Bioinformatic analysis of immune-related transcriptome affected by *IFIT1* gene in childhood systemic lupus erythematosus

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Background: The interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) gene is strongly associated with disease activity index of childhood systemic lupus erythematosus (SLE). However, whether *IFIT1*-regulated gene expression is the molecular basis of the pathogenesis of SLE has not been fully investigated.

Methods: Dataset GSE11909 was used to analyze the expression profiles of *IFIT1* gene in 103 SLE cases and 12 healthy individuals. Differentially expressed genes (DEGs)-affected by *IFIT1* gene were screened between the case group and control group, followed by gene function analysis. The clinical diagnostic potential of the least absolute shrinkage and selection operator (LASSO) model, established based on the expression profiles of *IFIT1* and *IFIFT1*-affected DEGs, was evaluated. Analysis of association between *IFIFT1*-affected DEGs and immune infiltration was performed.

Results: *IFIT1* was highly expressed in childhood SLE patients. *IFIT1* and *IFIT1*-affected DEGs showed the potential to serve as a diagnostic marker for childhood SLE with area under the curve (AUC) value of 0.947. Childhood SLE patients showed 826 upregulated DEGs and 4,111 downregulated DEGs compared to the control group. Among them, 208 upregulated DEGs and 214 downregulated DEGs were identified in the *IFIT1*-high group compared to the *IFIT1*-low group. The LASSO model for the diagnosis of childhood SLE involved 7 marker genes that were related to immune checkpoint and tertiary lymphoid structure in SLE.

Conclusions: Our results confirmed the clinical diagnostic potential of *IFIT1* and *IFIT1*-affected genes in childhood SLE. Moreover, this study elucidated that *IFIT1*-induced changes in the transcriptome are involved in immune checkpoint and tertiary lymphoid structure in childhood.

Keywords: Childhood systemic lupus erythematosus; interferon-induced protein with tetratricopeptide repeats 1 (IFIT1); immune infiltration; tertiary lymphoid structure

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Introduction

Systemic lupus erythematosus (SLE) is defined as a chronic multisystem autoimmune/inflammatory disease presenting heterogeneous clinical features ranging from mild cutaneous symptoms to multiple organ failure (1,2). Childhood SLE shows great disease activity, a high incidence of irreversible organ lesions, and a more aggressive clinical course, which may be profoundly due to infection and disease recurrence (3-6). This autoimmune disease is characterized by abnormal inflammatory responses due to genetic, epigenetic, immunoregulatory, ethnic, hormonal, and environmental factors (7-11). Immunological abnormalities are increasingly implicated in the pathogenesis of SLE (12,13). Researchers have identified that a subset of immune cells is associated with the development of SLE, including T helper (Th)17 memory cells, naïve CD4+ T cells, B cells, macrophages, and neutrophils (14-18).

The pathophysiology of SLE includes environmental factors that trigger the activation of the innate and adaptive immune systems (19). It has been reported that SLE may be related to type I interferon-induced hypomethylation in naïve CD4+ T cells, suggesting a genetic mechanism for type I interferon hyperresponsiveness in lupus T cells (20). In SLE, type I interferon is a primary pathogenic cause, and high systemic type I interferon activity results in a propensity for severe manifestations such as lupus nephritis (21). Recent evidence has well established the association between high type I interferon activity and clinical manifestations of lupus nephritis and specific autoantibodies, including anti-ribonucleoprotein, anti-Ro,

anti-Sm, and anti-double-stranded antibodies (22,23). To diminish chronic inflammation and end-organ injuries, type I interferon has been described as a potential target (24).

Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) is an antiviral protein that recognizes 5'-triphosphate RNA of microbial structures during the process of antiviral innate immunity (25). Viral infection enhances the specific abundance of the IFIT1 protein, which is antagonized by the IFIT complex through sequestering specific viral nucleic acids (25). Interferon-induced *IFIT1* is strongly expressed in cutaneous lupus erythematosus skin (26). Furthermore, the interferon-related immune pathway involving *IFIT1* has been related to the pathogenesis of SLE (27). The *IFIT1* gene may play roles in SLE by inducing the activation of Rho protein by interacting with Rho/Rac guanine nucleotide exchange factor (28). The *IFIT1* gene is described as a potential candidate target of SLE for therapeutic intervention (28). However, the expression profile of *IFIT1* gene has not been investigated in childhood SLE.

