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Bioinformatics Analysis Identifying Key Genes and Signaling Pathways Involved in the Egg Allergy in Young Children: a Retrospective Study

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ABSTRACT

Objective: Identify key genes and signaling pathways involved in IgE-mediated food allergy in young children using bioinformatics analysis.

Methods: The GSE114065 dataset from GEO was utilized for bioinformatic analysis. DEGs were identified using the GEO2R web tool. GO, KEGG, and Reactome functional analyses were performed using the Enrichr platform. The PPI network for DEGs was constructed with the STRING website and visualized in Cytoscape. The cytoHubba plugin was used to identify hub genes. Nonparametric Mann-Whitney test was employed to compare groups.

Results: Of the 490 DEGs identified, 402 were upregulated and 88 were downregulated. Dowregulated DEGs showed no significant enrichment in biological processes or molecular functions but were associated with Golgi apparatus-related cellular components. In contrast, upregulated DEGs exhibited pronounced enrichment in biological processes linked to antiviral defense, immune regulation, and IL-27 signaling, alongside extracellular matrix-related cellular components. Molecular functions included cytokine activity, receptor ligand binding. KEGG and Reactome analyses highlighted significant pathways involved in cytokine signaling, immune response, and antiviral defense. 10 DEGs were identified as hub genes, including USP18, OAS3, IFIH1, MX1, DDX58, OAS1, IFIT2, OAS2, IFI35, and IFIT3.

Conclusion: The results demonstrate that the aberrant activation of genes related to the interferon response and antiviral defense plays a central role in the pathogenesis of IgE-mediated food allergy. The 10 identified hub genes are key regulators of innate immunity, significantly influencing inflammatory and antiviral pathways. Our findings suggest that the upregulation of these genes contributes to the immune imbalance characteristic of food allergy, opening new avenues for understanding disease mechanisms and identifying innovative diagnostic and therapeutic targets.

Keywords: bioinformatics analysis, food allergies, hub genes, young children.

Introduction

IgE-mediated food allergy in children is a substantial clinical and social issue. In modern pediatrics, the prevalence of food allergy among young children is 6-8% and has continued to rise in recent decades [1]. IgE-mediated hypersensitivity is marked by the rapid onset of clinical symptoms, such as anaphylaxis, angioedema, and gastrointestinal disorders, which pose significant risks to patients' health and quality of life, as well as to their families [2].

Despite extensive research, the pathogenesis of IgE-mediated food allergy is still not fully understood [3].

Previous studies indicate an important role for both innate and adaptive immune responses [4]. Recent research highlights that changes in DNA methylation, histone modifications, and non-coding RNA, which together constitute epigenetic dysregulation, play a key role in the loss of immune tolerance in food allergy [5]. Conversely, epigenetic mechanisms may also help restore the disrupted immune balance in food allergy, acting as immunomodulatory factors in the disease's development [6].

The modern development of high-throughput technologies for gene expression analysis, along with the availability of extensive bioinformatics resources, offers unprecedented opportunities for in-depth study of the molecular mechanisms behind allergic diseases.

Databases like Gene Expression Omnibus are valuable tools for studying differentially expressed genes (DEGs) and associated signaling pathways. Analyzing high-quality expression arrays not only helps identify key target genes but also enables the construction of interactive protein-protein networks, which enhances a system-wide understanding of disease development. Research on food allergy in young children is especially important due to its rising prevalence and the unique features of the immune system during this stage.

Objective of the study: Identify key genes and signaling pathways involved in IgE-mediated food allergy in young children using bioinformatics analysis.

Methods

Collecting data from the GEO database

High-throughput sequencing data from food allergy-related mRNA expression profiles were collected and downloaded from the Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Information (NCBI).

The search query included the following terms: "Food allergy", "mRNA", "Children" and was filtered by organism "Homo sapiens". The dataset GSE114065, based on the Illumina HiSeq 4000 platform GPL20301 (Homo sapiens), was selected for analysis. The dataset comprises RNA-seq experiments performed on sorted naive CD4+ T cells isolated from peripheral blood of children with challenge-confirmed IgE-mediated egg allergy and non-allergic controls. Cells were profiled under two conditions, quiescent and polyclonal activation. In our study, the group of children with IgE-mediated egg allergy included 1-year-old children with an activated cell profile. Controls were non-atopic infants who tested negative to the panel of foods. The original study and GEO record provide cohort and activation protocol details [7].

