

Hyper-IgE Syndrome: A Case Report with Insights from Bioinformatics Analysis of Key Pathways and Genes

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Purpose: This study reports on a patient with High IgE Syndrome (HIES), focusing on clinical manifestations and pathogenic mechanisms through bioinformatics to enhance understanding and treatment.

Patients and Methods: The patient received appropriate interventions and was currently undergoing treatment with close monitoring. Additionally, bioinformatics analyses were conducted to investigate potential signaling pathways and key genes associated with HIES.

Results: A 28-year-old woman presented with a 6-month history of cough, worsening dyspnea, and eczema was diagnosed with HIES after elevated immunoglobulin levels and a STAT3 mutation. Initially, she declined immunoglobulin therapy, but showed improvement with sulfamethoxazole-trimethoprim and subsequently required intravenous immunoglobulin therapy for ongoing management. KEGG pathway analysis revealed that these genes were primarily associated with infection-related signaling pathways, consistent with the susceptibility to infections observed in HIES patients. Protein-protein interaction (PPI) network analysis highlighted the importance of key genes such as IL6, CDH2, and CLDN1.

Conclusion: Increased HIES awareness among healthcare providers is crucial for patients with recurrent infections, requiring a multidisciplinary approach. Our study identified IL6, CDH2, and CLDN1 as key factors in HIES progression, suggesting naive B cells and dormant mast cells may be involved.

Keywords: HIES, infection, IL6, CDH2, CLDN1, STAT3 mutation

Introduction

Hyper-IgE Syndrome (HIES), was first described by Davis and Wedgwood in 1966.¹ They identified two girls who suffered from recurrent infections with *Staphylococcus aureus* abscesses, pneumonia, and newborn eczema.² However, since this original report predates the identification of IgE, they did not observe significantly elevated levels of IgE in their serum at that time.² Further characterization of this syndrome was conducted by Buckley, who observed a correlation between recurrent staphylococcal abscesses, chronic eczema, and abnormally high concentrations of IgE in the bloodstream.³ Their work helped establish the association between these clinical manifestations and elevated IgE levels in HIES patients.³ Patients often experience symptoms such as multiple dermatitis, chronic allergic rhinitis, and airway infections (such as bronchiectasis and lung infections).⁴ Additionally, the disease is accompanied by severe skin itching, eczema, and idiopathic lung abscess.⁵ HIES can be classified into two forms: familial and non-familial.⁶ Familial HIES is typically inherited through autosomal dominant inheritance, while non-familial HIES is associated

with other factors such as genetic mutations and environmental factors.⁶ Specifically, STAT3 gene mutation is the most common form of mutation in familial Hyper-IgE syndrome.⁷ HIES is a rare disease with an incidence rate of 1/1,000,000 per year.⁸ There have been no reports of enrichment in specific ethnic or racial groups, which poses significant challenges in understanding its pathogenesis and developing effective treatments.⁹ As a result, the disease is prone to misdiagnosis or underdiagnosis. This further highlights its rarity and the substantial burden it imposes on patients and healthcare systems.

In recent years, research on HIES has made significant progress, particularly in understanding its pathogenesis and treatment options.^{1,10} Researchers have utilized gene sequencing techniques to identify multiple mutation sites associated with HIES, further exploring the dysregulation of immune system signaling pathways.^{4,11,12} Current diagnostic and therapeutic approaches primarily rely on clinical evaluation and symptom management, which often fail to address the underlying genetic and molecular mechanisms of the disease.¹³ Although advancements in genetic sequencing have provided some insights, the complexity of HIES pathophysiology remains inadequately understood. Bioinformatics offers a powerful approach to uncovering the genetic and molecular mechanisms of rare diseases like HIES, which may not be evident through clinical observation alone.¹ By integrating genomic, transcriptomic, and proteomic data, novel genetic variants and molecular pathways associated with HIES can be identified.^{1,14} Whole-exome sequencing (WES) is employed to detect mutations in key immune-related genes, while RNA sequencing (RNA-seq) analysis provides insights into differential gene expression patterns, highlighting dysregulated immune signaling pathways and offering a comprehensive view of the molecular landscape of HIES.⁹

Although HIES is a rare disorder, as our understanding of it deepens, we look forward to providing more effective treatment options and strategies to improve the quality of life for patients. Future research will continue to unveil the pathogenesis of HIES and explore novel therapeutic approaches to help patients better manage and cope with this condition. By advancing our knowledge in this field, we aim to enhance the overall care and outcomes for individuals affected by HIES. In this report, we presented a case diagnosed with HIES and conducted bioinformatics and immune infiltration analyses to reveal underlying genetic variants and molecular pathways that were difficult to detect through traditional clinical observation. By leveraging bioinformatics tools, this study aimed to elucidate the complex mechanisms behind HIES, ultimately contributing to the identification of new therapeutic targets and enhancing the overall understanding of this rare disease.

Material and Methods

Case Presentation

A 28-year-old female patient presented with a primary complaint of persistent cough and sputum production over the past six months, which had exacerbated and was accompanied by dyspnea in the preceding two weeks. She had previously been treated with penicillin-based medications in an outpatient setting, but without notable improvement. The patient has a history of recurrent eczema since one month postnatally. Subsequently, she developed facial cysts, which progressively evolved into multiple cysts distributed across various body regions, including the face, ears, neck, limbs, and breasts. These cysts were associated with pain, pruritus, and lax skin. The cysts progressively enlarge until they rupture, discharging pus and blood. Post-drainage, the cysts diminish in size, but the symptoms recur. The patient has undergone multiple cyst incision and drainage procedures. She reports exacerbation of symptoms during perceived periods of immunodeficiency. Additionally, she experiences significant dyspnea and an inability to participate in physical activities such as running, along with general fatigue. Upon admission, her vital signs were as follows: body temperature of 36.5°C, heart rate of 89 beats per minute, respiratory rate of 23 breaths per minute, and blood oxygen saturation of 92%. The physical examination demonstrated facial erythema, laxity of the skin, and multiple palpable breast masses bilaterally, with protrusion through the skin. These masses included larger formations enveloping several smaller ones, accompanied by visible pigmentation. Auscultation of the lungs revealed coarse breath sounds and fine moist rales bilaterally. The patient's medical history was significant for cellulitis in the right lower extremity and pulmonary tuberculosis.