Compared to adult SLE, there is a great challenge to manage childhood SLE. It is needed to delineate *IFIT1*-mediated immunopathogenesis, which may provide new insights to the diagnostic therapy. Here, this study aimed to investigate the diagnostic potential of *IFIT1* and differentially expressed genes (DEGs) affected by *IFIT1* in childhood SLE. Particularly, it is unclear whether *IFIT1* mediates immune cell infiltration. The current study then assessed immune cell infiltration, immune checkpoints and tertiary lymphoid structures in childhood SLE. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-365/rc).

Highlight box

Key findings
- *IFIT1*-affected transcriptome is involved in immune cell infiltration and tertiary lymphoid structure formation in childhood SLE.

What is known and what is new?
- The interferon-related immune pathway involving *IFIT1* gene is associated with the pathogenesis of SLE.
- *IFIT1* gene changes the transcriptional features, which affects immune cell infiltration and tertiary lymphoid structure formation in child SLE.

What is the implication, and what should change now?
- This study provides a comprehensive overview of *IFIT1*-regulated genes in childhood SLE, and functional annotation requires experimental validation.

Methods

Data collection and normalization

Dataset GSE11909 (Platform: GPL96) was downloaded from the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/gds). The dataset provides the transcriptional profiles of peripheral blood mononuclear cells (PBMCs) from 103 cases and 12 healthy individuals. The clinical and demographic information has been listed in the study of Chaussabel *et al.* (29). Data normalization was performed using the R package "Limma". The study was conducted in accordance with the Declaration of Helsinki (as

revised in 2013).

Principal component analysis and IFIT1 expression analysis

Principal component analysis (PCA) was implemented using the R packages "FactoMineR" and "FactoExtra". PCA plots were computed, and the *IFIT1* expression level was presented. The transcription level of the *IFIT1* gene is shown in the violin plot using the function ViolinPlot from the R package.

Receiver operating characteristics (ROC) analysis of the diagnostic potential of the IFIT1 gene

The ROC curve is commonly used in clinical settings to assess the performance of classifiers. In the case of an area under the curve (AUC) >0.5, the closer the AUC is to 1, the better the diagnosis. The ROC assessment has low accuracy when the AUC is between 0.5 and 0.7, some accuracy when the AUC is between 0.7 and 0.9, and high accuracy when the AUC is above 0.9. Here, ROC analysis was performed to differentiate between *IFIT1*-high and -low subjects. The diagnostic performance of *IFIT1* gene expression for SLE was analyzed by calculating AUC. The ROCs were plotted using the R package "pROC".

Analysis of differentially expressed genes (DEGs) between the case and control groups

To screen the DEGs between the case and control groups, the R packages "Limma" and "DESeq2" were used to analyze gene expression data. The cutoff criteria were log2(fold change) more than 1 and corrected P values less than 0.05. Childhood SLE patients were grouped into two groups: higher-than-median (high group) and low-than-median (low group) *IFIT1* gene expression groups. DEGs between the high group and low group were identified with log2(fold change) more than 1 and corrected P values less than 0.01. A Venn diagram was plotted using the R package "VennDiagram". The distribution of *IFIT1*-affected dysregulated DEGs was presented using a 4-quadrant plot, and the expression profile was illustrated using a heatmap. Functional analysis of *IFIT1*-affected dysregulated DEGs, including biological process (BP) and Kyoto Encyclopedia of genes and genomes (KEGG) pathway analyses, was

performed using the R package "clusterprofiler".

IFIT1-based least absolute shrinkage and selection operator (LASSO) model

The R package "LASSO" was used to select the effective marker genes (AUC >0.85) for diagnosis from the gene set of *IFIT1*-affected dysregulated DEGs. Regression coefficients were narrowed toward zero. The optimal lambda was selected according to the minimum cross-validation error in 10-fold cross-validation. The expression profile of the selected marker genes was presented in the box plot using the R package "ggplot2". The semantic similarity among gene ontology terms and marker genes was measured using the R package "GOSemSim".

Immune infiltration analysis

Analysis of immune infiltration was performed using the R package "CIBERSORT". Immune cell infiltration was analyzed by machine learning and deconvolution algorithms to assess the relationship between gene expression and immune cell infiltration. The infiltration abundance of immune cells was plotted using the R package heatmap. The R package PlotCor was used to plot correlation scatter plots, which aimed to indicate the correlation between the abundance of infiltrating immune cells and *IFIT1* expression.