Identification of differentially expressed genes (DEGs)

The GSE114065 dataset was thoroughly analyzed using the GEO2R web tool to identify DEGs. GEO2R, integrated with the GEO database, employs the R programming language to perform statistical analyses, including t-tests or analysis of variance (ANOVA), enabling comparisons between two or more experimental groups. Specifically, DEG identification in this study relied on the limma framework within GEO2R, which uses linear modeling with empirical Bayes moderation to perform moderated t-tests. The significance thresholds were set at $p<0.05$ and $|LogFC|\geq 1$, with p-values adjusted using the Benjamini-Hochberg method to control the false discovery rate. The results were visualized with various plots, such as volcano plots, UMAP, box plots, and Venn diagrams, using GEO2R.

Gene ontology analysis and pathway enrichment analysis

To gain a deeper understanding of the biological functions and molecular mechanisms behind the observed phenotypes, a comprehensive analysis of DEGs was conducted. Gene Ontology (GO) enrichment analysis provided a detailed characterization of the molecular functions, biological processes, and cellular components related to the identified DEGs. Additionally, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome pathway analyses were performed to identify key metabolic and signaling pathways involved in the processes being studied. All of these analyses were performed using the bioinformatics tool Enrichr. Benjamini–Hochberg correction was applied to account for multiple testing in pathway enrichment analyses, and pathways with an adjusted p-value < 0.05 were considered statistically significant.

Analysis of protein-protein interaction (PPI) networks and identification of hub genes

The online tool STRING was used to analyze known PPIs, including both direct and indirect interactions as well as their functional correlations. Interaction network was built using active interaction sources and a minimum required interaction score threshold of 0.4. In this study, 490 DEGs were analyzed, with 88 being dowregulated and 402 upregulated in the allergy group relative to the control group.

The data obtained were exported to Cytoscape software (version 3.10.3) for further visualization of PPI networks. The cytoHubba plugin was used to identify hub genes within the network. The analysis was conducted using the Maximal Clique Centrality (MCC) algorithm, which helped identify central nodes that play a key role in the biological processes under study.

Statistical analysis

IBM SPSS software (version 29.0) was used for statistical analysis. The statistical significance of differences in the expression level of hub genes between the study groups was assessed using the nonparametric Mann-Whitney test.

Results

Sample data information

To evaluate the distribution of data and identify differences between the food allergy and control groups, an analysis of 44 datasets from GEO2R was conducted. The control group included 18 participants, while the study group had 26 subjects. All participants in the study were 1 year old. The gender distribution was equal in both groups. Egg allergy was confirmed by a challenge test in infants within the study group.

Visual analysis of the box-and-whisker plots (Figure 1A) helped us evaluate how much the data deviated from a normal distribution. The UMAP technique was used to reduce the data's dimensionality and visualize its structure. The results from UMAP demonstrated that samples from the food allergy and control groups formed distinct clusters on the two-dimensional plot (Figure 1B), showing significant differences between these groups.

DEG analysis

During data analysis with GEO2R, 490 differentially expressed genes were identified using thresholds adjusted p (BH) < 0.05 and $|\log2FC| \geq 1$ out of a total of 17,628 genes analyzed (Figure 2A). Of these, 402 genes were upregulated and 88 were

downregulated in the allergy group relative to the control group. The volcano plot (Figure 2B) clearly shows the extent of gene expression changes and their statistical significance.

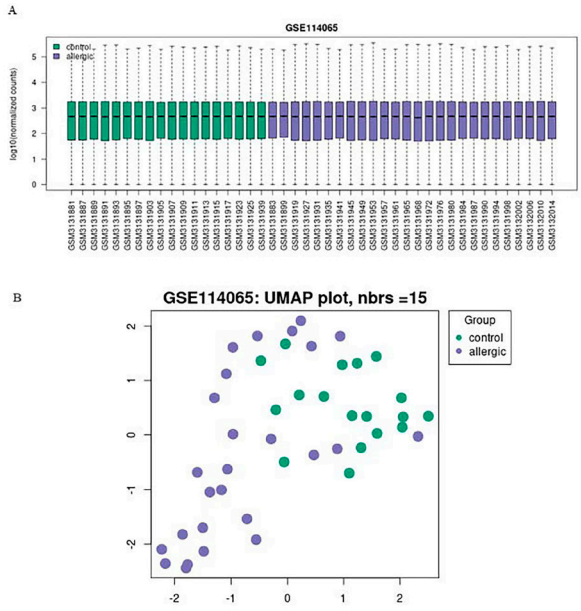

Figure 1 – Gene set evaluation

(A) A box plot with whiskers, where the horizontal axis shows the samples and the vertical axis demonstrates the log2-transformed gene expression values. (B) UMAP analysis was performed on two groups.

