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Hypomethylation of *OAS2* and *OAS3* Gene Promoters: Insights Into the Pathogenesis of Systemic Lupus Erythematosus

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ABSTRACT

Background: DNA methylation plays a key role in systemic lupus erythematosus (SLE) by regulating gene expression and impacting immune system functions. In SLE, abnormal DNA methylation patterns can lead to the overexpression of pro-inflammatory genes and downregulation of the regulatory genes, contributing to autoimmunity. This dysregulation can increase susceptibility to SLE. Understanding these methylation changes could help discover new therapeutic strategies for managing SLE.

Objective: To evaluate methylation levels of *OAS2* and *OAS3* in peripheral blood mononuclear cells (PBMCs) in volunteers with SLE were evaluated.

Methods: In this case-control study, we collected 207 peripheral blood samples from 102 SLE patients and 105 healthy subjects. After isolating the PBMCs, methylation analysis was performed using the methylation-quantification of endonuclease-resistant DNA (MethyQESD) method.

Results: The control group had an average *OAS2* methylation percentage of 40.02%±24.59%, whereas the SLE group had a significantly lower average of 19.46%±21.98%. This finding indicates a significant hypomethylation of *OAS2* in the SLE cohort (p<0.001). Additionally, a significant difference was observed in the mean methylation levels of *OAS3*, with SLE patients exhibiting 14.11%±19.50% compared to healthy controls at 25.32%±20.82% (p<0.001). Patients with renal damage also showed significantly lower *OAS2* methylation levels than SLE individuals without renal damage (p<0.001). Furthermore, a negative connection was found between the *OAS2* methylation level and creatinine (r=-0.266, p=0.007).

Conclusion: The pattern of methylation levels observed in *OAS2* and *OAS3* within PBMCs may provide valuable insights into the mechanisms underlying SLE development.

Keywords: Methylation, OAS2, OAS3, Systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by inflammation and damage to connective tissues in various organs, including the skin, joints, kidneys, heart, gastrointestinal system, and lungs. The exact etiology of SLE is still unknown, but it is believed to result from a combination of genetic predisposition, environmental factors, and hormonal influences (1, 2). Multiple genetic loci play a role in different aspects of the immune system, affecting the onset and progression of SLE, by regulating immune responses and autoantibody production (3, 4).

Irregular DNA methylation patterns have been identified in patients with systemic SLE, leading to alterations in gene expression and disruptions in immune system function. DNA methylation dysregulation is fundamental in the development of SLE (5, 6). Identifying specific SLE-associated DNA methylation signatures could offer insight into understanding SLE pathogenesis.

OAS2 and *OAS3* are Type I IFN-inducible antiviral effectors that are upregulated in autoimmune diseases, particularly in SLE (7-10). Studies have shown that dysregulation of OAS2 and OAS3 expression in SLE is associated with lupus nephritis, disease activity, and specific clinical manifestations (7, 11, 12). Additionally, studies have reported hypomethylation of the OAS2 and OAS3 promoter regions, leading to increased expression in individuals with rheumatoid arthritis (RA), SLE, systemic sclerosis (SSc), and Sjögren's syndrome (SS) (8, 13-17). For the first time, we aimed to determine the methylation status of OAS2 and OAS3 in peripheral blood mononuclear cells (PBMCs). Additionally, we explored the correlations between the methylation levels of these target genes and clinical characteristics in patients with SLE.

MATERIALS AND METHODS

Samples

Blood samples (5 ml) were collected in EDTA-containing tubes from 102 SLE patients and 105 healthy subjects of the same ethnic background. All patients were referred from the rheumatology clinic at Shariati Hospital of Tehran University of Medical Sciences and diagnosed according to the classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (18). The criteria items for SLE were determined by rheumatologists with expertise in the disease. All individuals in the study were from the same ancestry but were not biologically related. Healthy controls had no personal or family history of autoimmune or immune-related disorders.

The demographic information, laboratory data, and clinical manifestations of the subjects were recorded using a standardized questionnaire. The study protocol was reviewed and approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences (Approval No: IR.USWR.REC.1402.041). All participants provided written informed consent after receiving complete information about the study and its procedures including the collection and use of blood samples and medical records.