Results

mRNA expression of IFIT1 gene in children with SLE

PCA was performed to reduce dimensionality, compress data, extract feature data, and visualize the distribution of the subjects. *Figure 1A* shows that the transcriptome data were able to stratify childhood patients with SLE. The childhood patients with SLE showed high mRNA levels of the *IFIT1* gene compared to the controls. The violin plot also showed higher mRNA levels of the *IFIT1* gene in the case group than in the control group (*Figure 1B*). Considering the high expression of the *IFIT1* gene in childhood patients with SLE, we estimated the predictive performance of the *IFIT1* gene. *Figure 1C* indicates that *IFIT1* showed the potential to serve as a marker for childhood SLE, which was evidenced by the results from
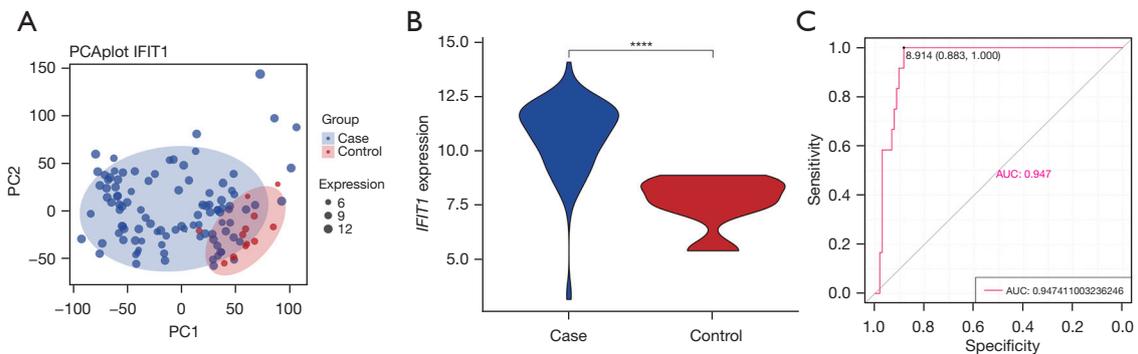
Figure 1 PCA and *IFIT1* transcription analysis for the enrolled subjects. (A) PCA for 103 cases and 12 healthy individuals based on the transcriptome data; (B) Comparison of relative mRNA expression of the *IFIT1* gene between SLE patients and healthy participants (****, P<0.0001); (C) ROC analysis of the diagnostic performance of the *IFIT1* gene for childhood SLE patients. PCA, principal component analysis; *IFIT1*, interferon-induced protein with tetratricopeptide repeats 1; ROC, receiver operating characteristics; SLE, systemic lupus erythematosus.
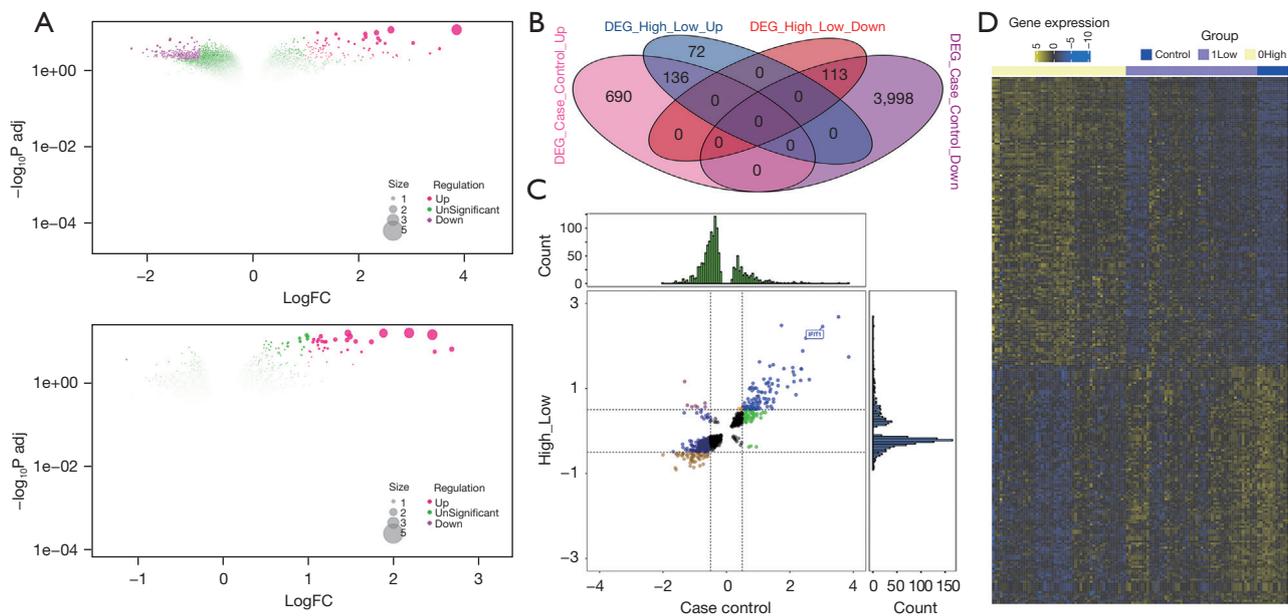

