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Serum level of interleukin-24 and its polymorphism in eczematic Iraqi patients

Aseel S. Mahmood, PhD[a,*], Wasan W. Al-Bassam, PhD[a]

Abstract

Eczema is a common skin disease associated with inflammation. Interleukin (IL)-24 is crucial in the pathogenesis of inflammatory diseases like eczema. The study objective was the assessment of IL-24 serum levels and its gene polymorphisms in eczematic Iraqi patients. This retrospective case-control study involved 145 participants, divided into 82 patients with eczema and 63 healthy controls. An enzyme-linked immunosorbent assay measured serum IL-24, while polymerase chain reaction and Sanger DNA sequencing were used for genotype analysis. Serum IL-24 level was significantly higher (*P* value < .001) in patients compared to controls (41.6 [interquartile range (IQR): 28.9–53.6] vs 9.8 [IQR: 0.8–19.6] pg/mL, respectively). DNA sequence illustrated 2 SNPs with polymorphic frequencies (rs1150256 G/A and rs3093425 del/ins). The first SNP (rs1150256 G/A) showed 3 genotypes (GG, AA, and G/A), while the second SNP (rs3093425) showed 3 genotypes (-/G del/Ins, G Ins/Ins, and - del/del). The subsequent investigation revealed the presence of the following findings within the DNA sequence of the PCR amplified region (329bp). In the control group, all participants had GG/G (wild type) genotype/allele for the rs1150256 SNP, while in eczematic patients, 24.4% GG, 50% GA, and 25.6% AA. For the second SNP genotype (rs3093425 del/ins), the genotype frequencies in patients vs control were (24.4% vs 84.1%, 50.0% vs 11.1%, and 25.6% vs 4.8; Del/Del, Del/Ins, and Ins/Ins, respectively). The presence of Ins compared to Del increased the risk of eczema by 8.91 (4.66–17.03); OR (95% CI). In conclusion, IL-24 is a good predictor of eczema and A-allele carrier for rs1150256 SNP, and insertion-allele carrier for rs3093425 SNP is associated with elevated serum IL-24 and higher risk of eczema.

Abbreviations: AD = atopic dermatitis, AUC = area under the curve, CI = confidence interval, HWE = Hardy-Weinberg equilibrium, IL = interleukin, IQR = interquartile range, OR = odd ratio, ROC = receiver-operating characteristic.

Keywords: allele, genotype, interleukin 24, polymorphism

1. Introduction

Eczema (atopic dermatitis [AD]) is a common skin disease characterized by inflammation. It can affect anyone at any age.[1] Eczema primarily manifests in children, although it can also occur in adults. Individuals afflicted with the condition typically experience dry, pruritic skin susceptible to infection.[2] Eczema has complex, distinctive features from multiple genetic and environmental factors.[3] Twin and familial clustering studies demonstrate that the illness has a strong hereditary component, indicating a substantial influence of genetic susceptibility.[4] Additionally, the notable rise in eczema prevalence in developed nations emphasizes the importance of environmental factors.[5] Studies indicate that AD has a genetic element; a prevalent mutation has been detected in the *Filaggrin* gene, which plays a crucial role in the maturation of skin cells. This gene is accountable for producing the resilient, planar corneocytes that constitute the outermost defensive barrier of the skin. The corneocytes are densely arranged and well-structured in an individual with normal skin cells. Patients harboring a Filaggrin mutation will exhibit a defective skin barrier due to the disordered arrangement of the skin cells.[4]

Dermatological changes in eczema are linked to immune system alterations originating at the stem cell level. Genetic defects in cytokines, such as interleukin 4 (IL-4) cluster, IL-12 receptor, IL-13 promoter, IL-4 receptor (IL-4R), stem cell factor (SCF), and tumor necrosis factor (TNF)-α, have been linked to the development of eczema; with cytokines play a crucial role in immune responses.[6–11] The cause-and-effect relationship between a specific locus and the occurrence of the AD phenotype has not been confirmed despite reports describing an association between the genetic locus and an atopy symptom.[12]

The expression of IL-24 is elevated in inflammatory skin diseases such as AD or psoriasis.[13] IL-24, along with other

Written informed consent was obtained from the participants.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was approved by the College of Science, University of Baghdad (Approval number: CSEC/1123/0109, date: 12th November 2023), and written informed consent was obtained from all participants in the study, per the Helsinki Declaration and its later amendments.

