International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 2.102

Unveiling the Protective Role of Hypoxia - Inducible Factor-1 Alpha Gene Polymorphisms (rs11549465 and rs11549467) in Psoriasis

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Abstract: ***Psoriasis is a chronic inflammatory skin condition influenced by genetic and environmental factors. The hypoxia - inducible factor 1 - alpha (HIF1A) gene, which regulates cellular responses to hypoxia and inflammation, has been linked to disease susceptibility. This study explores the association of two HIF1A single nucleotide polymorphisms (SNPs), rs11549465 and rs11549467, with psoriasis risk in a North Indian population. A case - control study was conducted with 200 psoriasis patients and 200 healthy controls. Genotyping was performed using TETRA - ARMS PCR, and statistical analyses assessed genotype and allele frequencies, odds ratios (ORs), and haplotypes. Results indicated that the T allele of rs11549465 and the A allele of rs11549467 were significantly associated with reduced psoriasis risk. Individuals carrying the T/T genotype (rs11549465) or A/A genotype (rs11549467) demonstrated the strongest protective effects. Haplotype analysis revealed that specific allele combinations further reduced susceptibility to psoriasis. This study highlights the potential protective role of specific HIF1A variants against psoriasis, offering new insights into its genetic basis. These findings may support future research into targeted therapies and precision medicine approaches for managing psoriasis.***

Keywords: Psoriasis, HIF1A gene, Single nucleotide polymorphisms (SNPs), Genetic susceptibility, Inflammatory skin disorders

1. Introduction

Psoriasis is a multifactorial, chronic inflammatory skin disorder characterized by the hyperproliferation of keratinocytes, immune dysregulation, and the formation of distinct erythematous plaques covered with silvery scales [1, 2, 3]. This condition significantly affects the quality of life, leading to physical discomfort and psychological distress among affected individuals [4, 5, 6]. The pathophysiology of psoriasis is complex, involving intricate interactions between genetic, immunological, and environmental factors [7, 8, 9]. Genome - wide association studies (GWAS) have identified numerous susceptibility loci, highlighting genes involved in immune regulation, epidermal differentiation, and inflammatory pathways[10, 11, 12].

Among the several genetic candidates implicated in psoriasis susceptibility, the hypoxia - inducible factor 1 alpha (HIF1A) gene has garnered considerable interest due to its critical role in cellular responses to hypoxia, inflammation, and metabolism [13, 14, 15]. HIF1A is a transcription factor that regulates the expression of a multitude of genes involved in angiogenesis, erythropoiesis, and cellular adaptation to hypoxic conditions [16, 17]. Dysregulation of HIF1A signaling pathways has been linked to various pathological conditions, including cancer, cardiovascular diseases, and inflammatory disorders such as psoriasis [18, 19, 20].

Single nucleotide polymorphisms (SNPs) within the HIF1A gene may have significant implications for disease susceptibility by affecting HIF1A expression and function [21]. Notably, SNPs rs11549465 and rs11549467 have emerged as important candidates in this context [22, 23, 24]. These SNPs have been associated with altered HIF1A expression levels and functional outcomes in various disease contexts, suggesting a potential role in modulating inflammatory responses critical to psoriasis pathogenesis.

The role of genetic factors in the susceptibility to psoriasis has been substantiated by multiple investigations. The International Psoriasis Genetics Consortium has identified numerous loci linked to the disease, with a significant enrichment of genes involved in immune system regulation and skin barrier integrity [25]. Furthermore, associations between various SNPs in immunologically relevant genes and psoriasis have been well - documented, underscoring the importance of genetic predisposition in the disease's multifactorial etiology [26, 27].

Despite the advances in understanding the genetic basis of psoriasis, the specific contributions of HIF1A SNPs to disease susceptibility remain inadequately explored. The present study aims to investigate the association between SNPs rs11549465 and rs11549467 in the HIF1A gene and the risk of developing psoriasis. Utilizing a robust case - control design involving genotyping methods such as TETRA - ARMS PCR, we seek to comprehensively evaluate

the association between HIF1A SNPs and psoriasis risk in a cohort of 400 participants (200 psoriasis cases and 200 healthy controls). Statistical analyses will include assessment of allele frequencies, genotype distributions, and odds ratios, providing insights into the genetic underpinnings of psoriasis.

