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Immunological Features in Hyper-IgE Syndrome: A Comparison of Infectious and Non-Infectious States—A Retrospective Study

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ABSTRACT

Background: This study aimed to clarify the impact of infections on the immune status of patients with hyper-IgE syndrome (HIES) and to explore cell-intrinsic immune homeostasis alterations associated with underlying genetic mutations.

Methods: A retrospective analysis was performed on five patients with *STAT3*-mutated HIES (STAT3-HIES) and one patient with a novel compound heterozygous *DOCK8*-mutated HIES (DOCK8-HIES). Comparisons were performed using the Mann–Whitney U test and Wilcoxon signed-rank test, as appropriate.

Results: In the cohort, *STAT3* mutations had minimal impact on lymphocyte subsets ($CD3^+$ T, $CD4^+$ T, $CD8^+$ T, $CD19^+$ B, and $CD16^+CD56^+$ natural killer (NK) cells), immunoglobulins (IgG, IgM, and IgA), and complement levels (C3 and C4). Importantly, patients with HIES exhibited a decline in lymphocyte subsets during infectious episodes, particularly in the single DOCK8-HIES patient, indicating that patients with HIES display dynamic immune profiles shaped by the infection status. Furthermore, elevated serum IgE levels were not universally observed and showed no clear correlation with infectious activity. Hematopoietic stem cell transplantation resulted in the normalization of markedly elevated IgE levels and favorable outcomes in the two patients with STAT3-HIES.

Conclusions: These findings highlight infection-associated variability in the immune profiles of patients with HIES and may inform therapeutic decision-making in complex

cases.

Keywords: Hyper-IgE syndrome, DOCK8, STAT3, Immunological characteristics, Infection

BACKGROUND

Hyper-IgE syndromes (HIES) are a group of inborn errors of immunity (IEI) originally described as Job syndrome by Davis et al. in 1966 [1]. In 1972, Buckley et al. reported high serum immunoglobulin E (IgE) levels in patients with this disorder and introduced the term HIES [2]. HIES is a rare multisystem disorder with immune and non-immune manifestations. Immunological features are characterized by pathologically elevated serum IgE, eczema, recurrent skin "cold" staphylococcal abscesses, pulmonary infections, and eosinophilia; non-immunological abnormalities include characteristic facial features, pathological fractures, scoliosis, osteoporosis, hyperextensible joints, and retention of deciduous teeth [3]. HIES can be caused by mutations in a number of genes, including signal transducer and activator of transcription 3 (*STAT3*), *d*edicator of cytokinesis 8 (*DOCK8*), *t*yrosine kinase 2 (*TYK2*), and others, and can be classified into two main forms based on inheritance patterns: autosomal dominant (AD-HIES) and autosomal recessive (AR-HIES), with the severity of immunological defects varying according to the underlying genetic mutations [4]. Mutations in the *STAT3* gene, which encodes a transcription factor implicated in cytokine signaling, especially in the immune system, are most frequently linked to AD-HIES. These mutations typically affect the T helper 17 (Th17) subset, which are

essential for defense against extracellular bacterial and fungal infections [5, 6]. Th17 cell deficits, impaired T cell responses, increased IgE levels, increased eosinophil counts, increased neutrophil cell death, and impaired regulatory T cell (Treg) induction are among the immunological characteristics of AD-HIES [5, 7, 8]. Mutations in the *DOCK8* gene, which encodes a protein implicated in regulating immune cell signaling, especially in T, B, and natural killer (NK) cells, are frequently linked to AR-HIES [9–12]. *DOCK8* mutations affect immune cell trafficking and function, resulting in more severe immunodeficiency than that in AD-HIES [13]. Serious immunological deficiencies, decreased T and B cell function, poor NK cell function, high IgE and eosinophilia, severe infections, and increased cancer risk are among the immunological characteristics of AR-HIES [14]. However, the mechanisms underlying these cardinal features of HIES have not yet been elucidated.

