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Correlation Between *FAS* Gene Polymorphism (rs:1800682) and their Serum Level with Psoriasis Patients

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Abstract: Psoriasis is a chronic, multifactorial inflammatory skin condition can be defined by keratinocyte hyper proliferation that is mediated by T cells. It is immune-mediated inflammatory skin disease with multiple phenotypically distinct subtypes it a major *gene*tic component, with heritability estimated to be (60-90%) The goal of the current study is genotyping of the *FAS (Fas* cell surface receptor *gene* (-671 A>G (rs:1800682), and evaluate its serum level in Iraqi patients with psoriatic.100 blood samples collected from December 2022 to February 2023. The blood samples split into two groups first 50 psorasis patients (30males and20 females) with age range (17-66years) second group 50 healthy individual (24 males 26 females) with age range (20-60 years) visit the Dermatology Department at Al-Yarmouk Teaching Hospital in Baghdad, Iraq. Two techniques were used in the research, the first is (PCR-HRM) to investigation *gene* polymorphism and the second technique is EIISA to detect *FAS* serum level. The aimed to investigate whether *FAS (Fas* cell surface receptor *gene* (-671 A>G (rs:1800682) with *FAS* serum level. the result suggest that there are three genotype (AA),(AG),(GG) in current study shows statistically significance in the (AA) genotype frequency in the *FAS gene* with a percentage in psoriasis patients (6%versus 24% in healthy individuals) respectively. The (AG) genotype shows non-significant differences between psoriasis patients and control the(P-value =0.612) respectively While the GG genotype shows non-significant frequency in psoriasis patients compared control group with (p-value =0.297). and findings that the *FAS* serum in patient high significantly different between psoriasis patients when compared to the healthy controls with (P 0.01). It was concluded that found correlation between genotyping and serum level for *FAS* (rs 1800682)*gene* (AA) genotype serum level that significant different from (GG) genotype serum level with p-value($P \leq 0.05$).

Keywords: *FAS*, Psoriasis, PCR-HRM, SNPs,ELISA.

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Introduction

Psoriasis (Pso) is the most common highly chronic inflammatory three decades the interplay of hereditary and environmental variables results in the complex disease. The reported prevalence of psoriasis in countries ranges between 0.09% and 11.43% (1) The prevalence of PSO in Iraq ranges from 0.7% to 2.3% (2)the most typically affected parts, the scalp, face, nails, palms, soles, and intertriginous regions also have a high rate of involvement stress.

The most important pathogenic trait of PSO is the hyper proliferation and cellular infiltration of keratinocytes and dermal vascular endothelial cells, which leads to vascular alterations and inflammation (3). The disease is usually manifested as raised, well-demarcated,

erythematous oval plaques with adherent silvery scales (4). The scales are a result of a hyper proliferative epidermis with premature maturation of keratinocytes (KC), (5) as show in the (Figure 1 -A,B).