In conclusion, elucidating the genetic determinants of psoriasis, particularly through the lens of HIF1A gene variations, may enhance our understanding of the disease and pave the way for targeted therapeutic interventions. Further investigations into the functional implications of these SNPs could illuminate novel pathways for the development of precision medicine strategies aimed at improving outcomes for patients with psoriasis.

2. Methodology

Sample Selection

Freshly diagnosed psoriasis patients were included, excluding those with other autoimmune disorders, acute or chronic infections, malignancies, or those who did not consent. For control group, age - and gender - matched healthy individuals without autoimmune disorders, infections, or malignancies were included, with non - consenting individuals excluded.

Ethical clearance for the study was obtained from the Institutional Clinical Ethical Committee of Punjabi University, adhering to the guidelines established by the Indian Council of Medical Research (ICMR). Blood samples (3 mL each) were collected from 200 psoriasis patients and 200 healthy controls by a certified technician after obtaining informed written consent. To ensure sample integrity, each sample was barcoded, transported on ice, and promptly stored at - 20°C until further analysis.

DNA Extraction

Genomic DNA was isolated from the whole blood using the phenol - chloroform method. DNA quality was assessed via agarose gel electrophoresis, and quantity was measured using a UV - visible spectrophotometer. DNA samples were stored at - 80°C for subsequent analysis.

Genotyping

The genotyping of SNPs rs11549465 and rs11549467 was performed using TETRA - ARMS PCR, a technique that employs allele - specific primers to selectively amplify the targeted regions. The primers for this study were designed using the Primer 1 tool (available at https: //primer1. soton. ac. uk/primer1. html), ensuring high specificity and efficiency for the amplification of the regions containing the SNPs. The detailed sequences of the primers used are provided in Table 1.

Table 1: Primer Sequences and Melting Temperatures for TETRA - ARMS PCR

SNP	Primer Sequence 5' - - - - - 3'	Melting temperature
HIF - 1A rs11549465	Forward inner primer (T allele) TCCAGTTACGTTCCTTCGATCAGTTGTAAT	65.3
	Reverse inner primer (C allele) AGGGCTTGCGGAACTGCTTTCTAAGGG	
	Forward outer primer GCTGAAGACACAGAAGCAAAGAACCCAT	
	Reverse outer primer TGTATGTGGGTAGGAGATGGAGATGCAA	
HIF - 1A rs11549467	Forward inner primer (G allele) TCAGTTGTCACCATTAGAAAGCAGTTACG	64.9ºC
	Reverse inner primer (A allele) TGAGGACTTGCGCTTTCAGGGCTGGT	
	Forward outer primer GCTGAAGACACAGAAGCAAAGAACCCATTT	
	Reverse outer primer ATGTGGGTAGGAGATGGAGATGCAATCA	

PCR amplification was conducted under optimized conditions, and the resulting amplicons were analyzed on a 2% agarose gel. Visualization of bands was achieved using a gel documentation system, with alleles identified based on the presence of specific bands corresponding to the inner primers. The details of the amplification conditions for SNPs rs11549465 and rs11549467 are provided in Table 2.

Table 2: PCR Amplification Conditions for SNPs rs11549465 and rs11549467

SNP	Initial Denaturation	Final Denaturation	Annealing	Initial Extension	Final Extension	Cycles
rs11549465	95ºC, 5 min	95ºC, 30 sec	63ºC, 45 sec	72ºC, 1 min	72ºC, 10 min	35
rs11549467	94ºC, 5 min	94ºC, 30 sec	60ºC, 45 sec	72ºC, 1 min	72ºC, 10 min	35

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (SPSS Inc., Chicago, IL) and the SNPstats Statistical Computation website. Characteristics of cases and controls were compared, and percentage analysis was conducted. Allele frequencies, genotype distributions, and odds ratios (ORs) with 95% confidence intervals were calculated to assess the association of SNPs with psoriasis risk. Codominant, dominant, overdominant, recessive and allele models were evaluated. Statistical significance was set at $p < 0.05$.