Figure 2 Analysis of DEGs between childhood SLE patients and healthy individuals. (A) DEGs between the case and control groups (up) or between the high group and low group (down); (B) Venn diagram presenting the intersections among the groups; (C) *IFIT1*-affected dysregulated DEGs in childhood SLE; (D) Heatmap demonstrating the mRNA expression profile of *IFIT1*-affected dysregulated genes and group clustering. FC, fold change; DEGs, differentially expressed genes; SLE, systemic lupus erythematosus; *IFIT1*, interferon-induced protein with tetratricopeptide repeats 1.

the ROC curve with an AUC value of 0.947.

DEGs in childhood SLE patients compared to healthy individuals

In this study, we obtained 826 upregulated DEGs and 4,111

downregulated DEGs in the case group compared to the control group (*Figure 2A* up). A total of 208 upregulated DEGs and 214 downregulated DEGs were identified in the high group compared to the low group (*Figure 2A* down). The Venn diagram shows the intersections of DEGs (*Figure 2B*). A total of 249 genes were recognized as DEGs
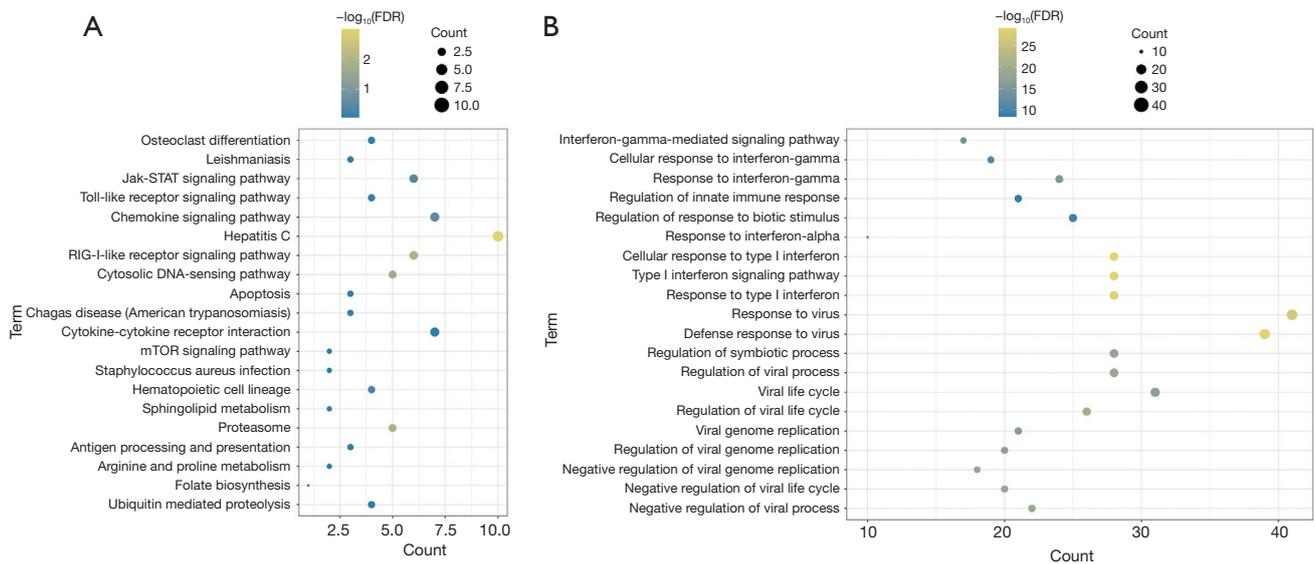
Figure 3 Functional analysis of *IFIT1*-affected dysregulated DEGs. (A) Biological processes and (B) KEGG pathways mediated by *IFIT1*-affected dysregulated DEGs. *IFIT1*, interferon-induced protein with tetratricopeptide repeats 1; DEGs, differentially expressed genes; KEGG, Kyoto Encyclopedia of Genes and Genomes.

