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Gene Expression and Polymorphism of Interleukin-36a in Psoriatic Iraqi Patients

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Abstract

Psoriasis is a common, persistent papulosquamous skin illness that affects people of all ages and has a high societal and personal burden. It is associated with various serious medical conditions like depression, psoriatic arthritis, and cardiometabolic syndrome. Interleukin-36a (IL-36a) is a key molecule in inflammation, coordinating the activation of critical pro-inflammatory cytokines and immune cells. The current study involved 84 Iraqi psoriatic patients (PoS) and 67 healthy controls. Real-time PCR and sequencing techniques were used to evaluate the gene expression and polymorphism of two SNPs (rs2305152 A/C and rs895497 G/A) of the IL-36a gene. The findings revealed that the IL-36a gene was up-regulated in psoriatic patients (1.29 [IQR: 1.12-1.55]) compared to healthy individuals. When we looked at how IL-36a gene activity varied based on specific genetic variations, only rs2305152 had a significant effect; the CC genotype was associated with significantly higher expression compared to the AA genotype (2.12 [IQR: 1.57-3.47] vs. 1.15 [IQR: 1.04-1.47]; p = 0.009). The genotypes of the SNPs showed that the AC genotype of IL-36a SNP rs2305152 (A/C) and GA genotype in rs895497 (G/A) presented a significantly amplified incidence in patients with psoriasis in comparison with the healthy control, and the associated OR values were 17.91 and 0.10, respectively. Hardy-Weinberg equilibrium value of SNP rs2305152 (A/C) was p-HWE = 0.033 in PsO. The haplotypes (rs2305152 A/C and rs895497 G/A) of the IL36A gene showed high significance. The results showed that the linkage disequilibrium values of IL-36a SNPs rs2305152 and rs895497 had a correlation coefficient value of R2 = 0.09 and an LD coefficient value of D' = 0.68, indicating that certain genetic variation (AC for rs2305152 and GA for rs895497) were more common in psoriasis patients compared to the control group, suggesting a potential association with the condition. This study suggests that the genetic variation rs2305152 (A/C) in the IL-36a gene may play a role in the risk of psoriasis.

Keywords: Gene expression, Interleukin 36a, Psoriasis, Single nucleotide polymorphisms SNPs.

التعبير الجيني وتعدد اشكال النيوكليوتيد للبين ابيضاض 36 الفا في مرضى الصدفية العراقيين

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الخلاصة

الصدفية هي حالة جلدية حطاطية حرشفية سائدة ومزمنة تؤثر على الأشخاص من جميع الأعمار ويشكل عبئًا كبيرًا على المجتمع والفرد. وقد تم ربطه بعدد من الاضطرابات الطبية الخطيرة، بما في ذلك الاكتئاب والتهاب المفاصل الصدفي متلازمة القلب والأوعية الدموية. البين ابيضاض 36 الفا هو جزيء رئيسي في الالتهاب، ينسق تنشيط السيتوكينات المؤيدة للالتهاب والخلايا المناعية الحرجة. شملت الدراسة الحالية 84 مريضاً عراقياً بالصدفية و67 شخصاً سليماً كمجموعة ضابطة. تم استخدام تفاعل البلمرة المتسلسل PCR الزمنية الحقيقية لتقييم التعبير الجيني والتعدد الشكلي لنوعين من النقاط الوراثية (SNPs) (rs2305152 A/C، وrs895497 G/A) لجين البين ابيضاض −36 ألفا. كشفت النتائج أن جين−IL 36aكان مفعلاً بشكل أكبر في المرضى المصابين بالصدفية ([IQR: 1.12−1.55] 1.29) مقارنة بالأشخاص الأصحاء. عند النظر في كيفية تباين نشاط جين IL−36a بناءً على التغيرات الجينية المحددة، كان للنقطة الوراثية rs2305152 تأثير ملحوظ؛ حيث كان النمط الجيني CC مرتبطًا بتعبير أعلى بشكل ملحوظ مقارنة بالنمط الجيني AA (2.12 [IQR: 1.04−1.47]; p vs. 1.15 [IQR: 1.57−3.47] = 0.009). اظهرت أنماط النقاط الوراثية ان النمط الجيني AC لتعدد اشكال النيوكليوتيدة المفردة لجين −IL 36a للنمط الوراثي (A/C) rs2305152 وGA للنمط الوراثي (G/A) rs895497 زيادة ملحوظة في الحدوث بين المرضى المصابين بالصدفية مقارنة بمجموعة الضابطة السليمة ، وكان معدل OR المرتبط 17.91 و0.10 على التوالي . كان توازن هاردي−وابنبرغ في النقطة الوراثية (A/C) rs2305152 هو−p HWE = 0.033مع مرضى الصدفية. بينت الأنماط الفردانية (rs2305152−rs895497) لجين−IL 36aأهمية كبيرة , C−G و A−A. للهابلوتايبات (rs2305152−rs895497) لجين IL−36a أهمية كبيرة، C−G وA−Aأظهرت النتائج أن التوازن الرابط لنقاط IL−36a الوراثيةrs2305152 ، و rs895497 كان له معامل ارتباط (R2 = 0.09) ومعامل(D' = 0.68) LD ، مما يشير إلى أن التغير الجيني معين (AC)لـ rs2305152 و GAلـ (rs895497 كان أكثر شيوعًا في المرضى المصابين بالصدفية مقارنة بمجموعة الضابطة، مما يشير إلى ارتباط محتمل بالحالة. تقترح هذه الدراسة أن التغير الجيني rs2305152 (A/C)في IL−36a قد يلعب دورًا في خطر الاصابة بالصدفية.