3. Results

The **rs11549465** genotype showed significant associations with psoriasis susceptibility. In the **codominant model**, individuals with the **C/T** genotype (OR = 0.61, p = 0.0045) or **T/T** genotype (OR = 0.34, p = 0.008) exhibited a lower risk of psoriasis compared to those with the **C/C** genotype. This suggests that the presence of the **T** allele may confer a protective effect. In the **dominant model**, carriers of the **C/T - T/T** genotypes showed a significantly reduced risk (OR = 0.55, p = 0.0032), further highlighting the protective role of the **T** allele. Similarly, in the **recessive model**, individuals with the **T/T** genotype demonstrated significant protection (OR = 0.41, p = 0.017). The **over dominant model**, however, showed no significant association. Allele frequency analysis confirmed the protective role of the **T** allele (OR = 0.60, p = 0.001). These findings suggest that **T** allele carriers might have a genetic advantage against psoriasis development.

Significant protective associations were also observed for the **rs11549467** genotype. In the **codominant model**, the **G/A** genotype (OR = 0.65, p = 0.049) and **A/A** genotype (OR = 0.22, p = 0.00006) were associated with a reduced risk of psoriasis compared to the **G/G** genotype. The results indicate that the **A** allele plays a protective role, especially in homozygous individuals (**A/A**). The **dominant model** also supported this protective association, with **G/A - A/A** carriers exhibiting a lower risk (OR = 0.53, p = 0.0021). Similarly, in the **recessive model**, the **A/A** genotype showed a significant protective effect (OR = 0.28, p = 0.00004). Allele analysis reinforced the finding that the **A** allele confers protection (OR = 0.53, p < 0.0001). These results suggest that the **A** allele, particularly in homozygous form, might reduce susceptibility to psoriasis.

Table 3: Genotypic Models and Allele Frequency Distribution of **rs11549465** and Association with Psoriasis Susceptibility.

Genotypic models	Genotype	Cases n (%)	Controls, n (%)	OR (95% CI)	p - value
Codominant (rs11549465)	C/C	103 (51.5%)	132 (66%)	Ref.	
	C/T	74 (37%)	58 (29%)	0.61 (0.40 - 0.94)	0.0045*
	T/T	23 (11.5%)	10 (5%)	0.34 (0.15 - 0.74)	0.008*
Dominant	C/C	103 (51.5%)	132 (66%)	Ref.	0.0032*
	C/T - T/T	97 (48.5%)	68 (34%)	0.55 (0.37 - 0.82)	
Recessive	C/C - C/T	177 (88.5%)	190 (95 %)	Ref.	0.017*
	T/T	23 (11.5%)	10 (5%)	0.41 (0.19 - 0.87)	
Overdominant	C/C - T/T	126 (63%)	142 (71%)	Ref.	0.089
	C/T	74 (37%)	58 (29%)	0.70 (0.46 - 1.06)	
Allele	C	280 (70%)	322 (80%)	Ref.	0.001*
	T	120 (30%)	78 (20%)	0.60 90.43 - 0.82)	

n - number of individuals; OR - Odds Ratio calculated at 95% Confidence Interval (CI); Ref. - Reference group (wildtype genotypes or alleles are taken as reference group); Statistically significant p≤ 0.05

Table 4: Genotypic Models and Allele Frequency Distribution of **rs11549467** and Association with Psoriasis Susceptibility