among the 4 groups. Here, we defined the 249 DEGs as the dysregulated genes affected by *IFIT1*. Next, *IFIT1*-affected dysregulated DEGs were classified based on the expression level of the *IFIT1* gene. *Figure 2C* shows that the intersections of upregulated DEGs between the case and high groups were defined as the positive-functional genes, as well as the intersections of downregulated DEGs in the case group and upregulated DEGs in the high group. The negative-functional genes were the intersections of downregulated DEGs between the case and high groups, as well as the intersections of upregulated DEGs in the case group and downregulated genes in the high group. *Figure 2D* indicates the mRNA expression signature of *IFIT1*-affected dysregulated DEGs. These *IFIT1*-affected dysregulated DEGs were involved in regulating the defense response to virus, type I interferon signaling pathway, and cellular response to type I interferon (*Figure 3A*) and mediating signaling pathways related to hepatitis C, proteasome, and RIG-I-like receptor (*Figure 3B*).

Clinical diagnostic potential of the LASSO model

LASSO regression is a common data mining method in machine learning. LASSO performs variable screening and complexity adjustment while fitting a generalized linear model, which can better solve the problem of

multicollinearity in regression analysis. Marker genes were selected from the *IFIT1*-affected dysregulated DEGs (AUC value >0.85). As a result, 7 marker genes were obtained, including *IFIT1*, *LGALS9*, *RPS10L*, *RP3-334F4.1*, *IFI44*, *RP6-11O7.2*, and *RPL7P52*. Lambda plots are shown in *Figure 4A*, demonstrating the predictive performance of the model. The LASSO model plot is shown in *Figure 4B*, which indicates the confidence level of the model under the corresponding log(lambda). The ROC curves of the LASSO model are shown in *Figure 4C*, suggesting that the *IFIT1*-based model showed good diagnostic efficacy for childhood SLE patients (AUC value =0.9950). In addition, the diagnostic efficacy was further proven (AUC value =0.9474), as shown in *Figure 4D*. Box plots were drawn to demonstrate the transcriptional profile of marker genes. *Figure 4E* indicates that *IFI44* mRNA was highly expressed in the case group compared to the control group. The semantic similarity among gene ontology terms and marker genes was analyzed. *Figure 4F* shows that *IFI44*, *IFIT1*, and *LGALS9* were significantly associated with biological processes of SLE.

Immune cell infiltration was affected by IFIT1

A large number of immune cells are present in the microenvironment of different diseases, including

