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Role of macrophage scavenger receptor 1 in the progression of dyslipidemia in acne vulgaris patients

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Abstract

Background: Macrophage scavenger receptor 1 gene (MSR1), is responsible for producing macrophage scavenger receptors. MSR1 is primarily located on the surfaces of various macrophage types and is known to exert a range of effects on the human body. These effects include influencing innate and adaptive immunological reactions, as well as contributing to the development of conditions such as atherosclerosis, dyslipidemia, liver and lung disease, and cancer. The unregulated assimilation of lipoproteins by MSR1 leads to the creation of macrophages rich in cholesterol that manifest as foam-like cells, ultimately contributing to dyslipidemia. This occurrence highlights the significance of MSR1 as a key player in the pathophysiology of dyslipidemia.

Aim: In this study, we aimed to estimate variation in lipid profile in acne vulgaris (AV) patients. Also, we aimed to investigate the role of MSR1 in lipid profile variation.

Subjects and methods: A case-control study consisting of 100 patients with AV and 104 healthy controls. Lipid profiles were assessed using normalized enzymatic processes and genotype analyses were performed by a polymerase chain reaction and standard Sanger sequencing. Predictions of variant effects were performed using in silico tools.

Result: Our results indicated that the levels of lipid profile were higher in patients with AV than in healthy patients. The two haplotypes that were most prevalent in the patients were TCAC (16.5%) and CAGG (15.47%), whereas the two haplotypes that were more prevalent in the controls were TAAC (16.43%) and CCAC (15.62%). IVS5.59 C > A and rs433235 A > G are in linkage disequilibrium. Additionally, rs433235 A > G has a significant linkage disequilibrium with rs3747531 C > G. In silico analysis, tools indicated that the rs433235 A > G variant was disease-causing.

Conclusion: Patients diagnosed with TCAC and CAGG exhibited a higher prevalence compared to healthy patients with TAAC and CCAC. The linkage disequilibrium

between rs433235 A > G and IVS5.59 C > A has been established. Furthermore, there appears to be significant linkage disequilibrium between rs3747531 C > G and rs433235 A > G. These findings support the notion that genetic variations may play a critical role in the pathogenesis of these conditions.

KEYWORDS
acne vulgaris, haplotypes analysis, linkage disequilibrium, MSR1 gene

1 | INTRODUCTION

Acne vulgaris (AV) constitutes the most typical chronic clinical entity, with inflammatory or non-inflammatory lesions or a combined effect of all of those. At the age of 16, 83% of girls and 95% of males have AV. AV in females is more chronic and frequently affects the face, whereas AV in males is more severe and typically affects the chest and back. In addition to teens, adults also experience AV. Skin flares such as whiteheads, blackheads, papules, pustules, and cysts characterize AV.[1]

The blood lipids profile of patients with AV deviates from that of healthy controls. Patients with AV, both males and females, have extremely diminished levels of high-density lipoprotein cholesterol (HDL-C) in their plasma. Patients with AV had greater total cholesterol (TC) and low-density lipoprotein cholesterol levels (LDL-C).[2,3]

Macrophage scavenger receptor 1 (MSR1) is a gene located on chromosome 8p22 that exhibits high expression in various organs including the kidney, colon, prostate, breast, and heart.[4] Its isoforms play a crucial role in the host defense mechanism. The first scavenger receptor identified was MSR1 or scavenger receptor class A type I (SR-A type I), which belongs to the class A scavenger receptors. The class A scavenger receptors consist of five members, namely MSR1, MARCO, SCARA3, COLEC12, and SCARA5. These receptors are characterized by collagen-like and coiled-coiled domains that form triple helical structures.[5]

Under physiological circumstances, the LDL receptor (LDLR) attaches to LDL and transports cholesterol esters into cells for steroid hormone synthesis, cell proliferation, and the production of bile acid salts. However, by different mechanisms, LDL is modified and engulfed by macrophages to avoid an increase in LDL levels.[6] MSR1 facilitates the uptake and degradation of modified LDL, leading to significant intracellular cholesterol deposition, and is essential for macrophage function, according to several studies.[6–10] So, we hypothesized that MSR1 may be associated with dyslipidemia risk. We selected the most common four variants in the MSR1 gene to study the effect of variants in the development of dyslipidemia.

Our goal was to estimate variation in lipid profile in AV patients. Also, we aimed to investigate the role of MSR1 (specially rs117359034 T > C, IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G variants) in lipid profile variation. We selected these variants in different positions promotor, exon, and intron at the MSR1 gene to investigate linkage disequilibrium (LD). We did not select variants near each other at the MSR1 gene for more accurate results about LD.

2 | SUBJECTS AND METHODS

2.1 | Subjects

This was case-control research with 100 patients with AV and 104 healthy controls. The year-long research was acted upon in the Dermatology Outpatient Unit in accordance with the Helsinki Declaration guidance. The participants were aware of the goal of the research, and their authorization was gained in the form of written consent. "Ethics Committee" authorized the protocol. ERC SU 20220088 is the agreement's reference number. All patients with AV and controls were given a thorough medical history, and data on demographic variables, the history, and duration of AV, and medications were collected. The severity of AV was graded as mild, moderate, or severe. Mild AV is defined by (at least 20 comedones, 15 inflammatory lesions, or a total lesion count of 30). Moderate AV is distinguished by (20—100 comedones, 15—50 inflammatory lesions, or a total lesion count of 30—125). Severe AV (more than five pseudocysts, a total comedones count of more than 100, a total inflammatory count of more than 50, or a total lesion count of more than 125).[11]

Patients with AV were between the ages of 15 and 45, regardless of gender, and a body mass index (BMI) between 18.5 and 24.9 were eligible. This research would include patients who did not use AV therapies in the past six weeks and were non-responsive to conventional topical agents or systemic antimicrobials.