الكلمات المفتاحية: التعبير الجيني، إنترلوكين 36أ، الصدفية، تعدد أشكال النوكليوتيدات المفردة.

Introduction

Psoriasis is an autoimmune skin disorder that affects both immune and resident skin cells, causing self-renewing inflammatory cycles. Psoriatic lesions are produced by the infiltration of effector leukocytes, appear as hyperkeratosis plaques, and cause angiogenesis, dermo-epidermal inflammation, and epidermal hyperproliferation with abnormal keratinocyte differentiation. The illness is distinguished by the proliferation of pro-keratinocytes, cytokines, and T cells, all of which have a role in the disease's development and maintenance. Type 1 T helper cells have been noticed to be the most prevalent in psoriasis patients [1].

Early upstream processes in psoriasis include the activation of pathways of innate immunity and the response of keratinocytes. Psoriasis lesions exert vascularized skin with substantial immune cell infiltration, including neutrophils, dendritic cells, and T cells [2].

Chronic plaque psoriasis vulgaris, the most frequent type, is caused by genetic predisposition, notably environmental triggers including alcohol intake, obesity, smoking, stress, and streptococcal infection, as well as the presence of the HLA-C*06:02 risk allele. Several psoriasis-related cytokines, including TNF-α, IL-22, and IL-17, have been

demonstrated to stimulate IL-36 production in organotypic skin models and primary human keratinocytes [3].

Among the various pathogenic mechanisms that occur in PsO, those mediated by cytokines, e.g. IL-36, have been identified as particularly important. IL-36 cytokine overexpression happens in both the primary and final phases of the illness [4]. Expression of IL-36 is triggered and maintained by adaptive or innate immune stimulation, which characterizes chronic and acute lesions of the skin, respectively [5].

Signal transduction, mediated by IL-36, has been identified to activate a variety of pathogenic pathways in kinds of psoriatic cells of the skin, including resident skin cells, like the endothelial cells and keratinocytes, which induce T-cell attraction and adhesion molecules in response to IL-36-dependent signaling [6]. The IL-36 cytokine family consists of one antagonist (IL-36Ra) and three agonists (IL-36 γ, IL-36 α and IL-36 β). Keratinocytes and immune system cells are cellular sources of IL-36 cytokines in the skin [6, 7].

This study aims to evaluate the role of polymorphism and gene expression of the IL-36a gene in the pathogenesis of psoriasis.

Methods

Subjects

The current case-control study was carried out on 84 Iraqi psoriatic patients and 67 healthy controls. Blood samples were collected from June to October 2023, and the diagnosis was made by the consulting medical personnel of AL-Yarmuk Hospital, Department of Dermatology. It was determined by a clinical examination of the skin, joints, and scaly areas.

