Peer Review File

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Reviewer A

1) First of all, my major concern for this study is the unclear and questionable focus of this study, the diagnostic accuracy of IFIT1 for SLE or its prognostic role in SLE. In different places of the paper, the authors described both but the two focuses are contradictory.

Reply 1: This inaccuracy description has been revised (see page 4, line 129).

Changes in the text: Here, this study aimed to investigate the diagnostic potential of *IFIT1* and differentially expressed genes (DEGs) affected by *IFIT1* in childhood SLE.

2) Second, the title did not indicate the research design of this study such as a bioinformatics analysis.

Reply 2: The tilte has been revised as "Bioinformatic analysis of immune-related transcriptome affected by IFIT1 gene in childhood systemic lupus erythematosus".

3) Third, the abstract needs some revisions. The background did not clearly indicate the research question to be answered and what the clinical significance of this focus is. In the methods, the authors need to describe the clinical and prognosis outcome data in the databases, and the research procedures and the questions to be answered by them, not the analytic procedures. The conclusion needs some comments for the implications of the findings.

Reply 3: The abstract has been revised.

4) Fourth, in the introduction of the main text, the authors need to review what has been known on the pathophysiological mechanisms of SLE and explain in pediatric patients why IFIT1 deserved to be studied. Please further clarify the questions to be answered by this study, i.e., the prognostic role or diagnostic role, and why there is a need to focus on this.

Reply 4: The introduction has been revised.

"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."

5) Fifth, in the methodology of the main text, please accurately describe the research design and the clinical data and samples in the datasets used. The small sample of 12 healthy individuals seems not able to answer the research questions in a reliable way. For the ROC analysis, the authors need to explain why there is a need to focus on the diagnostic value of IFIT1. Is the diagnosis of SLE a clinical concern and is the IFIT1 a convenient and costly diagnostic marker?

Reply 5: The research design and the clinical data and samples in the datasets used have been described (see page 5, line 138-144).

Changes in the text: *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 Chaussable et al. (27). 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".*

The need to focus on the diagnostic value of IFIT1 has been described in the Introduction (see page 4, line 111-122).

Changes in the text: *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 (23). Viral infection enhances the specific abundance of the IFIT1 protein, which is antagonized by the IFIT complex through sequestering specific viral nucleic acids (23). Interferon-induced IFIT1 is strongly expressed in cutaneous lupus erythematosus skin (24). Furthermore, the interferon-related immune pathway involving IFIT1 has been related to the pathogenesis of SLE (25). The IFIT1 gene may play roles in SLE by inducing the activation of Rho protein by interacting with Rho/Rac guanine nucleotide exchange factor (26). The IFIT1 gene is described as a potential candidate target of SLE for therapeutic intervention (26).* However, the expression profile of *IFIT1* gene has not been investigated in childhood SLE.

Finally, please consider to review and cite some related papers: 1. Huang Y, Yang DD, Li XY, Fang DL, Zhou WJ. ZBP1 is a significant pyroptosis regulator for systemic lupus erythematosus. Ann Transl Med 2021;9(24):1773. doi: 10.21037/atm-21-6193. 2. Zhan Y, Cheng L, Wu B, Ji L, Chen P, Li F, Cao J, Ke Y, Yuan L, Min Z, Sun L, Chen H, Hua F, Cheng Y. Interleukin (IL)-1 family cytokines could differentiate primary immune thrombocytopenia from systemic lupus erythematosus-associated thrombocytopenia. Ann Transl Med 2021;9(3):222. doi: 10.21037/atm-20-4729.

Reply: The references have been cited in this manuscript.

Reviewer B

The paper titled "Interferon-induced tetratricopeptide repeat 1 mediates immune-related transcriptomic changes in childhood systemic lupus erythematosus" is interesting. IFIT1-induced changes in the transcriptome in childhood SLE are involved in immune infiltration and tertiary lymphoid structure. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply 1: The abstract has been revised.

2) Some fonts need to be enlarged, as shown in Figures 2 and 3.

Reply 2: The figures have been revised.

3) The transcriptomics data is still premature without in-depth analysis and the authors' own perspective. Please supplement in the discussion.

Reply 3: It has been revised in the manuscript.

Changes in the text:

(see page 9, line 273-275): 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.

(see page 9, line 285-286): These results indicated that *IFIT1* could be detected for the diagnosis of childhood SLE.

(see page 9-10, line 300-302): Hence, we speculated that *IFIT1* may participate in mediating inflammation in SLE through affecting immune gene expression and immune cell composition.

4) What are your future work plans? What is the guiding significance of this study?

Reply 4: Our study still showed limitations in some aspects (see page 10, line 322-326).

Changes in the text: 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.

5) There are many genes that regulate childhood systemic lupus erythematosus. Why did the author choose IFIT1 for research? Please describe the reason.

Reply 5:It has been described in the Introduction (see page 4, line 111-122).

Changes in the text:

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.

6) What is the correlation between IFIT1 and the immune microenvironment? What are the possible goals of future drug development? It is recommended to add relevant content to the discussion.

Reply 6: "*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."* Our findings suggested that *IFIT1* could be targeted to relieve inflammation in childhood SLE. The description has been added in the manuscript.