Genotypic models	Genotype	Cases n (%)	Controls, n (%)	OR, (95% CI)	p - value
Codominant (rs11549467)	G/G	64 (32%)	94 (47%)	Ref.	
	G/A	99 (49.5%)	94 (47%)	0.65 (0.42 - 0.99)	0.049*
	A/A	37 (18.5%)	12 (6%)	0.22 (0.11 - 0.46)	0.00006*
Dominant	G/G	64 (32%)	94 (47%)	Ref.	0.0021*
	G/A - A/A	136 (68%)	106 (53%)	0.53 (0.35 - 0.80)	
Recessive	G/G - G/A	163 (81.5%)	188 (94%)	Ref.	0.00004*
	A/A	37 (18.5%)	12 (6%)	0.28 (0.14 - 0.56)	
Overdominant	G/G - A/A	101 (50.5%)	106 (53%)	Ref.	0.62
	G/A	99 (49.5%)	94 (47%)	0.90 (0.61 - 1.34)	
Allele	G	227 (57%)	282 (70%)	Ref.	<0.0001*
	A	173 (43%)	118 (30%)	0.53 (0.39 - 0.72)	

n - number of individuals; OR - Odds Ratio calculated at 95% Confidence Interval (CI); Ref. - Reference group (wildtype genotypes or alleles are taken as reference group); Statistically significant p≤ 0.05

Haplotype analysis further elucidated the combined effect of **rs11549465** and **rs11549467** on psoriasis susceptibility. The **HT2 (C - A)** haplotype was significantly associated with a lower risk of psoriasis (OR = 0.57, p = 0.0067). Similarly, the **HT4 (T - A)** haplotype demonstrated a strong protective effect (OR = 0.34, p = 0.0001). The global haplotype association was highly significant (p < 0.0001), indicating the combined contribution of these SNPs in modulating disease risk. These findings highlight the potential importance of haplotypes involving the **T** and **A** alleles in providing genetic protection against psoriasis.

Table 5: Haplotype Frequencies **rs11549465** and **rs11549467** and Their Association with Psoriasis Susceptibility

Haplotype	SNP1	SNP2	Cases (%)	Controls (%)	OR (95% CI)	p - value
HT1	C	G	42.64%	58.08%	1	Ref.
HT2	C	A	27.36%	22.42%	0.57 (0.38 - 0.85)	**0.0067***
HT3	T	G	14.11%	12.42%	0.67 (0.40 - 1.12)	0.13
HT4	T	A	15.89%	7.08%	0.34 (0.20 - 0.58)	**0.0001***
Global haplotype association p - value: <0.0001						

*p value < 0.05 (statistically significant); **p value < 0.001 (highly significant)

Linkage disequilibrium (LD) analysis revealed a weak but statistically significant relationship between **rs11549465** and **rs11549467** (p = 0.0101). While the LD was low, the significant association suggests potential interaction or co - regulation between these SNPs, which may jointly influence psoriasis susceptibility.

Table 6: Linkage Disequilibrium Statistics Between **rs11549465** and **rs11549467**

Statistic	Value
D statistic	0.0292
D' statistic	0.1715
r^2 statistic	0.1286
P - value	0.0101*

*p value < 0.05 (statistically significant); **p value < 0.001 (highly significant)

4. Discussion

Psoriasis is a complex, chronic, and inflammatory skin disorder influenced by the interplay of genetic, environmental, and immunological factors. The findings of this study highlight the potential role of polymorphisms in the hypoxia - inducible factor - 1 alpha (HIF1A) gene in influencing susceptibility to psoriasis, particularly in the North Indian population. This research provides insights into the genetic architecture of psoriasis and suggests protective associations for specific single nucleotide polymorphisms (SNPs) of the HIF1A gene, namely rs11549465 and rs11549467.

The T allele of rs11549465 demonstrated a significant protective effect against psoriasis across codominant, dominant, and recessive genetic models. Similarly, the A allele of rs11549467 was associated with a reduced risk of psoriasis, particularly in individuals homozygous for this allele (A/A genotype). These findings align with previous research that suggests HIF1A polymorphisms play a critical role in modulating inflammatory and hypoxic responses in various inflammatory diseases [15, 18, 19]. Given that psoriasis is characterized by hyperproliferation of keratinocytes, angiogenesis, and immune dysregulation, alterations in HIF1A gene function due to these SNPs may have a profound impact on disease pathogenesis [20].