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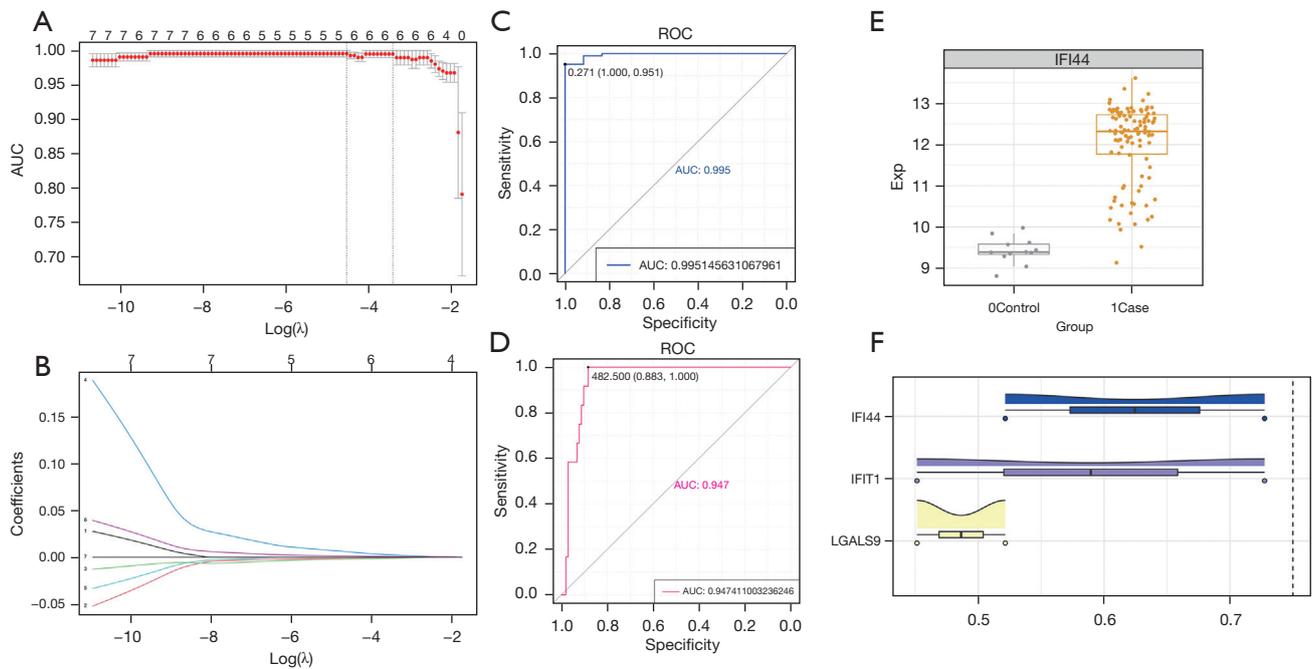
Figure 4 LASSO Cox regression analysis. (A) Tuning parameter selection in the LASSO model based on ten-time cross validation; (B) LASSO coefficient of the 7 *IFIT1*-affected dysregulated DEGs; (C) ROC curves showing the diagnostic accuracy of the 7 genes (AUC value =0.9951); (D) the diagnostic efficacy of *IFIT1*-based model; (E) box plot indicating increased mRNA level of *IFI44* in the case group compared to the control group; (F) the semantic similarity among gene ontology terms and marker genes was indicated by the semantic similarity scores (x-axis). LASSO, least absolute shrinkage selection operator; *IFIT1*, interferon-induced protein with tetratricopeptide repeats 1; ROC, receiver operating characteristics; AUC, area under the curve; *IFI44*, interferon induced protein 44.

lymphocytes, dendritic cells, monocytes/macrophages, granulocytes, and mastocytes. Immune cells play an important role in the development of SLE. *Figure 5A* suggests that the level of immune cell infiltration was low in *IFIT1* high expression samples. *Figure 5B* shows that *IFIT1* expression was significantly and positively correlated with the infiltration abundance of cells such as activated mast cells. The results in *Figure 5C* show that the marker genes of the *IFIT1*-based model were significantly related to immune cell abundance. Immune checkpoints are a set of molecules expressed on immune cells that regulate the degree of immune activation. *Figure 5D* shows that *IFIT1*-based model genes were significantly correlated with some immune checkpoint-related genes and tertiary lymphoid structural marker genes.

Discussion

SLE is a complex and multifactorial disease that manifests as significant immunological abnormalities (1,2). Its etiologies

may be related to hormonal, genetic and environmental factors (30). *IFIT1* was identified as an interferon-induced gene that plays roles in SLE by interacting with Rho/Rac guanine nucleotide exchange factor (28). In the current study, we revealed that *IFIT1* altered the transcriptional signatures in childhood SLE. *IFIT1*-affected genes were related to immune cell infiltration, immune checkpoints, and tertiary lymphoid structure formation.