Exclusion criteria include being pregnant, lactating, using oral contraceptives, or being postmenopausal. Patients with other medical disorders that primarily affect lipid metabolism (nephrotic syndrome, hyper- and hypothyroidism, pancreatitis, uremia, obstructive liver problems, and unregulated diabetes mellitus), patients with active malignant tumors or other chronic systemic ailments, patients on regular treatment for other ailments, and an isotretinoin historical record used in the previous 3 months are all excluded.

2.2 | Anthropometry assessment

Patients in both groups had an anthropometric assessment. The International Biological Curriculum recommended that body weight, height,

TABLE 1 Primer sequence and PCR condition for detection of MSR1 four variants.

Variants	Primer sequence	PCR condition	PCR product
rs433235A > G	Forward: 5′-TGCTTTCTACTGCAAAGATGTGG-3′ Reverse: 5′- AACTGCAAACACGAGGAGGT-3′	35 cycles of 15 s at 94°C, 58°C for 15 s, and 72°C for 30s	236 bp
IVS5.59C > A	Forward: 5′- GCCCTGCTTCTGTTTCTCAAA –3′ Reverse: 5′- TCATTTCCAAGAAAAACTAGTCCAG –3′	35 cycles of 15 s at 94°C, 55°C for 15 s, and 72°C for 30s	194 bp
rs117359034T > C	Forward: 5′-TATGCATTCAAGGATCAGGCCAT –3′ Reverse: 5′- CATGTCCCTGGACTGAGGAA –3′	35 cycles of 15 s at 94°C, 55°C for 15 s, and 72°C for 30s	343 bp
rs3747531C > G	Forward: 5′- AAGTACCTTGACAGATGACTAACCC –3′ Reverse: 5′- TCCTCGTGGACCACTTTCTC –3′	35 cycles of 15 s at 94°C, 58°C for 15 s, and 72°C for 30s	140 bp

rs: Reference SNP cluster ID, bp: Base Pair, °C: Celsius, s: second.

TABLE 2 Clinical and laboratory characteristics of both patients and controls.

Variables	Acne patients $N = 100$	Healthy controls $N = 104$	p-Value
Age (mean ± SD)	24.8 ± 5.23	32.2 ± 3.8	0.005**
Gender (Male/Female) (N/%)	51 (51 %) / 49(49%)	55 (52%) / 49 (48%)	NA
BMI			
Underweight < 18.5	32	25	NA
Normal 18.5–24.9	68	79	NA
Obese 30–34.9	NA	NA	NA
Extremely obese 35<	NA	NA	NA
Duration of disease (years)			
< 5	42	NA	NA
≥ 5	58	NA	NA
Chronic illness			
No	100		NA
Others	NA	NA	NA
Acne vulgaris severity			
Mild	38	NA	NA
Moderate	32	NA	NA
Severe	30	NA	NA
TG (mg/dl) (mean ± SD)	139.6 ± 8.4	91.8 ± 3.5	0.003**
TC (mg/dl) (mean ± SD)	132.8 ± 4.3	78.3 ± 5.9	0.005**
LDL-C (mg/dl) (mean ± SD)	214.9 ± 6.6	111.9 ± 8.3	0.004**
HDL-C (mg/dl) (mean ± SD)	50.3 ± 8.1	62.9 ± 6.3	0.002**

N: number, %: percentage, SD: standard deviation, **: mild significant differences $p \leq 0.005$, BMI: Body mass index, NA: not applied.

and waist measurement be monitored.[7] Using a Seca Scale Balance, the weight of the body was estimated to have an accuracy of 0.01 kg while wearing minimal clothing but without shoes. A Holtain Portable Anthropometer was used to estimate the height of the body to the closet 0.1 cm. Waist circumference was evaluated to the closest 0.1 cm using plastic tape that isn't stretchy in the standing posture, with the face oriented forward, shoulders comforted, and normal breathing. BMI was determined by dividing the weight of the body by height squared (kg/m^2).

2.3 | DNA extraction and genotypes analysis

2.3.1 | DNA extraction and purification

The blood was collected using Na2EDTA as an anticoagulant. The QIAamp DNA BloodMini Kit was utilized to wash away genetic DNA from 200 μl of entire blood in accordance with the package recommendations for the Blood protocol (Qiagen, Hilden, Germany).

TABLE 3 Association of genetic variants in MSR1 gene in acne vulgaris patients and healthy controls.

SNP	Model	Patients N (%)	Healthy controls *N* (%)	OR (95%CI)	*p*-Value
rs117359034T > C					
C/C	P (HWE)	0.069 [a*]	0.16		
C/T		33 (33%)	37 (35.6%)	1.00	
T/T	Co-dominant	40 (40%)	44 (42.3%)	1.02 (0.54–1	0.79
		27 (27%)	23 (22.1%)	.92)	
C/C				1.27 (0.61–2.63)	
C/T-T/T	Dominant	33 (33%)	37 (35.6%)	1.00	
		67 (67%)	67 (64.4%)	1.10 (0.62–1.97)	0.74
C/C-C/T					
T/T		73 (73%)	81 (77.9%)	1.00	
	Recessive	27 (27%)	23 (22.1%)	1.25 (0.66–2.39)	0.49
IVS5.59C > A					
	P (HWE)	0.4[a*]	0.17		
C/C		36 (36%)	26 (25%)	1.00	
C/A	**Co-dominant**	51(51%)	44 (42.3%)	0.84 (0.44–1.60)	0.001*
A/A		13 (13%)	34 (32.7%)	0.25 (0.11–0.58)	
C/C	**Dominant**	36 (36%)	26 (25%)	1.00	
A/C-A/A		64 (64%)	78 (75%)	0.58 (0.32–1.07)	0.007**
C/C-A/C		87 (87%)	70 (67.3%)	1.00	
A/A	**Recessive**	13 (13%)	34 (32.7%)	0.28 (0.14–0.59)	0.001*
rs433235A > G					
	P (HWE)	0.00042*[b]	<0.0001		
A/A		27 (27%)	77 (74%)	1.0	
A/G	Co-dominant	31 (31%)	16 (15.4%)	5.53 (2.62–11.65)	0.001*
G/G		42 (42%)	11 (10.6%)	10.63 (4.79–23.58)	
A/A	Dominant	27 (27.3%)	77 (74%)	1.0	
A/G-G/G		72 (72.7%)	27 (26%)	7.60 (4.08–14.18)	0.001*
A/A-A/G	Recessive	58 (58%)	93 (89.4%)	1.00	
		42 (42%)	11 (10.6%)	5.98 (2.85–12.55)	0.006**
rs3747531C > G					
	P (HWE)	0.51[a*]	0.19		
C/C	Co-dominant	21 (21%)	48 (46.1%)	1.00	
C/G		40 (40%)	43 (41.4%)	2.13 (1.09–4.15)	
G/G		39 (39%)	13 (12.5%)	6.68 (2.97–15.05)	0.001*
C/C	Dominant	21 (21%)	48 (46.1%)	1.00	
C/G-G/G		79 (79%)	56 (53.9%)	3.18 (1.72–5.90)	0.001*
C/C-C/G	Recessive	61 (61%)	91 (87.5%)	1.00	
G/G		39 (39%)	13 (12.5%)	4.36 (2.15–8.86)	0.001*

SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval, HWE: Hardy-Weinberg equilibrium, a*: significant with Hardy-Weinberg equilibrium, b*: not significant with Hardy-Weinberg equilibrium *: highly significant, **: mild significant %: percentage, rs: Reference SNP cluster ID.

2.3.2 | Genotypes analysis

The primer design: Using NCBI web site https://www.ncbi.nlm.nih.gov/tools/primer-blast/ MSR1 gene data as DNA FASTA sequence collected from human ensemble web site https://asia.ensembl.org/Homo_sapiens/Info/Index . We used MSR1 Genedata ENSG00000038945 and transcript ID: ENST00000262101.10.

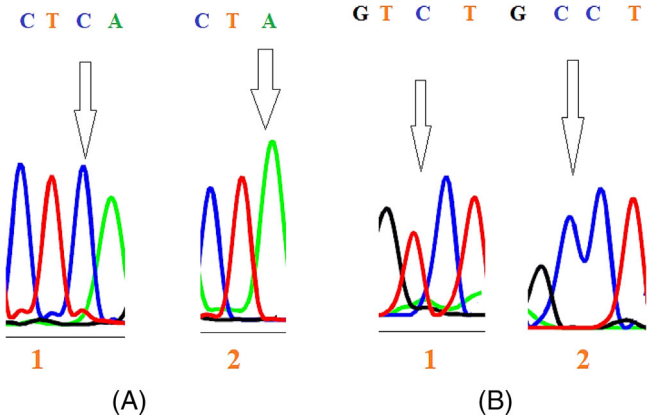

FIGURE 1 (A) Partial sequence MSR1 gene PCR fragment IVS5.59C > A variant. 1. Showing only C peak indicating C/C genotypes . 2. Showing only A peak indicating A/A genotypes. (B) Partial sequence MSR1 gene PCR fragment rs117359034 T > C variant . 1. Showing only T peak indicating T/T genotypes . 2. Showing only C peak indicating C/C genotypes.

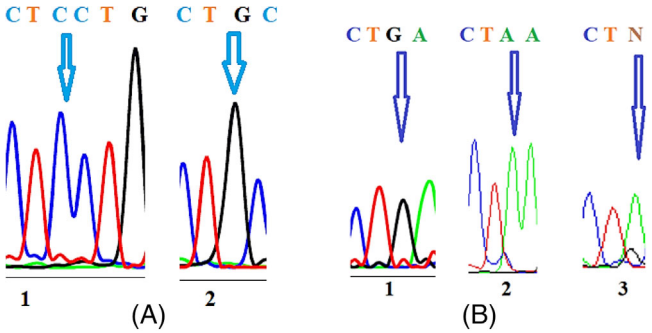

FIGURE 2 (A) Partial sequence MSR1 gene PCR fragment rs3747531C > G variant . 1. Showing only C peak indicating C/C genotypes . 2. Showing only G peak indicating G/G genotypes. (B) Partial sequence MSR1 gene PCR fragment rs433235A > G variant . 1. Showing only G peak indicating G/G genotypes . 2. Showing only A peak indicating A/A genotypes. 3. Showing both A and G peaks indicating A/G genotypes.

In a 50 μl reaction mixture, the genomic DNA was subjected to a polymerase chain reaction (PCR) (2xTaq PCR Master mix, cat. no. KT201; Tiangen Biotech Co., Ltd.). Table 1 summarizes the primer details and PCR conditions.

Genotypes analysis by DNA sequencing

Samples were processed on 1.5% agarose gels, anticipated size bands were cut, and purifying was passed through the gel extraction kit according to the manufacturer's protocol (QIA quick columns; Qiagen). Extracted samples were loop sequenced with the Big Dye Terminator v3.1 Kit and infused into the ABI 3100 Genetic Analyzer (Applied Biosystems). The sequencer-analyzed PCR products were attached to the gene bank registry at https:// WWW .blast.ncbi.nlm.nih.gov/Blast.cgi .