Haplotype analysis further reinforced the protective roles of these polymorphisms. Haplotypes containing the T allele of rs11549465 and the A allele of rs11549467 showed significant protective associations, emphasizing the importance of studying genetic interactions in disease risk assessment. The combined analysis of these two SNPs also revealed a weak but significant linkage disequilibrium, suggesting potential synergistic effects. However, the exact biological mechanisms underlying this interaction remain unclear and warrant further investigation.

The findings of this study contribute to the growing body of literature on the genetic basis of psoriasis. Previous studies have highlighted the role of HIF1A in regulating immune responses and keratinocyte behavior, processes central to psoriasis pathology. The protective associations observed in our study are consistent with these findings, as they indicate that specific genetic variations in HIF1A may mitigate the aberrant inflammatory and epidermal responses characteristic of psoriasis.

A meta - analysis conducted by Harun - Or - Roshid et al. (2022) also identified significant associations between HIF1A polymorphisms and inflammatory diseases [22]. Our results partially align with these findings, particularly in the context of Asian populations.

Contrasting findings have been reported in studies conducted on Turkish population, where the associations between HIF1A polymorphisms and psoriasis have been less consistent [28]. These discrepancies may arise from differences in genetic backgrounds, environmental exposures, and lifestyle factors across populations. For example, North Indian populations are exposed to unique environmental stressors such as high levels of air pollution, which may interact with genetic predispositions to influence disease outcomes.

The haplotype analysis conducted in this study provides additional insights into the genetic interactions underlying psoriasis susceptibility. Haplotypes combining the T allele of rs11549465 and the A allele of rs11549467 were associated with a significantly reduced risk of psoriasis, suggesting that these alleles may act synergistically to confer protection. The weak but significant linkage disequilibrium observed between these SNPs further supports this hypothesis.

The functional implications of these haplotypes remain to be elucidated. It is possible that they influence HIF1A gene expression or protein function in a manner that enhances the regulation of hypoxic and inflammatory responses. Future studies involving functional assays and gene expression analyses are needed to validate these findings and explore their biological significance.

This study focused on the North Indian population, where lifestyle and environmental factors such as dietary habits, high - calorie diets, physical inactivity, and air pollution may interact with genetic predispositions to influence psoriasis risk [29, 30]. The high prevalence of obesity and metabolic syndrome in this population further complicates the clinical profile of psoriasis, as these conditions are known to exacerbate inflammatory responses [29, 31].

The protective associations observed in this study may be specific to the North Indian population, highlighting the importance of conducting genetic research in diverse populations. Studies in other populations have reported varying associations between HIF1A polymorphisms and inflammatory diseases, underscoring the need for context - specific investigations [21, 24, 28].

5. Conclusion

This study provides compelling evidence for the protective role of specific single nucleotide polymorphisms (SNPs) in

the HIF1A gene, particularly rs11549465 and rs11549467, in reducing susceptibility to psoriasis. The findings suggest that the T allele of rs11549465 and the A allele of rs11549467 are significantly associated with lower psoriasis risk, highlighting the potential of these genetic variants as biomarkers for disease protection. The haplotype analysis further supports the contribution of specific allele combinations in mitigating the risk of developing psoriasis.

These results deepen our understanding of the genetic factors underlying psoriasis and reinforce the importance of the HIF1A gene in modulating inflammatory responses. The identified SNPs may serve as potential targets for future genetic screening and personalized treatment strategies, paving the way for more precise and effective interventions for psoriasis patients.

Further studies focusing on the functional implications of these variants and their role in immune modulation are warranted to elucidate the molecular mechanisms linking HIF1A to psoriasis pathogenesis. The integration of genetic research into clinical practice has the potential to revolutionize the management of psoriasis, improving outcomes for patients worldwide. Ultimately, this research contributes to the ongoing efforts to uncover the genetic architecture of psoriasis and develop targeted therapeutic approaches for this debilitating condition.

Acknowledgment
This research was funded by the Indian Council of Medical Research (ICMR), and the authors sincerely thank them for their support.

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