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members of the IL-10 family, such as IL-19 and IL-20, promotes the growth of keratinocytes in 2D cell cultures.[14] Like IL-19 and IL-20, IL-24 causes an increase in the thickness of the outer layer of the skin and the growth of skin cells in a human epidermis culture system.[15] This effect is directly proportional to the amount of IL-24 utilized. IL-24 reduces the expression of keratin-10 (KRT10) mRNA while simultaneously increasing the expression of KRT16.[16] The latter protein is increased in the upper layers of the interfollicular epidermis, indicating excessive cell growth and aberrant cell development. Therefore, it is also used as a marker for psoriasis.[17] IL-24 can hinder the movement of keratinocytes produced by Transforming growth factor alpha in a laboratory wound healing model and disrupts the growth of keratinocytes caused by TGFα.[18] When fibroblasts are grown together with organotypic co-cultures, IL-24 and IL-20 hinder differentiation and decrease the expression of Filaggrin and KRT10. IL-24 induces an augmentation in the thickness of the outermost layer of the skin in transgenic mice.[18–21] These data demonstrate that the function of IL-24 is different in normal skin compared to skin with an inflammatory response.[22] In the former scenario, IL-24 promotes cell growth and hinders the process of normal cell specialization. However, in inflamed skin, IL-24 suppresses the growth and movement of keratinocytes; this implies that the effects of IL-24 are regulated or counteracted by other cytokines/signals present during inflammation.[18,23] Defining the nature of these variables that interact with IL-24 signaling is an intriguing task.[24] To better understand the effect of IL-24 on eczematic patients biochemically and genetically, we undertook this study. The present study aims to evaluate serum levels of IL-24 and its gene polymorphisms in eczematic Iraqi patients.

2. Material and methods

2.1. Study design

A retrospective case-control study was conducted on 145 participants divided into 82 patients with eczema and 63 healthy controls. A consultant dermatologist diagnosed eczematic patients based on 2023 American guidelines.[25]

2.2. Study settings

The study was conducted in the biotechnology department of the College of Science, University of Baghdad. Patients were recruited from several hospitals in Baghdad (At Al Imamain Al-Kadhimein Medical City and Al-Yarmouk Teaching Hospital) from November 15th, 2023 to January 15th, 2024.

2.3. Eligibility criteria

Adult patients newly diagnosed with eczema were the inclusion criteria. The following patients were excluded: pregnant women, those diagnosed with other skin conditions aside from eczema, autoimmune disease, and chronic diseases like liver and kidney failure, and those who refused to participate.

2.4. IL-24 immunological test

Three milliliters of venous blood from each subject were drawn into a clear tube. After the blood had clotted, the tube was centrifuged (3000rpm for 15 minutes at 4°C), and the serum was then removed and stored at −20°C until analysis. The manufacturer directions were followed when the commercial enzyme-linked immunosorbent assay kit (CUSABIO) was used to measure the serum level of IL-24. The kit measurement range was 3.12 to 200 pg/mL.

2.5. Molecular method

DNA (Genomic) was extracted from EDTA blood using the ReliaPrep Blood gDNA Mini prep system (Promega) and subjected to PCR amplification after being evaluated for purity and concentration. Designed 2 primers forward5'-AGGTCAGAAGGCACCACAAG-3' and Reverse5'-GAGATGGGAGGAAATAAGCC-3' for genotyping of *interleukin-24* gene rs3093425 SNP and rs1150256. A total volume of 25μL was used for the PCR reaction, including 8.5μL nuclease-free distilled water, 2μL DNA sample (50 ng), 1μL from each (forward and reverse) primer (10 μM), and 12.5 μL Go Taq Green Master mix. The PCR condition initial denaturation (one cycle) step occurred at 95°C for 5 minutes. There were 35 cycles of denaturation cycles at 95°C for 30 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds, with the final extension at 72°C for 7 minutes; an ABI3730XL automatic DNA sequencer (Macrogen Corporation—Korea) used for Sanger sequencing for the amplified PCR fragments. After the genotypes were aligned with a reference sequence from the GenBank, Geneious Prime software disclosed the genotypes.