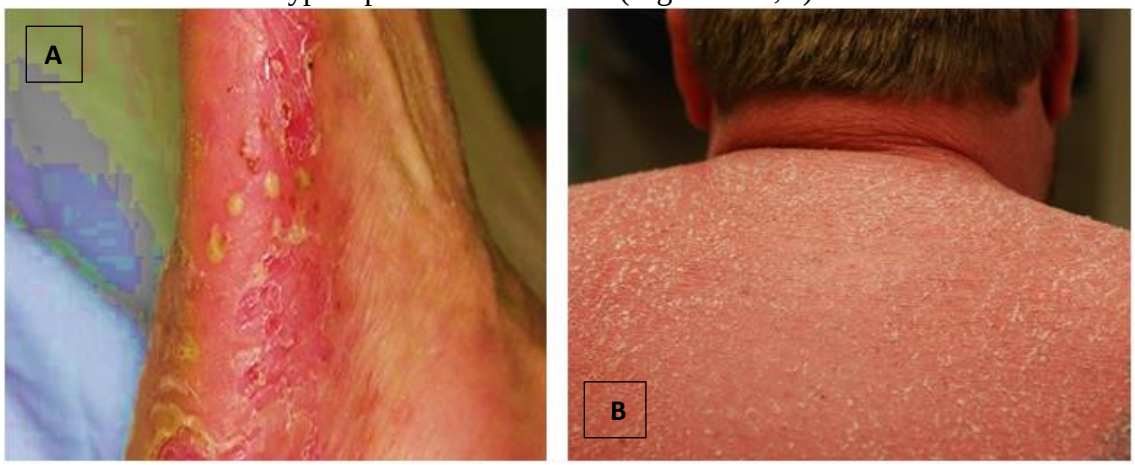

Figure (1):(A, B) patient with psoriasis

FAS gene is apoptosis *gene*s (Apo The *Fas*/ signal)(6) *Fas*, a 40–50 kDa type I trans membrane glycoprotein also known as, APO-1, is a member of the tumor necrosis family receptor (TNFR) superfamily that also performs non-apoptotic signaling (7).The human *Fas gene*, located at 10q23.3-4 on chromosome 10, has 335 amino acids.

Encodes the human *Fas*/ TNFRSF6/ CD95 protein, which has nine exons and eight introns. Exon 1 include the 5' untranslated region (UTR) and Exons 2-5 encode for the extracellular region and exon 6 encodes for the trans membrane region. The membrane proximal cytoplasmic 36 amino acids of the receptor are encoded by exons 7 and 8 whereas the remaining 109 amino acids, including the "death domain". *FAS* The best-known technique is apoptosis induction, which is an essential first step in the onset of psoriasis and is supported by activated lymphocytes Several studies have found an association between *FAS* polymorphisms and autoimmune disease (8). The interaction between *Fas* and receptor results in the formation of the death-inducing signaling complex (DISC), which contains the *Fas*-associated death domain protein (FADD), caspase-8 and caspase-10, There is a death domain in this receptor.

It has been demonstrated to play a crucial part in the physiological control of programmed cell death and has been linked to the development of numerous immune system disorders such as AIDS, hepatitis and cancers(This receptor interacts with *FAS* ligand to *gene*rate a signaling complex that causes death and contains (FADD), caspase 8, and caspase10 single nucleotide polymorphisms (SNP) of the *Fas* (cell surface receptor) *gene* , especially in the promot¬er region, can be affected by the expression of these *gene*s, and because *FAS* soluble in the serum any defects in keratinocytes lead to increase serum level in patients with psoriasis (9). one of the TNF receptor superfamily members that is Trans membrane receptor *Fas* is expressed in the thymus, liver, kidney, pancreas, brain, heart, and renal tissues. It is a member of the family of death receptors. *FAS gene*, Different autoimmune disorders and other cancers are related with risk and severity due to mutations in the APO-1/*Fas* promoter. The interaction between T-cell receptors

(TCRs) and antigen-presenting cells (APCs) results in the expression of the APO-1/*Fas* receptor by many different types of cells. These cells, on binding to *Fas*-expressing T-cells, lead to activation-induced cell death (10). the current study aimed to investigate that the *FAS* -671 A>G (rs: 1800682) polymorphisms were correlated with soluble *Fas (sFas*) levels in psoriasis Iraqi patient.

Material and methods

Samples were collected according to the Iraqi Health Ministry agreement by taking into consideration medical ethics. The study was conducted and was approved by the council of the University of Baghdad's Institute of *Gene*tic Engineering and Biotechnology for Postgraduate Studies.

Writing informed consent and medical history were obtained from all patients and healthy control groups, and all volunteers have been informed they will be enrolled in this research. The study involved a total 100 blood samples that were collected from December 2022 to February 2023. The blood samples included 50 Iraqi patients (30males and20 females) age average(17-66 years) with the psoriasis disease who most regularly visit the Department of Dermatology, Al-Yarmouk Teaching Hospital in, Baghdad, Iraq . In addition, 50 blood samples of apparently healthy volunteers (24males and 26 females) age average (20-60 years) two milliliters of venous blood were collected from each volunteer by using a disposable syringe transferred immediately (EDTA) tube for Molecular test and stored at (-20 c) *FAS* -671 A>G polymorphisms were analyzed with polymerase chain reaction-high resolution melting (PCR-HRM) technique. The 3 ml blood samples given to the study participants were collected into gel tubes for the sandwich ELISA test, which was centrifuged at 1.000 rpm after being allowed to clot for an hour. The collected patients serum samples were separated to portions and storage at -80 °C until needed. Using sandwich ELISA kits for detection *FAS* serum level.

