes in target tissues mainly the keratinocytes and fibroblasts which in turn show further increase in the production of various chemokines, cytokines, antimicrobial peptides, and other mediators.

Another aim of this study was to study the association between the SNPs of IL-17A gene and the severity of psoriasis. Our results revealed that PASI score increased gradually with GG, GA, and AA (mean ± SD = 6 ± 1.9, 8.7 ± 1.2, 11.8 ± 3.9, respectively; $p < 0.001$). Also, the results of this study showed that the frequency of progressive course increased gradually with GG, GA, and AA (12.5%, 20.8%, 55.6%,

TABLE 5 Regression analysis for prediction of fungal infection susceptibility

	Univariable			Multivariable		
	p	OR	95% CI	*p*	OR	95% CI
Smoking	**<0.001**	3.293	1.769–6.131	0.087	1.987	0.906–4.358
Positive family history	**0.339**	1.478	0.664–3.293			
Psoriasis	**<0.001**	8.677	4.709–15.986	**<0.001**	5.668	2.416–13.299
PASI	**0.055**	1.174	0.997–1.382			
IL-17A	**<0.001**	4.705	2.715–8.151	0.345	1.499	0.647–3.476

Abbreviations: OR, odds ratio; CI, confidence interval.

PASI, psoriasis area and severity index.

*$p \leq 0.05$ (Significant).

respectively; $p = 0.031$); these results could also be supported by the explanation proposed by Kaur et al.[5] who reported that the gene polymorphisms of IL-17A (rs10484879) may led to increased expression of IL-17 which upregulates the expression of various other inflammation-related genes which in turn show further increase in the inflammation mediators that were associated with psoriasis.

Psoriasis pathogenesis may involve a breakdown of immune tolerance to cutaneous microorganisms in genetically predisposed individuals who already have a dysregulated immune response to various environmental factors.[20] Skin microbiome has been recognized as an important triggers for initiation or progression of psoriasis in humans. Fungal dysbiosis has been recently associated with several chronic immune-mediated diseases including psoriasis.[9]

The results of this study showed that psoriatic cases were significantly associated with higher frequency of fungal growth when compared to the healthy control group. This result is similar to that reported by Takemoto et al.[21] who found that the psoriatic skin had higher fungal diversity compared to controls. Also, Stehlikova et al.[9] showed a specific correlation between different fungal species and psoriasis. However, they reported that the presence of diverse fungal growth on psoriatic skin still remains to be elucidated whether the observed microbial shift and specific relationship pattern are of primary etiological significance or secondary to the presence of psoriasis.

Sanchez et al.[22] reported that the pathobiology or genetically determined variations in stratum corneum properties might result in a dysbiosis that changes the abundance and diversity of commensal species, which disturbs skin barrier function and aggravates chronic skin diseases such as what occur in psoriasis.

As regard the isolated *Candida* species, the results of this study found that all the isolated *Candida* yeast were *C. albicans*, with a significant increase in isolation of *Candida* from psoriatic plaques than in controls. Our results were in agreement with different studies[23,24] who showed a higher rate of *C. albicans* colonization in patients with psoriasis in comparison with controls.

Kashem and Kaplan[23] explained the increased colonization of C. albicans on skin of patients with psoriasis as under normal circumstances, the fungus does not cause disease but dysregulation of the immune response, as occurred in psoriasis, can lead to the inability to control C. albicans colonization. The invasion of the skin by C. albicans directly activates cutaneous sensory nerves to induce the release of calcitonin gene related peptide that acts on dermal dendritic cell, with subsequently release of IL-23 that in turn acts on dermal γδ T cells to drive IL-17 production in the skin.

Our results showed that *Malassezia* species were found in 22% of cases and 2% of controls reflecting a noteworthy significant difference between psoriatic patients and healthy individuals ($p = 0.002$). In agreement with our results, Findley et al.[25] published that Malassezia is the dominant fungal genus occurring on the human skin and that psoriatic lesions display greater fungal diversity than healthy skin.

The role of *Malassezia* spp. in inflammation is thought to be through the production of lipases and phospholipases leading to damage of the epidermal barrier function; aggravation of local immune response by production of inflammatory cytokines from keratinocytes; and production of cross-reactive allergens leading to sensitization.[26] However, *Malassezia* role in pathogenesis of psoriasis is, still, undetermined. Although it may contribute to the inflammation associated with the disease, via complement activation and neutrophil recruitment, convincing evidence that it is of prime importance in the pathogenesis of the disease is still lacking.[27]

The results of our study showed that the genus *Aspergillus* had the highest frequency among the isolated fungal growth. It was found in 56% of cases and in 8% of controls denoting a significant difference between the 2 groups ($p < 0.001$). In line of our results is that reported by Stehlikova et al.[9] who found discriminative association of the species and the genus *Aspergillus* with psoriatic skin compared to normal controls.

To explain the abundant presence of *Aspergillus* in psoriatic skin, we can propose that it may be attributed to the fact that in psoriasis the skin is traumatized due to the extensive itching and scratching. So, the colonization of the traumatized psoriasis skin is more common due to the high exposure to environmental conidia as *Aspergillus* species is the most ubiquitous fungi seen in soil, water, and decaying vegetations. The abundant presence of the fungus facilitates the contamination of the skin and the establishment of colonization with *Aspergillus*.

Although the results of the present study revealed a significant correlation between fungual growth and psoriasis and also that

psoriatic patients showed significantly higher distribution frequency of IL-17A GA, AA, and total polymorphism (GA+AA) than control groups, the number of the study groups should be increased and also more one SNP should be studied.

5 | CONCLUSIONS

Psoriasis cases are significantly associated with fungal growth, which may be a contributing factor in its pathogenesis. Regarding the frequency of IL-17A GA, AA, and GA+AA genotypes in psoriasis cases, it was found to be significantly higher than in controls. Smoking, presence of psoriasis, and IL-17A GA+AA genotypes might be associated with fungal infection susceptibility.

CONFLICT OF INTEREST

No conflict of interest.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and an informed consent approved by the local ethics committee of research of Benha Faculty of Medicine was taken from all individuals before being enrolled in this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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