Expression of *IL-36a* gene

Blood was drawn from psoriatic individuals. The reverse transcription-quantitative polymerase chain reaction (RT-qPCR) method was used to evaluate the *IL36a* gene expression. Extraction of RNA was performed for each sample using the TRIzolTM Reagent technique and reverse-transcribed to cDNA. To determine gene expression, the GoTaq® One-Step RT qPCR System kit (Promega, USA) was utilized. The sequence of the forward primer was 5'-CATAAATTAGAGGTCCAAAATCG-3' and that of the reverse primer was 5'-AAGGGGCTGGGTCAGCTAT-3', while those for the housekeeping gene -Globin forward and reverse primers were 5'-ACACAACTGTGTTCACTAGC-3' and 5'-CAACTTCATCCACGTTCACC-3', respectively.

The test was run in a reaction volume of 20µl that contained 2.5µl of nuclease-free water, 5µl of RNA, 1µl of each primer, 0.5µl of RT mix, and 10µl of master mix. The following PCR cycling conditions were used: one cycle for RT Enzyme Activation at 37˚C for 15mins, one cycle for initial denaturation at 95˚C for 5mins, then 40 cycles for denaturation at 95˚C for 20 secs, annealing at 65˚C and 20secs, and extension at 72˚C or 20 secs. The IL36a gene expression was evaluated using the Livak equation Ct method, with β-Globin serving as a housekeeping gene. The results were displayed as the change of fold ($2^{-\Delta\Delta Ct}$) in gene expression level relative to the calibrator, which is the control of the gene of interest, and was normalized to the housekeeping gene, which is an endogenous control [7].
($\Delta CT = CT_{\text{gene}} - CT_{\text{Housekeeping gene}}$, $\Delta\Delta CT = \Delta CT_{\text{Treated or Control}} - \Delta CT_{\text{Control}}$, Folding $= 2^{-\Delta\Delta CT}$).

Gene polymorphism of IL36a

The genomic DNA was extracted from a tube of EDTA using the Relia-Prep ^{TM} Blood gDNA Mini-prep System (Promega, USA) kit, after assessing purity and concentration. Then, the amplification of PCR 329bp product size and agarose gel electrophoresis (1% agarose) were performed. Sequencing of DNA was utilized to look for SNPs in the *IL36a* promoter

gene (rs2305152 and rs895497). The forward (5'-GCCCTCATGTTTCAGGTTGC-3') and reverse (5'-AGGAGCTGCCTTTCACAGAC-3') primers were created. The PCR reaction process involved 25µl total volume, which included 12.5µl Master mix, 1µl of each primer, 2µl DNA sample (50ng), and 8.5µl nuclease-free distilled water. Initial denaturation at 95C for 5 minutes, then 30 cycles of denaturation at 95˚C for 30 secs, annealing at 60˚C for 30 secs, and extension at 72˚C for 30 secs, were achieved. The PCR product was sent for Sanger Sequencing using an ABI3730XL automated DNA sequencer (Macrogen Corporation – Korea).

Statistical analyses

Continuous variables are reported as mean± standard deviation (SD) if normally distributed; if the data is distorted, a median interquartile range (IQR) of 25-75% is applied. Categorical variables are shown as a percentage of total counts (counts/total counts). Differences between groups were analyzed using the Mann-Whitney U test (two groups), and we showed allele and genotype frequencies as percentages following HWE: Hardy-Weinberg equilibrium. Measures of relation between genotype or allele and PsO, including confidence interval (CI) and odds ratio (OR), were also computed. Two-tailed probability of Fisher's (p) and Bonferroni's correction for multiple testing (padj) were used to determine whether or not their distributions differed significantly between PsO patients and controls. Adjusted probability was corrected for the comparisons' number done at each location. D' and R2 are the linkage disequilibrium (LD) and correlation (R) coefficients, respectively. SHEsisPlus (http://shesisplus.bio-x.cn/SHEsis.html) was used for the construction of haplotypes and linkage disequilibrium analysis. The 25.0 edition of the statistical software tool SPSS was used for this study.