Molecular analysis

DNA extraction

2ml of blood Samples in EDTA tubes that collect from each psoriasis patients and healthy individual as control that are stored at -20 °C for using to DNA extraction By Easy Pure® Genomic DNA Kit After the DNA extraction process, Use gel electrophoresis to find out the presence of DNA and show the bands on the gel. The concentration (ng/l) and purity of the DNA were determined using the NanoDropTM OneC spectrophotometer, The A260/A280 ratio range (1.8 – 2.0) which suggested that the DNA samples were pure.

Primers designing and preparations

The primers were designed using the Primer 3plus, V4, and double checked by the University Code of Student Conduct (UCSC) programs, and with their reference sequences in the National Center for Biotechnology Information (NCBI) database. They were synthesized and lyophilized by Alpha DNA Ltd. (Canada), as shown in (Table 1).

Table (1): Oligonucleotide Primers that were used for amplification in this research

Primer	Sequence 5'- 3'	Product size (bp)	Tm	
***FAS gene* for (rs 1800682)**		100	58	Design in This study
Forward	**CCTATGGCGCAACATCTGTA**			
Reverse	**GACTGGGCTGTCCATGTTG**			

Primer sequence matching

Gene sequence matching as done by NCBI for *FAS gene* (rs 1800682) is shown in (Figures 2).

Quantitative Real-Time PCR (qRT–PCR) amplification runs High Resolution Melting (HRM).

Quantitative Real time PCR (qRT-PCR) was carried out byusing the Qiagen Rotor *gene* Q-Real-time PCR system (Germany)The *FAS gene* polymorphisms levels was quantified by measuring the 2x HRM PCR super mix kits components (Table 2).

***Fas gene* (rs1800682)**

TTGTTTTCCTCTTGAGAAATAAAAACTAAGGGGCCCTCCCTTTTCAGAGC**CCTATGGCGCAA CATCTGTA**CTTTTTCATATGGTTAACTGTCCATTCCAGAACGTCTGTGAGCCTCTCA

Forward primer) (CCTATGGCGCAACATCTGTA

TGTTGCAGCCA**CAACATGGACAGCCCAGTC**AAATGCCCCGCAAGTCTTTCTCTGAGTGACT CCAGCAATTAGCCAAGGCTC

CAACATGGACAGCCCAGTC (Revers primer)

Figure (2)*: FAS Gene* sequence matching

Table (2): Components of the reaction mixture for amplification for *Fas gene* SNPs

Component	Volume (µl)
N.F.Water	4
DNA Template	4
Forward Primer	1
Reverse Primer	1
TransStart® Tip master mix	10
Total volume	20

High Resolution Melting analysis principle

High Resolution Melting is a closed-tube, post-PCR analysis method that has raised enormous scientific interest. HRM characterized double-stranded PCR products based on their dissociation (melting) behavior as they transition from doublestranded DNA (dsDNA) to single-stranded DNA (ssDNA) with increasing temperature, (Table 3), (Figure 3).

Table (3): Thermal profile of HRM for SNP *FAS*

Step	Temperature (ºC)	Duration	
Enzyme activation	94	1 min	1
Denaturation	94	5 sec	40
Annealing	58	15 sec	
Extension	72	20 sec	1
HRM	65-90	0.2 sec for 1 degree	1

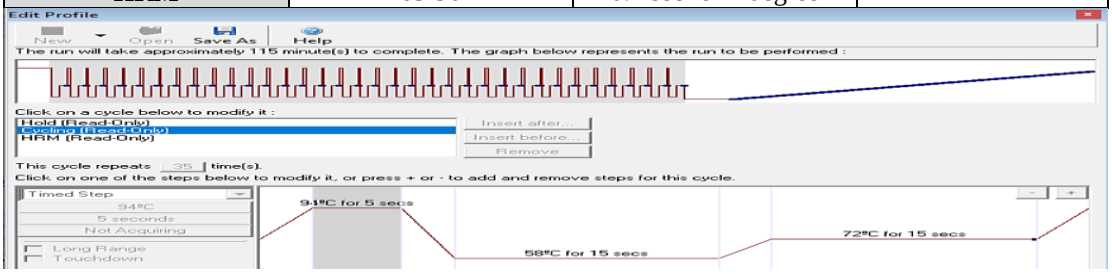

Figure (3): Thermal profile of HRM for SNP *FAS*. This picture was taken direct from rt-PCR Machine.