Processing of Blood Samples and Isolation of PBMC-DNA

The process of isolating PBMCs from peripheral blood was carried out using the Ficoll-Hypaque (Sigma, Germany) density gradient centrifugation (19). DNA was then extracted from the PBMC pellet using the AddPrep genomic DNA extraction kit, following the the manufacturer's instructions (AddBio Inc. Ltd., Korea). The quality and purity of the DNA were assessed through UV spectrophotometry and gel electrophoresis. The extracted DNA was stored at -20 °C for future procedures.

Methylation Analysis

To analyze the methylation of the OAS2 and OAS3 promoter regions, we utilized the methylation quantification endonuclease-resistant DNA (MethyQESD) method. This method combines methylation-sensitive digestion with real-time PCR (20). It involves two sets of restriction enzymes, a methyl-sensitive enzyme (Hin6I; G^CGC) for methylation quantification digestion and methyl-insensitive enzymes (DraI: TTT^AAA & XbaI: T^CTAGA) for methylation-independent calibrator digestion. The amount of methylated DNA resistant to Hin6I digestion was quantified using real-time PCR and normalized against a reference DNA that remains uncut. Real-time PCR amplification of the promoter region flanking the *OAS2* and *OAS3* genes was performed. The 10 µl PCR reactions included 0.5 µl each of forward and reverse primers, 1 µl of template DNA, and 5 µl of 2×SYBR Green PCR Master Mix (Thermo Fisher). Analysis was carried out with the ABI StepOne Plus real-time PCR system (Applied Biosystems). Table 1 lists the forward and reverse sequence-specific primers used for fragment amplification around the promoter sites. The cycling conditions for both genes were as follows: hot start by heating to 95 °C for 5 minutes as initial denaturation, followed by 45 cycles of denaturation at 95 °C for 15 s, annealing at 59 °C for 20 s, and extension at 72 °C for 30s. Finally, the methylation level was determined using the formula (Percent of methylation=$E^{\Delta Ct}$×100, where ΔCt=Ct of Calibrator – Ct of methylation quantification (E: PCR efficiency)).

Statistics

All data were analyzed using SPSS (version 25). The student's t-test was employed to compare the two groups. The clinical features of the participants were evaluated using the Kruskal-Wallis test for continuous variables and the Mann-Whitney U-test, along with the $\chi 2$-test for categorical variables. Receiver operating characteristic (ROC) curves were created for each gene by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) to determine the optimal threshold for distinguishing between individuals with SLE and healthy volunteers. The diagnostic accuracy for each gene was assessed by calculating the area under the ROC curve (AUC) and the corresponding 95% confidence intervals (CI). Furthermore, the Pearson correlation coefficient test was applied to explore the relationship between methylation levels and clinical characteristics. Data is presented as means±SD, with statistical significance set at $p<0.05$.

RESULTS

Clinical Characteristics of Subjects

In this research, we examined 102 individuals with SLE (33 males and 69 females; mean age: 41.93±12.13) and 105 healthy individuals (26 males and 79 females; mean age: 43.85±11.47). We found significant differences in blood pressure (both diastolic and systolic) and body mass index (BMI) between the SLE and control groups ($p<0.05$). The mean age of disease onset in SLE subjects was 25.20±9.83 years. Table 2 summarizes the clinical parameters of SLE patients and control volunteers, as well as a comparison between the two groups.

Table 1. Primer sequences for amplifying fragments around the promoter region of target genes.

Gene	Primer sequence	PCR product length (bp)	Annealing temperature
OAS2	F: AATCCTACGAGAGAGCTGCC R: ACCTGCTAGATGTCTGTCCT	100 bp	59°C
OAS3	F: TTGGGGAAGACAGGAACTGC R: GGGGTGCTGTACAAGTCCAT	192 bp	59°C

Table 2. Baseline features of patients with SLE and control volunteers who participated in this study