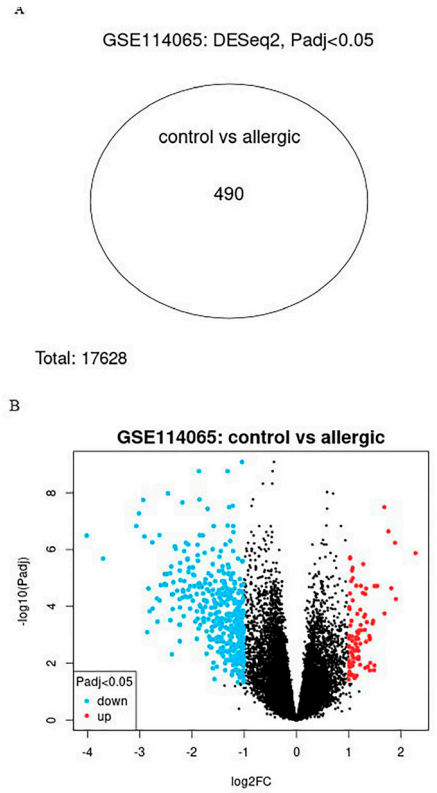

Figure 2 – Results of differential gene expression analysis

(A) A Venn diagram showing the number of differentially expressed genes. (B) A volcano plot of gene expression in two groups. The horizontal axis shows the log2FC (log2-fold change) values, and the vertical axis displays the -log10(adjusted p-value). Upregulated genes are shown in red, while downregulated genes are shown in blue. Genes that do not meet the significance criteria of p < 0.05 and |Log FC| ≥ 1 are shown in black.

Pathway enrichment analysis for up- and down-regulated DEGs

The analysis results showed that no statistically significant annotations were found for the downregulated DEGs in the categories of biological processes and molecular functions. However, in the cellular components category, four significant annotations were identified, all closely related to the Golgi apparatus. Nonetheless, the analysis of the KEGG and Reactome databases did not reveal any statistically significant signaling pathways passed the adjusted $p < 0.05$ cutoff for the downregulated DEG set.

Regarding the upregulated DEGs, the analysis identified 90 significant annotations in the biological processes category, including antiviral defense response, negative regulation of viral replication, and IL-27-mediated signaling pathway. In the cellular components category, one significant annotation related to the extracellular matrix was found. Additionally, the molecular functions were characterized by annotations related to cytokine activity, receptor ligands, and binding to single-stranded and double-stranded RNA (Figure 3). The KEGG database analysis revealed 25 significant pathways, such as cytokine-cytokine receptor interaction and extracellular matrix receptor interaction. The Reactome database analysis identified 18 significant pathways, including cytokine signaling in the immune response and interferon-alpha and beta signaling pathways. The top ten signaling pathways from the KEGG and Reactome databases are displayed in Figure 4 A and B, respectively.