Identification and Functional Analysis of Differentially Expressed Genes (DEGs)

To identify DEGs in HIES, a comprehensive database search was undertaken. The dataset GSE153886 was retrieved from the Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov>).¹⁵ Subsequent analyses were executed utilizing R software (version 4.3.1). A functional analysis of the DEGs was conducted to elucidate their biological significance. Gene Ontology (GO) analysis was employed to classify the DEGs according to categorize the DEGs based on their molecular functions (MF), biological processes (BP), and cellular components (CC).¹⁶ Additionally, pathway enrichment analysis was conducted using databases such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) to identify the pathways that were significantly enriched with DEGs.¹⁶

Construction of Protein-Protein Interaction (PPI) Network for DEGs

The STRING database is a comprehensive resource for protein-protein interaction networks, synthesizing information from public databases and literature sources. It aggregates data from multiple public repositories, such as UniProt, KEGG, NCBI, and Gene Ontology, to construct an extensive protein-protein interaction network database.¹⁷ Beyond facilitating the visualization of protein-protein interaction networks, STRING also offers insights into protein families, pathways, subcellular localization, and other related aspects. In this study, the STRING database was accessed via its official website (<https://string-db.org/>).¹⁷ By employing the search tool to input DEGs, we were able to generate a PPI network pertinent to the query results.

Immunoinfiltration Analysis of Hyper-IgE Syndrome

CIBERSORT (Cell-type Identification By Estimating Relative Subsets Of RNA Transcripts) is a computational technique employed to evaluate the relative abundance of various cell types within heterogeneous tissue samples.¹⁸ It can be used to analyze merged expression data and calculate immune cell infiltration.¹⁸ In this study, analysis of the GSE51587 dataset was conducted using the CIBERSORT package.¹⁹

Results

Case Presentation

Laboratory investigations revealed the following results: hemoglobin level of 98 g/L, serum amyloid A >320 mg/L, C-reactive protein 119.5 mg/L, interleukin-6649.92 pg/mL, total immunoglobulin E(IgE) 1203IU/mL (165IU/mL), immunoglobulin G(IgG)21.27 g/L(8.6–17.4 g/L), and immunoglobulin M(IgM) 2.85 g/L(0.5–2.8g/L). The breast exhibited the presence of multiple cysts, which have been addressed through the implementation of multiple incisions for the purpose of abscess drainage. Additionally, the surface displayed visible scars and areas of pigmentation (Figure 1A). Molybdenum target imaging showed multiple abscesses in both breasts (Figure 1B). The ultrasound examination revealed the presence of multiple cystic and solid masses within both breasts, indicative of a diagnosis of breast cysts (Figure 1C).

Based on the findings from the chest CT scan, multiple patchy and irregular high-density opacities with well-defined borders were present in the right lung. Some of these opacities exhibited a fluffy appearance at their peripheries, and their internal density was heterogeneous. Partial cavitation and air-fluid levels were noted, with the cavities displaying smooth internal walls. Additionally, multiple small “tree-in-bud” patterns were observed within the right lung field. Bronchiectasis was evident in certain regions of the right lung, characterized by thickened walls and indistinct margins, particularly pronounced in the right middle lobe (Figure 2A). During bronchoscopy, white viscous secretions were noted adhering to the walls of the right main bronchus, upper lobe bronchus, right middle lobe bronchus, and right middle lobe segmental bronchus. A brush sample was obtained from the visibly affected area in the right middle lobe for pathological examination. Pathological analysis of the brush sample revealed the presence of bronchial mucosal epithelium and a substantial number of degenerating neutrophils (Figure 2B). Considering that young patient was susceptible to multiple pathogens, including some opportunistic pathogens, we carefully reviewed the patient’s medical history. Surprisingly, she had suffered from eczema and itching all over her body since childhood. At the age of 23, she underwent surgical treatment for cellulitis in her right lower limb. In the

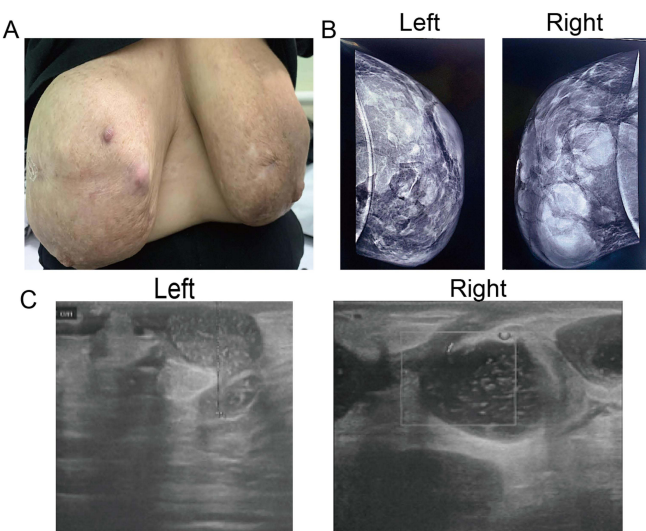


Figure 1 Breast examination results using different methods. (A) Visual examination results of the patient's breasts; (B) The results of mammography; (C) Ultrasound examination results of the patient's breast.

