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Comparison of Myxovirus Resistance Gene 2 Expression among Adult and Juvenile SLE Iraqi Patients

Sahar Aldhahir[1,*], Izzat A. M. Al-Rayahi[1], and Salwa S. Muhsin[2]

[1]Department of Medical Laboratory Techniques, College of Health and Medical Techniques, Middle Technical University, Iraq
[2]Department of Community Health Medical Technical Institute, Middle Technical University, Iraq

*Correspondence author; E-mail: sahar.aldhahir2020@gmail.com

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs in the body. The disease may affect juveniles, referred to as juvenile-onset SLE (jSLE), but it is less common than adult-onset SLE (aSLE). SLE is characterized by the excessive production of autoantibodies, and genetic background that is not fully understood. The human myxovirus resistance gene (MX2), classified as an immune regulatory gene, has not yet been studied in juvenile-onset SLE. Only a few studies have explored its connection to rheumatic diseases in adults. The current study aimed to investigate its expression and its correlation with the disease activity index across different age groups. This study included 50 patients with SLE, 25 adults and 25 juveniles who all met the ACR criteria, along with a control group of 30 healthy individuals., Total RNA was extracted from PBMCs from fresh whole blood samples of all participants to detect human (MX2) levels through quantitative real-time polymerase chain reaction (qRT-PCR), and disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). The human (MX2) gene was overexpressed in all patients involved, and there were no statistically significant differences in expression rates between the studied groups (p=0.76). There was a non-significant negative correlation (p=0.092) between the fold change in gene expression and the SLEDAI-2K score. The SLEDAI-2K scores for jSLE and aSLE indicated a statistically significant difference between the two groups (p=0.04). Understanding the genes linked to SLE is crucial, as MX2 could potentially serve as a diagnostic marker, and may also provide insights into disease mechanisms and targeted therapies.

Keywords: *juvenile-onset SLE; adult-onset SLE; MX2 gene*

1. Introduction

Systemic lupus erythematosus (SLE) is a long-term autoimmune condition that exhibits a variety of clinical symptoms and a relapsing-remitting pattern (Sandhu, & Quan, 2017), Its clinical presentation range from minor mucocutaneous symptoms to severe involvement of multiple organs (Justiz Vaillant et al., 2023). The disease process of SLE involves impaired nucleic acid clearance, elevated type I interferon (IFN) response, dysregulated B-cell tolerance leading to elevated autoantibody production, development and deposition of immune-related complexes that are causing damage to several organs (Nandakumar, & Nündel, 2022). In terms of prevalence, systemic lupus erythematosus is the most common forms of lupus, accounting for around 70% of lupus cases (Lao et al., 2023). Juvenile-onset SLE is an