Results

Gene expression of IL-36a

The IL-36a mRNA expression (fold change; $2^{-\Delta\Delta Ct}$) in psoriatic patients is highly significant when compared to healthy control (Expression of the IL-36A gene was up-regulated in PsO patients (1.29 [IQR: 1.12-1.55])), as shown in Fig. 1; plot A. According to gender, both males and females show insignificant differences in IL-36a mRNA expression (Fig.1; plot B). Fig; plot C shows that the IL-36a mRNA expression is not associated with the disease duration. The figure also illustrates the results of the genotypes of IL-36a SNPs rs2305152 (plot D) and rs895497 (plot E). The solid circle indicates the median, while the bars indicate the interquartile range (IQR: 25-75%). When *IL-36A* gene expression was evaluated according to the SNP genotypes, only rs2305152 had a significant effect; the CC genotype was significantly associated with higher expression compared to the AA genotype (2.12 [IQR: 1.57-3.47] *vs*. 1.15 [IQR: 1.04-1.47]; $p = 0.009$).

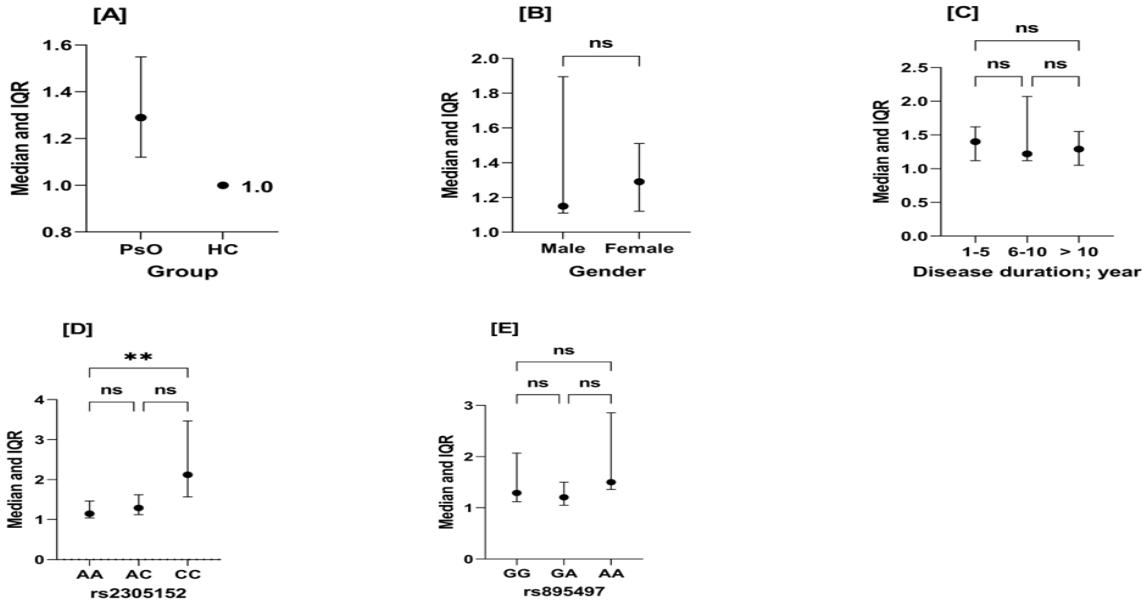

Figure 1: IL-36A mRNA expression (fold change; $2^{-\Delta\Delta Ct}$) in patients with psoriasis with (PsO; plot A), (plot B Sex), (plot C disease duration), (plot D genotypes SNP rs2305152), and (plot E SNP rs895497).

IL-36a gene SNPs

Two SNPs with polymorphic frequencies (rs2305152 A/C and rs895497 G/A) were assigned in the DNA sequence of the PCR amplified region (329bp), as exhibited in Figure 2. The genotype frequencies of these SNPs were in good agreement with HWE in PsO patients and healthy subjects. The first SNP was rs2305152 A/C. It was observed that three genotypes in PsO patients (AA, AC, and CC) had frequencies of 29.8, 65.5, and 4.8 %, respectively. The AC genotype showed a corrected, significantly increased frequency in the patients compared to the control (OR=17.91; 95% CI=7.21-44.48; *P*< 0.001). While the genotype CC showed a significantly decreased frequency in PsO patients (OR=3.04; 95% CI; *P*=0.209). Regarding the second SNP, rs895497G/A, three genotypes were observed (GG, GA, and AA), which have frequencies of 48.8, 45.2, and 6.0 %, respectively in PsO patients. The heterogenotype GA showed a highly significant difference (OR= 0.10; 95% CI= 0.04-0.25; *p*< 0.001). On the other hand, the genotype AA showed non-significantly decreased frequency in PsO patients (OR = 0.24; 96% CI = 0.05-1.20; *P* = 0.113), as illustrated in Table 1.