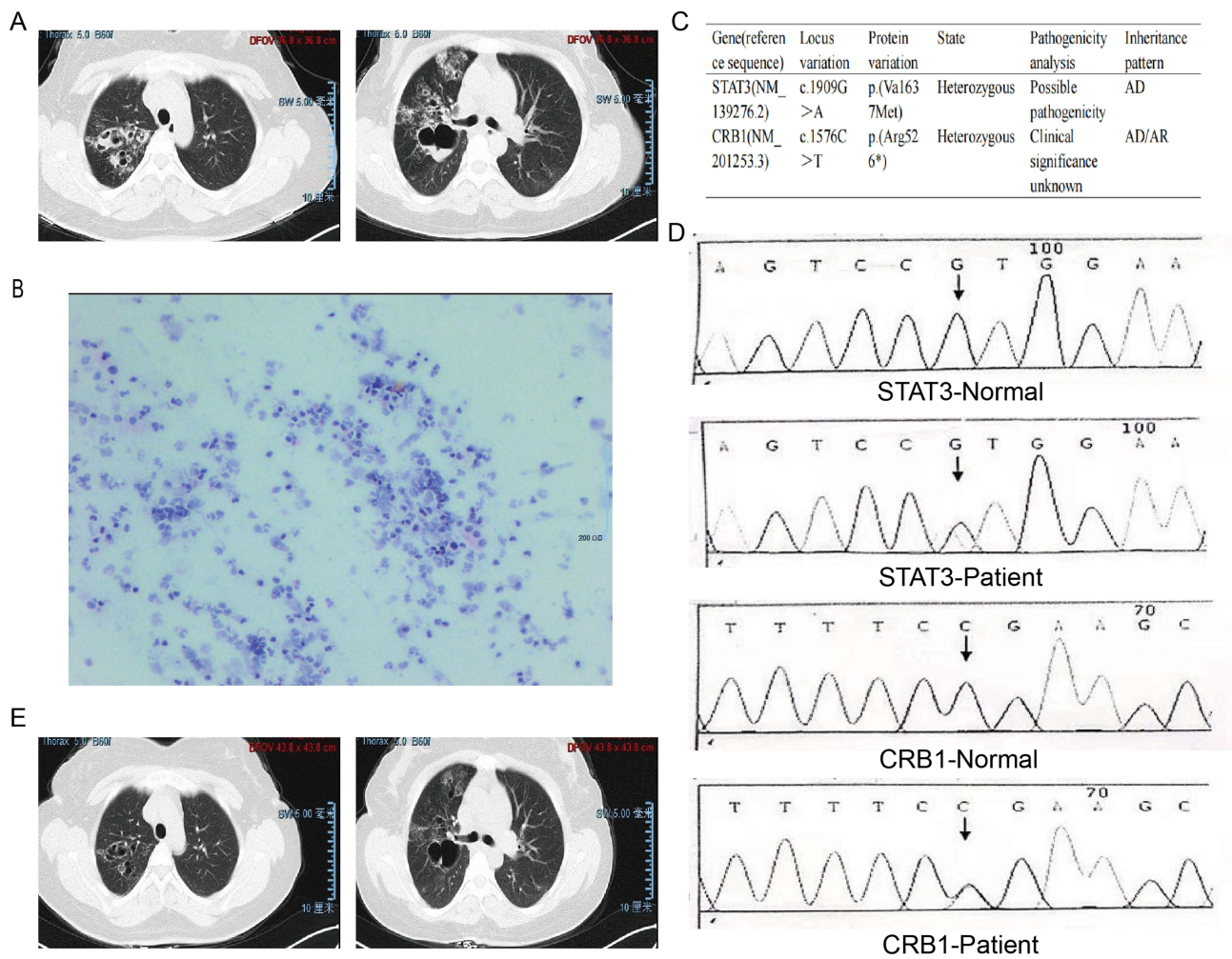


Figure 2 Patient examination results. (A) The results of chest CT scan on admission; (B) The results of tracheal brush cytology examination; (C and D) Whole exome sequencing result: STAT3 and CRB1 gene mutation; (E) The results of Chest CT examination at discharge.

past three years, she had recurrent incision and drainage for abscesses in the breast and face. The patient had recurrent infections with different strains, including MRSA, and presented with rashes and significantly elevated IgE levels. HIES was suspected. According to the HIES diagnostic scoring system developed by the National Institutes of Health (NIH), which evaluates parameters such as IgE levels, the frequency and severity of pneumonia, and respiratory tract infections, a score of 40 or higher is generally indicative of HIES.⁴ Scores between 20 and 40 warrant further monitoring and evaluation, while a score below 20 may effectively rule out an HIES diagnosis. In this study, the patient achieved a score of 55 points on the NIH-HIES diagnostic scale, strongly suggesting a diagnosis of HIES. This elevated score reflects a high probability of HIES, based on the integration of clinical manifestations, laboratory results, and other pertinent criteria. Consequently, the diagnosis of HIES is confirmed for the patient under investigation. Whole-exome sequencing of peripheral blood revealed a heterozygous mutation in the STAT3 gene at the c.1909G>A locus, corroborating a diagnosis of autosomal dominant Hyper-IgE Syndrome (AD-HIES) (Figure 2C and D). Due to financial constraints, the patient declined immunoglobulin therapy and was treated with a combination of sulfamethoxazole-trimethoprim, vitamins, and other medications. Subsequently, the patient's condition improved and was discharged from the hospital.

Since discharge, the patient has been taking oral sulfamethoxazole-trimethoprim as a prophylactic measure against infections. During this period, she was readmitted for treatment of a pulmonary infection and received intravenous immunoglobulin therapy (0.2 g/kg per infusion) twice to boost their immune system. Simultaneously, she received vancomycin treatment for an infection due to the detection of MRSA in her sputum culture, after which her condition improved and she was discharged from the hospital. During the 6-month follow-up, the patient did not experience any recurrent infections. A chest CT scan showed improvement in the infiltrates (Figure 2E).

Identification and Functional Analysis of DEGs

In the dataset GSE153886, gene expression profiles of Epstein-Barr virus-transformed B cells (EBV-B cells) were analyzed from 18 healthy individuals and 18 patients with elevated IgE levels following stimulation with IL-21, IL-6, IL-23, IL-10, and IFN- α . Differential expression analysis identified a total of 98 DEGs, comprising 40 upregulated and 58 downregulated genes (Figure 3).

In this study, GO and KEGG analysis were performed using the BiocManager package in R software.²⁰ The GO analysis included three categories: BP, CC, and MF. The results revealed several associations with differentially expressed genes (DEGs) in each category.

In the BP analysis, DEGs were found to be related to behavioral response to pain, response to pain, and cell-cell junction assembly. In the CC analysis, associations were observed with the apical part of the cell, apical plasma membrane, and synaptic membrane. The MF analysis indicated links to phosphatidylinositol-4,5-bisphosphate binding, gated channel activity, and monoatomic ion gated channel activity (Figure 4A).

In-depth analysis utilizing circle plots identified 11 DEGs, namely PIP5KL1, ORM2, IL6, UGT8, TLN2, CLDN16, CLDN1, CDH2, VWA1, TRPV1, and SCN3A, which were associated with five enriched GO terms, including acute-phase response, behavioral response to pain, cell-cell junction assembly, negative regulation of mitochondrial membrane potential, and response to pain. Notably, TRPV1 was associated with multiple GO terms, while cell-cell junction assembly was associated with multiple genes, including UGT8, TLN2, CLDN16, CLDN1, and CDH2 (Figure 4B).

Moreover, KEGG pathway analysis using circle plots revealed that 15 DEGs (HSPA6, MYO1B, CLDN16, CLDN1, SERPINB6, LAMB4, TPM2, ITGA10, IL6, TRPV1, P2RY1, HCRTR1, GRIA3, CHRM5, and AVPR1B) were involved in five pathways: Amoebiasis, Hypertrophic cardiomyopathy, Legionellosis, Neuroactive ligand-receptor interaction, and Pathogenic *Escherichia coli* infection. Among these, IL-6 expression was associated with four signaling pathways, and Neuroactive ligand-receptor interaction was associated with multiple genes (TRPV1, P2RY1, HCRTR1, GRIA3, CHRM5, and AVPR1B) (Figure 4C).