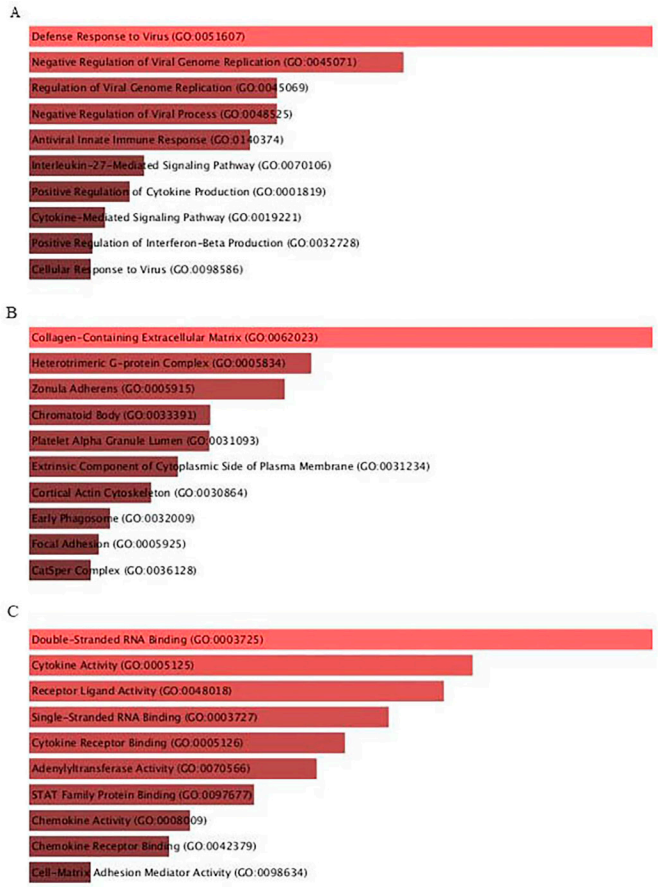

Figure 3 – Graphical illustration of GO ontology enrichment analysis for downregulated genes

(A) Biological Processes; (B) Cellular Components; (C) Molecular Functions

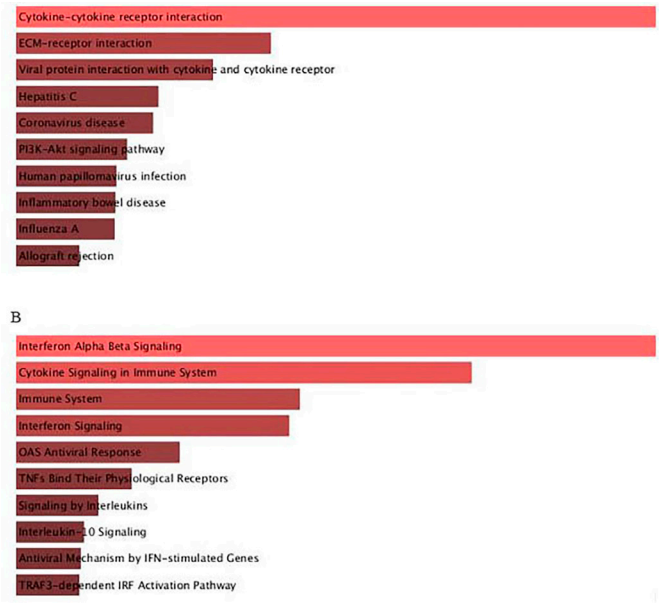

Figure 4 – Graphical illustration of KEGG and Reactome pathway analysis for downregulated genes

(A) The top 10 most significantly enriched KEGG pathways are shown. (B) The top 10 results for the Reactome pathway are shown.

PPI construction and identification of hub genes

To analyze the functional relationships among the 490 differentially expressed genes, a molecular interaction network was built using the STRING database. The network consisted of 275 nodes connected by 3928 edges (Figure 5A). Using the Maximal Clique Centrality (MCC) algorithm, 10 hub genes were identified that likely have central roles in the studied processes: USP18, OAS3, IFIH1, MX1, DDX58, OAS1, IFIT2, OAS2, IFI35, and IFIT3 (Figure 5 B). When comparing the expression levels of these genes between groups, all showed significant differences except for OAS2 (Table 1).

Table 1 Results of comparative analysis of gene expression levels in the study groups

Gene Symbol	log2(fold change)*	Group	Mean Rank	p-value
USP18	2.524	Control	15,28	0.003
		Allergy	26,84	
IFI35	1.474	Control	13,83	<0.0001
		Allergy	27,88	
IFIH1	1.419	Control	15,33	0.003
		Allergy	26,80	
IFIT2	2.128	Control	15,61	0.005
		Allergy	26,60	
IFIT3	2.835	Control	15,89	0.007
		Allergy	26,40	
MX1	2.33	Control	15,17	0.002
		Allergy	26,92	
DHX58/DDX58	1.63	Control	13,89	<0.0001
		Allergy	27,84	
OAS1	2.087	Control	14,83	0.001
		Allergy	27,16	
OAS2	1.484	Control	22,56	0.805
		Allergy	21,60	
OAS3	1.815	Control	14,67	0.001
		Allergy	27,28	