As an interferon-induced gene, the expression profile of the *IFIT1* gene has been related to the diverse immune phenotype of SLE, and the *IFIT1* gene was overexpressed in SLE patients (28). It has been reported that *IFIT* genes may be involved in immune microenvironment of cardiovascular disease (31). However, the exact mechanisms have not been reported. The expression level of *IFIT1* in childhood SLE remains uninvestigated. Our results consistently showed that *IFIT1* mRNA expression was higher in childhood SLE patients than in controls. Additionally, Mähönen *et al.* found that *IFIT1* and *IFIT2* were strongly upregulated in keratinocytes in cutaneous lupus erythematosus (26). A
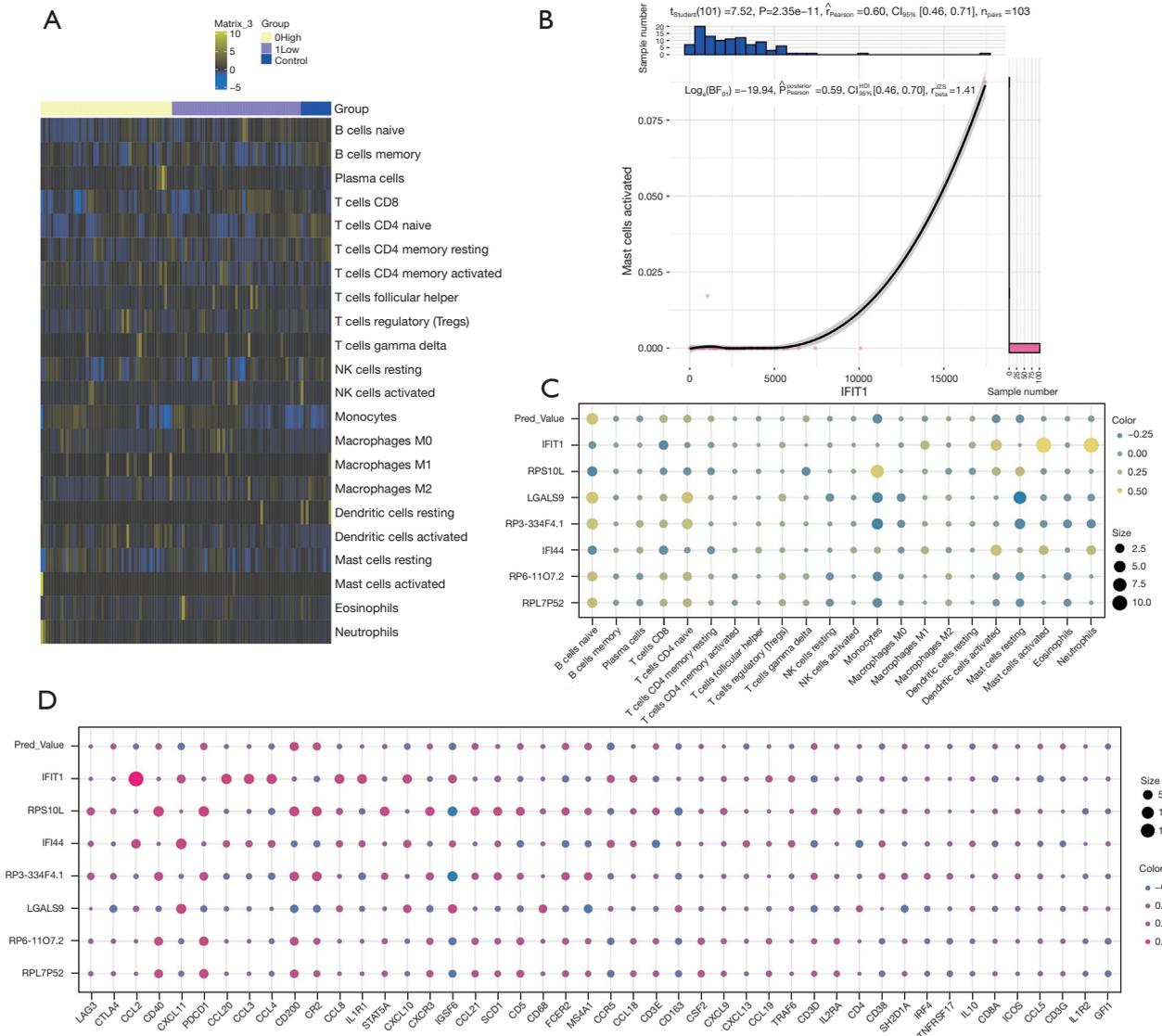
Figure 5 Analysis of immune cell infiltration in childhood SLE. (A) Heatmap suggesting the abundance of immune cell populations; (B) Scatter plot showing the correlation between the abundance of immune cell infiltration and *IFIT1* expression; (C) Bubble plots suggesting the correlation of the predictive marker genes and immune cell infiltration abundance; (D) Bubble plots demonstrating the correlation of predictive marker genes and immune genes related to checkpoint and tertiary lymphoid structure signatures. SLE, systemic lupus erythematosus; IFIT1, interferon-induced protein with tetratricopeptide repeats 1.