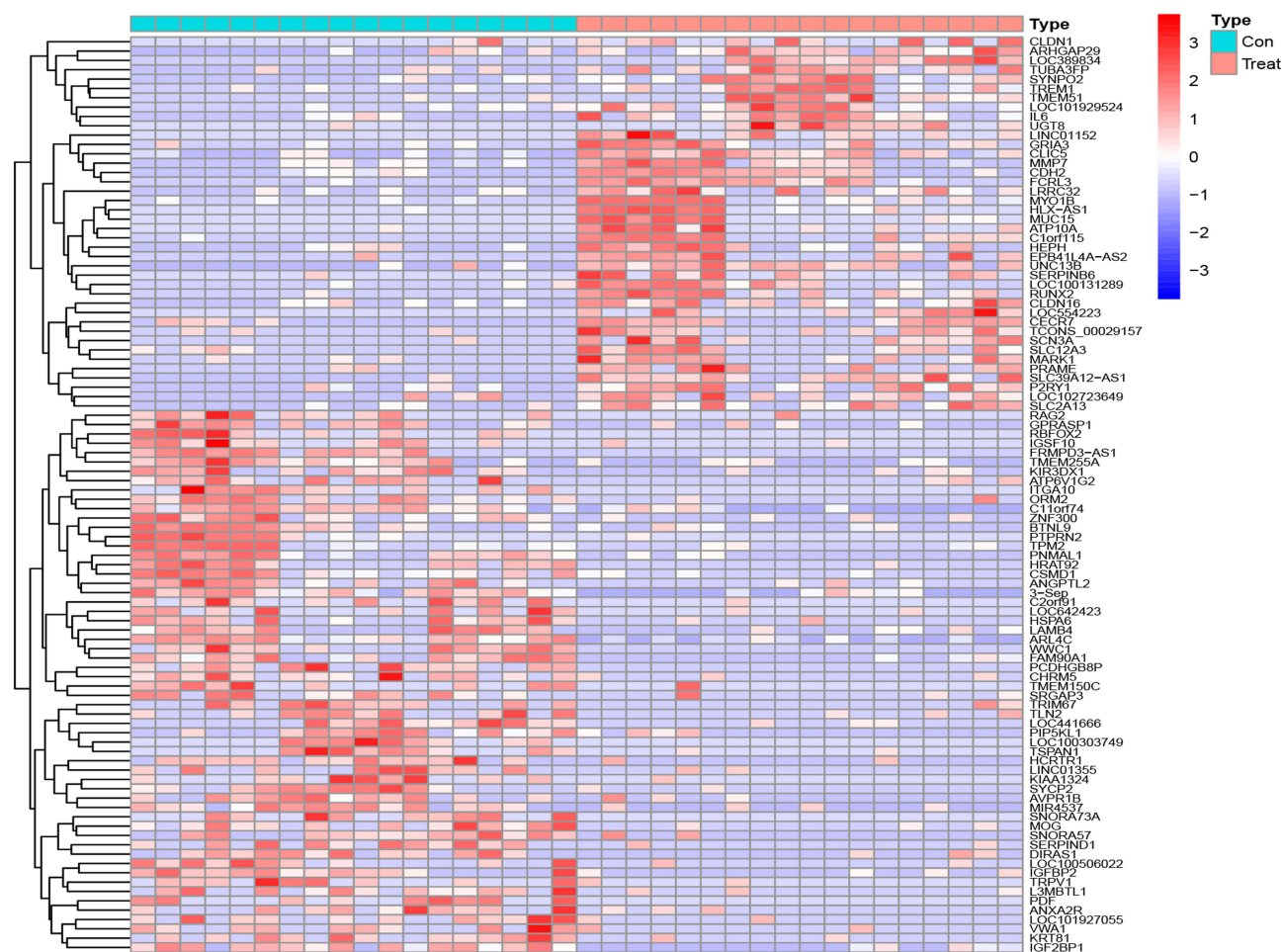


Figure 3 Heatmap of DEGs.

Protein-Protein Interaction (PPI) Network Construction of DEGs and Network-Core Gene Screening

The PPI network of DEGs can be obtained from STRING (<https://string-db.org/>), with a minimum interaction score requirement of 0.4 (18) (Figure 4D). The core genes of the network are generated based on count values using R software (R 4.3.1). The bar chart showed that the top three core genes in the network were IL6, CDH2, and CLDN1 (Figure 4E).

Analysis of Immune Cell Infiltration Associated with Hyper-IgE Syndrome

The proportions of various immune cell types in each sample were calculated and presented in a bar chart (Figure 5A). Figure 5B illustrated a heatmap depicting the expression levels of 22 immune cell types. The heatmap revealed that, in comparison to healthy individuals, activated dendritic cells demonstrate a positive correlation in expression among patients with elevated IgE levels. Additionally, this study performed a correlation analysis of infiltrating immune cells (Figure 6). The findings indicated a significant positive correlation between the expression of CD8 T cells and monocytes ($r = 0.84$), and a negative correlation between the expression of activated dendritic cells and plasma cells ($r = -0.81$).

Furthermore, this study compared the expression levels of 22 immune cells between healthy individuals and patients with HIES (Figure 7A). The violin plot results show significant differences in the expression of B cells naïve and Mast cells resting between different groups, with higher expression of B cells naïve in healthy individuals and higher expression of Mast cells resting in patients with HIES, with p-values of 0.031 and 0.019, respectively. We also conducted