**Positive log2(fold change) values indicate higher expression in the Allergy group compared to the Control group*

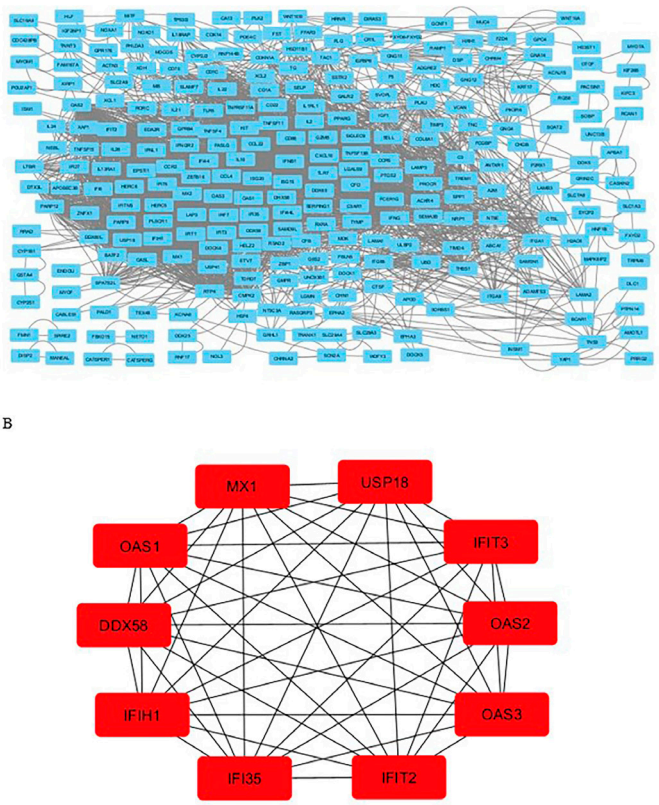

Figure 5 – PPI network analysis and hub genes identification

(A) Analysis of the PPI network using the STRING database. (B) The top 10 hub genes identified by the MCC ranking method.

Discussion

This study performed a comprehensive bioinformatics analysis to identify key genes and signaling pathways associated with IgE-mediated egg allergy in young children. Using the GSE114065 dataset from GEO, 490 differentially expressed genes were identified. Among these, 402 were upregulated and 88 were downregulated in the allergy group relative to the control group.

Genes upregulated in allergies exhibited the most pronounced functional enrichment. Ninety significant annotations were identified in the biological processes category, primarily related to antiviral defense, negative regulation of viral replication, and the IL-27 signaling pathway. This suggests significant modulation of the immune response and aberrant activation of innate immune mechanisms in food allergies. The enrichment of the IL-27 signaling pathway deserves special attention in the context of immune regulation. As a pleiotropic cytokine, IL-27 plays a critical role in maintaining the balance between Th1 and Th2 responses, and its activation may indicate an attempt by the system to limit excessive allergic inflammation [8]. Thus, the IL-27 pathway acts as an important control mechanism modulating the intensity of the immune response during food sensitization. At the molecular function level, these genes are associated with cytokine and receptor activity, as well as single- and double-stranded RNA binding. KEGG signaling pathway analysis identified 25 significant pathways, and Reactome analysis identified 18 significant pathways, confirming the dominant role of cytokine-receptor interactions, interferon-alpha and beta signaling pathways, and matrix interactions in disease pathogenesis. Our findings are consistent with broader molecular patterns observed across various food allergy phenotypes. For instance, integrated

transcriptomic and proteomic analyses in cow's milk protein allergy have highlighted significant enrichment in complement and coagulation cascades, immune activation, and cytokine-receptor interaction pathways, directly paralleling the interferon signaling signatures identified in our study [9]. Furthermore, multi-omics investigations integrating plasma proteomics with metabolomics have confirmed alterations in cytokine networks (including IL-4, IL-6, and IL-13 signaling), which aligns with our emphasis on immune regulation via the IL-27 and interferon pathways [10].

The identification of key genes such as USP18, OAS3, IFIH1, MX1, DDX58, OAS1, IFIT2, IFI35, and IFIT3 through protein-protein interaction network construction further confirms the critical role of the interferon response in the development of allergic disease. Notably, these transcriptomic findings are reinforced by proteomic data from other allergy models. Proteomic investigations in wheat intolerance have identified differentially expressed proteins involved in immune response and complement cascades, highlighting the cross-phenotype importance of these pathways at the protein level [11].