The diagnosis of HIES involves a multistep process: HIES is initially suspected based on clinical symptoms and laboratory findings, and the diagnosis is subsequently confirmed through molecular genetic testing. Therefore, understanding the clinical and immunological features of the disease is crucial for reducing missed diagnoses and enabling early detection. Although much research has focused on the immunological mechanisms and clinical characteristics of patients with HIES, these patients are prone to recurrent infections, and acute pathogen-induced inflammation can worsen and mask the underlying immune deficiencies caused by genetic mutations. However, the immunological differences between patients with HIES with and without active infections have not been well defined. This study aimed to provide a preliminary

investigation of the clinical and immunological characteristics of patients with HIES during infection-free and active infection states.

METHODS

This retrospective study was conducted at Wuhan Children's Hospital to investigate the clinical and immunological characteristics of patients with HIES during active infection and infection-free states.

Patients

We included five patients with HIES caused by *STAT3* mutations (STAT3-HIES) and one patient with HIES caused by *DOCK8* mutations (DOCK8-HIES) from six unrelated families of diverse ethnic backgrounds, all of whom were diagnosed by whole-exome sequencing (WES) between 2016 and 2024 at Wuhan Children's Hospital. Patients with coexisting autoimmune diseases, malignancies, or severe congenital malformations, as well as those who had received intravenous immunoglobulin therapy or any dose of corticosteroids (intravenous or oral) within 12 months were excluded. Healthy controls (HCs) consisted of 17 volunteers recruited during routine physical examinations or elective surgeries. The exclusion criteria for HCs included 1) any acute infection or illness within four weeks prior to blood collection, 2) a history of chronic inflammatory, autoimmune, or allergic disorders, and 3) any vaccination (including live or inactivated vaccines) within eight weeks before sampling. Statistical comparisons revealed no significant differences in age or sex

composition between HCs and patients. This study was approved by the Wuhan Children's Hospital Committee for Research Ethics (2025R015-E01) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients' legal guardians.

Definitions

The definition of infection required the simultaneous fulfillment of both clinical and laboratory criteria. Specifically, patients with HIES were classified as having an active infection if they exhibited clinical signs and symptoms (e.g., fever or localized inflammation) together with a significant elevation in at least one inflammatory biomarker: high-sensitivity C-reactive protein (hs-CRP) > 6 mg/L or procalcitonin (PCT) > 0.5 ng/mL. The non-infectious state refers to patients who do not show clinical signs or laboratory evidence of ongoing infections at the time of assessment. This includes the absence of fever, pus formation, or other typical symptoms associated with bacterial, viral, or fungal infections. Diagnostic tests such as blood cultures, polymerase chain reaction (PCR), and imaging do not reveal pathogens indicative of active infection. The non-infectious period was defined as a stable clinical phase with no signs or symptoms of active infection for at least 4 weeks following the complete resolution of the last documented acute infectious episode.

Timing of Blood Sampling

Peripheral blood samples for immunological analysis during the non-infectious

state were collected at least four weeks after the resolution of any clinical infection and prior to any subsequent infection. Samples designated as during active infection were collected at the time of initial clinical presentation for an acute infectious episode, before initiation of targeted antimicrobial therapy. Peripheral blood samples were collected from patients with HIES and HCs. White blood cell counts, lymphocyte subsets, serum immunoglobulin levels (IgE, IgA, IgM, and total IgG), and complement C3 and C4 levels were assessed according to routine measures at Wuhan Children's Hospital.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 8.0.1 (San Diego, CA, USA). Because of the small sample size and non-normal data distribution, nonparametric tests were used. Comparisons between patients with HIES (with or without infection) and HCs were performed using the Mann–Whitney U test, whereas paired comparisons between infection and infection-free states within the same patients were performed using the Wilcoxon signed-rank test. Data are presented as medians with interquartile ranges (IQRs), and statistical significance was indicated by $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$. The effect sizes were calculated where applicable.

