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**Research Article**

# Screening of Hub Genes Associated with Lupus Nephritis by Integrated Bioinformatic Analysis

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## Abstract

Lupus Nephritis (LN) is one of the commonest complications of systemic lupus erythematosus which is characterized by autoimmune and tissue destruction. Elucidating the process in detail would be of great significance for clinical practice, however, the molecular mechanism underlying LN is not clear. In the study, GSE112943 and GSE81622 were retrieved from Gene Expression Omnibus database (GEO), and the differentially expressed genes (DEGs) were identified by GEO2R. Among these DEGs, 42 genes were up-regulated, and 7 genes were down-regulated. The functions and signaling pathways of these DEGs were analyzed systematically, and protein-protein interaction (PPI) networks of these DEGs were established through the search tool for the retrieval of interacting genes (STRING) database. 10 hub genes (IFI44, RSAD2, IFI44L, IFI27, MX1, IFIT3, IFIT1, IFI6, OAS3 and IFIT2) were screened out by the plug-in CytoHubba in Cytoscape. Expression level, diagnosis value as well as correlation with glomerular filtration rate (GFR) expression of these hub genes for LN patients were investigated in GEO datasets and Nephroseq v5 online platform. The results showed that eight of these hub genes were found highly expressed in LN tissues and significantly related to the diagnosis (AUC>0.7; $p<0.05$). In addition, these hub genes were negatively related to the GFR level of LN patients. In conclusion, the hub genes and pathways that were related to the development of LN were screened out, which could provide a new insight for the future molecularly targeted therapy and diagnostic evaluation.

**Key words:** Lupus Nephritis (LN), Bioinformatics, Differentially Expressed Genes (DEGs), Hub Genes, diagnosis.

## Introduction

Systemic lupus erythematosus (SLE) is a common autoimmune disease characterized by the presence of nuclear autoantibodies, which can cause immune complex formation and inflammation of multiple organs like joints, skin, kidneys, heart, hematopoietic system and the nervous system (1). Lupus nephritis (LN), a form of glomerulonephritis, constitutes one of the most severe organ manifestations of SLE and leads the death rate in patients (2). Although understanding of the genetic and pathogenetic basis of LN has improved substantially over the past few decades, there're also many obstacles. Therefore, looking for reliable biomarkers is of great importance for improving the prognosis and reducing the mortality of LN patients.

Based on RNA sequencing or microarray gene expression profiles, high-throughput screening technique has been widely used for gene detection and diseases analysis. Academics can rapidly and precisely get the knowledge of key genes associated with serious diseases including SLE via many biological information data mining. Zhao et al. found that IFI27 may be closely related pathogenesis of SLE and represents a new candidate molecular marker of the occurrence and progression of SLE via integrated bioinformatics analysis (3). In addition, a circRNA-miRNA-mRNA regulation network was built in SLE by screening the differentially expressed circRNAs from GEO database (4). The discovery and the lucubration of these key genes obtained through bioinformatics analysis contribute to the discovery of effective biomarkers, which can be applied to understand the initiation and development of LN.

The purpose of our study was to perform multiple analyses towards key genes of LN through integrated bioinformatics methods. First, we downloaded two microarray datasets containing mRNA expression data from Gene Expression Omnibus (GEO) and the differentially expressed genes (DEGs) were screened out via GEO2R online tool. Next, gene expression profiles were obtained, and functional analysis was performed for DEGs, then we established protein-protein interaction (PPI) network and further investigated the hub genes's expression level , their diagnosis value as well as correlation with glomerular filtration rate (GFR) expression in LN patients in GEO datasets and Nephroseq v5 online platform. All these analyses may provide new biomarkers for research on the initiation and development of LN.

## Materials and methods

### 1. Acquisition and processing of GEO data

We used "lupus nephritis" as the keyword for searching and two SLE datasets were obtained from GEO database (available online: http://www.ncbi.nlm.nih.gov/geo) (5), which are GSE112943 (expression profiling by array, 14 lupus nephritis, 7 control kidney), and GSE81622 (expression profiling by array, 30 lupus nephritis, 25 control kidney). Both datasets were based on the GPL10558 platform (Illumina HumanHT-12 V4.0 expression beadchip). DEGs were screened and identified via GEO2R online tools (available online: https://www.ncbi.nlm.nih.gov/geo/geo2r/ ) with the cut-off $|\log2FC|\geq1$ and adj. $p < 0.05$. DEGs co-occurred in two datasets were integrated together and showed in a Venn diagram (available online: https://bioinfogp.cnb.csic.es/tools/venny/index.html ).

### 2. GO and KEGG Pathway enrichment analyses and visualization

Functional annotations and pathway enrichment analyses on DEGs were carried out through R packages, which included the visual results of Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. GO can be used to study gene-related biological process (BP), cellular component (CC) and

molecular function (MF)，while KEGG can simulate and analyze the pathways that DEGs were enriched in. *P*-values were calculated based on the cumulative hypergeometric distribution; they were corrected by the Benjamin-Hochberg method. The most representative enrichment analysis results were selected with $p < 0.05$.

### 3. PPI network and acquisition of hub genes

Protein and protein interaction (PPI) network can explain the underlying associations of the genes involved in some biological processes. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, available online: https://stringdb.org/, Version11.0 ) (6) was first applied to establish a PPI network of DEGs, and then the results were imported into Cytoscape software (version 3.6.1) (7) to further visualize. In addition, the plug-in CytoHubba in Cytoscape was applied to identify the hub genes that were generated top ten through the score of Maximal Clique Centrality (MCC) algorithm.