Enzyme-linked Immunosorbent Assay (ELISA) kit for the detection serum level of *Fas* This kit was based on sandwich enzyme-linked immune-sorbent assay technology According to the constriction of the company (Fine test). Capture antibody was pre-coated onto 96-well plates. And the biotin conjugated antibody was used as detection antibodies. The standards, test samples and biotin conjugated detection antibody were added to the wells subsequently, and washed with wash buffer Streptavidin conjugate (SABC) was added and unbound conjugates were washed away with wash buffer.

TMB substrates were used to visualize HRP enzymatic reaction. TMB was catalyzed by (SABC) to produce a blue color product that changed into yellow after adding acidic stop solution. The density of yellow is proportional to the target amount of sample captured in plate. Read the O.D. absorbance at 450nm in a micro plate reader, and then the concentration of target can be calculated.

Statistical analysis

The Statistical Analysis System-SAS (2018) application was used to determine the impact of various factors on study parameters. The T-test and Least Significant Difference (LSD) test were used to significantly compare between means. Chi-square test was used to compare percentages (0.05 and 0.01 likelihood) in a significant way. The study's estimated odds ratio and confidence interval.

Results and discussion

Genomic DNA was extracted from blood samples of the study subjects using the Easy Pure® The concentration (ng/l) and purity of the DNA were determined using the NanoDropTM OneC spectrophotometer, The A260/A280 ratio range (1.8 – 2.0) which suggested that the DNA samples were pure. Genomic DNA Kit in order to investigate *gene*tic polymorphisms of *FAS* for (rs 1800682) gene in Iraqi psoriasis patients and healthy controls, (Figure 4).

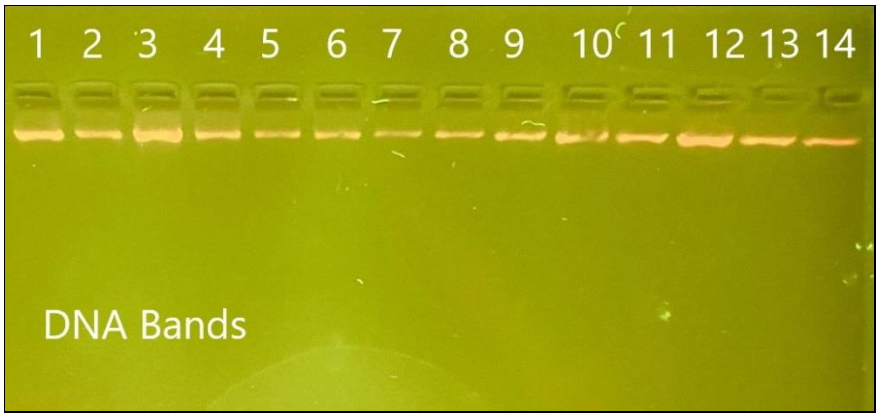

Figure (4): DNA Bands on 1% Agarose Gel at 7 Volts for 60 min. Genomic DNA extracted from blood samples, visualized under UV light after staining with Ethidium Bromide

Using HRM real-time PCR, it was possible to compare the genotype of the *FAS gene* (*Fas* cell surface receptor *gene*) -671 A>G (rs:*1800682*) polymorphism with allele frequencies (AG) between the study groups of psoriasis patients and apparently healthy individual as controls. Displays the thermal cycler output for the three genotypes as a result in (Figures 5-A,B).