Table 1: Single nucleotide polymorphism genotypes of the *IL-36a* gene analyzed for association with psoriasis.

IL36a SNP	Genotype	PsO: n = 84		HC: n = 67		OR	95% CI	*p*	p_{adj}
		n	%	n	%				
rs2305152	AA	25	29.8	57	85.1	Reference			
	AC	55	65.5	7	10.4	17.91	7.21-44.48	< 0.001	< 0.001
	CC	4	4.8	3	4.5	3.04	0.65-14.32	0.209	1.0
***p*-HWE**		0.033		0.149					
rs895497	GG	41	48.8	6	9.0	Reference			
	GA	38	45.2	58	86.6	0.10	0.04-0.25	< 0.001	< 0.001
	AA	5	6.0	3	4.5	0.24	0.05-1.20	0.113	1.0
***p*-HWE**		0.855		< 0.001					

IL: Interleukin; SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; PsO: Psoriasis; HC: Healthy controls; OR: Odds ratio; CI: Confidence interval; p: Two-tailed

Fisher's probability; padj: Bonferroni-adjusted probability; NA: Not applicable. Significant p-value is indicated in bold.

A study of the allelic frequencies of the two SNPs showed that the first SNP rs2305152 has two alleles; A and C. C allele was increased highly significantly (OR = 5.58; 95% CI = 2.91-10.72 and $\boldsymbol{p} < 0.001$). While the second Snp observed two alleles G and A. Allele A showed an increased highly significant difference in PsO patients (OR = 0.44; 95% CI=0.27-0.70 and $\boldsymbol{p} < 0.001$), as Table 2.

Table 2: Single nucleotide polymorphism alleles of the *IL-36a* gene analyzed for association with psoriasis.

***IL-36a* SNP**	**Allele**	**PsO; n = 84**		**HC; n = 67**		**OR**	**95% CI**	***p***	$\boldsymbol{p_{adj}}$
		n	**%**	**n**	**%**				
rs2305152	*A*	105	62.5	121	90.3	Reference			
	C	63	37.5	13	9.7	5.58	2.91-10.72	< 0.001	< 0.001
rs895497	*G*	120	71.4	70	52.2	Reference			
	A	48	28.6	64	47.8	0.44	0.27-0.70	< 0.001	< 0.001

IL: Interleukin; SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; PsO: Psoriasis; HC:

Healthy controls; OR: Odds ratio; CI: Confidence interval; p: Two-tailed Fisher's probability; padj : Bonferroni-

adjusted probability; NA: Not applicable. Significant p-value is indicated in bold.

When studying the haplotypes, it was revealed that there are three types (A-G, C-G, and A-A), which had frequencies of 37.5, 33.9, and 25.0 %, respectively, in PsO patients. Compared to the control, the expression of the A-G haplotype was not significantly changed (OR =0.74; 95% CI=0.47-1.17 and P = 0.238), whilst that of the haplotype C-G had a very highly significant difference (OR = 6.37; 95% CI=3.10-13.07; P < 0.001). As for the haplotype A-A, the study showed a highly significant difference (OR = 0.40; 95% CI= 0.25-0.65 and P < 0.001). These results are shown in Table 3.

Table 3: Single nucleotide polymorphism haplotypes (rs2305152-rs895497) of the *IL-36a* gene analyzed for association with psoriasis.

***IL-36a* haplotype**	**PsO; n = 168 Ch**		**HC; n = 134 Ch**		**OR**	**95% CI**	***p***	$\boldsymbol{p_{adj}}$
	n	**%**	**n**	**%**				
A-G	63	37.5	60	44.8	0.74	0.47-1.17	0.238	0.714
C-G	57	33.9	10	7.5	6.37	3.10-13.07	< 0.001	< 0.001
A-A	42	25.0	61	45.5	0.40	0.25-0.65	< 0.001	< 0.001

PsO: Psoriasis; HC: Healthy controls; Ch: Chromosome; OR: Odds ratio; CI: Confidence interval; p: Two-tailed Fisher's probability; padj: Bonferroni-adjusted probability; NA: Not applicable. Significant p-value is indicated in bold.