2.6. Sample size

It was determined using the G*Power version (3.1.9.7),[26,27] the effect size was 0.5, α-level 0.05, β-level 0.09 (power of detection 91%), with one-tailed, and the sample size was 144 for both groups, based on t-test family.

2.7. Statistical analysis

The categorical variable was presented in terms of both numerical and percentage frequencies. Significance was detected using the Mann–Whitney U test (***$P < .001$). The column represents the median, while the bars represent the interquartile range (IQR). The allele frequencies of IL-24 SNPs were determined using direct gene counting. Additionally, any substantial deviation from the Hardy-Weinberg equilibrium (HWE) was assessed using an HWE calculator for the 2 alleles (https://www.had2know.org/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html); in addition, the Confidence interval (CI), Odds ratio (OR); Two-tailed *P* value was also estimated to define an association between allele or genotype and eczema. Receiver-operating characteristic (ROC) curve analysis; the cutoff values, CI, area under the curve (AUC), specificity, and sensitivity are displayed; all analyses are carried out using the statistical software SPSS version 25.[28]

3. Results

3.1. Demographic data

As Table 1 illustrates, there was no significant difference in age, sex, and weight between both groups.

Table 1

Demographic data.

Parameters	Eczematic patients	Control	*P*
Number	82	63	
Age (yr)	37.8 ± 14.7	33.6 ± 12.4	.068
Sex			.292
Female	49 (59.8%)	43 (68.3%)	
Male	33 (40.2%)	20 (31.7%)	
Weight (kg)	71.3 ± 17.2	71.8 ± 14.4	.867

3.2. IL-24 concentration

Patients exhibited markedly elevated levels of serum IL-24 compared to the control group 41.6 [IQR: 28.9–53.6] vs 9.8 [IQR: 0.8–19.6] pg/mL, respectively; $P < .001$, as illustrated in Figure 1.

ROC curve analysis showed that IL-24 had a high predictive capability to differentiate eczematic patients from control. This cytokine had a remarkable AUC value of 0.887 (good predictor), with an optimal cutoff value of 25 pg/mL, a sensitivity of 80%, and a specificity of 80.3%, as illustrated in Figure 2.

3.3. IL-24 gene SNP

DNA sequence illustrated 2 SNPs with polymorphic frequencies (rs1150256 G/A and rs3093425 del/ins). The first SNP (rs1150256 G/A) showed 3 genotypes (GG, AA, and G/A), while the second SNP (rs3093425) showed 3 genotypes (-/G del/Ins, G Ins/Ins, and - del/del). The subsequent investigation revealed the presence of the following findings within the DNA sequence of the PCR amplified region (329bp), all shown in Figure 3.

Both SNPs followed HWE in eczematic patients; the rs1150256 SNP in the control group followed HWE, but the rs3093425 SNP deviated from HWE. In the control group, all participants had GG/G (wild type) genotype/allele for the rs1150256 SNP; when compared to eczematic patients, there was a statistically significant difference in the distribution of genotype/ allele, as illustrated by Table 2.

For the second SNP genotype (rs3093425 del/ins), the genotype frequencies in patients were 24.4%, 50.0%, and 25.6%; Del/Del, Del/Ins, and Ins/Ins, respectively, while for control, it was 84.1%, 11.1%, and 4.8; Del/Del, Del/Ins, and Ins/Ins respectively. The risk of having eczema in patients with Del/Ins compared to Del/Del was 15.52 (6.04–39.91); OR (95% CI), the risk of having eczema in patients with Ins/Ins compared to Del/Del was 18.55 (5.05–68.19); OR (95% CI). The presence of Ins compared to Del increased the risk of eczema by 8.91 (4.66–17.03); OR (95% CI), as illustrated by Table 2.