2.3.3 | Biochemical analysis

Estimation of a lipid profile

Triglyceride (TG), HDL-C, and TC levels in blood were assessed using normalized enzymatic processes on the Olympus AU 400 computer-aided diagnosis chemistry analyzer using kits provided by Roche Diagnostics (Mannheim). LDL-C was determined by calculating using Friedwald et al formulas.[12]

2.3.4 | In silico analysis for prediction with 4 MSR1 variants pathogenicity and protein effect

MSR1 gene data as DNA sequence and cDNA sequence collected from human ensemble web site https://asia.ensembl.org/Homo_sapiens/Info/Index . We used MSR1 gene data ENSG00000038945 and transcript ID: ENST00000262101.10. For the detection of variants, we used https://www.ncbi.nlm.nih.gov/dbvar/ . For variant analysis as well as prediction of the variant effect, we used the mutation taster website: https://www.mutationtaster.org/ . and Rare Exome Variant Ensemble Learner (REVEL) website: https://genome.ucsc.edu/cgi-bin/hgTrackUi?db = hg19&g = revel , Polymorphism Phenotyping v2 (PolyPhen-2) website: http://genetics.bwh.harvard.edu/pph2/,and mutation assessor website: http://mutationassessor.org/r3/

2.3.5 | Statistical analysis

The Arlequin software (version 3.1) and SNPstats (http://bioinfo.iconcologia.net/SN Pstats) were used to calculate allele frequency, genotypes, LD, and haplotypes. The statistical tool for social science (SPSS) software package 20 was used to investigate the data (Chicago, IL, USA). The mean and standard deviation of all numerical variables were evaluated. When comparing qualitative data, the Chi-square test was used. A one-way analysis of variance test was used to compare three variables. The statistical significance level was set at $p \leq 0.05$.

3 | RESULTS

3.1 | General data for both patients and controls

The present study identified patients with AV and lipid profiles. The study population comprised 100 patients with AV, having a mean age of 24.8 ± 5.23 years, while the control group consisted of 104 healthy patients matched for age and gender. According to body mass index, more than two-thirds were normal (68% and 79% in patients and normal participants, respectively), while, (32% and 25% in patients and normal participants, respectively) were underweight. The levels of TG, TC, and LDL-C were found to be significantly higher in patients with AV

TABLE 4 Four MSR1 gene SNPs were standardized for linkage disequilibrium coefficients (D') in patients with acne vulgaris.

SNP	ex4V113A	IVS5.59	PRO3	P275A
rs117359034T > C	NA	0.4919/0.001*	0.1361/0.1217	0.0967/0.2193
IVS5.59C > A	−0.3579	NA	0.276/ 0.008**	0.2087/0.005**
rs433235A > G	−0.11	−0.1869	NA	0.6385/ 0.001*
rs3747531C > G	0.0873	0.137	0.6189	NA

The upper diagonal values are D'/P (with red color), and the lower diagonal values are the correlation coefficients (r) (with green color), *: Strong linkage disequilibrium, rs: Reference SNP cluster ID.

TABLE 5 Analysis of haplotypes for the genotypes of the MSR1 gene in acne patients, healthy volunteers, and the entire study population.

	Haplotypes analysis						
S	rs117359034T > C	IVS5.59C > A	rs433235A > G	rs3747531C > G	Patients *N* = 100	Healthy controls *N* = 104	Total *N* = 204
1	T	C	A	C	0.1654*	0.0909	0.1269
2	C	C	A	C	0.0427	0.1562*	0.1067
3	C	A	A	C	0.1026	0.1272	0.1062
4	C	A	G	G	0.1547*	NP	0.0924
5	T	C	G	G	0.1407*	NP	0.0887
6	T	A	A	C	0.0153	0.1643	0.0885
7	C	C	A	G	0.1032	0.0507	0.0784
8	C	A	A	G	NP	0.1034	0.0594
9	C	C	G	C	NP	0.1192	0.0465
10	T	A	A	G	NP	0.0802	0.0459
11	T	C	G	C	0.0598	NP	0.0403
12	T	A	G	G	0.0779	0.0529	0.039
13	C	C	G	G	0.1094	NP	0.0357
14	C	A	G	C	0.0227	0.0106	0.0263
15	T	C	A	G	NP	0.0445	0.016
16	T	A	G	C	0.0056	NP	0.0029

N: Number, NP: Not present, *: highly significant P≤0.001, and rs: Reference SNP cluster ID.

as compared to healthy patients ($p = 0.003$, $p = 0.005$, and $p = 0.004$, respectively). Moreover, there was a significant difference in HDL-C levels between healthy controls and patients (62.9 ± 6.3 vs. 50.3 ± 8.1), with a *p*-value of 0.002, as shown in Table 2. These findings suggested that patients with AV have an altered lipid profile, which may have implications for their overall health and well-being.

We amplified specific segments MSR1 gene by PCR and then detected the genotypes of four variants by sequencing analysis as shown in Figures 1 and 2.

3.2 | Genotypic and allelic frequencies in association analysis

Hardy-Weinberg assumptions were met by all four variants (all $p > 0.05$; Table 3). Genotype and allele frequency ranges were computed and compared to find differences between the control and patients with AV groups. IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G frequencies exhibited significant variations between the two groups ($p = 0.001$, $p = 0.001$, and $p = 0.001$, respectively). variants rs117359034 T > C results among the two groups did not differ significantly ($p = 0.79$) Table 3. These results suggested that patients with AV may be more susceptible than healthy controls to the effects of variants IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G on blood lipid profile.

Dominant and recessive models for the rare allele were built to check the variations' associations and generate odds ratios (ORs) and 95% confidence intervals (95% CIs) to validate the associations of the four variants with AV. The genotypes and observed allele frequencies for patients with AV and controls are displayed in Table 3.

For IVS5.59 C > A, the C/A, and A/C+C/C genotypes were substantially more common than the C/C genotypes (OR = 0.84 and

95%Cis = 0.44–1.60 and 0.58 and 0.31 and 1.07, respectively). On the other side for rs433235A > G, the G/G and A/G+G/G genotypes were substantially more prevalent than A/A (OR = 10.63 and 95% CIs = 4.79–23.58) and OR = 7.60 and 95% CIs = 4.08–14.18, respectively. Additionally, in rs3747531 C > G, the G/G genotype was substantially more common than other genotypes (OR = 6.68 and 95% CIs = 2.97–15.05; Table 3).