Characteristics	Controls	SLE patients	*p*
Total number	105	102	
Age (mean±SD)	43.85±11.47	41.93±12.13	0.28
Gender n (%)			
Male	26 (24.8%)	33 (32.4%)	0.281
Female	79 (75.2%)	69 (67.6%)	
Age of disease onset (mean±SD)	--	25.20±9.83	--
BMI (mean±SD)	23.92±3.46	26.14±2.22	<0.001*
SBP (mean±SD)	119.95±9.54	126.84±16.13	<0.001*
DBP (mean±SD)	79.04±8.46	82.45±6.43	0.023*
Positive family history n (%)	0	22 (21.6%)	--
Neurological symptoms n (%)	0	28 (27.5%)	--
Skin manifestations n (%)	0	65 (63.7%)	--
Hematological manifestations n (%)	0	49 (48.0%)	--
Oral ulcers n (%)	0	76 (74.5%)	--
Arthritis n (%)	0	73 (71.6%)	--
Renal involvement n (%)	0	43 (42.2%)	--

SD: Standard deviation; SLE: Systemic lupus erythematosus; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *p<0.05

The results of laboratory tests showed that in cases of SLE, the serum levels of erythrocyte sedimentation rate (ESR), creatinine, C-reactive protein (CRP), blood urea nitrogen (BUN), and anti-double stranded DNA (anti-dsDNA) antibody were significantly higher compared to non-SLE subjects (p<0.05). Conversely, the platelet count (PLT), hemoglobin levels, and serum concentrations of C3 and C4 were significantly lower in SLE cases compared to the control group (p<0.05). There were no significant differences in other laboratory parameters including, white blood cell (WBC) count, triglyceride and high-density lipoprotein (HDL) levels between the case and control groups (p>0.05). For more details refer to Table 3, which outlines the laboratory parameters and provides a comparison between the two groups.

OAS2 Methylation

The average percentage of methylation in the control group was 40.02%±24.59%, while in the SLE group, it was 19.46%±21.98%. This indicates a significant hypomethylation of *OAS2* in the patient group (P<0.001) (Figure 1A). However, there was no significant difference in methylation levels between SLE subjects with an age of onset ≤20 years and those with an age of onset >20 years (p=0.145). ROC curve analysis demonstrated that *OAS2* promoter methylation can distinguish individuals with SLE from healthy subjects with 83.33% sensitivity and 74.28% specificity (Figure 2, Table 4).

We found a significant association between the methylation levels of *OAS2* and renal damage. Notably, we observed lower methylation levels in SLE patients with lupus nephritis (12.57%±15.02%) compared to patients without kidney manifestations (34.43%±25.72%) (p<0.001). There was also a negative correlation between the methylation level of this gene and creatinine levels (r=-0.266, p=0.007). However, no significant associations were found between OAS2 promoter methylation and other laboratory parameters, including CRP, complement factors (C3, C4), and anti-dsDNA level in SLE patients (p>0.05, Figure 3).

Table 3: Laboratory parameters of patients and control groups

	Controls (105)	SLE (102)	$p_{\text{Controls vs SLE}}$
ESR (mm/h)	15.29±6.89	39.93±17.36	<0.001*
CRP (mg/l)	3.83±2.02	18.74±9.89	<0.001*
White blood cell (10^9/l)	6.47±1.49	6.70±1.62	0.296
Hemoglobin	14.13±1.43	11.66±1.46	<0.001*
PLT (10^9/l)	241.74±67.79	219.42±56.94	0.011*
Creatinine (mg/dL)	0.864±0 .19	1.38±0. 71	<0.001*
BUN	15.96±4.76	18.52±9.03	0.012*
FBS	89.97±18.82	88.50±14.96	0.535
HDL	50.06±11.71	50.16±7.31	0.941
LDL	107.32±37.49	107.93±29.82	0.897
TG	152.65±59.29	158.29±46.63	0.449
Anti-dsDNA (IU/ml)	10.67±4.67	219.80±180.96	<0.001*
C3 level (mg/dl)	146.66±34.88	48.20±35.76	<0.001*
C4 level (mg/dl)	20.69±5.89	10.05±7.05	<0.001*

Data is presented as mean±SD, or n (%). SD: Standard deviation; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BUN: Blood urea nitrogen; PLT: Platelet; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; FBS: Fasting blood sugar; dsDNA: Double-stranded DNA; C3: Complement component 3; C4: Complement component 4; SLE: Systemic lupus erythematosus; *p<0.05.