In contrast, Enrichr functional analysis did not reveal significant enrichment within KEGG or Reactome signaling pathways for genes with reduced expression in children with allergies. However, the identified association of these genes with the Golgi apparatus in the cellular components category may indicate specific impairments in post-translational modification and protein secretion processes necessary for proper immune system function. This observed decrease in the expression of genes associated with the Golgi apparatus may indicate the development of endoplasmic reticulum stress in the studied cells. It is likely that the massive biosynthesis and intense secretion of proinflammatory cytokines, characteristic of activated T-helper cells in allergy, lead to an overload of the secretory apparatus, causing adaptive or destructive changes in the functions of vesicular transport organelles [12].

The discovery of interferon response-related genes among our hub genes is especially significant because it suggests their potential role in the development of food allergies. In our study these genes showed significantly increased expression in children with food allergy. For instance, the USP18 gene encodes an enzyme that acts as a key negative regulator of the type I interferon (IFN) signaling pathway. The observed upregulation of USP18 might represent a compensatory mechanism to control the heightened cellular response to inflammation. This contrasts with conditions like vitiligo, where USP18 expression is notably decreased [13]. In cancer studies, loss of USP18 reduces the growth of lung cancer cell lines, particularly those with activated KRAS, indicating its influence on cell proliferation [14]. Additionally, in a metabolic hypertension model, USP18 overexpression inhibited the JAK/STAT pathway, which enhanced cell proliferation and reduced apoptosis, highlighting its involvement in metabolic regulation and cellular stress responses [15].

The 2'-5'-oligoadenylate synthetase (OAS) gene family is a group of highly conserved, ubiquitously expressed genes in mammals that play a key role in innate immunity against viral infections. The family includes four members: OAS1, OAS2, OAS3, and OASL. Our results demonstrate a significant increase in OAS1 and OAS3 expression in the allergy group. Particular attention is given to OAS1 as one of the most well-studied members, with its functionality being critical for modulating the immune response. OAS1 expression is significantly increased during viral, bacterial, and parasitic infections [16]. Moreover, OAS1 has also been linked to the development of several autoimmune diseases. Notable differences in OAS1 expression have been observed between patients with systemic lupus erythematosus and healthy individuals, leading to its consideration as a potential biomarker for this disease [17].

In turn, the OAS3 gene also plays a crucial role in antiviral immunity, where its activation causes the destruction of viral RNA. Studies have demonstrated that OAS3 is a key regulator of innate antiviral immune responses, and its absence results in increased viral replication [18]. Additionally, increased expression of this gene is observed in various autoimmune and systemic diseases, such as lupus nephritis and Sjogren's syndrome [19].

The upregulation of these genes in our study suggests a state of pre-activated innate immunity in children with food allergies. Notably, while OAS1 and OAS3 were significantly elevated, OAS2 did not show a significant difference between the groups ($p = 0.805$).

The IFIT2 and IFIT3 genes are also crucial in the innate immune response and were found to be overexpressed in the allergy group. The increased expression of IFIT2 observed in our study is consistent with findings in patients with seasonal allergic rhinitis, where its expression rises in response to allergens to regulate mucosal barrier function [20]. Additionally, IFIT2 deficiency has been shown to increase vulnerability to autoimmune inflammation [21]. During neurotropic coronavirus infection, IFIT2 is essential for limiting viral replication and preventing the development of encephalitis [22]. Furthermore, the link between IFIT3 and autoimmune diseases like psoriasis, where it promotes inflammation, supports our finding that interferon-inducible genes are overexpressed during allergic inflammation [23,24].

The IFI35 gene, which encodes an interferon-inducible protein of approximately 35 kDa, was also identified in our study as a hub gene with significantly increased expression in infants with IgE-mediated food allergy. This finding aligns with the overall elevation in the expression of genes involved in the interferon response observed in our analysis [25].

Intracellularly, IFI35 interacts with components of the RIG-I pathway and can suppress RIG-I-mediated IFN-I induction. Additionally, IFI35 interacts with viral proteins, which modifies the antiviral response depending on the specific pathogen. Besides its intracellular role, IFI35 also has extracellular functions. When cells are injured or strongly stimulated, IFI35 is released into the extracellular space, acting as a DAMP. This activity allows it to activate macrophages via TLR4, leading to NF-κB activation and the secretion of proinflammatory cytokines. This response has been linked to the severity of systemic inflammation [26-28].