As a result, AV had higher rates of the unusual alleles of the IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G variants than did controls, and these variants were predominately linked to altered lipid profiles.

3.3 | LD and haplotypes analysis for four variants in AV patients

We conducted LD and haplotype analysis to investigate the relationships between four variants and lipid profile alteration and AV. IVS5.59 C > A and rs433235 A > G are in LD, as demonstrated in Table 4, and rs117359034 T > C as well as IVS5.59 C > A are both substantially LD. Additionally, rs433235 A > G has a significant LD with rs3747531 C > G. Additionally, the outcomes showed that IVS5.59 C > A and rs3747531 C > G were in LD (Table 4).

The haplotypes TCGC, CCGG, and TAGC, were solely present in patients and lacking in healthy controls, according to a haplotype analysis of patients and healthy controls (Table 5).

The two haplotypes that were most prevalent in the patients were TCAC (16.5%) and CAGG (15.47%), whereas the two haplotypes that were most prevalent in the controls were TAAC (16.43%) and CCAC (15.62%; Table 5).

3.4 | Analysis of four variants haplotypes in patients with AV based on the severity of the condition

We divided patients into mild, moderate, and severe illness categories. rs117359034 T > C T/ IVS5.59 C > AC/ rs433235 A > G G/ rs3747531 C > G G was the most prevalent haplotype in mild (25.13%), rs117359034 T > C C/IVS5.59C > A C/ rs433235 A > G A/ rs3747531 C > G G was the most prevalent in moderate (28%), and rs117359034 T > C T/ IVS5.59 C > A C/rs433235 A > G A/ rs3747531 C > G C was the most prevalent in severe (24.14%; Table 6).

3.5 | Compare the variation in lipid profile with four variants genotypes

As shown in Table 7, we tried to shed some light on the association between four variants and changes in the lipid profile.

On the other hand, T/T genotypes of rs117359034 T > C had greater LDL-C levels than C/C and C/T, with extremely significant differences ($p \leq 0.001$) between the two. HDL-C and cholesterol, also part of the lipid profile, did not significantly vary across all genotypes. TG was higher (135 ± 6.4) among patients with T/T genotypes than C/C or C/T (107 ± 3.6 and 129 ± 24.9, respectively) in the rs117359034 T > C study (Table 7A). In variants IVS5.59 C > A, no significant variation between IVS5.59 C > A genotypes and all lipid profile parameters (Table 7B). G/G genotypes of rs433235 A > G variant have high levels of TC and HDL-C ($p \leq 0.001$ and $p \leq 0.001$, respectively; Table 7C).

Consequently, there is extremely significant variance in HDL-C for patients with G/G genotypes compared to C/G, and C/C P≤ 0.001 for the rs3747531 C > G variants, which affects both cholesterol and LDL-C ($p = 0.002$ and $p = 0.006$, respectively; Table 7D).

TABLE 6 Depending on the severity of acne, the most prevalent haplotypes for scavenger receptor gene genotypes in acne patients.

Parameters	Haplotypes analysis
Mild N = 38	1- rs117359034 T/ IVS5.59 C/ rs433235 G/rs3747531 G (25.13%) 2- rs117359034 C/ IVS5.59 A/ rs433235 G/rs3747531 G (21.8%)
Moderate N = 32	1- rs117359034 C / IVS5.59 C / rs433235 A/rs3747531 G (28%) 2- rs117359034 T / IVS5.59 C/ rs433235 A /rs3747531 C (17.19%)
Severe N = 30	1- rs117359034 T / IVS5.59 C/ rs433235 A/rs3747531 C (24.14%) 2- rs117359034 C/ IVS5.59 A/ rs433235 G/rs3747531 G (18.97%)

N: Number, and rs: Reference SNP cluster ID.

3.6 | Disease severity and changes in lipid levels

Patients with mild conditions had greater LDL-C and HDL-C with mild significant variance ($p = 0.0082$ and $p = 0.0021$, respectively). There is no significant difference in triglycerides and cholesterol between mild, moderate, and severe patients ($p = 0.209$ and $p = 0.552$, respectively; Table 8).

3.7 | Examine the relationship between the genotypes of four variants and the variation in the lipid profile in patients with mild, moderate, and severe patients

All genotypes of the four variants are dominant in patients with mild AV, including homozygotes, heterozygotes, and recessive homozygotes. Different rs117359034 T > C genotypes differ somewhat in terms of TG and LDL-C ($p = 0.004$ and $p = 0.003$, respectively). No significant variation was found between lipid profiles and IVS5.59C > A genotypes in mild AV. The G/G genotypes of rs433235 A > G variant have high cholesterol levels and HDL-C ($p \leq 0.001$ and $p = 0.007$, respectively). Also, the G/G genotypes of rs3747531 C > G have high cholesterol levels with significant variation ($p = 0.006$, Table 9A).

TABLE 7 Comparisons of the lipid profile between patients with acne vulgaris and the genotype of the Scavenger receptor gene's four variants.

Parameters	A) rs117359034T > C				B) IVS5.59C > A				C) rs433235A > G				D) rs3747531C > G			
	C/C	C/T	T/T	*p*-Value	A/A	A/C	C/C	P -Value	A/A	A/G	G/G	*p*-Value	C/C	C/G	G/G	*p*-Value
TG (mg/dl) (mean ± SD)	107 ± 3.6	129.2 ± 4.9	135 ± 6.4	0.002**	117 ± 5.2	121 ± 5.8	136 ± 3.6	0.386	123 ± 9.3	124 ± 8.7	129 ± 7.9	0.896	130 ± 4.9	118 ± 8.4	132 ± 7.7	0.513
TC (mg/dl) (mean ± SD)	122 ± 9.6	147 ± 9.3	135 ± 6.3	0.234	124 ± 6.4	147 ± 6.9	126 ± 5.3	0.279	115 ± 4.6	125 ± 6.1	159.1 ± 9.5	0.001*	116 ± 5.2	126 ± 9.6	158 ± 6.3	0.002**
LDL-C (mg/dl) (mean ± SD)	125 ± 6.7	160 ± 4.6	170 ± 8.5	0.001*	136 ± 7.1	148 ± 6.1	160 ± 4.2	0.217	147 ± 5.6	146 ± 8.9	160 ± 6.8	0.495	162 ± 4.7	137 ± 3.8	163 ± 5.6	0.006**
HDL-C (mg/dl) (mean ± SD)	75.2 ± 3.9	78 ± 5.3	77.9 ± 1.3	0.591	77 ± 7.7	80 ± 7.4	73 ± 8.0	0.140	71 ± 5.3	72 ± 4.1	80.3 ± 7.2	0.001*	71 ± 3.8	73 ± 2.6	86 ± 3.2	0.001*