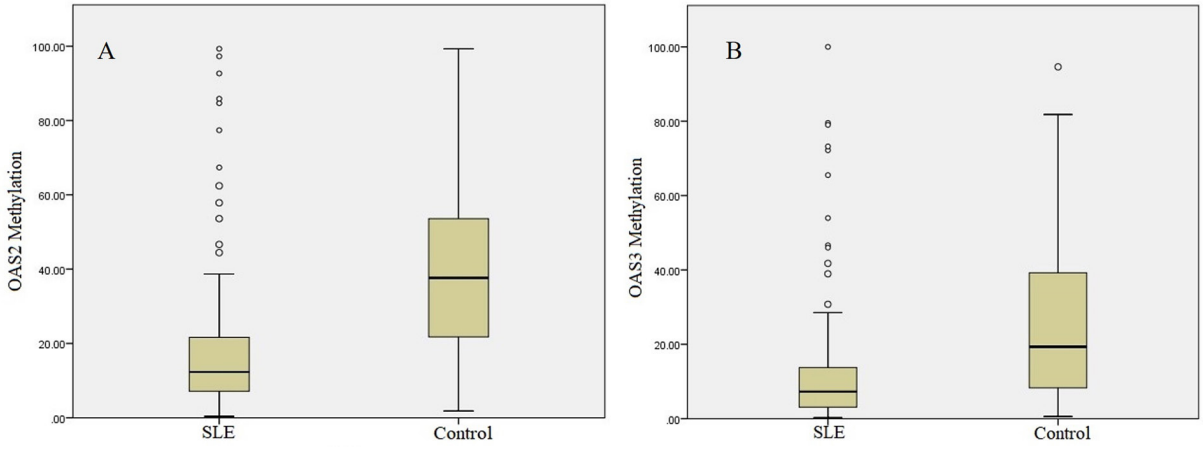

Fig. 1. Comparison of *OAS2* (A) and OAS3 (B) promoter methylation status between patients with SLE and non-SLE controls p<0.001.

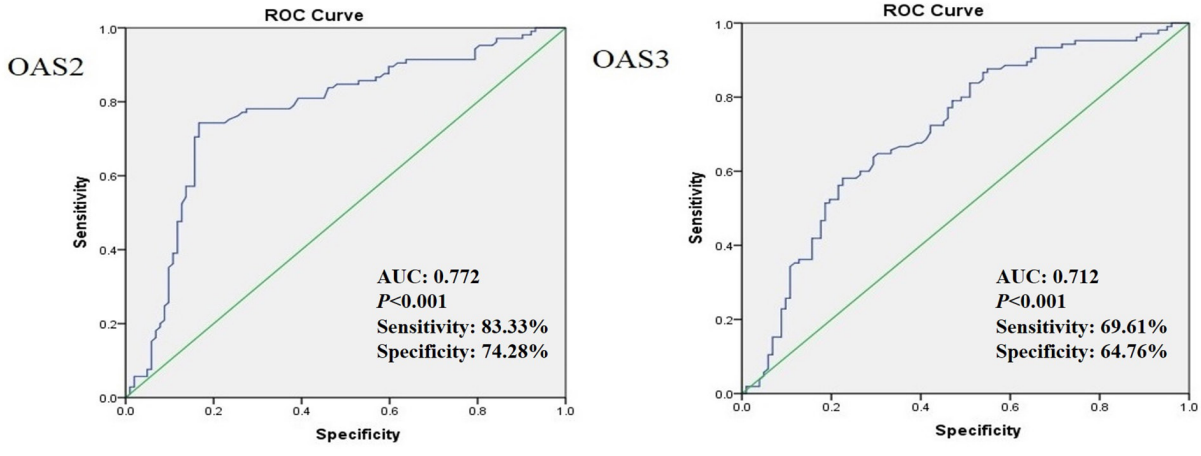

Fig. 2. The receiver operating characteristic (ROC) curves of *OAS2* and *OAS3* promoter methylation levels in participants with SLE compared to those in the control group.

Table 4: The levels of methylation in the *OAS2* and *OAS3* genes in both the SLE and control groups, as well as their diagnostic significance.