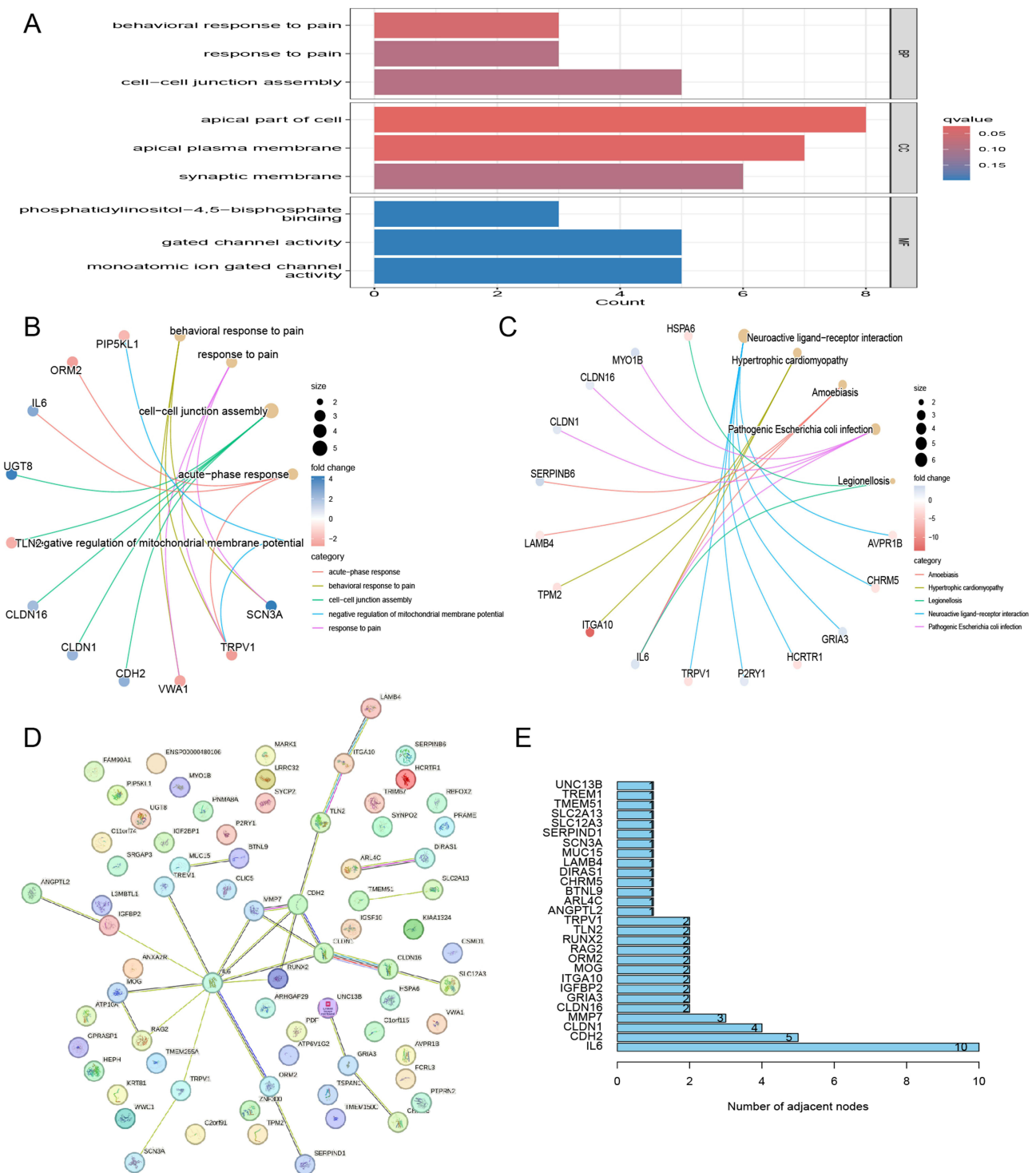


Figure 4 Functional analysis of DEGs. (A) Bar-plot of GO analysis; (B) Circle-plot of GO analysis; (C) Circle-plot of KEGG analysis; (D) PPI network analysis of DEGs; (E) Bar-plot of DEGs.

differential expression analysis of immune cells between different paired samples, and the results were consistent with the above results. Among the 18 matched samples, B cells naïve showed higher expression in healthy individuals (Figure 7B), while Mast cells resting showed higher expression in patients with HIES, with statistically significant differences (Figure 7C).

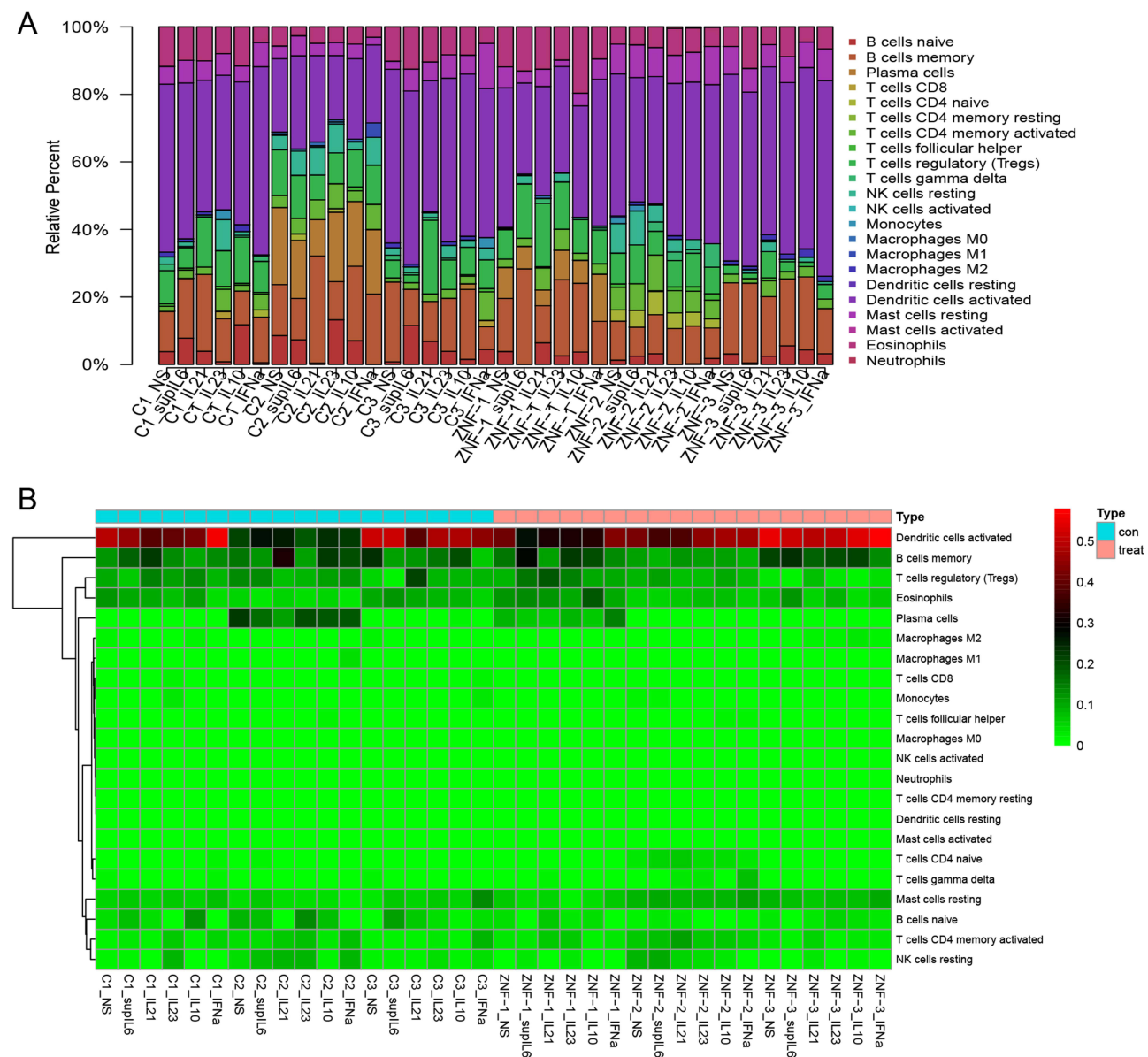


Figure 5 Bar plot and heatmap of immune cell infiltration analysis of 22 types in the GSE153886 dataset. **(A)** Bar plot of immune cell infiltration analysis of 22 types in the GSE153886 dataset; **(B)** Heatmap of immune cell infiltration analysis of 22 types in the GSE153886 dataset.