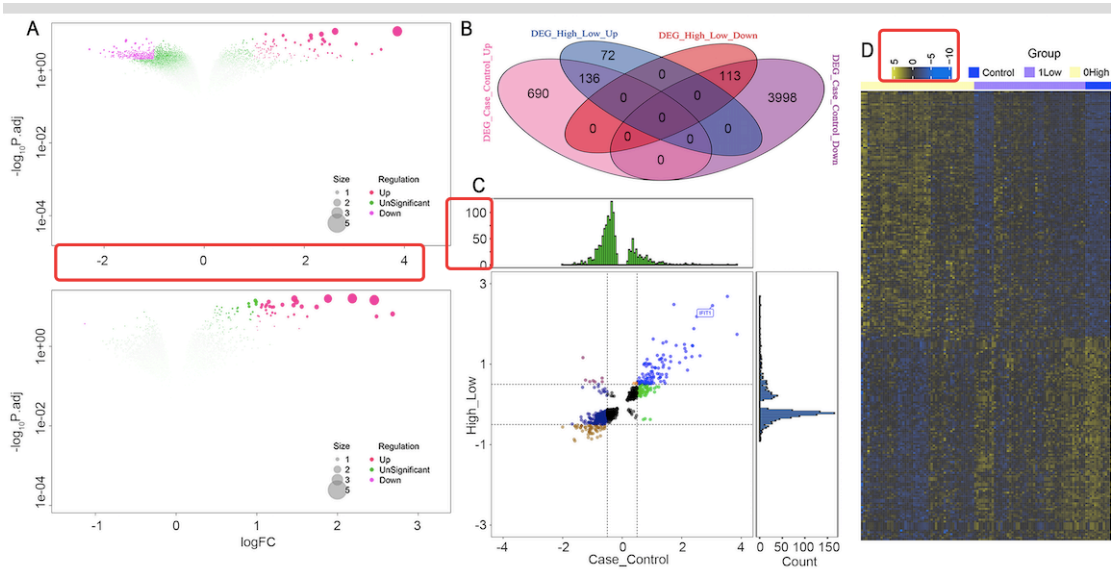
7) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Interleukin (IL)-1 family cytokines could differentiate primary immune thrombocytopenia from systemic lupus erythematosus-associated thrombocytopenia, J Thorac Dis, PMID:33209364”. It is recommended to quote the article.
Reply 7: It has been quoted.

8) It is recommended to add in vivo experiments to study the biological function of IFIT1.
Reply 8: Thanks for your suggestion. It is our next work, which will be implemented in our future study.

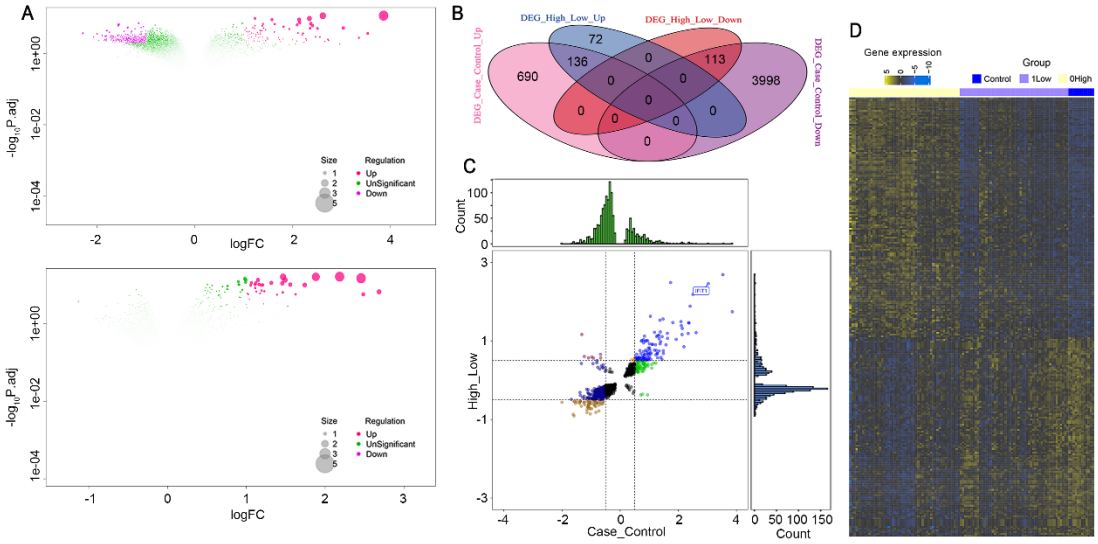
Reviewer C

1. Figure 1
Please explain the meaning of “****” in the legend.
Reply: It has been revised in the manuscript as ****P<0.0001.