Group	AM %	*p*	Cutoff	Sensitivity	Specificity	AM% in age of onset ≤20	AM% in age of onset>20	*p*
OAS2								
SLE (n:102)	19.46±21.98	<0.001*	22.68%	83.33%	74.28%	23.90±25.61	16.82±19.24	0.145
Control (n:105)	40.02±24.59					_	_	_
OAS3								
SLE (n:102)	14.11±19.50	<0.001*	12.07%	69.61%	64.76%	14.95±21.89	13.61±18.11	0.739
Control (n:105)	25.32±20.82					_	_	_

*p<0.05; AM: Average percent of methylation; SLE: Systemic lupus erythematosus.

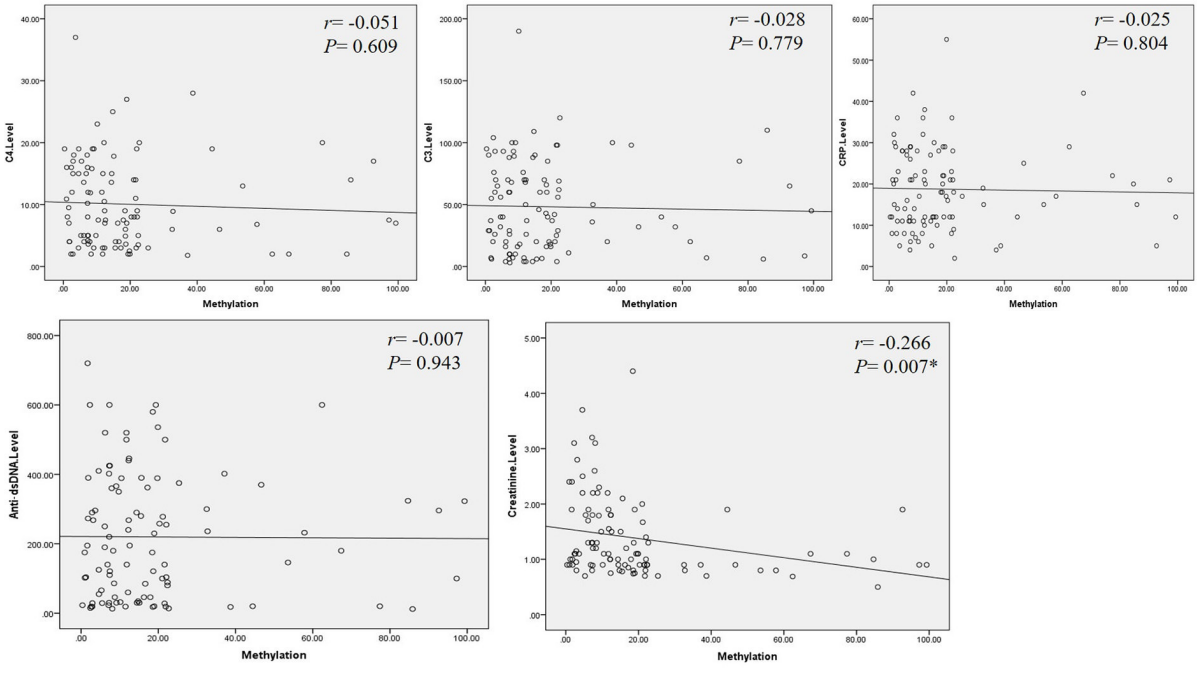

Fig. 3. Correlations between methylation of *OAS2* and levels of C4, C3, CRP, Anti-dsDNA, and creatinine in patients with SLE.

OAS3 Methylation

We observed a significant difference in mean methylation levels between SLE patients (14.11%±19.50%) and healthy participants (25.32%±20.82%) (p<0.001) (Figure 1). Using an optimal cutoff point (12.07%) based on the OAS3 promoter methylation level, the test demonstrated a sensitivity of 69.61% and specificity of 64.76% in discriminating SLE subjects from non-SLE individuals (Table 4).