study pointed out that the expression level of the *IFIT1* gene may be positively correlated with the SLE activity index (32). *IFIT1* overexpression was considered to be related to renal affection of SLE patients, which appears to be the molecular basis for the diverse immune phenotype of SLE (32). Considering the high expression of the *IFIT1* gene in SLE, we assessed the diagnostic potential of *IFIT1* for SLE patients. ROC analysis further confirmed the diagnostic

performance of *IFIT1* for childhood SLE patients. These results indicated that *IFIT1* could be detected for the diagnosis of childhood SLE.

RNA sequencing data uncovered the distinct transcriptome architectures of SLE and showed specific marker genes related to autoimmunity (33,34). Next, we studied whether *IFIT1* is implicated in the regulation of the transcriptome in patients with SLE. Compared to

healthy individuals, 249 DEGs were defined as dysregulated genes affected by *IFIT1*. Functional analysis showed the enrichment of biological processes for the 249 DEGs, including defense response to virus, type I interferon signaling pathway, cellular response to type I interferon, and mediating signaling pathways related to hepatitis C, proteasome, RIG-I-like receptor. Type I interferon is a primary pathogenic factor of SLE, and a high level of type I interferon may result in the activation of immature myeloid dendritic cells, autoreactive T cells, B cells and cytotoxic CD8+ T cells (35). Its increase in circulation contributes to the presence of lupus nephritis, arthritis, mucocutaneous, and autoantibodies (23). Hence, we speculated that *IFIT1* may participate in mediating inflammation in SLE through affecting immune gene expression and immune cell composition.

Among these 249 DEGs, 7 marker genes showed predictive potential for childhood systemic lupus erythematosus, including *IFIT1*, *LGALS9*, *RPS10L*, *RP3-334F4.1*, *IFI44*, *RP6-11O7.2*, and *RPL7P52*. The 7 marker genes were strongly related to immune cell infiltration, which has been consistently reported in previous studies (36-39). *IFIT1* was correlated with CD8 T cells, activated mast cells and neutrophils. *LGALS9* was related to naïve B cells and monocytes. *RPS10L* was predicted to be linked to naïve B cells, naïve CD4 T cells, and resting mast cells. *RP3-334F4.1* may be associated with naïve B cells, naïve CD T cells, monocytes, and resting mast cells. *IFI44* was correlated with naïve B cells, CD8 T cells, and activated dendritic cells. *RP6-11O7.2* may mediate the function of naïve B cells, naïve CD4 T cells, and monocytes. *RPL7P52* may be involved in the cellular function of naïve B cells, naïve CD4 T cells, and monocytes. In particular, the 7 marker genes were significantly correlated with a number of immune checkpoint-related genes and tertiary lymphoid structural marker genes, such as *CCL* (40), *IGSF* (41), and *CXCL* (42). For example, *IFIT1* was positively related to *CCL2*, *CCL20*, *CCL3*, *CCL4*, *CCL8*, and *IL1R1*. *RP6-11O7.2* and *CD40* were positively related to *PDCD1*. These findings suggested that *IFIT1* could be targeted to relieve inflammation in childhood SLE.

However, our study still showed limitations in some aspects, such as participants should be enrolled for the validation of the prediction model. Besides, the predictive genes or genes-related to childhood SLE should be experimentally confirmed, and their biological or clinical functions should be further studied. These mentioned limitations will be our future study focus.

Conclusions

This comprehensive study provides a detailed comparative overview of the DEGs regulated by *IFIT1* in childhood SLE. Functional annotation revealed the important roles of these genes in mediating the defense response to virus, type I interferon signaling pathway, cellular response to type I interferon, and regulating signaling pathways related to hepatitis C, proteasome, RIG-I-like receptor. The identified predictive genes (*IFIT1*, *RPS10L*, *IFI44*, *RP3-334F4.1*, *IGALS9* and *RP6-11O7.2*) might be responsible for the distribution landscape of immune cell infiltration. There were obvious correlations between the 7 marker genes and immune checkpoint genes, as well as signature genes related to tertiary lymphoid structure formation in childhood SLE.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-365/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-365/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-365/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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