RESULTS

Clinical characteristics and genetic mutation profiles in HIES patients

This study enrolled six patients: five with STAT3-HIES and one with DOCK8-HIES **(Table 1)**. For Patient 1, whole-exome sequencing (WES) identified novel compound heterozygous mutations in exons 1 and 41 of *DOCK8* **(Figure 1A, B)**. Structural analysis revealed that the c.36C>G mutation resulted in p.Phe12Leu, whereas the c.5346C>G mutation, which has not been reported in the Genome Aggregation Database (gnomAD), resulted in p.Ile1782Met within the Dock Homology Region 2 (DHR-2) domain **(Figure 1B)**. Genetic analysis revealed a compound heterozygous state of the variants, consistent with an autosomal recessive mode of inheritance for *DOCK8*-related disease (**Figure 1B**). Clinically, the patient presented with scattered impetigo on the head, nose, and extremities; bilateral conjunctival congestion with purulent discharge; pharyngeal erythema; and tonsillar exudates complicated by herpes virus and *Pseudomonas aeruginosa* skin and soft tissue infections **(Table 1)**. The clinical phenotype was consistent with DOCK8 deficiency. However, the study was limited by the lack of confirmatory protein expression or functional assay data for this patient. For Patients 2–6, WES confirmed *STAT3* mutations. Patients 2 and 3 carried the same variant, c.1145G>A (exon 13, p.Arg382Gln) **(Figure 1C)**. Patients 4, 5, and 6 harbored the mutations c.1954G>A (exon 21, p.Glu652Lys), c.1909G>A (exon 21, p.Val637Met), and c.1907C>T (exon 21, p.Ser636Phe), respectively **(Figure 1C)**. These mutations have been previously reported [15–17]. Clinically, patients with *STAT3* mutations exhibited eczema, recurrent infections, and characteristic facial features **(Table 1)**. Imaging revealed severe pulmonary inflammation and consolidation with focal necrosis in patient 2 **(Figure 2A)**, whereas patient 3 had right lower lobe

pneumonia with consolidation, cavitation, and necrosis **(Figure 2B)**.

All patients received supportive treatment including prophylactic antibiotics, skin care, and intravenous immunoglobulin (IVIG). However, Patients 2 and 3 continued to experience recurrent respiratory infections and skin abscesses despite standard management. To restore immune function, they each underwent hematopoietic stem cell transplantation (HSCT) from human leukocyte antigen (HLA)-matched donors during infection-free intervals—Patient 2 at age 11 years and Patient 3 at age 2 years 11 months. Post-transplantation short tandem repeat (STR) analysis confirmed 100% myeloid and lymphoid engraftment, leading to complete infection control and full resolution of eczema.

Changes in leukocyte profiles in HIES patients with and without active infections

The main subtypes of white blood cells (WBCs) include neutrophils, lymphocytes, monocytes, and eosinophils. Our results showed that the absolute WBC count as well as the counts and percentages of lymphocytes, neutrophils, and monocytes were generally within the normal range in all patients without infections. However, Patient 3, who had a *STAT3* mutation, had a decreased absolute count and percentage of neutrophils without infections, and Patient 1, who had DOCK8 deficiency, exhibited markedly low absolute lymphocyte counts during infectious episodes **(Figure 3A-D)**. Eosinophilia in some patients with HIES has been previously reported [3, 18, 19]. We also found that the absolute count and percentage of eosinophils in four patients reached or exceeded the upper limit of the normal range **(Figure 3E)**. Additionally, we

dynamically assessed the differences in WBCs and their subtypes between active infectious and non-infectious states within the same patients, as well as the differences between STAT3-HIES patients and HCs **(Figure 3F-J)**. Unexpectedly, no statistically significant differences in lymphocyte counts or percentages were observed between STAT3-HIES patients and HCs, regardless of infection status, indicating a limited effect of *STAT3* mutations on lymphocyte homeostasis. However, a decreasing trend was observed during infection relative to the infection-free periods, suggesting a possible, though statistically insignificant, suppressive effect of infection ($p > 0.05$; **Figure 3G**). Further studies with larger sample sizes are needed to confirm this observation. In comparison, Patient 1 with DOCK8 deficiency exhibited a more pronounced reduction in both parameters during infection (from 5.4 × 10^9/L to 1.68 × 10^9/L and from 60.2% to 35.5%; **Figure 3B**), indicating the infection state is a critical determinant of immune variability in HIES. In addition, compared with HCs, STAT3-HIES patients exhibited significantly elevated WBC counts both during active infection and infection-free periods [10.99×10^9/L (IQR: 8.7-16.43) vs. 5.6×109/L (IQR: 4.64-6.61), $p = 0.0022$; 8.74×10^9/L (IQR: 7.92-8.84) vs. 5.6×10^9/L (IQR: 4.64-6.61), $p = 0.0003$; **Figure 3F**].