Discussion

HIES is a primary immunodeficiency disorder characterized by a combined T and B cell defect.²⁰ Its main features include chronic eczema, recurrent skin abscesses, recurrent staphylococcal infections, elevated serum IgE levels, and eosinophilia.²¹ Other variable immune abnormalities may include defects in neutrophil chemotaxis, abnormal T lymphocyte subsets, impaired antibody production, and decreased generation or response of certain cytokines.^{21,22} Some patients may also exhibit distinctive facial appearance, dental abnormalities, joint hyperextensibility, and fractures, which are non-immunological features.²³ Additionally, some patients may have vascular abnormalities such as medium-sized artery tortuosity and aneurysms, which can be associated with symptoms like myocardial infarction and subarachnoid hemorrhage.²⁴

HIES can be classified into two categories based on the inheritance pattern: (1) Autosomal dominant hyper-IgE syndrome (AD-HIES): This type is primarily caused by mutations in the STAT3 gene, accounting for more than 60–70% of cases. AD-HIES affects multiple systems, including the immune system, connective tissues, skeletal system, teeth, and

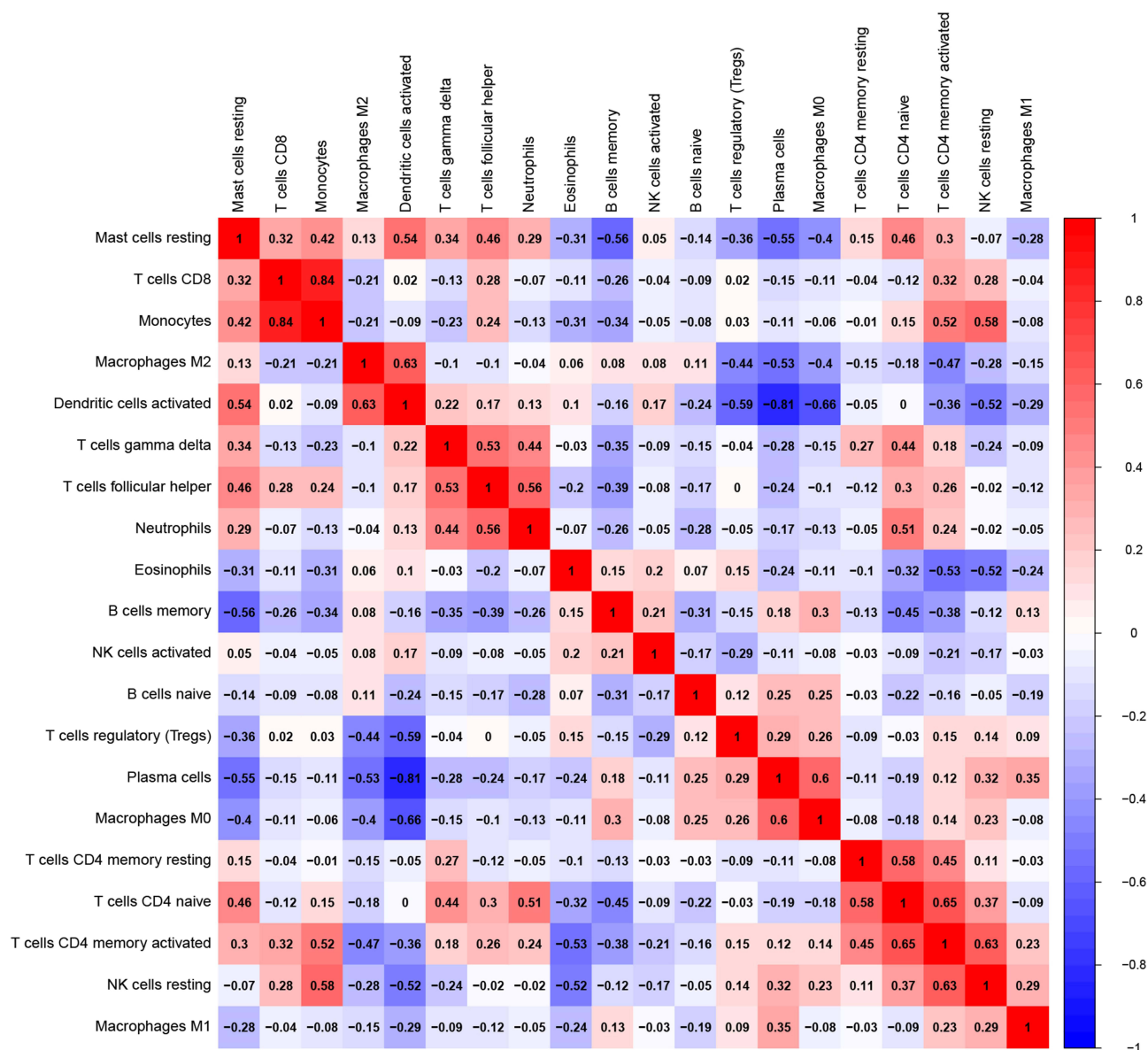


Figure 6 Correlation analysis of 22 immune infiltrating cell types.

blood vessels; (2) Autosomal recessive Hyper-IgE syndrome (AR-HIES): AR-HIES is mainly caused by mutations in genes such as TYK-2, DOCK8, ZNF431, and PGM3. Unlike AD-HIES, AR-HIES primarily affects the immune system without involvement of connective tissues or skeletal changes.^{24–26}

This study presents a case of STAT3-related AD-HIES. The diagnosis of AD-HIES relies on clinical manifestations and laboratory investigations, with genetic testing aiding in confirmation. In this particular case, the infant experienced recurrent infections affecting various sites such as the facial region, limbs, breasts, and lungs since one month after birth. There was no history of long-term immunosuppressant use. Elevated serum IgE levels were observed, and according to the scoring system developed by NIH, the patient scored 55 points. Combined with distinctive facial features and the detection of a STAT3 mutation through genetic testing, a definitive diagnosis of Hyper-IgE syndrome was made.²⁴ In this case, IgE, IgG, and IgM levels were significantly elevated, but eosinophilia, which is typically associated with HIES, was not prominent. This suggests that not all cases of HIES exhibit elevated eosinophil levels, and eosinophil levels can vary dynamically throughout the course of the disease.