uncommon but severe multisystem illness that can cause significant tissue damage. Between 15% and 20% of SLE patients are children whose disease begins before the age of 18. Compared to adult-onset SLE, Juvenile-onset SLE is characterized by greater aggression, higher levels of disease activity, more serious organ manifestations, and a greater risk of renal, cardiovascular, and neuropsychiatric involvement. These factors contribute to the increased morbidity and mortality associated with the disease (Jawad kadhum et al., 2021; Charras et al., 2021; Robinson et al., 2020). The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is the most commonly used in observational studies. The SLEDAI, first released in 1992, was later updated in 2002 (SLEDAI-2K) to account for current disease activity (Gladman et al., 2002). The prevalence of SLE in familial clusters and the notable rise in relative risk seen in monozygotic twins compared to dizygotic twins, where the concordance rate is reported to be 24% and 2%, respectively, provide strong evidence for the impact of genetic susceptibility (Catalina et al., 2020). Genetic variations and environmental factors can be responsible for this difference. There is insufficient epidemiological data on SLE for 79.8% of the world's countries. Although the globally estimated incidence of SLE is 5.14 (1.4 to 15.13) per 100,000 person-years, with approximately 0.40 million people newly diagnosed annually (Tian et al., 2023). More than 100 gene loci with polymorphisms, or less frequently, mutations of a polygenic nature, are linked to most SLE cases, while it has been found that around 30 genes have been found to be monogenic nature causing SLE or SLE-like diseases (Qian et al., 2020). These genes play a role in disease pathogenesis by stimulating the activation of both innate and adaptive immune systems. A few atypical gene mutations are thought to carry a very high risk of developing SLE mutations vary in their contribution to risk factors (Coss et al., 2023). Several bioinformatic studies have identified various aberrant gene expression levels linked to the onset of SLE (Zhao et al., 2016). A large number of genes upregulated in SLE and other rheumatic disease patients are related to type I interferon-mediated immune responses and make up the IFN gene signature (Cooles, & Isaacs, 2022; Demers-Mathieu, 2023). Human Myxovirus resistance gene 2, a member of the GTPase family, (also known as MX2 or MXB) is found on chromosome 21q22.3 (Haller et al., 2015). Despite thorough investigation into the role of MX2 in different immune-related conditions such as RA (Sanayama et al., 2014), hepatitis B (Wang et al., 2020), hepatitis C (Yi et al., 2019), and acquired immune deficiency syndrome (AIDS) (Moschonas et al., 2023), its connection with SLE remains limited. However, there are few recent studies that have identified elevated MX2 expression in SLE (Zhao et al., 2023). In addition to genetic factors, biomarkers such as the antinuclear antibody (ANA) play a significant role in SLE diagnosis due to their high sensitivity (Pisetsky et al., 2019). Antibodies targeting double-stranded DNA (dsDNA) were the initial disease-specific markers identified for SLE, and can be utilized for tracking the progression of disease (Mummert et al., 2018). Anti-dsDNA is crucial for diagnosing, categorizing, and treating SLE, and often seen as more clinically significant and specific for SLE (Orme et al., 2022). Similarly, renal involvement is another common complication in SLE, and laboratory measures like creatinine and urea levels correlate with renal injury (Gounden et al., 2024). However, renal damage is more frequently observed in children (Tektonidou et al., 2017). Lupus nephritis is observed in approximately 50-82% of cases, while in adults, it affects about 20-40% of cases (Samanta et al., 2017). Since the MX2 gene has been previously studied in relation to various diseases in adults, the purpose of this study was to measure its expression in both children and adults with SLE, given its importance in immune regulation and its impact on disease severity. This is particularly relevant as the disease tends to be more severe in children, and we sought to determine whether this gene also plays a role.

2. Objectives

To investigate the gene expression of the MX2 gene in Iraqi adult and juvenile patients with systemic lupus erythematosus, in comparison to the control group, and to assess its expression in relation to disease activity index, as well as to evaluate the clinical differences between the two groups.

3. Materials and Methods

3.1 Study Design

The current study aimed to include 60 patients from various age groups, every patient included in this study was diagnosed with SLE based on the 1997 American College of Rheumatology (ACR) guidelines

(Hochberg, 1997). Present clinical features, and SLEDAI-2K calculation were assessed by physicians through patient assessment. They visited the Rheumatology Unit at Baghdad Teaching Hospital (for adults), and Welfare Teaching Hospital (for children), from January to May 2024. Ten patients were excluded due to having other immune-related diseases or chronic viral infections. The total number of eligible cases was divided into two groups based on age: Adult-onset SLE (Group I): 25 patients aged >20 years, and Juvenile-onset SLE (Group II): 25 patients aged <16 years. The control group consisted of 30 healthy volunteers matched with patients by both age and sex and with no history of any form of lupus or other autoimmune diseases. Subjects were enrolled at any time after their diagnosis. All participants were included in the MX2 gene expression analysis, which was measured by qPCR, and disease activity was observed to determine the SLEDAI-2K score for systemic lupus erythematosus disease activity index 2000 (Gladman et al., 2002). Every participant provided consent. Ethics approval numberd:193/3; date:09/01/2024.