The sequence chromatograms of IL-36a gene SNPs rs2305152 and rs895497 were then analyzed. The Geneious Prime software was used to generate the chromatogram, as shown in Figure 2. This figure illustrates each SNP with its genotypes, as SNP rs2305152 A/C has three genotypes AA, AC, and CC, whereas SNP rs895497 has three genotypes GG, GA, and AA.

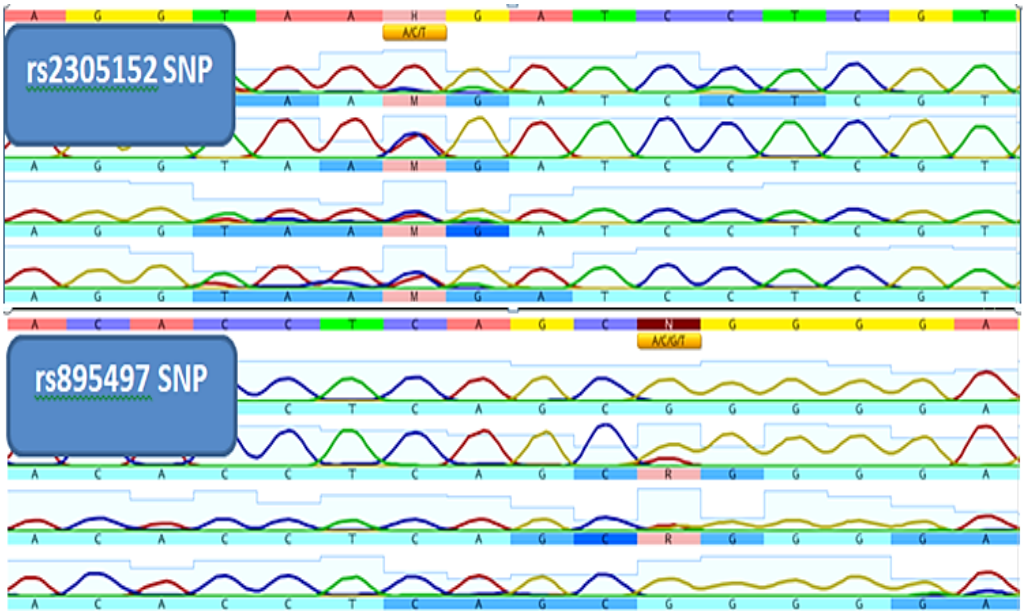

Figure 2: DNA sequence chromatograms of *IL36a* gene single nucleotide polymorphisms (rs2305152 and rs895497). Geneious Prime software was used to generate the chromatogram.

Figure 3 clarifies the linkage disequilibrium (LD) values of the two SNPs (rs2305152 A/C and rs895497 G/A). The two-locus linkage disequilibrium plots for the two SNPs showed values of LD coefficient (D') = 0.68 and correlation coefficient (R^2) = 0.09. The plots were generated using SHEsisPlus software (http://shesisplus.bio-x.cn/SHEsis.html).