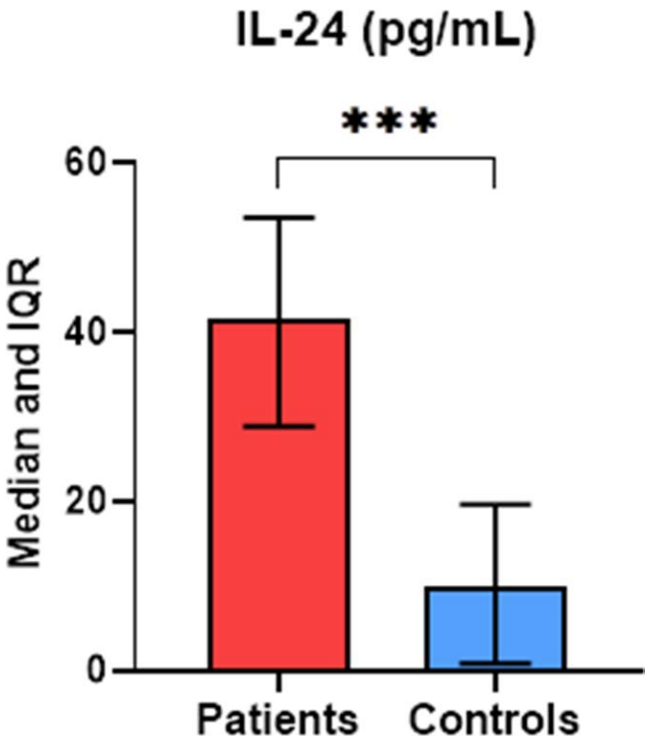

Figure 1. Serum IL-24 level in patients and controls. The column represents the median, while the bars represent IQR. Significance was detected using the Mann–Whitney U test (***$P < .001$). IL = interleukin, IQR = interquartile range.

3.4. Impact of genotypes on IL-24 concentration

The rs1150256 SNP genotypes impacted the concentration of the *IL-24* gene in eczema patients. Elevated IL-24 level was significantly seen in the serum of individuals with the genotypes AA (41.6 [IQR: 26.9–54.7] pg/mL; $P < .001$) and GA (35.5 [IQR: 27.7–52.9] pg/mL; $P < .001$) compared with the GG genotype (13.4 [IQR: 1.0–35.8] pg/mL), while there were non-significant difference between individuals GA and AA ($P = .88$) as shown in Figure 4.

The rs3093425 SNP genotypes impacted the concentration of the *IL-24* gene in eczema patients. Elevated IL-24 levels were significantly seen in the serum of individuals with the genotypes Ins/Ins (41.6 [IQR: 24.8–53.7] pg/mL; $P < .001$) and Del/Ins (34.2 [IQR: 19.8–50.5] pg/mL; $P < .001$) than in individuals with the Del/Del genotype (14.8 [IQR: 1.0–36.9] pg/mL), while there was non-significant difference between individuals with the genotypes Del/Ins and Ins/Ins ($P = .43$) as in Figure 4.

4. Discussion

The current study results show a significant elevation in the concentration of IL-24 in the serum of patients compared to healthy subjects, and this indicates a strong relationship between IL-24 and eczema. IL-24 is a crucial cytokine in inflammation because it may trigger the production of other cytokines like interferon-γ, IL-6, and TNF-α. In reaction with specific stimuli, immune cells such as macrophages, mast cells, natural killer cells, T and B lymphocytes, and monocytes, IL-24 production is stimulated by non-immune cells such as melanocytes and keratinocytes.[29,30]

Previous research has shown that individuals with AD had an increased expression of the *IL-24* gene in the affected skin.[31] Expression of the IL-24 protein was high in the basal layer compared to the spinous cell layer of skin tissues in AD patients, whereas no increase was observed in the granular and cornified layers. The expression of IL-24 was elevated in the epidermis of mice exposed to mites and in animals with the *IL-4* gene inserted in mouse models of AD.[32] In other studies, IL-24 was elevated in autoimmune illnesses such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis.[33,34]

As previously stated, eczema primary characteristics are abnormal skin colonization by pathogens, chronic pruritus, immune dysregulation, and skin barrier disruption. When treated with imiquimod, HaCaT cells (a cell line of immortalized keratinocytes) expressed IL-24 likewise elevated.[35,36] Loss of self-tolerance in autoimmune disorders causes autoreactive T and/or B cells to become active and cause tissue inflammation.[37,38]