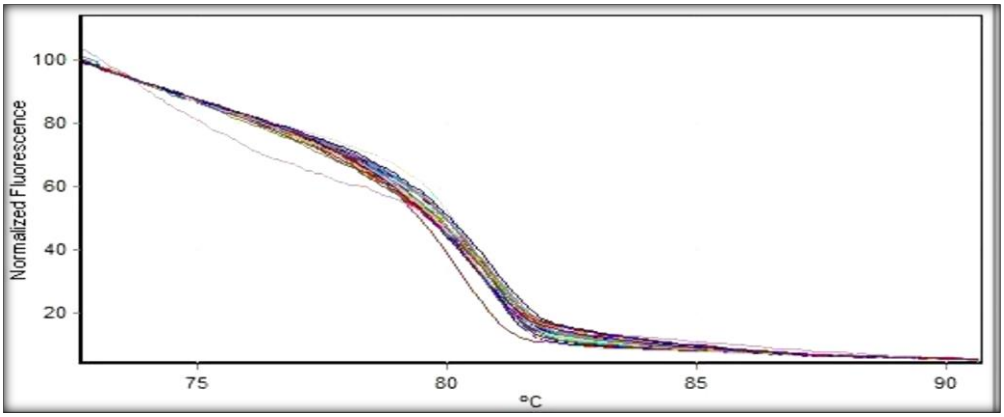

Figure (5-A) :The result output of HRM for the three genotypes in *rs*1800682 SNP of *FAS gene*.

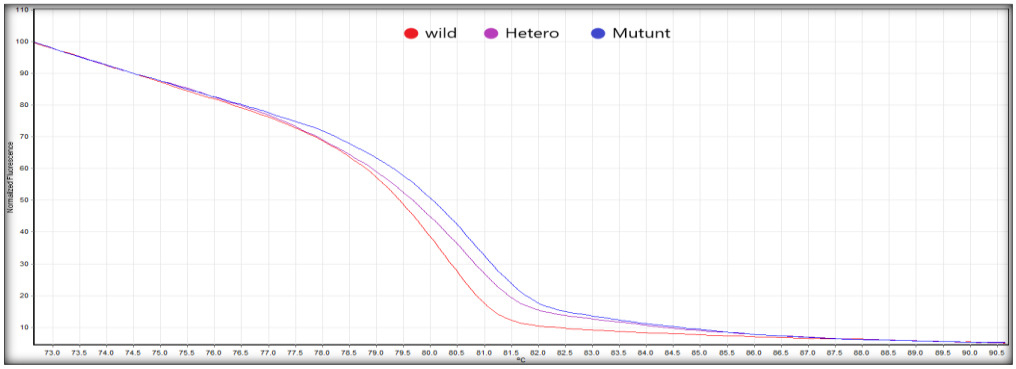

Figure (5-B):of HRM for the genotypes (rs1800682) SNP for *Fas gene*.

Detection of the genotype of *FAS* (*rs1800682) gene* polymorphism with allele frequencies between the study groups (patients and control) was carried out using HRM real-time PCR (Table 4). Shows statistically significance in the AA genotype frequency in the *FAS gene* with a percentage in psoriasis patients (6%versus 24% in healthy individuals). The AG genotype shows non-significant differences between psoriasis patients (66.0%) versus in healthy individuals (56.0%), the (P-value =0.612) While the GG genotype shows non-significant frequency in psoriasis patients (28%) compared to the control group (18%) and (p-value =0.297). the A allele frequency values were (0.39and 0.53)) for apparently healthy individual and psoriasis patients, respectively The values of allele frequency of the G allele were (0.61 and 0.47) of apparently healthy and psoriasis patients, respectively.

Table (4): Genotype and allele frequency of *FAS* rs(1800682) *gene* in patients and control groups

Genotype *FAS* rs (1800682)	Patients No. (%)	Control No. (%)	Chi-Square ($\chi 2$)	P-value	O.R. (C.I.)
AA: Wild	3 (6.00%)	12 (24.00%)	5.40 *	0.0201	1: Reference
AG: Hetero.	33 (66.00%)	29 (58.00%)	0.258 NS	0.612	0.219 (0.09-0.82)
GG: Mutant	14 (28.00%)	9 (18.00%)	1.087 NS	0.297	0.161 (0.05-0.75)
Total	50 (100%)	50 (100%)			
Allele	**Frequency**				
A	39 (0.39)	53 (0.53)	P-value = 0.144 NS		
G	61 (0.61)	47 (0.47)	P-value = 0.178 NS		
*** (P≤0.05), NS: Non-Significant.**					