### 4. Diagnosis value evaluation of hub genes

Two datasets, GSE112943 and GSE81622 were used to evaluate the diagnosis value of hub genes. We applied SPSS (version 24.) to obtain the Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC) represents the diagnosis value. Patients were defined as “1” while the normal controls were defined as “0”. Then the expression of each hub gene was test variable and the “0/1” was regarded as state variable.

### 5. The expression of hub genes and their relationship with clinical features in LN patients

The expression of hub genes between LN patients and healthy living donors were detected by Nephroseq v5 online tool (http://v5.nephroseq.org), which provides unique access to datasets from the Applied Systems Biology Core at the University of Michigan, incorporating clinical data which is often difficult to collect from public sources. We also used it to analyze the correlation between hub genes and clinical features in LN patients. Unpaired t test for comparisons was performed between groups and the criterion of two-tailed value of $p < 0.05$ was set as statistically significant.

## Results

### 1. Identification and screening of DEG

Two microarray datasets: GSE112943 and GSE81622 (Fig.1) were obtained from GEO database, which included 44 samples from LN patients and 32 samples of normal tissues. The DEGs were identified by online GEO2R analysis tool with the cut-off criterion of $|\log_2 FC| \geq 1$ and adj. $p < 0.05$. Afterwards, a Venn diagram (Fig. 2) was used to get an intersection of DEGs from the 2 datasets and there were 42 up-regulated genes and 7 down-regulated genes (Table 1) in the LN samples compared to the normal samples.

### 2. GO analysis of DEGs

To evaluate the function of DEGs, we performed functional annotations and pathway enrichment analyses via GO and KEGG. Based on the GO analysis, the top 10 most significantly enriched GO terms in the BP, CC and MF of DEGs were listed in Fig. 3 and Table 2. It showed that up-regulated DEGs mainly participated in the biological processes (BP) of response to virus, defense response to virus, type I interferon signaling pathway, cellular response to type I interferon and so on. The analysis of cellular component (CC) emerged that these genes mainly encoded the components of secretory granule lumen. The molecular function (MF) included endopeptidase activity, serine-type endopeptidase activity, serine-type peptidase activity and so on.

### 3. KEGG pathway analysis of DEGs

Depending on the analysis of KEGG pathway,

significant genes were mainly enriched in six KEGG pathways (Fig. 4; Table 3), they were Hepatitis C, Influenza A, COVID-19, IL-17 signaling pathway, Measles and Bladder cancer. Numerous pathways involved in the development of LN which included IL-17 signaling pathway. IL-17 has a potential to induce the production of additional inflammatory cytokines and to promote recruitment of inflammatory cells such as monocytes and neutrophils to the inflamed organ (8). It has been confirmed that there's elevated level of Th17 cells as well as IL-17 in SLE patients (9) and high levels of IL-17 predicts poor histopathological outcome after immunosuppressive therapy in patients with LN (10).

## 4. Analysis of PPI network and identification of hub genes

Exploring the PPI in organisms can help to study molecular mechanisms of some diseases from a perspective of system. We built a PPI network only about up-regulated DEGs via STRING website (Fig. 5A) and visualized it by Cytoscape tool. CytoHubba plug-in was applied to confirm ten hub genes according to the score of MCC. The results were shown in Fig. 5B. We can see that IFI44, RSAD2, IFI44L and IFI27 rank first and then MX1, IFIT3, IFIT1, IFI6. OAS3 and IFIT2 rank ninth together. The hub genes and their full names as well as functions were shown in Table 4.

## 5. Diagnosis value evaluation of hub genes

Based on GSE112943 and GSE81622, we evaluated the diagnosis value of hub genes. From GSE112943, the AUC of IFI44, IFI44L and IFIT2 ranked first but IFIT1's AUC was only 0.439. From another dataset, GSE81622, IFI44 also had the biggest AUC, followed by IFI44L, RSAD2, IFI6, IFI27, OAS3, IFIT1, IFIT3, IFIT2 and MX1 (Fig. 6, Table 5). Combining these two results, we speculated IFI44 might have the most valuable of the diagnosis in LN.