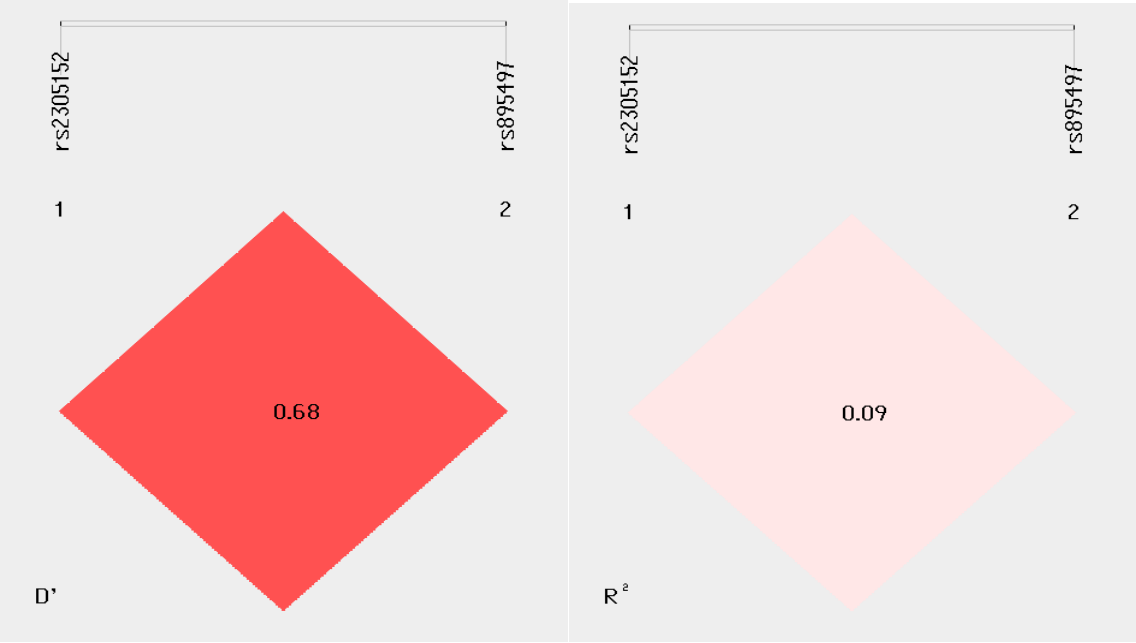

Figure 3: Two-locus linkage disequilibrium (LD) plot for the *IL36A* single nucleotide polymorphisms rs2305152 and rs895497 showing the LD coefficient (D') and correlation coefficient (R^2).

Discussion

The Δ Ct of IL-36a mRNA expression revealed a significantly higher mean in psoriasis patients compared to the control, suggesting that gene expression of IL-36a was up-regulated in psoriasis patients. The relative expression value was higher than one, according to the folding value of $2^{-\Delta\Delta Ct}$. When comparing psoriasis patients to healthy controls. The current study found a highly significant difference in the IL-36a gene expression, as shown in Figure 1 (plot A). Based on the preliminary findings, this may have a role in the severity of the psoriasis condition. In a previous investigation, IL-36 was shown to be increased in the serum of psoriasis patients, and this elevation was related to psoriasis activity. IL-36 functions as a central node cytokine by regulating the hyperactivation of important proinflammatory cytokines as well as activating immune cells, particularly neutrophilic accumulations [8]. *In vivo* preclinical investigations in knockout and transgenic mice revealed that IL-36 signaling is important in the formation of psoriatic lesions. IL-36 signaling acts as a gatekeeper, perhaps connecting innate immunity to the development of psoriasis [9]. Previous research has shown that IL-36a expression is highly related to the severity of psoriasis [10].

According to studies, IL-36a cytokines have an important role in the attraction and activation of Th17 and neutrophil cells in psoriatic skin [9]. The cytokines mediated by the IL-36a receptor impair epidermal differentiation and cornification and enhance pathological angiogenesis and endothelial cell activation. TNF-α and IL-17 both greatly increase the production of IL-36 cytokines in the psoriatic epidermis [11, 12].

In addition to its pathogenic effect on the skin, recent studies have shown that IL-36a may have a role in the extracutaneous clinical symptoms of Generalized Pustular Psoriasis and plaque psoriasis [9, 10]. According to a previous study, patients with GPP displayed a significant IFN Type-I signature, which is associated with abnormal IL-36 activity.

The current study discovered two SNP genotypes when analyzing the gene polymorphism of IL-36a. The pathogenic-etiological effect of IL-36a will be better understood once the gene polymorphism of this cytokine is identified [13].

The genotype study in this current research analyzed the genotypes of the two SNPs (rs2305152 A/C and rs895497 G/A), as shown in Table 1; the results demonstrated that the AC genotype of IL36a SNP rs2305152 (A/C) showed a significantly increased frequency in PoS patients compared to controls, and the associated OR was 17.91. Such difference was more pronounced when the comparison was based on allele frequencies; the C allele showed a corrected significantly increased frequency (susceptibility allele), while the A allele frequency was significantly decreased (protective allele). Another IL-36a SNP, rs895497 (G/A), showed a corrected significantly increased frequency (susceptibility allele), while G allele frequency was significantly decreased (protective allele), as listed in Table 2. When the rs2305152 and rs895497 haplotypes of the IL-36a gene were analyzed for the association with psoriasis, a significant relation was found between the haplotypes C-G and A-A, as shown in Table 3. Many previous studies have proven the existence of a relationship between genotypes and several autoimmune diseases [12, 14]. Figure 2 shows the sequence chromatogram of rs2305152 A/C and rs895497 G/A in psoriasis patients, illustrating the heterozygous genotype of each SNP. Figure 3 shows a two-locus linkage disequilibrium (LD) plot for the rs2305152 and rs895497, showing the values of LD coefficient (D' = 0.68) and correlation coefficient (R2= 0.09). Previous studies validated the effects of IL-36 cytokines on genes that are relevant to pathogenesis. The strongest among them is concerned with SNPs