3.2 Primers

The primers were designed by downloading the human MX2 gene nucleotides from NCBI and then using the primer-plus 3 software to complete the process. The required information was entered to design appropriate and precise primers. The GAPDH primer sequence was obtained from Al-Rayahi et al., (2017). The source of all primers used in this study was macrogen® (Korea). The name and sequence are given in table (Table 1).

3.3 Isolation and Quantitation of Total RNA

Total RNA was extracted from fresh whole blood samples (PBMCs) using TRIzol™ reagent (Invitrogen Company, USA). The manufacturer's protocol included the following: adding 0.5 mL blood sample into 1 mL TRIzol™. In time to start the process, chloroform was used for cell lysis and precipitation of cell content when RNA was transferred to the new tube in the aqueous phase. RNA precipitation was performed using isopropyl alcohol. RNA washing was done by using 70% ethanol, the pellet was rehydrated in 100 µL of nuclease free water and then incubated to ensure RNA solubility. The RNA quantitation was done by using a Qubit® RNA HS kit from ThermoFisher® (USA).

3.4 Quantitative Real-Time Polymerase Chain Reaction Analysis (qRT-PCR)

cDNA was synthesized by qPCR by ProtoScript® First Strand cDNA Synthesis Kit from NEB (UK). MX2 expression evaluated by NEB Luna Universal qPCR Master Mix for real-time qPCR detection and quantification of target DNA sequences using the SYBR®/FAM. Results were analyzed by Livak $2^{-\Delta\Delta Ct}$ formula (Livak, & Schmittgen, 2001).

3.5 Anti-ds-DNA and Anti-nuclear Antibody

Anti-ds-DNA IgG and Anti-nuclear antibody (IgG) by enzyme-linked immunosorbent assay (ELISA system reader Agilent BioTek 800 TS), USA. Kits from (Demeditec, Germany) following the manufacturer's instructions.

3.6 Laboratory Tests for Renal Assessment

Blood urea and serum creatinine tests was measured by (Mindray BS-240 chemistry full-automated analyzer, China). RBCs count done by microscopic examination and the albumin was estimated using a reagent strip test from (CYBOW, Germany) following the manufacturer's instructions.

Table 1 Primers used in this study: Names, Sequences, and Product Sizes

Name of gene	Sequence of primer	Size (bp)		Tm	Excision number
MX2	MX2-F (5′-ACTTGGTGGTGGTTCCCTGTA3′) : MX2-R (5′- TGGTCAGGATACCGATGGTCC-3′)	105 bp	Newly diagnosed	86	NM_002463.2
GAPDH	GAPDH-F (5′-GTCTCCTCTGACTTCAA-3′) GAPDH-R (5′-ACCACCCTGTTGCTGTA-3′)	131 bp		84	NM_0080848

3.7 Statistical Analysis

The Statistical Analysis System (SAS) 2018 program (Cary, 2012) was used to assess the impact of various sets (patients and control group) on the study variables. A t-test was used to compare means in groups for significance. Chi-square test was utilized to assess significant differences between percentages at probabilities of 0.05 and 0.01. The correlation coefficient was calculated to determine the association between SLEDAI-2K and fold change in MX2 expression.