N: Number, SD: Stander deviation, and **: mild significance P≤0.005, TG: triglycerides, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, rs: Reference SNP cluster ID.

IVS5.59 C > A C/A, rs433235 A > G G/G, and rs3747531 C > G G/G genotypes do not show symptoms of moderate AV. A significant extreme difference was found when going to compare the lipid profile with the rs117359034 T > C variant in a patient with T/T. Compared to other genotypes in the moderate group, they have greater levels of TG and LDL-C. TG was greater in patients with G/G genotypes, according to rs3747531 C > G analysis for moderate patients, P = 0.003. In contrast, moderate patients with A/A had increased LDL-C levels in variant rs433235 A > G, ($p = 0.003$, Table 9B).

IVS5.59 C > A A/A is absent in the group of severe cases (Table 8C). variant rs117359034 T > C, IVS5.59 C > A, and rs433235 A > G had no significant variance with any lipid profiles, according to the analysis of lipid profiles with four SNP genotypes in severe patients. In comparison, severe C/C patients in variant rs3747531 C > G have higher LDL-C levels than other genotypes ($p = 0.002$, Table 9C).

3.8 | In silico analysis for MSR1 four variants pathogenic effect and impact upon the protein

We used in silico analysis tools to confirm the harmful effect of the four variations. The findings suggested that the rs433235 A > G (c.138G > A) variant might be a causal variant in Figure 3A–C, which may support the patient's clinical diagnosis. Table 10 summarizes the predictions made for four variations using the mutation taster program.

We used several bioinformatics tools for the identification pathogenicity of variant rs433235 A > G as REVEL, PolyPhen-2, and mutation assessor where the probability of damage score for rs433235 A > G were 0.582, 0.999, and 0.676, respectively and this data matching with mutation taster program.

4 | DISCUSSION

The four MSR1 variants (rs117359034 T > C, IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G) and their relationship to lipid profile alterations in patients with AV in the Saudi Arabian population are thoroughly analyzed in this work. As far as we are aware, this was the first study to attempt to clarify the relationship between rs117359034 T > C, IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G and the alteration of lipid profile in patients with AV in our communities.

We found that greater HDL-C levels were identified in healthy controls ($p = 0.002$), while higher levels of TC, TG, and LDL-C were found in patients with AV ($p = 0.0051$, $p = 0.0032$, and $p = 0.0041$, respectively). AV sufferers in Jordan had considerably reduced HDL-C, according to El-Akawi et al.[2] findings ($p = 0.000$).

Additionally, patients with AV TG and LDL-C levels were considerably higher than those of controls ($p = 0.004$ and $p = 0.000$, respectively) in patients with AV.[2] Furthermore, case-control research in China found that patients with AV had greater TC and LDL-C levels than healthy controls.[13] In case-control research of female

TABLE 8 Comparisons of the lipid profile based on the severity of acne vulgaris.

Parameters	Mild acne $N = 38$	Moderate acne $N = 32$	Severe acne $N = 30$	*p*-Value
TG (mg/dl) (mean ± SD)	134.1 ± 9.7	130.5 ± 8.9	110.8 ± 5.7	0.209
TC (mg/dl) (mean ± SD)	145 ± 6.4	131.2 ± 8.9	130.5 ± 5.8	0.552
LDL-C (mg/dl) (mean ± SD)	170.2 ± 6.6	151.6 ± 9.8	130.8 ± 7.01	0.008**
HDL-C (mg/dl) (mean ± SD)	83.7 ± 11.7	74.2 ± 15.2	72.4 ± 14.5	0.002**

N: Number, SD: Stander deviation, and **: mild significance $p \leq 0.005$, TG: triglycerides, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

FIGURE 3 (A) Results from MutationTaster for the observed substitution indicate that the rs433235A > G variant may be a disease-causing mutation. (B) Genomic and cDNA sequence original and altered for rs433235A > G mutation. (C) Protein amino acid sequence wild and mutated for rs433235A > G variant.

patients with AV, changes in lipid profiles and BMI were found to be substantially correlated with AV.[3]

Increased TG, TC, and LDL-C levels in patients with AV and their impact on the condition's progression can be explained by a key mechanism where cholesterol enters sebocytes by LDL-C receptor-mediated endocytosis, and its synthesis is blocked at the squalene's levels.[14] Because androgens of adrenal and gonads are produced from inner cholesterol, raised serum total cholesterol levels influence the progression of AV by raising androgens.[15] Lipoprotein lipase, which has been demonstrated to be displayed in sebaceous glands at the mRNA level, releases exogenous fatty acids from lipoproteins into cells to a lesser amount than de novo production.[14] Additionally, research indicates that dietary fat consumption boosts sebum production.[16]

The lipid profile of patients with AV is undoubtedly affected by hereditary variables, so we chose groups of variants in a distinct region of the MSR1 gene and looked at how they correlated with lipid profiles. Our findings showed that while rs117359034 T > C had no significant difference among patients with AV and controls, IVS5.59 C > A, rs433235A > G, and rs3747531 C > G genotype analysis revealed significant differences among patients with AV and controls. In addition, we noted that rs117359034 T > C, rs433235 A > G, and rs3747531 C > G different genotypes were associated with variation in lipid profiles.