In current study found no significant difference between the AG, GG, genotype but significant different in AA genotypes between healthy individual and psoriasis patients. And that computable with (11) found the genotype distribution and allele frequencies for *FAS* -671 A>G. There was not a significant distinction between the psoriasis and control groups when we investigated *FAS* -671 AG and GG genotypes and G allele frequencies. (AG, p=0.521; GG, p=0.726; G, p=0.929) of the *FAS* polymorphism (p>0.05) in Turkish psoriasis patients.

while (12,13) that found significant different in genotypes in healthy subjects and psoriasis patients in other SNP *IL12B* (rs6887695) *IL23R* (rs11209026) and *TNF* (rs36152) are all well-known polymorphism associated with susceptibility to Psoriasis and not found in *FAS* (*rs*1800682) but (15) the analysis showed the(rs1800682) polymorphism was associated with an increased risk of colorectal cancer (CRC)and A statistically significant association was found between *Fas* rs1800682 and increased breast cancer risk and that study above not computable with current study. One of the study's unexpected findings is how many people with the AA genotype in the control group have high levels of *Fas*. in current study found *FAS* serum level (Table 5), (Figure 6) is deferent between control and mild, sever psoriasis patients and study showed that the serum level *FAS* in severe cases of psoriasis was higher (mean340.21 pg/ml) than that of mild cases (mean303,68 pg/ml), and the serum level in control cases was lower (mean265,9 pg/ml) compared to patients with psoriasis.

Table (5): Relationship of Severity and parameters study in difference groups.

Severity	Mean ± SE pg/ml
	FAS serum level
Mild	303.68 ±37.06
Sever	340.21 ±24.61
Control	265.99 ±19.12
T-test	106.07 NS
P-value	0.242
NS: Non-Significant.	

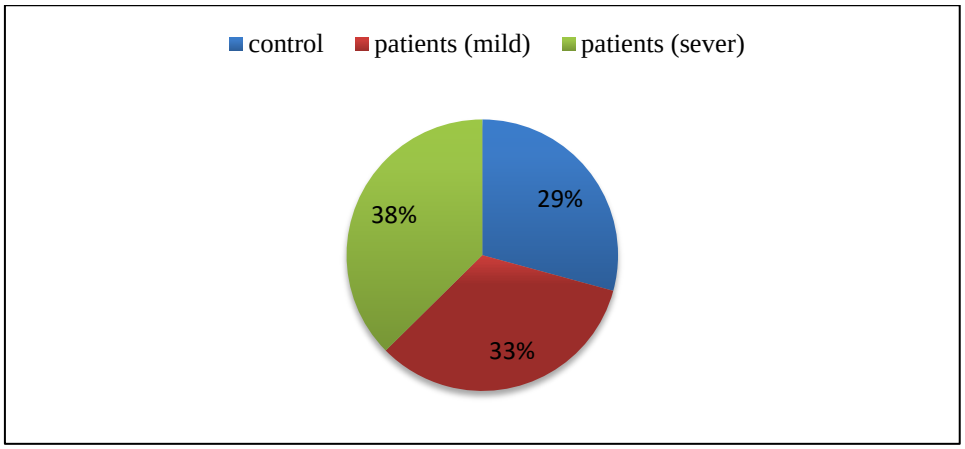

Figure (6): Relationship of Severity and parameters with *FAS* serum level.

Because our sample is of comparable ethnic origin and comes from an isolated region, more research in a larger population is necessary.

Serological Investigations

Measurement serum level of *FAS gene* In current study serum level of *Fas gene* that show high significant different between control and patient with P value (P≤0.01) Table(6).

Table (6) Sample study distribution based on *Fas* levels in the serum in the patient and control groups

	Control	Patients	P-Value
Mean pg/ml	265.998	316.70	0.000**
Std. Deviation	101.143	147.843	
T-test	13.916	15.147	
P-Value	0.000**	0.000**	
** (P≤0.01).			