During active infection, the neutrophil count was higher in STAT3-HIES patients than in HCs ($p = 0.0373$, **Figure 3H)**, and the absolute monocyte count was higher in STAT3-HIES patients than in both HCs and infection-free STAT3-HIES patients [0.75×10^9/L (IQR: 0.485-1.16) vs. 0.36×10^9/L (IQR: 0.295-0.6300), $p = 0.0062$; 0.75×10^9/L (IQR: 0.485-1.16) vs. 0.38×10^9/L (IQR: 0.25-0.58), $p = 0.0625$, **Figure 3I**].

STAT3-HIES patients exhibited significantly higher eosinophil counts and percentages than HCs in the absence of active infection [0.68×10⁹/L (IQR: 0.495–1.31) vs. 0.17×10⁹/L (IQR: 0.1125–0.3625), $p = 0.0018$; 9.0% (IQR: 5.7–14.9) vs. 2.6% (IQR: 1.625–5.175), $p = 0.0039$; **Figure 3J**]. In STAT3-HIES patients, elevated WBC counts might be driven by distinct cellular profiles depending on the infection status: eosinophils predominated during infection-free periods, whereas neutrophils and monocytes were the main contributors during active infection, indicating that infection specifically modulates leukocyte composition in these patients.

Characteristics of lymphocyte subsets in patients with HIES in both infectious and non-infectious states

Lymphocyte subsets in patients with HIES can vary between infectious and non-infectious states because of both immunodeficiency and the ongoing immune response to infections. Here, we provide an overview of how lymphocyte subsets typically behave in patients during different states. Initially, we investigated the alterations in lymphocyte subsets induced by gene mutations. Our results showed that in uninfected HIES patients, the absolute count and proportion of $CD3^+$ T, $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, and $CD19^+$ B lymphocytes, and the $CD4^+/CD8^+$ T cell ratio did not fall below the normal reference range **(Figure 4A-E)**. However, during active infection, the single *DOCK8*-deficient patient (Patient 1) exhibited absolute counts and percentages of CD3 +, CD4 +, and CD8 + T cells below the normal range, even at the lower end of the spectrum observed in the *STAT3*-deficient cohort. **(Figure 4A-F)**. Moreover, the

number and proportion of $CD16^+CD56^+$ NK cells were low in this patient **(Figure 4F)**.

Surprisingly, no significant differences were observed in the absolute counts of $CD3^+$ T cells, $CD3^+CD8^+$ T cells, $CD19^+$ B cells, or the $CD4^+/CD8^+$ ratio between STAT3-HIES patients and HCs, either during infection or in the infection-free period ($p > 0.05$ for all, **Figure 4G-L**). However, in specific comparative analyses, the absolute $CD3^+CD4^+$ T cell count showed a nonsignificant trend toward higher values in infection-free patients relative to HCs ($p = 0.0648$, **Figure 4H**), indicating that *STAT3* mutations appear to have minimal impact on these lymphocyte subsets. Furthermore, during active infection, patients showed lower absolute counts and proportions of $CD16^+CD56^+$ NK cells compared to HCs ($p = 0.0237$, $p = 0.0032$, respectively; **Figure 4K**), which is in agreement with previous reports that $CD16^+CD56^+$ NK cell levels are decreased as a consequence of cell exhaustion upon persistent infection [20]. Moreover, the proportion of $CD16^+CD56^+$ NK cells in the infection-free state was lower than that in HCs ($p = 0.0693$; **Figure 4I**), which might be influenced by other immune cell populations.