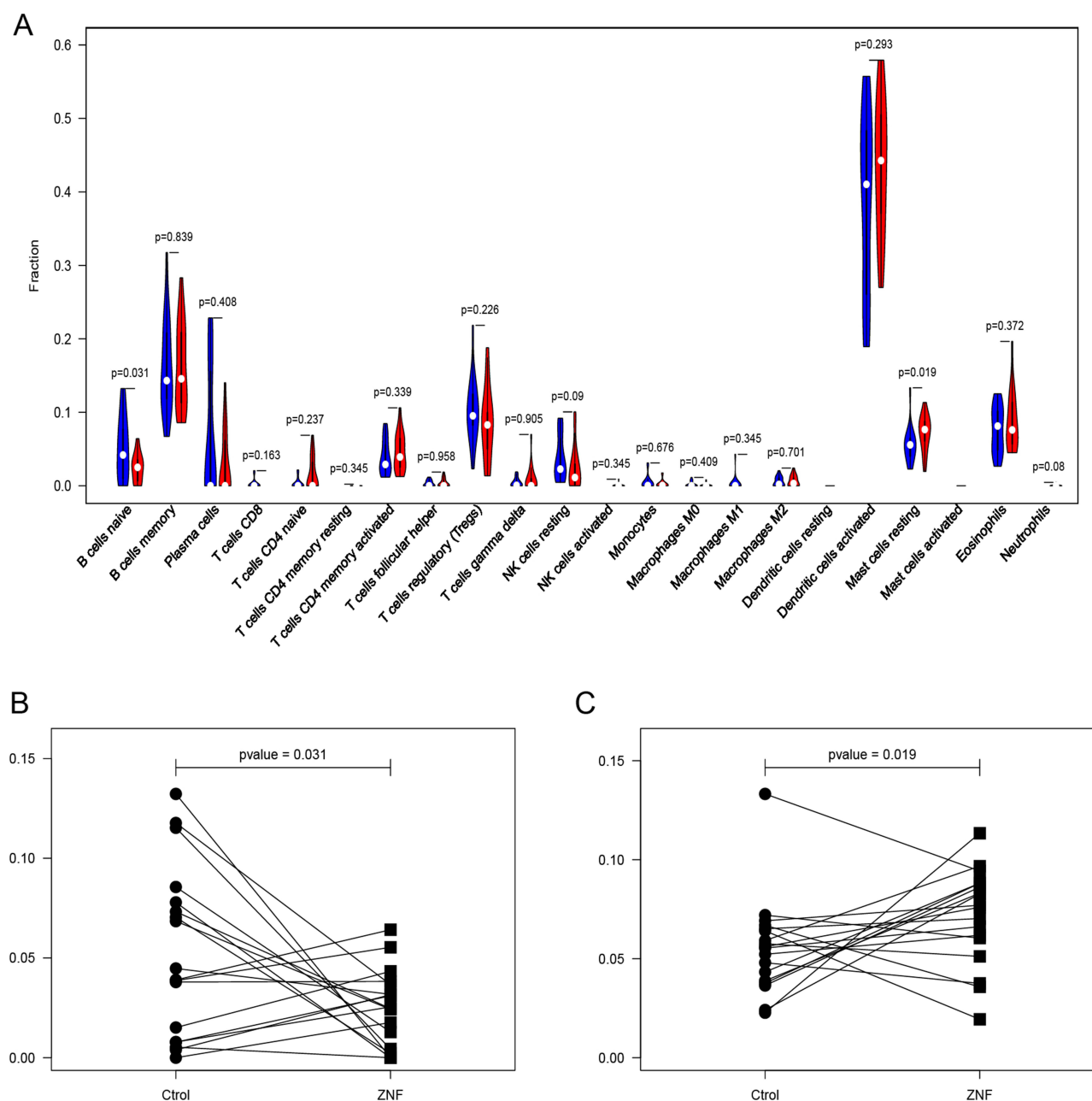


Figure 7 Differential expression analysis of 22 immune cell types between healthy individuals and HIES patients. **(A)** Violin plot of differential expression analysis of 22 immune infiltrating cell; **(B)** Volcano plot of paired analysis of B cells naïve; **(C)** Volcano plot of paired analysis of Mast cells resting.

This case highlights the intricate nature of HIES and its impact on the patient's overall health and quality of life. The patient's presentation, characterized by recurrent respiratory infections and extensive cyst formation, aligns with the known complications associated with HIES. Current literature emphasizes the diverse clinical manifestations of HIES, which can include not only recurrent infections but also autoimmune phenomena and various dermatological issues. The presence of multiple cysts, particularly in the context of immunodeficiency, raises important considerations regarding the management of such patients and the potential for secondary infections. The treatment approach for this patient involved a combination of sulfamethoxazole-trimethoprim and supportive care, which ultimately led to an improvement in her condition. This aligns with current recommendations for managing infections in patients with HIES, where prophylactic antibiotic therapy is often necessary to prevent recurrent infections. However, the decision to forego immunoglobulin therapy due to financial constraints underscores the challenges faced by patients with rare diseases in accessing appropriate care.

The exact pathogenesis of HIES remains unclear. Studies suggest that AD-HIES is primarily caused by mutations in the signal transducer and activator of transcription 3 (STAT3) gene, while most cases of AR-HIES are associated with mutations in genes such as Dedicator of Cytokinesis 8 protein (DOCK8) and Tyrosine Kinase 2 (TYK2).^{24,27} To elucidate the potential molecular mechanisms underlying Hyper-IgE Syndrome (HIES), this study leveraged the GEO database to obtain HIES-related datasets and performed comprehensive analyses of differential gene expression and immune infiltration. Our analysis identified a total of 98 differentially expressed genes (DEGs) in HIES samples compared to controls. Functional enrichment analysis of these DEGs revealed their significant involvement in biological processes such as the acute-phase response, cell-cell junction assembly, and negative regulation of mitochondrial membrane potential. Recent studies have highlighted the association between the acute-phase response and HIES.²⁸ The acute-phase response represents a systemic reaction of the body to inflammation or infection, characterized by marked changes in the levels of various proteins and cells in the bloodstream. In HIES patients, abnormalities in this response have been observed, suggesting a dysregulation in the immune system.²⁸ This immune dysregulation may contribute to the characteristic susceptibility to recurrent infections seen in HIES.

Furthermore, KEGG pathway analysis identified significant associations between the DEGs and several infection-related pathways, including amoebiasis, Legionellosis, neuroactive ligand-receptor interaction, and pathogenic *Escherichia coli* infection. The prominence of infection-related signaling pathways among the DEGs aligns with the increased susceptibility to infections observed in HIES patients. Dysregulation of these pathways may compromise the immune response, thereby enhancing vulnerability to infections in individuals with HIES.⁷ These findings underscore the importance of investigating the interplay between immune dysregulation and infection susceptibility in HIES, highlighting potential targets for therapeutic intervention.