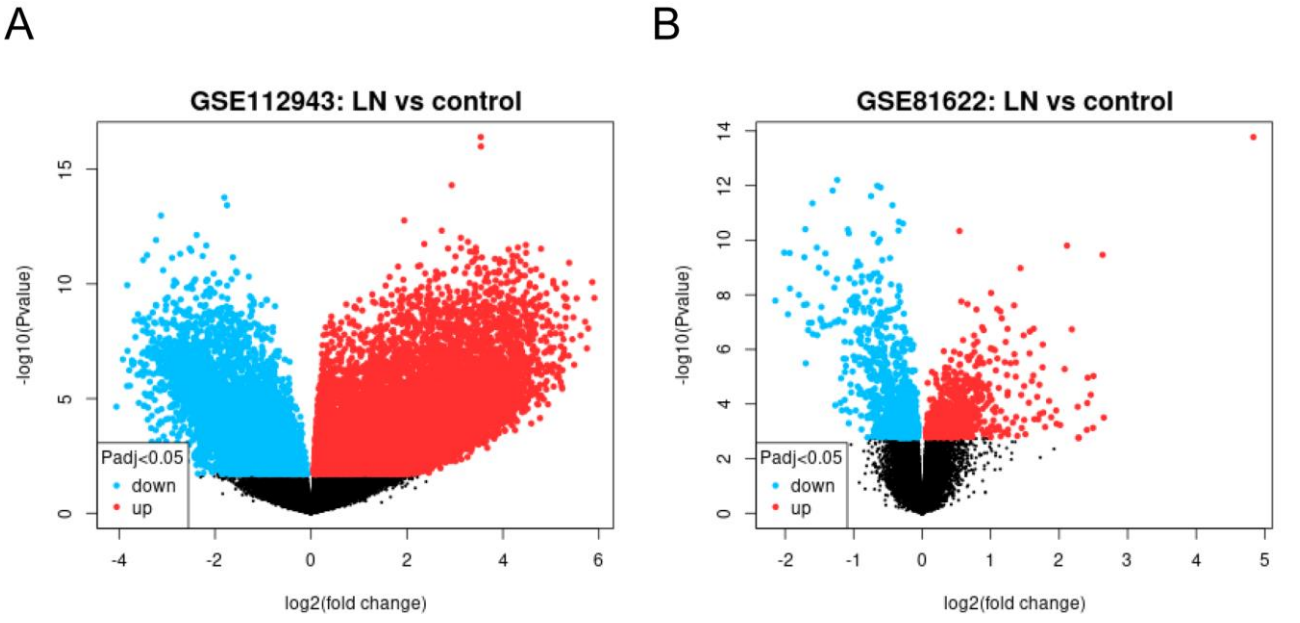


**Figure 1. The expression of DEGs in GSE112943 and GSE81266.** The red dots mean up-regulated genes in LN compared to normal while blue dots mean down-regulated genes. (A) GSE112943; (B) GSE81622. The intersecting areas represent the commonly altered DEGs. DEGs, differentially expressed genes, LN, lupus nephritis.

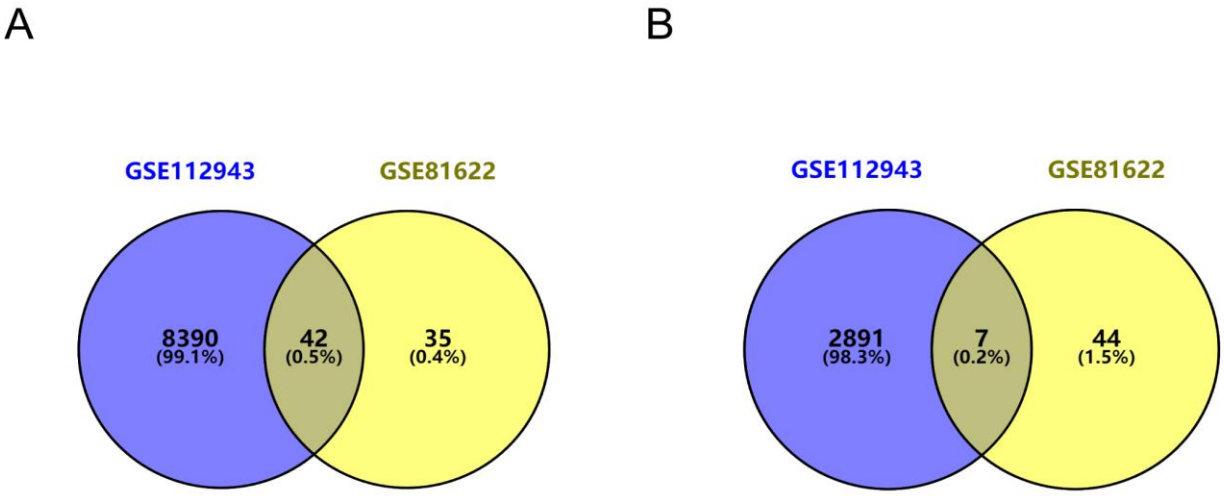


**Figure 2. The intersection of DEGs from GSE112943 and GSE81266 via Venn diagram.** (A) Up-regulated genes; (B) Down-regulated genes.