The current study findings revealed that, compared to controls, eczematic patients had a significantly higher frequency of the GA and AA genotypes and the A-allele for the IL-24 rs1150256 SNP, and this suggests a significant role of the A-allele in eczema susceptibility.[29] There is a relationship between IL-24 polymorphisms and both metabolic and cardiovascular risk factors, which indicates that IL-24 polymorphisms may have functional impacts by raising the production of IL-24 and, as a result, pro-inflammatory cytokines.[39] IL-24 overexpression is implicated in psoriatic skin lesions[40] and other inflammatory autoimmune diseases.[29]

The current findings indicate that the rs3093425 SNP del/ins and ins/ins exhibited a notably higher frequency in patients with eczema than in the control group; the associated odd ratios were 15.52 and 18.55, respectively.

When analyzing allele frequencies, the Ins-allele displayed a significantly higher frequency (indicating susceptibility), while

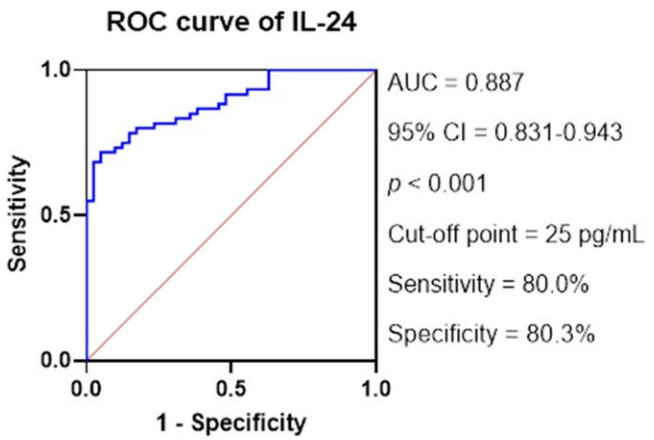

Figure 2. The ROC curve analysis of IL-24 in patients versus controls. AUC = area under the curve, CI = confidence interval, IL = interleukin, ROC = receiver-operating characteristic; specificity and sensitivity.

the del allele was found to be protective, in which the presence of Ins-allele increased the risk by 8.91 folds; the genotypes del (GGG) and ins (GGGG); this is the first study to examine the rs3093425 SNP in eczema.

The current study examined the correlation between serum IL-24 levels and the gene polymorphism of 2 SNPs. The IL-24 rs1150256 SNP AA and GA genotypes were significantly linked to higher IL-24 serum levels than the GG genotype; this suggests that this SNP may affect the gene expression of IL-24 and subsequently impact its serum level in patients with eczema.

Regarding the second SNP rs3093425 and its relationship to the serum level, it is clear from the results that serum IL-24 level was significantly higher in individuals with the genotypes Ins/Ins and Del/Ins than with the Del/Del genotype. These SNPs have also been suggested to influence IL-24 serum levels in eczematic patients. Previous studies have demonstrated that IL-24 polymorphism has been linked to numerous pathological conditions involving inflammation and may be involved in viral infection, tuberculosis, rheumatoid arthritis, cardiovascular disease, psoriasis, and inflammatory bowel disease.[29,41]