4. Result

The study included fifty patients, categorized by age. Individuals over the age of 20 years were classified as having adult-onset systemic lupus erythematosus (aSLE) (mean ± SD, 32.73 ±1.76 years; Male: Female 2:23). Those under 16 years were classified as having juvenile-onset systemic lupus erythematosus (jSLE) (mean ± SD, 9.48 ±0.59 years; Male: Female ratio is 5:20). The control group consisted of 30 healthy individuals: 15 children (mean ± SD, 8.44 ± 1.50 years; Male:Female ratio 3:12), and (15 Adult, mean ± SD, 34.2 ±1.82 years: Male: Female 2:13. Differences in clinical features were observed between the two groups. In the jSLE group, fatigue (97.14% vs. 82.8%), lymphadenopathy (8.57% vs. 0.0%), nausea (60.0% vs. 31.4%), hemolytic anemia (14.2% vs. 0.0%), and acute nephrotic syndrome (62.86% vs. 14.29%) were more common compared to the aSLE group. Conversely, Raynaud's phenomenon (34.29% vs. 0.0%) and photosensitivity (65.71% vs. 11.43%) were more common in the aSLE group than in the jSLE group. Other symptoms were less common, with fever observed in 51% of individuals and pericarditis in only 3% (Figure 2). In the aSLE group, 97% of individuals experienced lupus headaches as a predominant symptom. The rest of the symptoms were reported by different percentages, with arthritis being the most common at 71% and pericarditis being the least common at 6% (Figure 3). MX2 was overexpressed in all patients compared to controls. As shown in Figure 1, the fold change in gene expression did not differ significantly between the jSLE and aSLE groups (p = 0.76). The SLEDAI mean score of jSLE (21.1±1.75) and aSLE (16.7±1.22) groups were compared, and the result indicated a statistically significant difference between the two means (p=0.04). A weak negative correlation (r = -0.351) between fold change in gene expression and the SLEDAI-2K score was observed, though it was not statistically significant (p = 0.092) (Table 2). In addition, some routine laboratory tests are shown in Table 3. Both the jSLE and aSLE groups had higher ANA levels than the control groups (p = 0.0322 and p = 0.0488, respectively). Although jSLE group experienced more positivity rate of ANA than aSLE and there are statistically significant between them p=0.049. jSLE and aSLE had higher level of anti-ds-DNA than control groups P=0.0247,0.0007 respectively. Additionally, jSLE and aSLE had elevated levels of urea when compared to control groups p=0.0019, 0.0489 respectively, and significant elevation in jSLE versus aSLE patient groups p=0.0021. Regarding creatinine, results showed a significant elevation in the jSLE group compared to the control group (p = 0.04), but no significant difference was observed in the aSLE group compared to the control group (p = 0.457). However, there is statistical difference between jSLE versus aSLE patients' groups p= 0.014.

Table 2 Correlation between fold change in MX2 expression and SLEDAI-2K

Correlations		**SLEDAI**	
Spearman's rho	Fold of expression	Correlation Coefficient	-0.351
		P value	0.092

Table 3 Routine laboratory tests in studied groups

Parameter Mean ± SD	Adults (n = 25)	Adult control (n = 15)	p-value	Juveniles (n = 25)	Juvenile control (n = 15)	p-value	p-value jSLE vs aSLE
ANA	1.47 ± 0.44	0.255 ± 0.004	0.048	3.26 ± 0.87	0.211 ± 0.04	0.003	0.0492
Anti-dsDNA IU/mL	29.37 ± 4.19	6.32 ± 0.86	0.0007	65.32 ± 15.56	7.76 ± 1.25	0.024	0.0312
Urea mg/dL	25.69 ± 1.93	19.67 ± 1.18	0.0489	39.20 ± 3.70	19.43 ± 1.93	0.0019	0.0021
Creatinine mg/dL	0.66 ± 0.04	0.503 ± 0.02	0.457	1.12 ± 0.12	0.378 ± 0.06	0.04	0.014
RBCs count in urine / HPF	16.75 ± 4.81	0.80 ± 0.11	0.0312	26.63 ± 4.14	0.7 ± 0.12	0.0003	0.0498
Albumin in urine positivity	20%	0%	0.001	60%	0%	0.000	0.0085