rs28947207, rs28947206, and rs28947211, which were associated with the entire psoriasis analysis but also with several subgroups [15].

When associated with gene expression, the current findings (Figure 1, plot D) indicated that only rs2305152 had a significant effect; the CC genotype was associated with significantly higher expression compared to the AA genotype (1.12 [IQR: 0.57-2.47] vs. 0.15 [IQR: 0.04-0.47]; p = 0.009). A recent study established the association of this polymorphism with gene expression in psoriasis patients, for whom no previous research had been conducted. In the current study, the relationship of IL-36a polymorphism SNP rs2305152 A/C with gene expression was clarified and it was found that there was a significant difference in CC genotype with gene expression, as exhibited in Figure 1 (plot D). Accordingly, the SNP rs2305152 A/C may play an essential role in psoriasis and may be related to the severity and advancement of psoriasis in Iraqi patients, leading to significantly increased susceptibility to the disease.

As for the other SNP (rs895497 G/A), the results did not show significant differences when linked with gene expression in psoriasis patients, as shown in plot E above. The findings of this study indicate that these two SNPs may increase risk factors for psoriasis. No previous studies indicated this relationship. Previous studies showed that other SNPs associated with psoriasis, such as the variant alleles in *IL-23R* rs11209026 [16], *IL12B* rs6887695 [17], and *TNF* rs361525 [18]. The only variable consistently linked to an elevated risk of all phenotypes was the variant allele of TNF (rs361525), highlighting the significance of TNF-α signaling in the development of psoriasis [19] [20].

Another study looked at IL-12B rs3212227 and rs2082412, which were both linked to a lower incidence of PsO [17] [21]. There were differences found between PsC and PsA for IL-12B rs2082412 [22]. In a prior research, the PPARG variant allele rs1801282 was linked to a lower incidence of PsA [23]. The IL-36 pathway's increasing relevance in additional autoinflammatory skin conditions establishes IL-36 as a critical node orchestrating a pathogenic autoinflammatory process [19]. Evidence suggests that IL-36 cytokines are involved in the stimulation of keratinocytes and APCs, as well as the proliferation of T lymphocytes [24,25]. Many investigations revealed that IL-36 cytokines may have a role in the etiology of psoriasis [3, 4, 26]. Cytokine increases the development and expansion of immune cells, and therefore the creation of a humoral immune response [27, 28]. Cytokines have an important role in the pathophysiology and etiology of numerous autoimmune disorders and the immunopathogenesis of infectious diseases, inflammatory diseases, and cancer [27, 29]. Cytokine genes, which are involved in both inflammation and metabolism, have garnered significant attention in the study of a wide variety of diseases. Many cytokines such as interleukins, interferons, chemokines, and tumor necrosis factors have pleiotropic effects that are strongly related to the pathogenesis of psoriasis types [17, 25, 30].

Conclusions

In people with psoriasis, the study found that the activity of the IL-36a gene was higher due to genetic differences in the rs2305152 (A/C) SNPs, specifically the CC genotype. This genetic variation is strongly linked to an increased risk of psoriasis in Iraqi patients. The findings show a clear connection between increased gene expressions and this SNP. The study suggests that IL-36a is not only important in the development of psoriasis but also in determining how severe the disease can become, making it an important biomarker in psoriasis patients.

Ethical Clearance

Scientific studies in Iraq require the Research Ethical Committee's permission before they can proceed. This work has received clearance from the University of Baghdad and the Ministry of Health (CSEC/1123/0108).

Conflict of Interest

Conflicts of interest are not present, according to the authors.

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