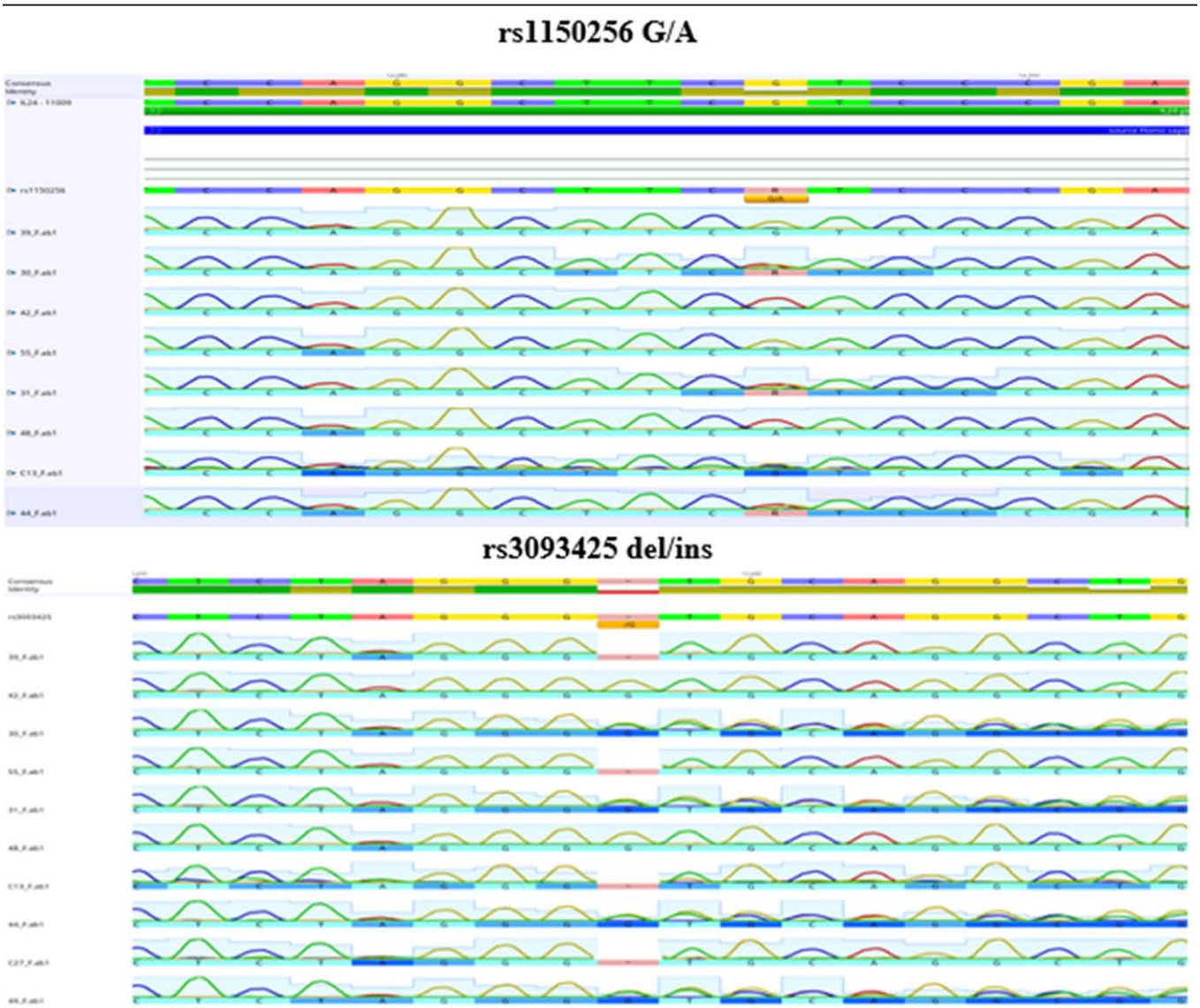

Figure 3. DNA sequence chromatograms of IL-24 gene single nucleotide polymorphisms (rs1150256 G/A and rs3093425 del/ins). Geneious Prime software was used to generate the chromatogram. IL = interleukin.

Table 2

Allele and genotype frequency of rs1150256 SNP in patients and controls.

	Eczematic patients (N = 82)		Controls (N = 63)				
Allele/Genotype	**N**	**%**	**N**	**%**	**OR**	**95% CI**	***P***
rs1150256 SNP							
G	81	49.4	126	100.0	Reference		<.001
A	83	50.6	0	0.0	-	-	
GG	20	24.4	63	100.0	Reference		<.001
GA	41	50.0	0	0.0	-	-	
AA	21	25.6	0	0.0	-	-	
HWE-*p*	0.998		1.000				
rs3093425 SNP							
Del	81	49.4	113	89.7		Reference	
Ins	83	50.6	13	10.3	8.91	4.66–17.03	<.001
Del/Del	20	24.4	53	84.1		Reference	
Del/Ins	41	50.0	7	11.1	15.52	6.04–39.91	<.001
Ins/Ins	21	25.6	3	4.8	18.55	5.05–68.19	<.001
HWE-*p*	0.998		0.002				

CI = confidence interval, Del = deletion, HWE = Hardy-Weinberg equilibrium, Ins = insertion, OR = odds ratio, p = two-tailed probability.