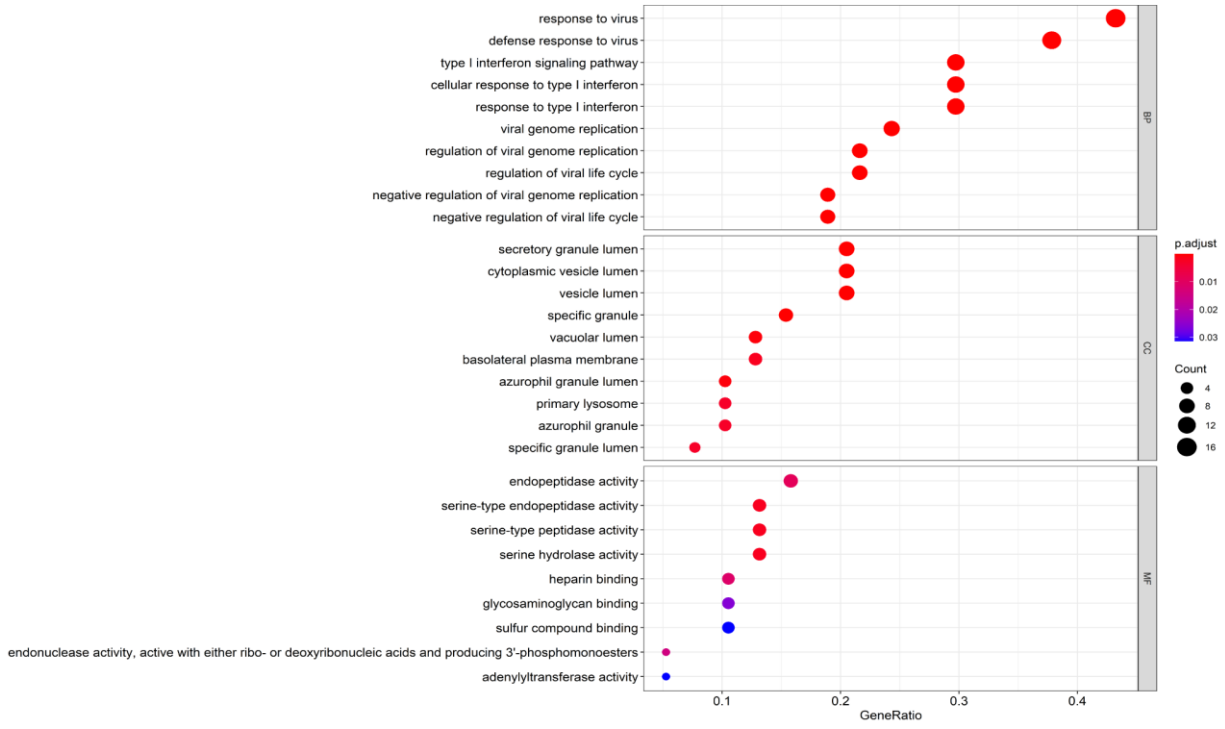


**Figure 3. The GO enrichment analyses on up-regulated DEGs.** The top ten items of GO are illustrated in the form of bubble plot via using the ggplot2 package for R software. The area of the nodes means the number of enriched genes and the color represents the significance of the item. BP, Biological Process; CC, Cellular Component; MF, Molecular Function. A p-value <0.05 was considered statistically significant.

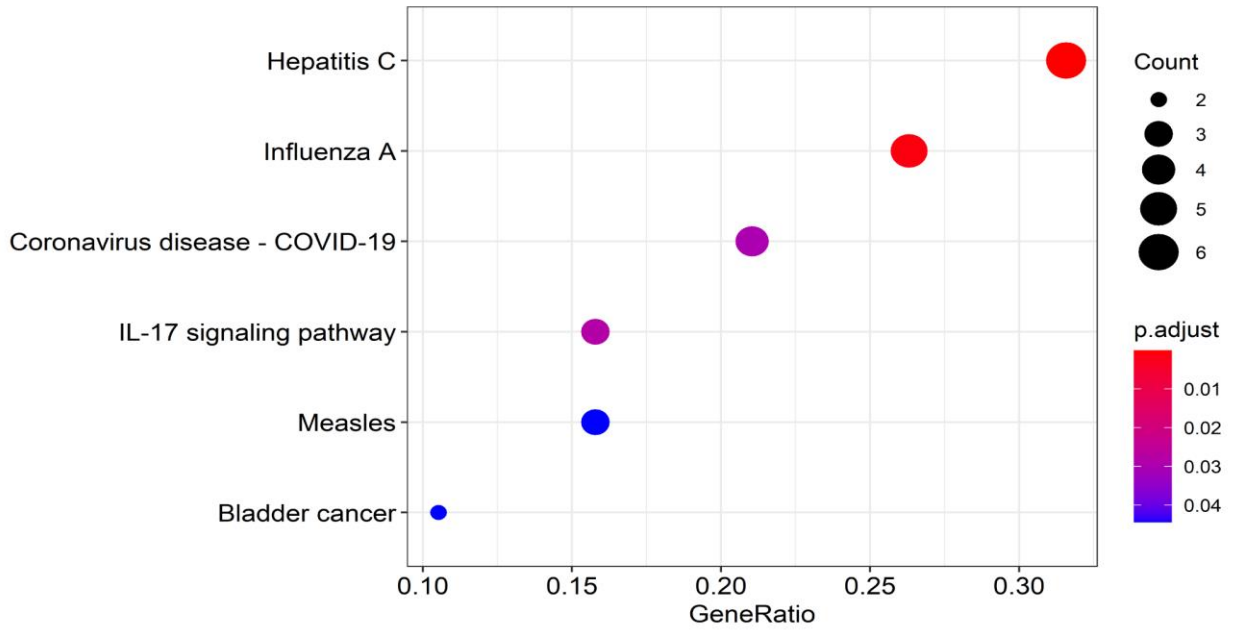


**Figure 4. The KEGG enrichment analyses on up-regulated DEGs.** The area of the nodes means the number of enriched genes and the color represents the significance of the item. A p-value <0.05 was considered statistically significant.