Additionally, protein-protein interaction (PPI) network analysis highlighted key genes that play significant roles in HIES, including IL-6, CDH2, and CLDN1. Interleukin-6 (IL-6) has been identified as a 26kDa secreted protein that stimulates B cell antibody production.²⁹ Subsequently, IL-6 was found to stimulate cells through various pathways and utilizes the shared IL-6 signal transducer, GP130.³⁰ Genetic variations in IL6ST, which encodes the shared cytokine receptor for the IL-6 cytokine family GP130, are associated with various clinical phenotypes and diseases.³⁰ These include autosomal dominant HIES caused by monoallelic variants of IL6ST and autosomal recessive HIES caused by biallelic variants.^{30,31} Genetic variations in IL6ST contribute to the dysregulation of IL-6 signaling, leading to immunological abnormalities observed in HIES patients.^{30,32} The involvement of IL-6 and its signaling pathway in immune responses highlights its significance in the pathogenesis of HIES.³² The involvement of IL-6 and its signaling pathway in immune responses highlights its significance in the pathogenesis of HIES. Targeting the IL-6 signaling pathway may provide therapeutic benefits for HIES by reducing inflammation. N-cadherin, also known as Neural-cadherin/Cadherin-2 (CDH2), is a calcium-dependent single-chain transmembrane glycoprotein that mediates homotypic and heterotypic cell adhesion.³³ As an important member of the cadherin family, N-cadherin plays a crucial role in the development and functional regulation of the nervous system, brain, heart, skeletal muscle, blood vessels, and hematopoietic microenvironment.^{33,34} Aberrant expression of N-cadherin has been closely associated with various aspects of human malignancies, including transformation, adhesion, apoptosis, angiogenesis, invasion, and metastasis.³⁵ Those indicated that CDH2 may affect the migration of immune cells and tissue integrity in HIES, making it a potential biomarker for assessing disease severity and a target for immune regulation. CLDN1 (Claudin-1) is a transmembrane protein and a member of the tight junction protein family.³⁶ It is expressed both within tight junctions (TJs) and outside TJs.³⁶ In cancer biology, CLDN1 has been found to be involved in promoting tumor cell migration, invasion, and metastasis by modulating the integrity and permeability of tight junctions.³⁷ It has also been implicated in fibrotic diseases, where it contributes to tissue remodeling and fibrosis progression.³⁶ In addition, CLDN1 has been associated with autophagy regulation and apoptosis modulation, influencing cellular homeostasis and survival.³⁸ CLDN1 is involved in the formation of tight junctions and epithelial barrier function. Mutations in CLDN1 have been implicated in various diseases, including ichthyosis and immune dysregulation.³⁹ In HIES, CLDN1 may serve as a biomarker for epithelial barrier dysfunction and become a potential therapeutic target aimed at restoring barrier integrity.

The analysis of immune infiltration revealed significant differences in the expression of B cells naïve and Mast cells resting between different groups. Specifically, healthy individuals showed higher expression of B cells naïve, while

patients with high IgE levels exhibited higher expression of Mast cells resting. Antibody production and functional defects are the main characteristics of primary immunodeficiency disorders affecting B cells.⁴⁰ Patients with these disorders are particularly susceptible to recurrent infections caused by encapsulated pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*.⁴⁰ The reduced expression of B cells naïve suggests that there might be impairment in B cells naïve development, maturation, or antibody production in HIES patients.^{41,42} This compromised B cells naïve function could contribute to their increased susceptibility to bacterial infections. Our analysis also revealed decreased expression of B cells naïve in patients with HIES. This impairment may be due to the fact that patients with HIES often suffer from abnormal immune regulation caused by defects in the STAT3 signaling pathway.⁴³ Dysfunction of STAT3 can prevent naïve B cells from differentiating normally into memory B cells, thereby leading to a significant increase in IgE levels.⁴³ Moreover, during the process of differentiating into plasma cells or memory B cells after antigen activation, naïve B cells may fail to effectively produce antigen-specific antibodies due to defects in the signaling pathways.⁴³ Mast cells are immune cells that play a key role in immune regulation and are important in the pathogenesis of HIES. Mast cells release histamine, cytokines, and chemokines through activation of the IgE-mediated FcεRI receptor, triggering allergic reactions and inflammation.⁴⁴ In HIES patients, the activation of mast cells may be closely related to the elevated levels of IgE. Research has indicated that the silencing of STAT3 in human mast cells primarily leads to a reduction in IgE-mediated degranulation.⁴⁵ This finding suggests that there may be distinct immunological mechanisms at play in HIES patients with varying levels of IgE, highlighting the role of these specific cell types in the disease pathogenesis. Further investigation is warranted to elucidate the functional implications of these immune cell populations in HIES.

The etiology of HIES, also known as Job's syndrome, remains unclear. It is believed to be an autosomal dominant genetic disorder with significant variability. It is often considered a subtype of congenital immunodeficiency syndromes. The long-term prognosis of HIES is not yet fully understood. However, early diagnosis and proactive treatment can reduce the risk of infections and improve outcomes. Without timely diagnosis and treatment, patients may face a higher risk of severe infections that can be life-threatening. Hence, early detection is crucial for effective management of HIES. Further research and clinical observations will contribute to a better understanding of disease progression and prognosis in HIES, enabling the development of more effective treatment strategies. Early diagnosis and comprehensive management can help reduce the risk of complications, enhance quality of life, and extend survival.

Conclusion

This case highlights the need for increased HIES awareness among healthcare providers, especially for patients with recurrent infections and unusual skin symptoms. Managing HIES requires a multidisciplinary approach, including genetic counseling and tailored therapies. Our study identified IL6, CDH2, and CLDN1 as key factors in HIES progression, and we suggest that naïve B cells and dormant mast cells may play a role in its pathogenesis. Future research should further explore the specific mechanisms of action of these genes in HIES, in order to develop more effective diagnostic and therapeutic strategies. Future practices should focus on early detection and intervention to improve patient outcomes.

Data Sharing Statement

Open databases were analyzed in our study. GSE153886 data was obtained from GEO database (<https://www.ncbi.nlm.nih.gov/geo/>).

Research Ethics and Consent

Written informed consent has been obtained from individuals for the publication of any potentially identifiable images or data contained in this article. This study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of Tai'an Central Hospital (Approval No.: 2021-06-67), with the application number being No. (110) of (2021). Given that this case report was a retrospective study and did not involve the disclosure of patient identification information, no additional approval was required to publish the case details according to the institutional regulations.

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Disclosure

The authors report no conflicts of interest in this work.

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