This data is consistent with (14) which showed for the first time that psoriasis patients have higher s*Fas* concentrations ratios than healthy controls but (15) Finding soluble *Fas* (s*Fas*) is crucial for psoriasis sufferers, and there are reports that treatment has altered serum levels. expression of the *gene*, which results in apoptosis, a form of programmed cell death. And disagree with other study (16) , is one of the most significant of these pathways In this study, we postulated that the hyper proliferation may cause the *Fas* signaling pathway to be disrupted in the apoptotic process. The higher s*Fas* levels in patients, however, imply that this theory might still be accurate.

Patients with Systemic Lupus Erythematosus (SLE) taking part in a study to find out more about the role of the *Fas* system in autoimmune illnesses. The Another study found that the concentration of the s-CD95 (*Fas*) *gene* in the serum of psoriasis patients did not differ from that of healthy controls. Moreover, in a different investigation SNPs in the promoter region have been discovered. Research on how Guillain-Barre syndrome (GBS) patients' blood levels are affected by *FAS* promoter area polymorphisms suggests that they may increase serum levels and be related to the condition(17). Patients' levels of s*Fas* were significantly greater than those of the control group, according to the current study (p 0.001).

Other Iraqi study that agree with current study (18) discovered that patients with diabetic foot lesions had when compared to patients without diabetic foot lesions and healthy control groups, there were considerably greater levels of s*Fas* (p 0.001, p 0.05, respectively), and that pregnant women with hypertension had significantly higher levels of *Fas* ligand (p0.001) than pregnant women with normotensive blood pressure (19) other Iraqi study found no significant increases in serum s*Fas* with chronic myeloid leukemia patient compared to healthy control with P=0.09. When the mean s*Fas* concentration was obviously highest in newly diagnosed (1163.6pg/ml) followed by optimally treated (1021.7 pg/ml) and lowest in healthy control (970.1pg/ml) (20). However, the fact that *FAS* levels are higher in patient groups than in the control group implies that more research is required in this area. The rise large in serum levels raises the notion the *Fas* signaling during pathway that broken. According to the amount of body surface area affected, which dermatologists evaluated and classified as mild and severe, psoriatic patients were separated into two groups in the current study In psoriasis patients, the levels of soluble *Fas* (*FAS*) are essential Additionally, there have been events of changing serum levels. as a result of treatment-induced production of the

gene, which causes apoptosis, a type of programmed cell death(In currant study, found higher level of *FAS* in the serum of patients with psoriasis than healthy individual. The Relationship between *FAS* (rs 1800682) and there serum level in psoriasis patients that show in (Table 7).

Table (7): Relationship between *FAS* rs (1800682) *gene* polymorphism and serum level in psoriasis patients and control groups

***FAS* rs (1800682) *gene* polymorphism**	**Mean ± SE pg/ml of *FAS* serum level**	
	Patients	**Control**
AA	223.15 ±50.82 b	263.68 ±40.79
AG	299.07 ±26.70 ab	258.86 ±28.09
GG	378.31 ±34.21 a	284.63 ±30.14
LSD value	153.34 *	110.78 NS
P-value	0.0498	0.841
*** (P≤0.05), NS: Non-Significant.**		

In current study found significant different between genotyping and serum level for *FAS* (rs 1800682)*gene*|(AA) genotype (mean 223.15 pg/ml) significant different from (GG) genotype (mean 378.31 pg/ml) with p-value (P≤0.05) but not different between (AA) genotype and (AG) genotype. The promoter regions of the *FAS gene* contain the *FAS* -671 A>G (rs: 1800682) polymorphisms which have been linked to a variety of disorders in several studies (21). It makes some autoimmune diseases more probable to develop., Other study (22) Patients with psoriasis need to have adequate amounts of soluble *Fas* (s*Fas*) (23).

Conclusion

The investigated *FAS* polymorphisms were not found to be directly associated with the psoriasis. The current research has shown that serum levels of the *FAS gene* which increase in patients with psoriasis, were found to be correlated with the severity of the illness. As a result, serum levels of the *FAS*, which were found to be connected with the clinical severity of psoriasis, may serve as an objective measure of therapy efficacy and may be used to monitor patients.

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