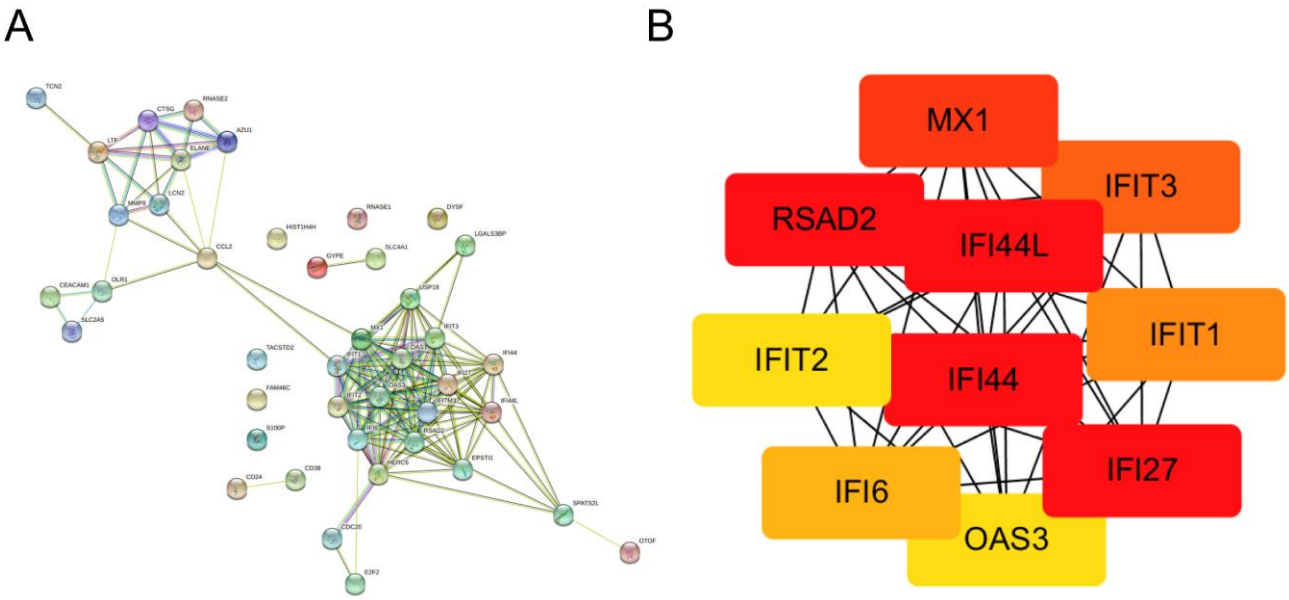


**Figure 5. The PPI network constructed by STRING online database and the identification of 10 hub genes.** (A) The PPI network of 42 up-regulated DEGs, the nodes meant different proteins and the lines meant interaction between the two proteins. (B) 10 hub genes were screened out by cytohubba app. The squares meant genes and the lines meant interaction between two genes, and the deeper the color was, the more significant the gene was.

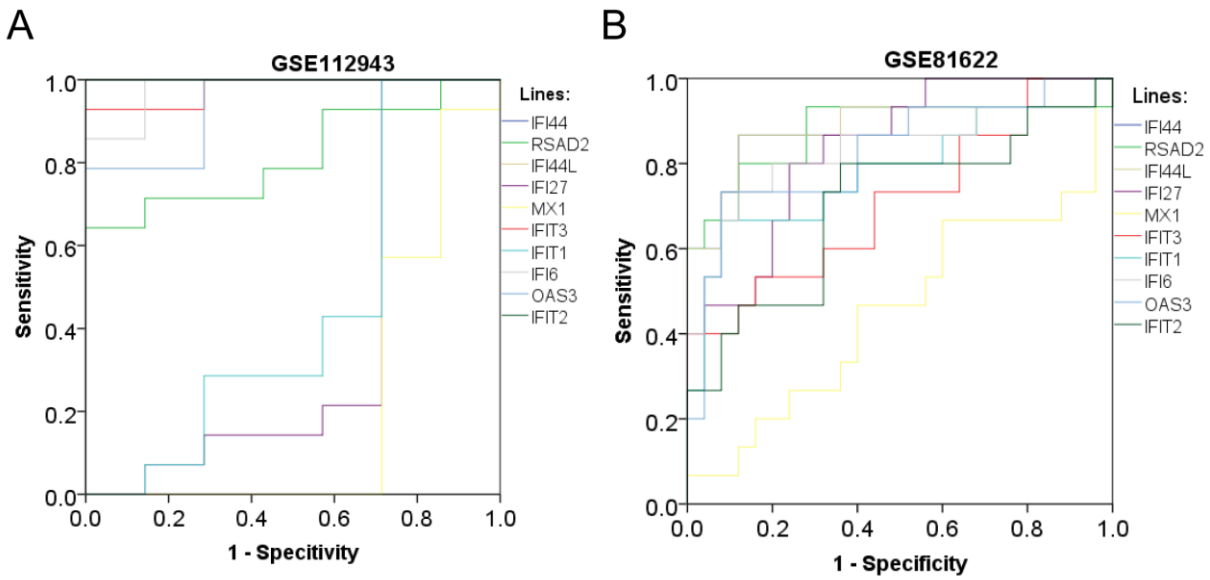


**Figure 6. The diagnostic performance of the hub genes.** The diagnostic performance of the calculated based on the ten hub genes expression in LN diagnosis in training (A) GSE112943 and (B) GSE81622, respectively. ROC, receiver operating characteristic; AUC, area under the curve.