Numerous organs have high MSR1 expression.[17–19] According to what its name implies, MSR1 is mainly affected by macrophage-associated with physiology and pathology, including atherosclerosis and lipid profile disruption.[20] The Ensembl database for the MSR1 gene currently lists 30,163 variations. Only three of these, however, have been linked to the pathophysiology and clinical consequences of NM 138715.3 (MSR1): c.520G > T (p.Asp174Tyr) and c.877C > T (p.Arg293Ter) in prostate cancer[21]; and c.760C > G (p.Leu254Val) specifically associated to stomach acid reflux.[22] Different transcription factors control the transcriptional expression of MSR1. Most of the binding sites for transcription factors are located around a single nucleotide variant in the upstream transcriptional domain of MSR1, indicating that the variants play an indirect function in the transcriptional control of MSR1. The serum TG and aspartate transaminase levels were also impacted by these variants.[23] This can show and clarify the role of the MSR1 gene in lipid disruption, rise, or decrease of various lipid profiles. The larger effects of variants rs117359034 T > C, IVS5.59 C > A, rs433235 A > G, and rs3747531 C > G on fluctuating blood lipids in patients with AV may now be predicted based on our findings as well as those of other researchers. Additionally, it has been hypothesized that the various genotypes linked to mild AV may be the source of high LDL-C in our study group's mild patients with AV more so than in severe and moderate cases.

TABLE 9 Comparisons of the Scavenger receptor gene polymorphism genotype in the lipid profiles of mild, moderate, and severe patients.

	A. Mild acne vulgaris *N* = 38															
	rs117359034T > C				IVS5.59C > A				rs433235A > G				rs3747531C > G			
Parameters	C/C	C/T	T/T	*p* -Value	C/C	C/A	A/A	P -Value	A/A	A/G	G/G	P -Value	C/C	C/G	G/G	P -Value
TG (mg/dl) (mean ± SD)	102 ± 5.1	147 ± 3.8	157 ± 7.3	0.004**	87 ± 8.5	132 ± 7.5	155 ± 6.9	0.522	135 ± 3.2	80 ± 4.7	136 ± 3.6	0.744	87 ± 6.7	132 ± 5.4	137 ± 7.1	0.721
TC (mg/dl) (mean ± SD)	120 ± 4.2	166 ± 8.5	151 ± 6.7	0.163	100 ± 4.1	156 ± 3.9	100 ± 4.3	0.115	85 ± 7.4	119 ± 5.3	161 ± 6.7	0.001*	100 ± 5.9	103 ± 4.8	159 ± 7.2	0.006**
LDL-C (mg/dl) (mean ± SD)	145 ± 3.6	196 ± 5.8	167 ± 3.7	0.003**	145 ± 4.2	173 ± 5.2	159 ± 5.1	0.624	157 ± 5.1	150 ± 5.6	174 ± 4.7	0.552	145 ± 3.9	165 ± 5.9	172 ± 4.6	0.751
HDL-C (mg/dl) (mean ± SD)	79 ± 4.2	85 ± 3.6	86 ± 4.8	0.279	78 ± 6.6	85 ± 7.2	75 ± 3.3	0.133	74 ± 4.6	85 ± 3.8	86 ± 2.5	0.007**	78 ± 3.9	77 ± 4.2	85 ± 3.7	0.171
	B. Moderate acne vulgaris N = 32															
	rs117359034T > C				IVS5.59C > A				rs433235A > G				rs3747531C > G			
Parameters	C/C	C/T	T/T	P -Value	C/C	C/A	A/A	P -Value	A/A	A/G	G/G	P -Value	C/C	C/G	G/G	P -Value
TG (mg/dl) (mean ± SD)	112 ± 5.3	125 ± 5.3	208 ± 3.8	0.006**	136 ± 7.4	NP	120 ± 7.7	0.454	147 ± 5.6	124 ± 10.1	NP	0.336	169 ± 6.7	119 ± 5.3	NP	0.003**
TC (mg/dl) (mean ± SD)	129 ± 3.8	128 ± 6.04	148 ± 8.1	0.872	133 ± 4.9	NP	126 ± 8.6	0.797	142 ± 7.5	127 ± 4.6	NP	0.586	120 ± 4.3	134 ± 6.1	NP	0.643
LDL-C (mg/dl) (mean ± SD)	123 ± 2.9	136 ± 9.2	197 ± 7.3	0.003**	160 ± 9.8	NP	135 ± 6.7	0.248	187 ± 5.8	139 ± 8.9	NP	0.003**	179 ± 4.6	143 ± 7.6	NP	0.138
HDL-C (mg/dl) (mean ± SD)	75 ± 4.6	70 ± 4.7	80 ± 4.3	0.484	72 ± 3.7	NP	76 ± 4.3	0.450	77 ± 9.4	72 ± 4.3	NP	0.432	78 ± 4.8	72 ± 10.5	NP	0.430
	C. Severe acne vulgaris N = 30															
	rs117359034T > C				IVS5.59C > A				rs433235A > G				rs3747531C > G			
Parameters	C/C	C/T	T/T	P -Value	C/C	C/A	A/A	P -Value	A/A	A/G	G/G	P -Value	C/C	C/G	G/G	P -Value
TG (mg/dl) (mean ± SD)	106 ± 6.3	111 ± 8.9	113 ± 10.3	0.955	126 ± .4.4	104 ± 5.5	NP	0.282	101 ± 3.3	129 ± 3.3	111 ± 9.9	0.574	113 ± 5.5	98 ± 5.3	117 ± 5.3	0.751
TC (mg/dl) (mean ± SD)	117 ± 4.8	154 ± 8.3	115 ± 9.3	0.361	125 ± 4.6	132 ± 6.5	NP	0.802	115 ± 4.4	118 ± 3.8	154 ± 8.7	0.361	115 ± 6.9	127 ± 8.6	153 ± 3.7	0.405
LDL-C (mg/dl) (mean ± SD)	92 ± 8.5	121 ± 4.9	162 ± 5.8	0.002**	179 ± 4.7	109 ± 7.5	NP	0.002	116 ± 5.6	174 ± 4.9	121 ± 6.3	0.101	153 ± 5.4	82 ± 7.3	132 ± 4.1	0.002**
HDL-C (mg/dl) (mean ± SD)	65 ± 5.6	79 ± 6.3	69 ± 6.7	0.155	74 ± 4.8	71 ± 8.8	NP	0.606	65 ± 6.8	73 ± 4.6	79 ± 3.8	0.091	68 ± 5.9	70 ± 7.1	80 ± 6.5	0.227