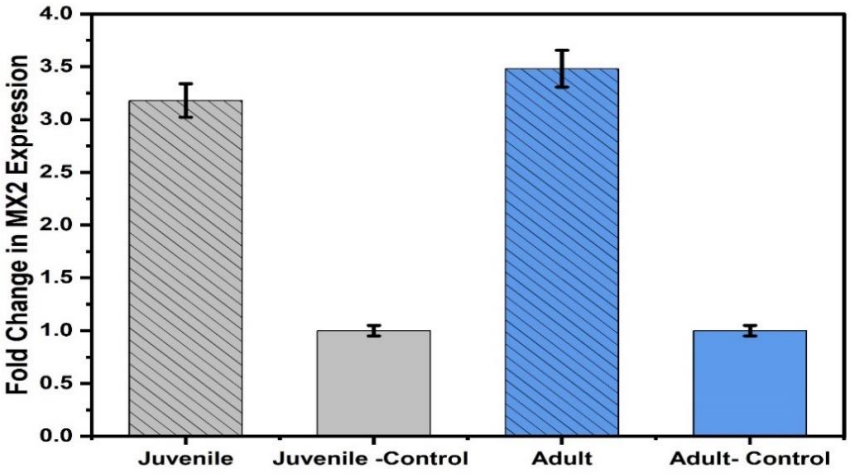

Figure 1 Mean fold change in MX2 gene expression among studied groups

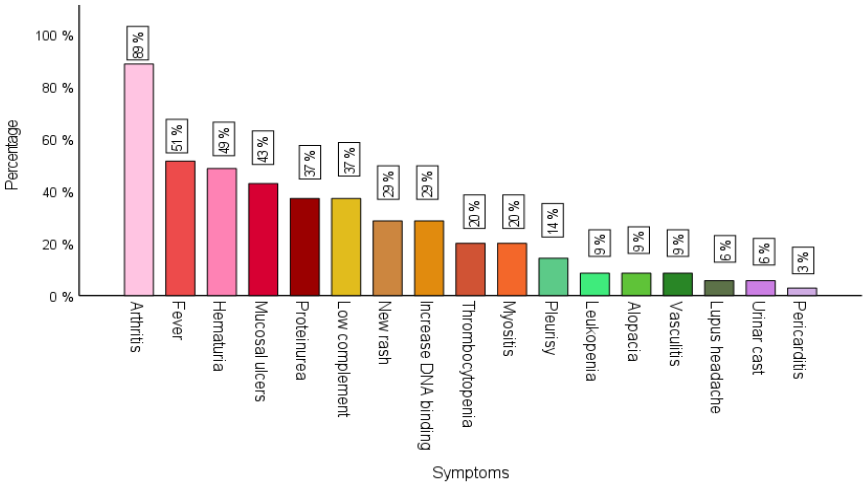

Figure 2 The percentage of the main symptoms in juvenile patients

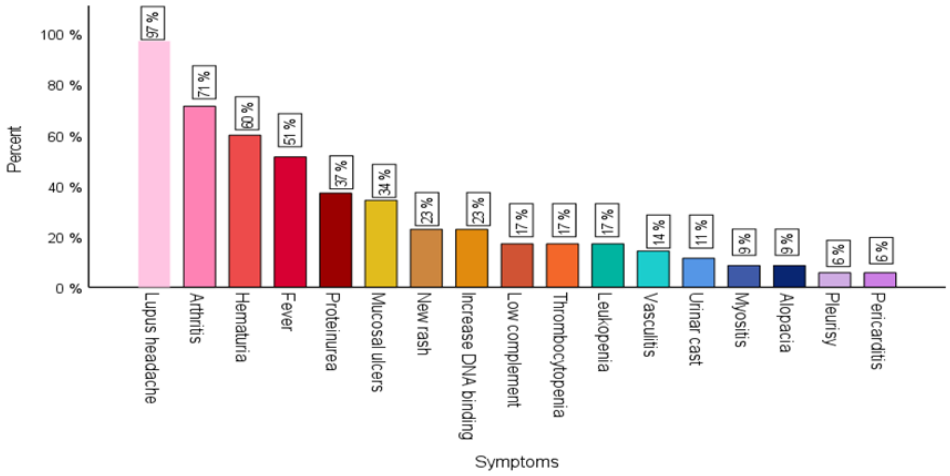

Figure 3 The percentage of the main symptoms in adult patients

5. Discussion

This research aimed to compare classical and major clinical features and MX2 gene expression between juvenile- and adult-onset SLE, as well as to track MX2 gene expression during disease activity. The SLE clinical phenotype shows wide variability, in general, fatigue is a common symptom in individuals with rheumatic diseases (Dey et al., 2021). SLE associated arthritis has long been established as a common feature (Ceccarelli et al., 2021). A recent study found interleukins, IL-17 and IL-6 levels were high in synovial fluid of SLE patients, beside T cells, suggesting a pathogenic role of T cells in lupus arthritis (Sippl et al., 2021). Lymphadenopathy may result from a disease flare, infections, or lymphoproliferative disorders (Soares et al., 2022). None of the aSLE patients developed lymphadenopathy, but a few jSLE patients exhibited cervical lymphadenopathy. Which might be carried due to current flare or to recurring upper respiratory infections induced by immunosuppressive medication they take. However, the Ryanoid phenomenon can be seen in a small percentage (10%) of children with SLE (Jiang et al., 2022). In our study, we did not observe any case in jSLE, maybe because it occurs in only a limited number of jSLE, since it has been reported in 60% of aSLE cases in large cohort study and has been associated with Anti-ribonucleoprotein