The IFIH1 gene encodes the MDA5 receptor, which acts as a cytoplasmic sensor for viral double-stranded RNA. Activation of this receptor initiates the signaling pathway through MAVS → IRF3/7 → IFN-I and NF-κB, a process essential for starting antiviral immunity [29]. In mouse model studies, the absence of IFIH1 results in decreased IFN-β production and increased vulnerability to viruses [30], while in humans, its functions are linked to the severity of respiratory tract infections and viral flare-ups of asthma [31]. Additionally, IFIH1 is associated with autoimmune disease. For instance, certain mutations in this gene offer a protective effect by lowering the risk of developing type 1 diabetes mellitus [32].

The DDX58 gene encodes the cytosolic receptor RIG-I, which is part of the RLR family and recognizes viral

5'-triphosphate and structured RNAs. RIG-I activation leads to signal transduction through the MAVS adapter, followed by activation of transcription factors IRF3/7 and NF-κB. This process triggers the production of type I interferons and proinflammatory cytokines, a key mechanism of innate antiviral response [33]. Clinically, the role of DDX58 is well established in RNA viral infections. Defects or reduced activity of RIG-I are linked to increased sensitivity to various respiratory viruses. Several studies on the interaction of antiviral RLR pathways with epithelial and immune cells of the respiratory tract have shown that impaired RIG-I signaling correlates with more severe virus-induced flares of allergic diseases [31,34]. This highlights the biological potential for cross-regulation between antiviral defense and allergic inflammation.

The MX1 gene encodes a protein that is a crucial part of the innate immune response, particularly in combating viral infections. Meanwhile, researchers have observed overexpression of MX1 in a group of patients with diabetes mellitus and atherosclerosis [35]. Additionally, other studies have found a connection between MX1 and the severity of viral asthma symptoms and asthma exacerbations [36].

The results of this study are exclusively based on bioinformatic analyses of transcriptome datasets. While computational modeling and statistical analyses enable identification of potentially significant markers and pathways, they cannot substitute for experimental validation. Challenges such as biological variability, post-translational modifications, and regulatory mechanisms, which are not always reflected in mRNA expression profiles, remain. Therefore, to confirm the validity and clinical relevance of the identified hub genes, functional studies both in vitro and in vivo, as well as clinical investigations with subsequent correlation analyses between gene expression and clinical outcomes, are essential.

Building upon these findings, the identification of key genes regulating the interferon response and antiviral defense mechanisms opens new horizons for the development of biomarkers for the diagnosis and prognosis of food allergies. Hub genes such as USP18, IFIT3, OAS1, and others demonstrate potential as targets for pharmacological modulation of the immune response aimed at restoring the balance between pro-inflammatory and anti-inflammatory processes. Their role can be realized within the framework of personalized medicine, enabling the early identification of children at risk of severe allergies and facilitating the development of targeted therapeutic strategies. Furthermore, understanding the mechanistic aspects of antiviral response dysfunction contributes to a deeper comprehension of the pathogenesis of allergic diseases, thereby improving clinical guidelines and preventive approaches.

Despite these promising insights, it is important to acknowledge certain limitations of the current study. Specifically, the cohort size in this study is relatively small, which may limit statistical power and reduce sensitivity to detecting some biological effects. However, this scale of study is common when examining highly specialized and clinically homogeneous groups, allowing for the collection of highly specific and relevant data. The homogeneity of the age group and the limited range of clinical characteristics reflect careful selection and decrease the influence of confounding factors, but also restrict the ability to account for genetic and epigenetic diversity. Nevertheless, this specificity also restricts the ability to fully account for broader genetic and ethnic diversity. While the identified interferon signature appears robust across the total cohort, it is essential to consider that the dataset originates from a multi-ethnic population. Given that innate immune response genes often possess well-documented genetic polymorphisms that vary by ancestry, their expression patterns may exhibit population-specific nuances. Consequently, further studies in more ethnically homogeneous or, conversely, specifically diverse populations are required to determine the universal applicability of these transcriptomic markers in the context of food allergy. To verify and build upon the results, it is recommended to conduct studies with larger and more diverse samples, enhancing the overall validity and reproducibility of the findings.

Conclusion

The bioinformatics analysis conducted identified key genes and signaling pathways associated with IgE-mediated food allergy in young children. Our results suggest that the upregulation of genes related to the interferon response and antiviral defense is associated with the disease's development. The ten identified hub genes are involved in regulating innate immunity and may influence inflammatory and antiviral activities. Therefore, changes in the expression of these genes suggest a potential immune imbalance in food allergy, highlighting them as candidate biomarkers and potential therapeutic targets that require further independent validation and experimental research to confirm their clinical utility.

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