We investigated the association between the methylation levels of the *OAS3* promoter and clinical factors. However, we found no clear link between the methylation levels of this gene and renal involvement. The methylation percentages in SLE subjects with and without renal involvement were 14.10%±23.02% and 14.11%±16.69%, respectively. Additionally, Pearson correlation analysis revealed that there was no significant correlation with laboratory findings such as creatinine, C3, C4, CRP, and anti-dsDNA concentration (p>0.05) (Figure 4). Moreover, there was no significant difference in methylation levels between SLE participants with an age of onset ≤20 years and those with an age of onset >20 years (p=0.739) (Table 4).

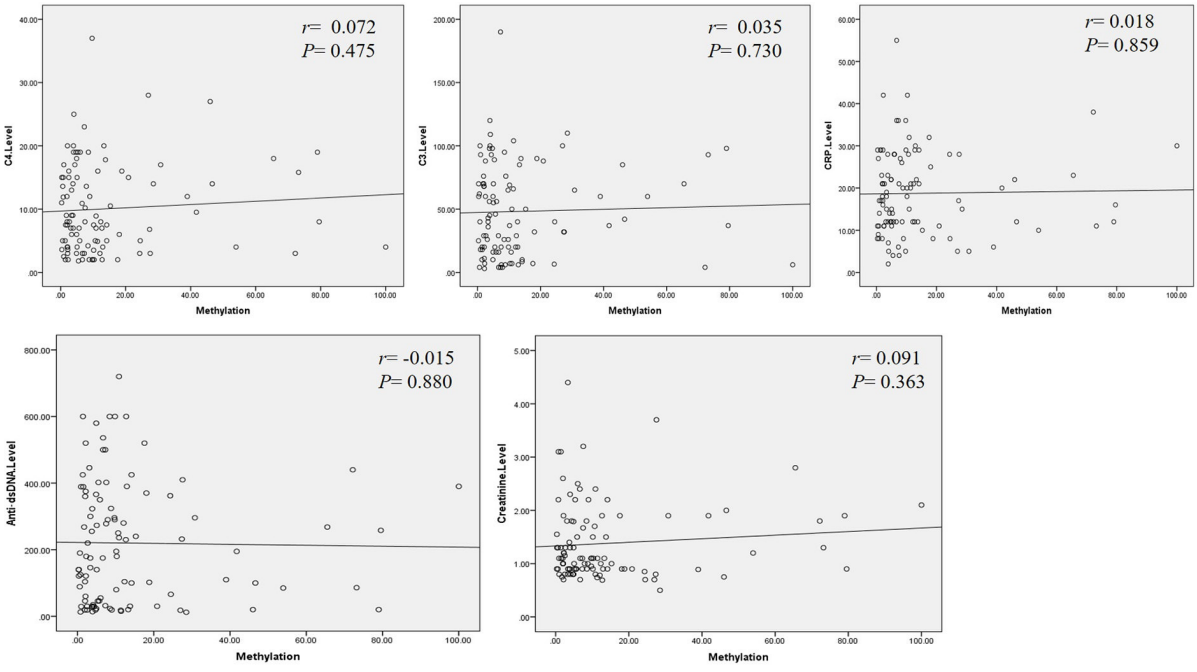

Fig. 4. Correlations between methylation of *OAS3* and levels of C4, C3, CRP, Anti-dsDNA, and creatinine in patients with SLE.

DISCUSSION

Aberrant DNA methylation patterns significantly contribute to the pathogenesis of autoimmune diseases such as SLE and RA. These abnormalities in DNA methylation can impact gene expression, resulting in immune dysregulation and disease initiation (21-23). Investigating DNA methylation in autoimmunity offers valuable insights into their pathogenesis and could help identify new therapeutic targets (24). Multiple studies have identified the aberrations in DNA methylation levels in SLE, affecting key immune-related genes such as *IFI44L*, *FOXP3*, *MX1*, *CDKN2A*, *MMP9*, *NR3C1*, *STX1B2*, *RAB22A*, *LGALS3BP*, *DNASE1L1*, and *PREX1* are dysregulated in SLE (5, 25-29).