To determine the effect of infection on lymphocyte profiles, we compared the immunophenotypes of STAT3-HIES patients during active infection and infection-free periods. A comparative analysis of STAT3-HIES patients revealed a downward trend in absolute lymphocyte counts during active infection compared with the infection-free state, illustrated by the following paired median values (with IQR): $CD3^+$ T cells [2988 (2118–5051) vs. 2164 (972–2827) cells/μL], $CD3^+CD4^+$ T cells [1519 (1176–2325) vs. 1076 (461.8–1483) cells/μL], $CD3^+CD8^+$ T cells [1409 (851.3–2504) vs. 1001 (385–

1250) cells/μL], and $CD19^+$ B cells [809.5 (666.8–1084) vs. 472 (384.3–602.5) cells/μL]. These reductions did not reach statistical significance (all $p > 0.05$; **Figure 4G–K**), a result that may be attributable to the limited sample size. Meanwhile, in the single DOCK8-HIES patient, infection induced pronounced reductions across all major lymphocyte subsets: $CD3^+$ T cells (from 5025 to 341 cells/μL), $CD3^+CD4^+$ T cells (from 3071 to 192 cells/μL), $CD3^+CD8^+$ T cells (from 1831 to 130 cells/μL), $CD19^+$ B cells (from 2154 to 981 cells/μL), and $CD16^+CD56^+$ NK cells (from 629 to 66 cells/μL) (**Figure 4A-F**). Based on these findings, patients with HIES exhibited a decline in lymphocyte subsets during infectious episodes, especially in the single DOCK8-HIES patient; this decrease may reflect a mutation-associated state of functional lymphocyte depletion.

Alterations in immunoglobulin and complement levels in response to infection

We examined the role of immunoglobulins and complement proteins in reflecting the immune status of patients with HIES by measuring the serum levels of immunoglobulins, C3, and C4 in different states. Our results showed that IgE levels in both infected and non-infected patients with HIES were significantly higher than the upper limit of the normal reference range, which is consistent with the hallmarks of HIES [3, 21] **(Figure 5A)**. Moreover, IgM and IgG levels were somewhat elevated above the normal range, but IgA levels were generally within the normal range, independent of infection status **(Figure 5B-D)**. IgE levels were significantly elevated in both infected and non-infected HIES patients compared to those in HCs **(**$p = 0.0032$

and $p = 0.0103$**)**, but there was no significant difference between the infection and non-infection groups **(**$p > 0.05$, **Figure 5E)**. During active infection, STAT3-HIES patients exhibited significantly elevated levels of IgG, C3, and C4 compared with HCs ($p < 0.05$), whereas IgM showed a nonsignificant increase ($p = 0.0566$); **Figure 5E–F**]. During infection-free periods, these parameters did not differ significantly from those in HCs. Moreover, comparisons within STAT3-HIES patients between the infected and non-infected states showed no significant changes in immunoglobulin or complement levels (**Figure 5E–F**). Overall, these findings indicate that *STAT3* mutations predominantly influence IgE levels while exerting negligible direct effects on the homeostasis of other immunoglobulins and complement proteins. Remarkably, in the single DOCK8-HIES patient, infection was associated with marked declines in IgM (from 2.58 to 0.67 g/L), IgG (from 16.3 to 4.46 g/L), IgA (from 0.63 to 0.25 g/L), C3 (from 0.91 to 0.59 g/L), and C4 (from 0.14 to 0.07 g/L) levels compared to the infection-free period, a finding that is hypothesis-generating and requires validation in larger studies of DOCK8 deficiency.

In this study, high serum IgE levels were defined as >1000 IU/mL, which is a hallmark of HIES [3]. However, the relationship between IgE levels and disease progression remains unclear. Therefore, we monitored three patients admitted to our hospital and determined their infection status. The serum IgE level of Patient 2 remained consistently high during infection **(Figure 5G)**. However, the IgE level of Patient 3 fluctuated between high and low levels regardless of infection **(Figure 5H)**. In Patient 5, the serum IgE levels remained low from 10 to 15 years of age during both

infectious and non-infectious periods. The sole exception was a single elevated level recorded during a non-infected state at the age of 16 years and 4 months **(Figure 5I)**. These findings indicate that IgE levels in these patients were not significantly related to the infection status. It is also important to note that not all patients with HIES have elevated IgE levels; therefore, clinicians should be aware of the possibility of HIES in patients lacking high IgE levels. Notably, a gradual decline in IgE levels was observed in two STAT3-HIES patients (Patients 2 and 3) following HSCT (**Figure 5G, H**), which is consistent with previous reports [22, 23].