N: Number, SD = Stander deviation, rs: Reference SNP cluster ID, NP: not present, **: mild significance P≤0.005, and *: highly significance P≤0.001, TG: triglycerides, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

TABLE 10 Summary of 4 variants prediction pathogenic effect and change in protein structure and function.

Variants	Predication	Effect	Probability	DNA change	Anino acid change	Alternation region	Alternation type
rs433235A > G	disease-causing	1- Protein features (might be) 2- affected splice site changes	1	c.138G > A cDNA.336G > A g.392225G > A	no AA changes	CDS	Single base exchange
rs117359034 T > C	Polymorphism	1- Amino acid sequence changed 2- Heterozygous in TGP or ExAC 3- Known disease mutation at this position (HGMD CM023577) 4- Protein features (might be) affected	0.99	c.338T > C cDNA.536T > C g.398741T > C	V113A Score:64	CDS	Single base exchange
IVS5.59C > A	Polymorphism	1- Protein features (might be) affected 2- Splice site changes	0.99	g.71758C > A	N/A	intron	Single base exchange
rs3747531C > G	Polymorphism	1- Amino acid sequence changed 2- Homozygous in TGP or ExAC 3- Known disease mutation at this position (HGMD CM100500) 4- Protein features (might be) affected 5- Splice site changes	0.005	c.823C > G cDNA.1021C > G g.412352C > G	P275A Score:27	CDS	Single base exchange

CDS: CoDing Sequence, rs: Reference SNP cluster ID, HGMD: Human Gene Mutation Database, N/A: Not Applicable, P: Proline amino acid, A: Alanine amino acid, V: Valine amino acid, g.: Genomic DNA, cDNA: complementary DNA, c.: Coding sequence.

In a particular population, Linkage disequilibrium is the non-random relationship between two or more loci alleles.[24] In the regulatory region of a gene, LD between variants alleles has been utilized to find haplotype matching with the disease in a population.[25,26] This occurs when there is a significant change in LD between variants alleles within haplotypes in a patient group especially in comparison to a reference point of population. In such circumstances, punitive binding alterations for transcription factors responsible for gene regulation can be found using LD between variants alleles. Such transcription factor binding sites (TFBS) alterations could lead to human illness or disease.[24]

Even in the absence of substantial genetic offspring reorganization, linkage SNP variants can develop. The MSR1 variants rs117359034 T > C and IVS5.59 C > A are both substantially LD, and there are strong LD links between IVS5.59C > A and rs433235 A > G, according to our study's LD and haplotype analysis. Furthermore, rs3747531 C > G and rs433235 A > G have a significant LD. The findings also demonstrated the presence of IVS5.59 C > A and rs3747531 C > G in LD.

The current investigation of MSR1 gene haplotypes broadens our understanding and establishes a foundation for understanding the connections between the polymorphisms under investigation. Our results indicate that TCAC (16.5%) and CAGG (15.47%) were the two haplotypes that were most common in patients, whereas TAAC (16.43%) and CCAC (15.62%) were the two haplotypes that were most common in controls. Another study on Chronic Obstructive Pulmonary Disease (COPD) discovered that the most prevalent haplotype in the patient group is ACCCdel (rs433235 A > G, IVS5-59, rs3747531 C > G, R293X, and INDEL7).[27]

Chen and his colleagues discovered that the most common haplotypes in prostate cancer patients were ACG, ACC, and GCG (rs433235 A > G, IVS5-59, and rs3747531 C > G variations)[28]; his findings mirrored ours.

According to variants allele frequency, the role of haplotypes and LD in the variation of lipid profiles can differ among both ethnic and ancestry groupings because of historical species limitations. This would impact the frequency of transcription factor binding sites (TFBSs) and transcription factors (TFs) and should influence populations more prone to disease.[24]

As the change of one variant may affect the change of other variants, creating a joint effect on the progression of hyperlipidemia, we can anticipate that the LD and haplotype analysis of variants could increase or decrease the risk of lipid profile variation. Our findings influence our capacity to assess the genetic underpinnings of a risk factor role more thoroughly for MSR1, possibly assisting in a more targeted response. Our findings provide a foundation for future research examining how different patients respond to different medications, allowing for the creation of personalized medicine strategies.

4.1 | Future recommendations

Other variants in the MSR1 gene must analyze for more information about gene role in lipid profile alternations. Also, other genes such as Apo E, Apo B, VLDL, and LDL should analysis for a complete vision of genes' role and lipid profile disturbance. Moreover, another group of patients with other diseases such as hypertension, diabetes, and coronary artery disease is most taken into consideration. We recommend carrying out the study with a larger number of patients. Also, consider the results in establishing the management protocol. Establishing a diet to normalize the lipid profile is imperative for treating acne.

5 | CONCLUSION

The most prevalent conditions in patients were TCAC and CAGG, whereas TAAC and CCAC were the most prevalent conditions in fit people. There is a linkage disequilibrium between rs433235 A > G and IVS5.59 C > A. Furthermore, there is a significant linkage disequilibrium between rs433235 A > G and rs3747531 C > G.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

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

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