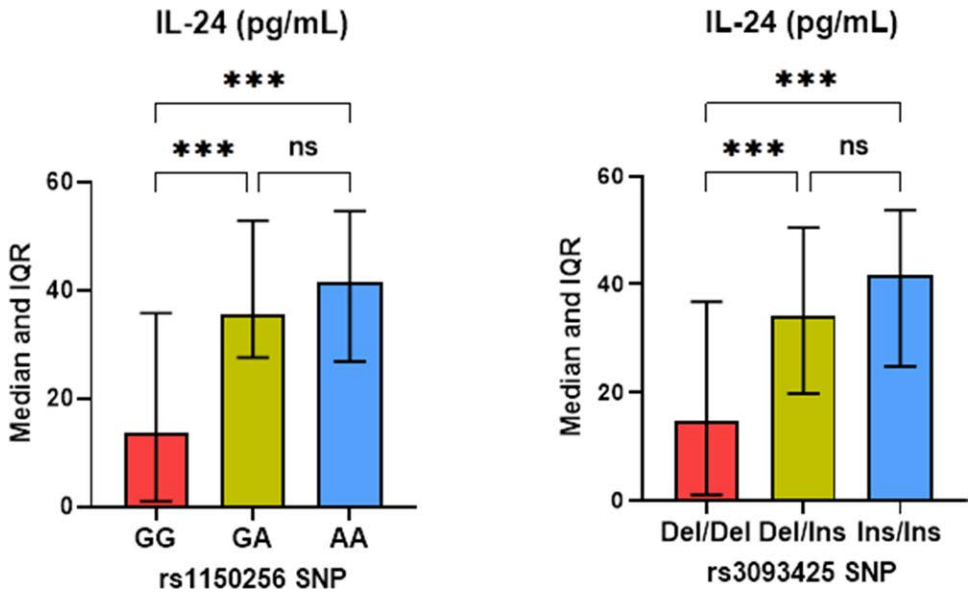

Figure 4. Serum IL-24 levels classified by rs1150256 SNP and rs3093425 SNP genotypes. The column represents the median, while the bars reflect the IQR. Statistical significance was determined using the Mann–Whitney U test (****P* < .001; ns: insignificant). IL = interleukin.

The *IL-24* gene is located within chromosome 1q32-3 and other cytokines clusters, such as the *IL-19* and *IL-20* genes. The *IL-24* gene is exclusive to the Th2 lineage and is highly activated by STAT6 in Th2 cells.[13,42] Mast cells secrete mediators, including TNFα, IL-4, IL-5, and IL-6, linked to allergic reactions. These mediators promote the recruitment of inflammatory cells.[43] Cytokines can have both pro- and anti-inflammatory functions based on the underlying disease. Previous research has identified several cytokines with important functions in the pathophysiology of autoimmune disease.[31,37,44]

5. Study limitations

Reproducing findings in genetic association research is intrinsically intricate, resulting in difficulties in making significant comparisons across many studies. The strongest evidence of a correlation is in reproducing this association in a separate population that possesses the same genetic makeup, physical characteristics, and direction of influence.[45] The majority of research examining genetic connections suffers from insufficient statistical power as a result of the limited number of individuals with the homozygous mutant genotype.[45] In addition to the limited sample of patients, the study examined single ethnic groups and did not include the children population; these factors limit the generalizability of the study findings.

6. Conclusion

In conclusion, our research shows that IL-24 polymorphisms are connected to eczema. There is an association between 2 IL-24 SNPs (rs1150256 and rs3093425) and the risk of eczema in Iraqi patients; these genetic polymorphisms influence the serum levels of IL-24 in eczematic patients.

Author contributions

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Writing – review & editing: Aseel S. Mahmood, Wasan W. Al-Bassam.

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