DISCUSSION

According to our retrospective investigation, STAT3-HIES patients exhibited clinical symptoms consistent with those previously documented, including eczema, recurrent skin and lung infections, and markedly elevated IgE levels [5, 24]. In this cohort, we identified a patient with novel compound heterozygous mutations in *DOCK8*, whose clinical and immunological characteristics aligned with those reported for other mutations in the gene [18, 25]. This suggests that mutations in the same gene may lead to similar deficiencies despite differences in mutation site. The single DOCK8-HIES patient showed more severe clinical and immunological abnormalities yet lacked the connective tissue and skeletal manifestations characteristic of STAT3-HIES, as previously described [4, 18].

Management of HIES primarily focuses on prophylactic and therapeutic interventions targeting infections, inflammation, and associated complications. In

contrast to DOCK8-HIES, HSCT is generally not advised as an initial treatment for STAT3-HIES because non-immunological symptoms persist, and serum IgE levels do not normalize post-transplantation [26]. In contrast to this general expectation, two STAT3-HIES patients (Patients 2 and 3) in our cohort achieved favorable outcomes following HSCT, including gradual normalization of serum IgE levels, a finding consistent with other reported cases in the literature [23]. These successful outcomes contribute to the evidence supporting HSCT as a treatment option for selected patients with severe disease manifestations.

It is a fundamental immunological tenet that infections can elicit immune responses, with different pathogens inducing distinct immune patterns [27, 28]. Accordingly, immunological characteristics in the absence of infection are more stable and reliable for analysis. Given that patients with HIES are often hospitalized for recurrent infections, previous reports of their immunological findings have not always distinguished between infected and non-infected states. This study showed that immune cell subsets during active infections differed from those observed during infection-free periods. In the absence of an active infection, alterations in immune cell subsets in patients with HIES are primarily driven by intrinsic immune system defects. In this cohort, compared with HCs, STAT3-HIES patients demonstrated significantly elevated peripheral white blood cell, neutrophil, and monocyte counts during active infection, along with sustained leukocytosis and increased eosinophil levels, even during infection-free periods. This pattern indicates a dual mechanism of leukocytosis in STAT3-HIES: during active infection, leukocytosis is primarily driven by increased

circulating neutrophils and monocytes, consistent with the classic innate immune response to pathogens [29, 30], whereas during infection-free periods, it appears to be predominantly mediated by eosinophils. Consistent with previous studies [31–33], our results confirmed an elevated eosinophil count in STAT3-HIES patients. Intriguingly, lymphocyte counts in STAT3-HIES patients did not differ significantly from those in HCs, irrespective of infection status. This immunophenotype stands in contrast to the marked infection-associated lymphopenia observed in the single DOCK8-deficient patient (Patient 1), which indicates that while *STAT3* and *DOCK8* deficiencies are both classified as HIES, they involve divergent underlying mechanisms of immune dysregulation, which in turn shape distinct clinical and immunological presentations during infection.

It should be noted that the data from the single DOCK8-HIES patient were presented descriptively as a single case rather than pooled with or directly compared statistically with the STAT3-HIES cohort. Thus, future studies with larger genetically defined cohorts are needed to validate and compare infection-induced lymphopenia between patients with STAT3-HIES and DOCK8-HIES.

The lymphocyte subset profiles of patients with HIES were analyzed. Except for $CD16^+CD56^+$ NK cells, the absolute counts and proportions of $CD3^+$ T cells, $CD3^+CD4^+$ T cells, $CD3^+CD8^+$ T cells, and $CD19^+$ B cells in infection-free HIES patients were generally within the normal reference range **(Figure 4A-E)**. As is well known, *STAT3* and *DOCK8* mutations share similar clinical manifestations [34] but differ in their regulatory mechanisms [24, 35]. *STAT3* mutations primarily affect Th17