The genes *OAS2* and *OAS3* encode enzymes that belong to the oligoadenylate synthetase (OAS) family which play a critical role in antiviral defense and are classified as type I IFN-inducible genes. When a cell is infected by a virus, OAS enzymes are activated to produce 2'-5'-linked oligoadenylates, which then trigger the enzyme RNase L. RNase L then degrades viral RNA, halting viral replication and spread (30-32). Through bioinformatics analysis and expression assays, it has been revealed that OAS2 and OAS3 are key genes that are upregulated in various cell types and tissues. Their increased expression is specifically associated with the progression of lupus nephritis in glomerular biopsies (11). Moreover, these genes are also upregulated in PBMCs of SS patients, skin lesions in discoid lupus patients, and multiple immune cell subsets (PBMCs, CD33+ myeloid cells, $CD4^+$ T cells, and $CD19^+$ B cells) in SLE patients with active disease, particularly those with renal complications and arthritis (7, 8, 10, 33).

Multiple studies have reported hypomethylation of *OAS2* and *OAS3* in various sample types. Fang and colleagues found that in $CD14^+$ monocytes and $CD19^+$ B cells from patients with SLE, *OAS2*, *OAS3*, *OAS1*, and *OASL* (other members of the OAS family) were hypomethylated compared to healthy controls. This hypomethylation was linked to increased expression of these genes in their samples. Moreover, they proposed that *OAS1*, *OAS2*, and *OASL* could be used as diagnostic biomarkers for SLE, demonstrating high sensitivity (AUC>0.70) in distinguishing

SLE from non-SLE individuals (8). Similarly, He et al confirmed hypomethylation and overexpression of the *OAS2* gene in SLE patients(34).

A genome-wide DNA methylation analysis in CD4+ T cells revealed a significant correlation between the methylation level of *OAS2* and the patient global assessment (PGA) in patients with RA (15). PGA a key component of disease activity scores is used to define remission in RA (35, 36). Similarly, hypomethylation of *OAS2*, was observed in minor salivary gland biopsies and PBMCs from patients with SS, correlating with elevated gene expression (13, 14). Independent studies also reported OAS3 hypomethylation in classical monocytes ($CD14^{+}$ $CD16^{-}$) and $CD4^{+}$ T cells from African American and Spanish SSc patients (16, 17).

In this study, we assessed the methylation levels of the promoter regions of the *OAS2* and *OAS3* genes in PBMCs, an easily accessible source of human immune cells, from SLE patients and healthy controls. To avoid DNA degradation and related artifact, we employed the MethyQESD, a bisulfite conversion-independent technique (20, 37). Our findings was consistent with previous reports, showing significant difference between *OAS2* and *OAS3* methylation between SLE and control groups (Table 4, Figure 1). Additionally, we demonstrated that methylation levels were significantly different in patients with and without renal involvement. Patients with renal damage and higher creatinine levels exhibited significantly lower *OAS2* methylation levels, consistent with previous studies linking *OAS2* overexpression to the progression of lupus nephritis. Notably, OAS2 expression was higher in SLE patients with renal involvement compared to those without (7, 11). However, this association was not observed in the study by Román-Fernández et al. (38), highlighting potential variability across cohorts. In our analysis, neither *OAS2* nor *OAS3* methylation levels correlated with standard disease activity markers (CRP, C3, C4, and anti-dsDNA). This contrasts with findings by Grammatikos et al, who reported association between the methylation level of *OAS2* and various SLE activity indices (12).

In summary, hypomethylation of the *OAS2* and *OAS3* genes leads to their increased expression though the precise mechanisms through which this overexpression contributes to SLE pathogenesis are not fully understood. However, this overexpression may hyperactivate the interferon response, promoting inflammation through enhanced pro-inflammatory cytokine secretion and autoantibody production, particularly antinuclear antibodies (ANAs). These antibodies are a hallmark of SLE and play a pivotal role in driving tissue damage and disease progression (39, 40).

Our findings demonstrate a significant association between the hypomethylation of *OAS2* and renal involvement in SLE patients, suggesting a potential role for *OAS2* promoter methylation in SLE pathogenesis. However, this study has certain limitations, including potential ethnic variations in gene methylation patterns and a relatively small sample size. Future studies should investigate larger, more diverse cohorts to validate these findings. Additionally, since the expression levels of *OAS2* and *OAS3* may serve as biomarkers for monitoring disease activity in SLE patients (12), longitudinal studies, rather than case-control design alone, would provide more comprehensive insights into disease progression and activity .

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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