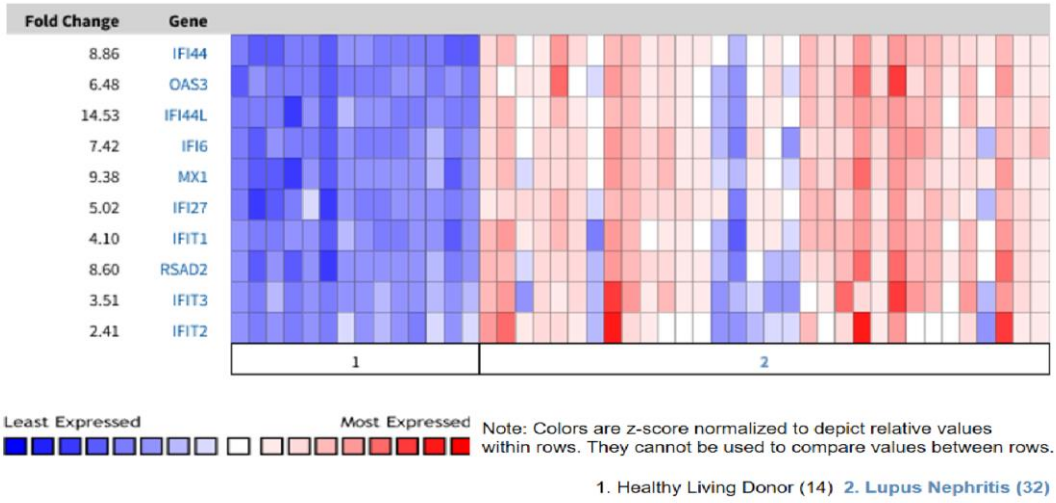


**Figure 7. The heat-map of hub genes expression.** The color of the diamonds is displayed in a gradient from red to blue according to the ascending order of gene expression level. The fold change is log2 median-centered intensity.

**Table 1 Differentially Expressed Genes**

| Up- or Down-regulated | Number | Differentially Expressed Genes |
|---|---|---|
| Up-regulated | 42 | RNASE2 AZU1 RSAD2 S100P HERC5 IFIT1 USP18 CEACAM1 SLC2A5 E2F2 SLC4A1 FAM46C LGALS3BP OAS1 CD24 OLR1 GYPE IFITM3 IFI6 ELANE TACSTD2 OTOF LCN2 LTF CTSG CD38 TCN2 HIST1H4H MX1 IFIT2 CDC20 MMP9 IFI44 RNASE1 DYSF SPATS2L IFIT3 IFI27 OAS3 CCL2 EPSTI1 IFI44L |
| Down-regulated | 7 | KIR2DS5 FEZ1 MATK KIR2DL1 ADGRG1 KIR2DL4 TTC38 |

**Table 2. GO Analysis of the Up-regulated DEGs**

| Term | GO number | Definition | P-value | Gene Count |
|---|---|---|---|---|
| **BP** | GO:0009615 | Response to virus | 1.21E-18 | 16 |
| | GO:0060337 | Type I interferon signaling pathway | 2.23E-17 | 11 |
| | GO:0071357 | Cellular response to type I interferon | 2.23E-17 | 11 |
| | GO:0051607 | Defense response to virus | 2.59E-17 | 14 |
| | GO:0034340 | Response to type I interferon | 3.58E-17 | 11 |
| | GO:0019079 | Viral genome replication | 2.26E-12 | 9 |
| | GO:0045069 | Regulation of viral genome replication | 1.59E-11 | 8 |
| | GO:0045071 | Negative regulation of viral genome replication | 2.47E-11 | 7 |
| | GO:1903901 | Negative regulation of viral life cycle | 2.94E-10 | 8 |
| **CC** | GO:0034774 | Secretory granule lumen | 1.95E-07 | 8 |
| | GO:0060205 | Cytoplasmic vesicle lumen | 2.14E-07 | 8 |
| | GO:0031983 | Vesicle lumen | 2.25E-07 | 8 |
| | GO:0042581 | Specific granule | 7.12E-07 | 6 |
| | GO:0005775 | Vacuolar lumen | 2.31E-05 | 5 |
| | GO:0035578 | Azurophil granule lumen | 3.18E-05 | 4 |
| | GO:0016323 | Basolateral plasma membrane | 0.000123 | 5 |
| | GO:0005766 | Primary lysosome | 0.000251 | 4 |
| | GO:0042582 | Azurophil granule | 0.000251 | 4 |
| | GO:0035580 | Specific granule lumen | 0.000256 | 3 |
| **MF** | GO:0004252 | Serine-type endopeptidase activity | 2.45E-05 | 5 |
| | GO:0008236 | Serine-type peptidase activity | 3.98E-05 | 5 |
| | GO:0017171 | Serine hydrolase activity | 4.40E-05 | 5 |
| | GO:0004175 | Endopeptidase activity | 0.000264 | 6 |

| | | | |
|---|---|---|---|
| GO:0008201 | Heparin binding | 0.000401 | 4 |
| GO:0016894 | Endonuclease activity, active with either ribo- or deoxyribonucleic acids and producing 3'-phosphomonoesters | 0.000626 | 2 |
| GO:0005539 | Glycosaminoglycan binding | 0.001311 | 4 |
| GO:0070566 | Adenylyltransferase activity | 0.001869 | 2 |
| GO:1901681 | Sulfur compound binding | 0.002046 | 4 |

**Table 3. KEGG Analysis of the Up-regulated DEGs**

| Rank | Term | P-value | Gene Count |
|---|---|---|---|
| 1 | Hepatitis C | 1.05E-06 | 6 |
| 2 | Influenza A | 3.70E-05 | 5 |
| 3 | IL-17 signaling pathway | 0.001277 | 3 |
| 4 | Coronavirus disease - COVID-19 | 0.001802 | 4 |
| 5 | Measles | 0.003903 | 3 |