2. Figure 2
Please provide the descriptions for the below three places (red boxes).

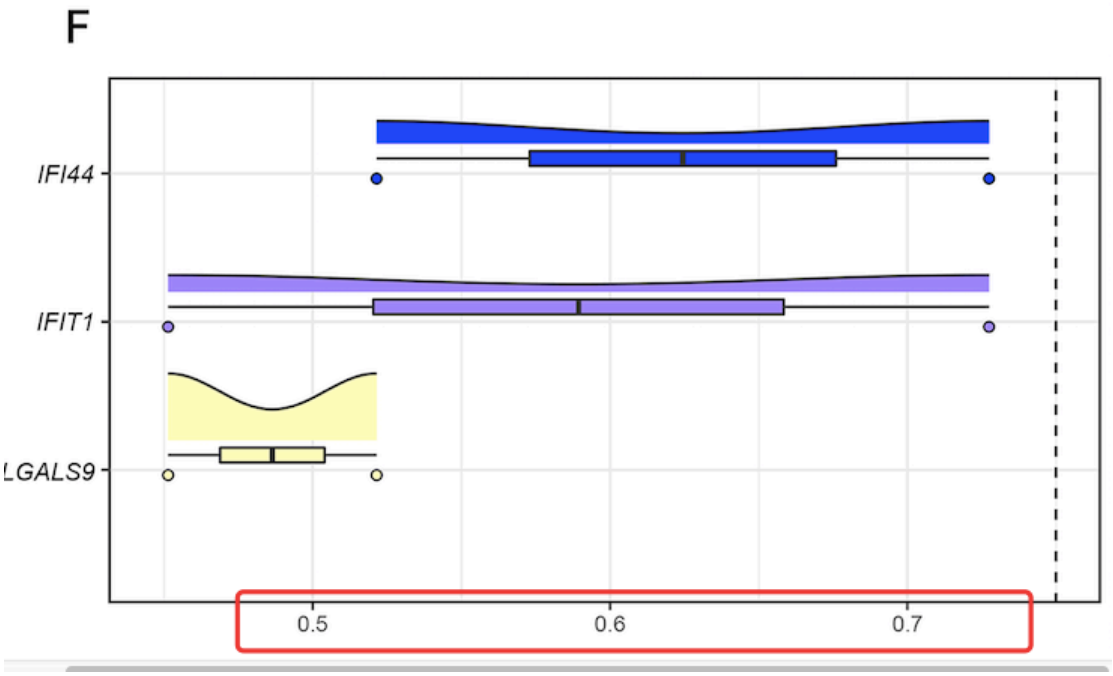


Reply: It has been marked in Figure 2.



3. Figure 4F

Please provide the descriptions of the x-axis.



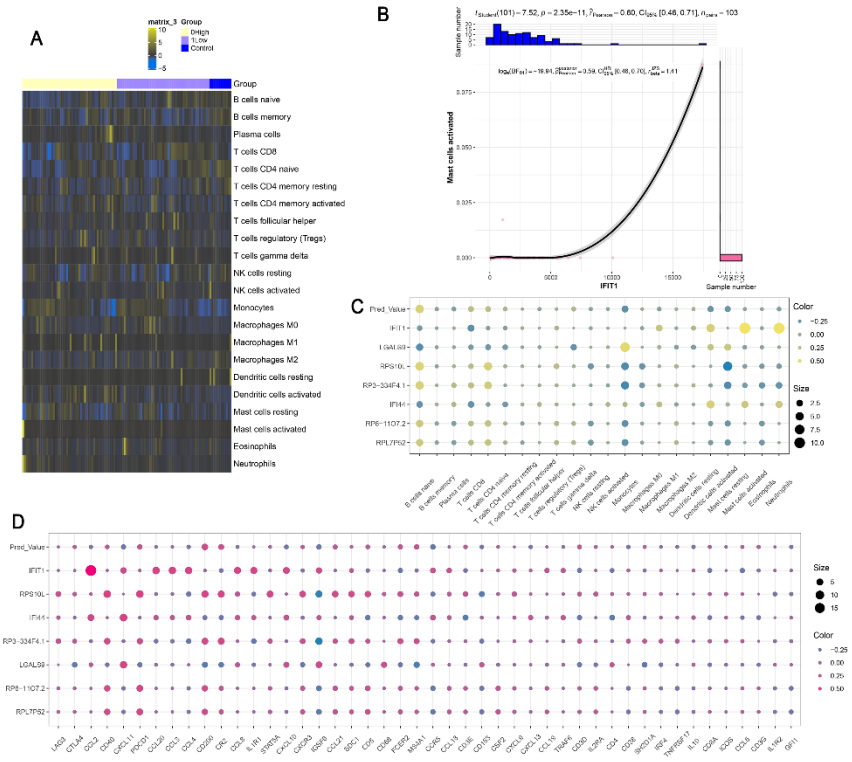
Reply: It has been revised in the text as: (F) the semantic similarity among gene ontology terms and marker genes was indicated by the semantic similarity scores (x-axis).

4. Figure 5B

1) The data are covered. Please revise.

2) Please provide the descriptions for it.

Reply: It has been re-marked in figure 5B.



5. The information of Ref. 29 in the main text differed from the information in the reference list. Please revise.

Main text:

The clinical and demographic information has been listed in the study of Chaussable et al. (29)

Ref list:

29. Chaussabel D, Quinn C, Shen J, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. Immunity 2008;29:150-64.

Reply: Confirmed.