antibody (anti-RNP antibody) and it is notably more prevalent in aSLE (Rodsaward et al., 2021). We observed significant differences between the two groups we studied in the disease activity and following clinical manifestations: Renal involvement (LN) and Hemolytic Anemia. Juveniles suffered more than adults. This can be attributed to several explanations. indeed, children's immune systems usually have a robust response, and there is a placebo-clinical trial that included 2200 young by testing a COVID-19 immunization revealed a 100% effectiveness rate and a robust immune reaction (Wallace, 2021). This was a subtle explanation by (Trindade et al., 2021). Another possible reason is that children's organs are still developing and may not effectively combat the disease. Additionally, the use of certain medications in children is often more restricted. A decade ago, MX2 was recognized as an immune-related indicator in rheumatoid arthritis (RA) (Sanayama et al., 2014). MX1 and MX2 have strong correlations and exhibit comparable domain architectures and structures (Dicks et al., 2016). Nevertheless, A recent study demonstrated the MxA, which is a member of the human Myxovirus resistance gene, and found it highly expressed and common in lupus myositis patients, serving as a useful marker to distinguish LM from other myositis conditions (Xing et al., 2024). It is known that an Interferon type I (IFN-I) is a crucial factor in the pathogenesis of SLE (Postal et al., 2020). It plays a critical part in both innate and adaptive immune systems through its role in activating immune responses, cell growth, and regulating apoptosis. Therefore, any disruption in its function can disrupt