**Table 4. The Full Name and Functions of Hub Genes**

| Rank | Name | Full name | Function | References |
|---|---|---|---|---|
| 1 | IFI44 | Interferon induced protein 44 | IFI44 can positively affects virus production and negatively modulates innate immune responses induced after viral infections | (11, 12) |
| 1 | RSAD2 | Radical S-adenosyl methionine domain containing 2 | The protein plays a role in cellular antiviral response and innate immune signaling. | (13, 14) |
| 1 | IFI44L | Interferon induced protein 44 like | The methylation level of IFI44L promoter can distinguish patients with SLE from healthy persons and other autoimmune diseases | (15, 16) |
| 1 | IFI27 | Interferon alpha inducible protein 27 | It can mediate the antiviral effects against different neurotropic viruses. | (17, 18) |
| 5 | MX1 | MX dynamin like GTPase 1 | This gene encodes a guanosine triphosphate (GTP)-metabolizing protein that participates in the cellular antiviral response. | (19, 20) |
| 6 | IFIT3 | Interferon induced protein with tetratricopeptide repeats 3 | IFIT3 Modulates IFIT1 RNA binding specificity and protein stability. | (21, 22) |
| | IFIT1 | Interferon induced | The encoded protein may inhibit viral replication | (23, 24) |

| | | | | |
|---|---|---|---|---|
| 7 | | protein with tetratricopeptide repeats 1 | and translational initiation. | |
| 8 | IFI6 | Interferon alpha inducible protein 6 | The encoded protein may play a critical role in the regulation of apoptosis. | (25, 26) |
| 9 | OAS3 | 2'-5'-oligoadenylate synthetase 3 | This enzyme family plays a significant role in the inhibition of cellular protein synthesis and viral infection resistance. | (27, 28) |
| 9 | IFIT2 | Interferon induced protein with tetratricopeptide repeats 2 | IFIT2 is instead repurposed by influenza virus to promote viral gene expression. | (29, 30) |

**Table 5. The Diagnosis Value of Hub Genes from Two GEO datasets**

| GSE112943 | | GSE81266 | |
|---|---|---|---|
| **Term** | **AUC** | **Term** | **AUC** |
| IFI44 | 1.000 | IFI44 | 0.896 |
| RSAD2 | 0.816 | RSAD2 | 0.877 |
| IFI44L | 1.000 | IFI44L | 0.896 |
| IFI27 | 0.908 | IFI27 | 0.827 |
| MX1 | 0.980 | MX1 | 0.456 |
| IFIT3 | 0.980 | IFIT3 | 0.709 |
| IFIT1 | 0.439 | IFIT1 | 0.781 |
| IFI6 | 0.980 | IFI6 | 0.829 |
| OAS3 | 0.939 | OAS3 | 0.827 |
| IFIT2 | 1.000 | IFIT2 | 0.704 |

**Table 6. The Correlation between Hub Genes and GFR expression in LN patients**

| Term | Sample numbers | P value | R value |
|---|---|---|---|
| IFI44 | 22 | 4.20E-6 | -0.813 |
| RSAD2 | 11 | 0.020 | -0.684 |
| IFI44L | 22 | 6.25E-4 | -0.671 |
| IFI27 | 16 | 2.87E-4 | -0.788 |
| MX1 | 22 | 3.25E-4 | -0.696 |
| IFIT3 | 16 | 0.001 | -0.729 |
| IFIT1 | 13 | 0.032 | -0.596 |
| IFI6 | 12 | 0.005 | -0.754 |
| OAS3 | 16 | 0.007 | -0.642 |
| IFIT2 | 16 | 0.010 | -0.623 |

### 6. The expression of hub genes and their relationship with clinical features in LN patients

By using Nephroseq v5, the expression of 10 hub genes (IFI44, RSAD2, IFI44L, IFI27, MX1, IFIT3, IFIT1, IFI6, OAS3 and IFIT2), especially IFI44L, MX1 and IFI44 showed higher expression in LN patients compared to healthy living donors (Fig. 7). In addition, all these hub genes were found negatively associated with GFR level of LN patients (Table 6). Therefore, the expression changes of these ten genes may play an important role in the occurrence and development of LN.

## Conclusion

SLE is a multi-system autoimmune disease and despite years of study, the etiology of SLE is still unclear (31). In recent years, bioinformatics is one of the newest fields of biological research, and viewed broadly as the use of mathematical, statistical, and computational methods for the processing and analysis of biological data. To understand the pathogenesis of LN, we performed an integrated analysis of tissues from patients with LN and normal controls to investigate the potential biomarker of the disease.