differentiation and Th17-mediated immune responses, leading to fungal and bacterial susceptibility, while preserving B cell function and having less impact on NK cells [6]. In our cohort of STAT3-HIES patients, the baseline lymphocyte subset counts during non-infectious states were comparable to the reference values. This suggests that, in STAT3-HIES, the mutated gene does not intrinsically cause severe baseline lymphopenia in these subsets. However, during active infection, STAT3-HIES patients showed a decreasing trend in the absolute counts of these lymphocyte subsets relative to their non-infectious state. Therefore, in STAT3-deficient patients, the reduction in lymphocyte counts observed during active infection may reflect a combination of factors, including immune exhaustion and lack of appropriate immune regulation during the inflammatory response, rather than an inherent immunological trait of the condition, which warrants further investigation. Unfortunately, the potential impact of STAT3 mutations on Th17 cell frequency could not be assessed in this study because of Th17 cells were not included in the flow cytometry analysis. Furthermore, B-cell and complement functions appeared to be preserved in patients with STAT3-HIES patients, as evidenced by comparable baseline levels to HCs and a significant infection-driven increase in IgM, IgG, C3, and C4. In contrast, *DOCK8* mutations cause widespread immune dysfunction, affecting T, B, and NK cells, resulting in more severe immune deficiency and chronic infections [11, 14]. In our cohort, the single DOCK8-deficient patient showed absolute counts and percentages of $CD3^+$ T, $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, $CD19^+$ B, and $CD16^+CD56^+$ NK cells below the normal range, together with widespread declines in lymphocyte subsets, immunoglobulins (IgM, IgG, and IgA) and

complement levels (C3 and C4) during active infection compared to the infection-free period. This observation further supports the hypothesis that DOCK8 mutations lead to broad immune dysregulation. Given the limitation of a single case, these findings should be considered hypothesis-generating and require validation in future studies involving larger DOCK8-deficient cohorts.

Serum IgE levels in HIES patients typically range from several thousand to even millions of IU/mL, according to previous studies [21]. However, our results showed that not all patients consistently exhibited extremely high IgE levels, even though elevated IgE levels are considered a hallmark of HIES **(Figure 5)**. The potential molecular regulatory mechanism of the IgE increase caused by HIES-related gene mutations requires further exploration. Therefore, when a child has recurrent abscesses or other immune-related features, even without elevated IgE levels (≤1000 IU/mL), clinicians should remain alert to the possibility of HIES. Whether caused by *DOCK8* or *STAT3* mutations, the diagnosis of HIES involves a multistep approach incorporating clinical assessment, immunological evaluation, and genetic testing. While genetic testing provides a definitive diagnosis, immunological profiling, such as flow cytometry analysis of T, B, and NK cells, as well as the measurement of serum IgE levels, can offer critical diagnostic clues, particularly in the early disease stages or in the absence of genetic confirmation.

Limitations of the study

This retrospective study has two primary limitations. First, because of the rarity of

the disease, its exploratory design, and small sample size, larger follow-up studies are needed to confirm the generalizability of the findings. Second, because of inherent practical and ethical constraints, the absence of an infected healthy control group prevents us from determining whether the observed immune changes are disease-specific or represent a general infection-driven response. Future studies should employ larger cohorts and appropriate control groups. Furthermore, experimental studies, including studies using animal models (e.g., mice), may help clarify the specific effects of immunodeficiency and infection on lymphocyte number and function.

CONCLUSIONS

In conclusion, this study provides key insights into infection-driven immune variability in HIES, challenges the diagnostic overreliance on serum IgE levels, and reports favorable post-HSCT immune changes in two patients with STAT3-HIES. Furthermore, this study provides a detailed phenotypic analysis by characterizing dynamic changes in immune parameters. It uses nonparametric tests for paired samples and emphasizes effect sizes and biological consistency, providing a clinical-level overview of the immune profile rather than delving into upstream molecular mechanisms. These findings may support informed clinical interpretation of laboratory results and highlight the importance of testing timing (“when to test”).