immune tolerance mechanisms, leading to the production of harmful autoreactive antibodies (Oon et al., 2016). Importantly, more than 50% of the identified genes related to SLE are responsible for producing or responding to type I IFN, either directly or indirectly (Deng, & Tsao, 2017). MX2 is predominantly expressed through IFN activation, particularly type I (Betancor et al., 2021; Juraleviciute et al., 2020). MX2 is classified as one of the IFN-stimulated genes (ISGs) (Wiesauer et al., 2015). When IFNs bind to receptors on the cell surface, intracellular signaling cascades are initiated, which results in the activation of interferon-stimulated genes (Lang et al., 2022). A recent study identified increased MX2 gene expression in patients with SLE compared to healthy individuals, and to further understand MX2 gene role in the disease, researchers found a significant association through correlation analysis in which MX2 activates the nucleotide oligomerization domain 2 (NOD2-like receptor) signaling pathway (Meng et al., 2022). Stimulation of NOD2-like receptors leads to the activation of various transcription factors and production of different cytokines, interferons, and chemokines (Saferding, & Blüml, 2020). Nevertheless, the specific cellular control processes of NOD2 activation and the distinct roles in various immune cell populations in SLE remain to be fully understood. In addition, Meng et al., (2022) in their study, discovered through immune infiltration analysis algorithms that MX2 exhibited a strong correlation with neutrophil infiltration, it also showed a significant association with neutrophils marker genes (Meng et al., 2022). These findings could be taken into consideration, as neutrophils have been shown to play an important role in the pathogenesis of SLE, by exhibiting multiple abnormalities for example, it has been documented that in the bone marrow of SLE patients, neutrophils can stimulate improper B-cell proliferation and create type-I IFN independently of toll-like receptor (TLR) stimulation (Palanichamy et al., 2014). Neutrophils may play a role in inducing $CD4^+$ T-cells to release TNFα and IFNγ. Since many researchers found SLE patients have a high concentration of low-density granulocytes (LDG), a subtype of neutrophils, in their peripheral blood, these cells are linked to the severity of the disease and the presence of the IFN signature (Rahman et al., 2019; Tay et al., 2020). Additionally, the MX2 gene may be induced by other SLE-related genes, such as interferon regulatory factor 1 (IRF1) (Liu et al., 2017). Which has been shown to be significantly elevated in MX2-overexpressing melanoma cells compared to controls (Juraleviciute et al., 2021). Furthermore, the transducer and activator of transcription 1 (STAT1) plays a critical role in regulating the transcription of ISGs, including MX2 (Wiesauer et al., 2015).This understanding of the interplay between MX2, type I IFN, and the immune mechanisms in SLE highlights the importance of further research to explore potential therapeutic targets and interventions. Disease activity tends to be higher in jSLE as previously mentioned, it likely leads to greater organ damage, which in turn results in elevated urea and creatinine levels compared to aSLE. In addition, research indicates a stronger connection between genetic loci linked to SLE susceptibility and LN in SLE diagnosed during childhood (Webber et al., 2020). In this current research, it showed there is no significant difference between MX2 and SLEDAI-2K, this may be due to many patients involved were receiving treatment, which in turn lead to reduce disease activity, but not seems to affect expression rates, since a previously study showed that many conventional SLE treatments had no effect on ISGs expression rates (Nikpour et al., 2008). In previous research, there have been contradictions regarding the relationship between ISGs and SLEDAI score, some studies have demonstrated a type of association between them (Nikpour et al., 2008). While others have found no correlation at all (Landolt-Marticorena et al., 2009; Shen et al., 2022). There is also a study that aimed to investigated the upregulation of ISGs over multiple time periods and their relationship with the SLEDAI score, it found that despite changes in SLEDAI score among patients, the genes expression remained stable across all measurements (Petri et al., 2019). jSLE group experienced a higher positivity rate of ANA than aSLE and there are statistically significant between them $p < 0.05$. This is consistent with (Kim et al., 2019; Massias et al., 2020). Most of patient with jSLE has positive antinuclear antibodies, ANA titers do not align with disease activity because they are not precise (Abd El Monem Teama et al., 2021; Avar-Aydın, & Brunner, 2024). jSLE group experienced a higher positivity rate of Anti ds-DNA antibody than aSLE and there are statistically significant between them $p < 0.05$. This finding aligns with the results reported by El-Garf et al. (2021). Moreover, anti-dsDNA antibodies have been shown to correlate with

disease progression across all age groups (Abd El Monem Teama et al., 2021; Damoiseaux, & van Beers, 2023). As well as with lupus nephritis (LN) (Hsu et al., 2023; Rodsaward et al., 2021; Vyasam et al., 2023). It became clear from the previous results that both lupus nephritis and disease activity are more prevalent in jSLE, which explains the outcome we observed of Anti ds-DNA antibody test and the increased presence of red blood cells and protein in jSLE which align with previous studies (Gilliam et al., 2012; Pinheiro et al., 2019)

6. Conclusion

Systemic lupus erythematosus is more common in adults but rare in children. While numerous studies focus on adults, fewer have been conducted on children. The sex distribution of the disease varies between these age groups, as do the clinical symptoms, with children generally experiencing more severe manifestations. Genetic factors play a crucial role, and in this study, we examined the MX2 gene, which was elevated in all age groups, suggesting its involvement in the disease. However, it was not associated with disease severity. The study could be expanded by increasing the sample size and comparing gene expressions in newly diagnosed patients.

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