In this study, DEGs in LN based on the GEO expression profiles of GSE112943 and GSE81622 were identified, which including 42 up-regulated and 7 down-regulated genes. Through R packages, we visualized the outcomes derived from GO and KEGG pathway enrichment analysis. As for the biological processes, these up-regulated DEGs were enriched in the response to virus, defense response to virus, type I interferon signaling pathway, cellular response to type I interferon and so on. As for the cellular component, it showed that these genes mainly encoded the components of secretory granule lumen. And the molecular function included endopeptidase activity, serine-type endopeptidase activity, serine-type peptidase activity and so on. Although there's few study that illuminates the association between response to virus and SLE or LN, however as a kind of auto-immune disease, LN may share the similar immune characteristics with response to virus. Type I interferon signaling pathway has been reported that involved in molecular and cellular processes of renal damage and the heterogeneity of LN (32, 33). Evan Der et al. applied scRNA-seq to identify clinically relevant signatures associated with LN and found an elevated IFN response signature in keratinocytes from patients with LN compared to healthy control subjects, indicative of a systemic response to IFN (34). In addition, there are also plenty of study targeted type I interferon signaling pathway to ameliorate LN (35). According to the result of KEGG, up-regulated DEGs emerged a high enrichment in the pathways of Hepatitis C, Influenza A, COVID-19, IL-17 signaling pathway, Measles and Bladder cancer. IL-17 has a potential to induce the production of additional inflammatory cytokines and to promote recruitment of inflammatory cells such as monocytes and neutrophils to the inflamed organ (8). Researches showed that IL-17 and Type I interferon had close relationship in many kind of diseases such as thyroid cancer (36), bronchopulmonary dysplasia (37), hepatocellular carcinoma (38) and so on. In LN, Type I interferon and Th17 pathways co-exist

and co-regulate the pathogenic processes (39). Additionally, IFN-α can induce IL-10 production and tilt the balance between Th1 and Th17 in Behçet disease (40). However, the underlying mechanism between IL-17 and Type I interferon needs more research. Next, the PPI network of DEGs was constructed via the STRING online database and Cytoscape software. By use of "CytoHubba" plug-in, the top ten hub genes, IFI44, RSAD2, IFI44L, IFI27, MX1, IFIT3, IFIT1, IFI6, OAS3 and IFIT2 were identified. As for IFI44, Siddiqi KZ et al. applied a systematic review of cross-sectional studies and found IFI27, IFI44, IFI44L, IFIT1, PRKR and RSAD2 expression clustered with the fraction of SLE cases having African ancestry or lupus nephritis (41). And other studies also used integrated bioinformatics analyses to confirm the role of IFI44 in LN (3, 42). Hu et al. carried out experiments that suggested Ifi44 is potentially involved in the inflammation associated with gentamicin-induced ototoxicity and nephrotoxicity (43).

Shimizu Y et al. found Interferon-inducible MX1 protein was highly expressed in renal tissues from treatment-naive lupus nephritis (44). Others utilized bioinformatics analyses and then got the relationship between MX1 and LN (45-47). Intense glomerular Mx1 expression was observed in biopsy specimens from patients with LN which at least in part indicated the theory of innate immune system activation in the pathogenesis of LN (48). In addition, as a IFN-inducible gene, MX1 was highly expressed in SLE patients, and increased levels were correlated with disease activity defined by several methods (49).

The IFN-signature genes, IFIT1 and IFIT3, they both proved have relationship with LN and might act as the potential biomarker, however, the underlying mechanism is still unknown (41, 50-52).

Other genes like RSAD2, IFI44L, IFI27 were simply detected their expression and IFI6 and IFIT2 even haven't been reported in LN. So our work was of great importance to further elucidate hub genes' internal regulatory mechanism.

After that, we analyzed the diagnosis value of the hub genes and the results showed that except IFIT1 and MX1, all eight hub genes had great diagnosis value and especially, IFI44 ranked first in both datasets. From the results in Nephroseq v5 tool, ten hub genes were all up-regulated and negatively related to GFR level in LN patients. IFI44, IFI44L, IFI27, MX1, IFIT3, IFIT1, IFI6 and IFIT2, they all belong to type I interferon signature genes, which is consistent with the results from enrichment analysis. It has been confirmed that in LN patients' skin and kidney, there is a high expression of interferon responsive genes compared to healthy control subjects (53) and this pathway also affects renal mesangial cells, contributing to the occurrence of LN (54). Other type I interferon related genes like IFI202, IFI203 have become the candidate genes for LN (55). Therefore, the understanding of type I interferon allows the development of treatment for this disease.

In summary, our study indicated that IFI44, RSAD2, IFI44L, IFI27, MX1, IFIT3, IFIT1, IFI6, OAS3 and IFIT2 might be involved in LN tumorigenesis and progression. Multiple database analyses demonstrated that eight of these hub genes may be regarded as the latent diagnosis biomarkers.

However, in our study, only bioinformatic analysis was performed, the role of identified hub genes in LN should be further verified in vivo and in vitro. Anyway, all our analysis may provide some potential biomarkers of LN.

## Abbreviations

SLE, Systemic lupus erythematosus; LN, Lupus Nephritis; GEO, Gene Expression Omnibus; DEGs, differentially expressed genes; GO, Gene Ontology; KEGG, The Kyoto Encyclopedia of Genes and Genomics; PPI, The protein-protein interaction; STRING, Search Tool for the Retrieval of Interacting Genes; BP, biological process; MF, molecular function; CC, cellular component; GFR, glomerular filtration rate. MCC, Maximal Clique Centrality.

## Declarations

**1)** ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

***2)*** ***Ethical approval and consent to participants***

Not applicable.

**3)** ***Disclosure of conflict of interests***

We declare that no conflict of interest exists.

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***5)*** ***Availability of data and material***

We declare that the data supporting the results reported in the article are available in the published article.

***6)*** ***Authors' Contributions***

BW designed and managed the whole study. MW wrote the manuscript and completed all figures and tables. XRZ, NZ, LP, JM, LH and YY helped to revise the manuscript. All the authors have read and approved the final manuscript

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