List of abbreviations

ACMG/AMP: American College of Medical Genetics and Genomics/Association for

Molecular Pathology

AD-HIES: Autosomal dominant hyper-IgE syndrome

AR-HIES: Autosomal recessive hyper-IgE syndrome

DOCK8-HIES: DOCK8-associated hyper-IgE syndrome

gnomAD: Genome Aggregation Database

HC: Healthy control

HIES: Hyper-IgE syndrome

HLA: Human leukocyte antigen

HRCT: High-resolution computed tomography

hs-CRP: High-sensitivity C-reactive protein

HSCT: Hematopoietic stem cell transplantation

IEI: Inborn errors of immunity

IQR: Interquartile range

IVIG: Intravenous immunoglobulin

MAF: Minor allele frequency

NK: Natural killer

PCR: Polymerase chain reaction

PCT: Procalcitonin

STAT3-HIES: STAT3-associated hyper-IgE syndrome

STR: Short tandem repeat

Th17: T helper 17

Treg: Regulatory T cell

VUS: Variant of uncertain significance

WBC: White blood cell

WES: Whole-exome sequencing

Declarations

Ethics approval and consent to participate

This study was approved by the Wuhan Children's Hospital Committee for Research Ethics (approval no. 2025R015-E01) and was performed in accordance with the Declaration of Helsinki. Written informed consent to participate was obtained from the patients' legal guardians.

Consent for publication

Not applicable.

Availability of data and materials

All data reported in this article are publicly available as of the date of publication. Zhong, Yucheng (2025), "Immunological Features in Hyper-IgE Syndrome: A Comparison of Infectious and Non-Infectious States", Mendeley Data, V1, doi: 10.17632/4jcmwxxhv7.1. This article does not report any original code.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Conceptualization, Hongxia Tang, Yi Liu and Yucheng Zhong; methodology, Hongxia Tang, Yi Liu, Wen Yin; Investigation, Yanmei Huang, Wen Yin, Yali Wu, and Yi Liu, writing—original draft, Hongxia Tang, Yi Liu and Yanmei Huang; writing—review & editing, Hongxia Tang, Yi Liu and Yucheng Zhong; funding acquisition, Hongxia Tang; resources, Yucheng Zhong and Hongxia Tang; supervision, Hongxia Tang and Yucheng Zhong

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Figure legends

Figure 1. Genetic characterization of *DOCK8* and *STAT3* mutations in patients with HIES

(A) Sanger sequencing results of patient 1 and his parents. (B) Schematic representation of the compound heterozygous DOCK8 mutations in patient 1. Variant interpretation of the DOCK8 gene. According to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) 2015 guidelines, both identified variants (c.5346C>G and c.36C>G) were classified as variants of uncertain significance (VUS). The c.5346C>G variant met PM1, PM2, and PP3 criteria, while the c.36C>G variant met PM1 and PM2. The proband carries these variants in a compound heterozygous state, consistent with the autosomal recessive inheritance pattern of DOCK8-related disease, and the clinical phenotype is concordant with DOCK8 deficiency. PM1: Missense variant located in a well-studied functional domain of the exon with no benign variants reported (no benign variants in ClinVar). PM2: Minor Allele Frequency (MAF) < 0.005, indicating a low-frequency variant. PP3: Multiple computational predictions suggest a deleterious effect on the gene product, based on conservation and protein structure analysis (SIFT, Polyphen2_HDIV,

642 Polyphen2_HVAR, PROVEAN, Mutation Taster, M-CAP, GERP). (C) Schematic
643 representation of STAT3 mutations identified in five patients.
644
645 **Figure 2. Chest HRCT findings in patients with STAT3 mutations**
646 (A) Patient 2 showing severe pulmonary inflammation and consolidation. (B) Patient 3
647 demonstrating right lower lobe pneumonia with consolidation, cavitation, and necrosis.
648 HRCT, high-resolution computed tomography.
649
650 **Figure 3. Changes in leukocyte profiles in HIES patients with and without active**
651 **infections**
652 (A–E) Graphical representation of white blood cell (A), lymphocyte (B), neutrophil
653 (C), monocyte (D), and eosinophil (E) counts in patients during infection-free and
654 active infection states. Shaded areas indicate age-adjusted normal ranges. (F–J)
655 Statistical comparisons of white blood cell (F), lymphocyte (G), neutrophil (H),
656 monocyte (I), and eosinophil (J) counts among HCs and patients with STAT3-HIES,
657 with or without active infections. Statistical analysis: The Mann–Whitney U test was
658 used for comparisons with healthy controls; the Wilcoxon signed-rank test was used for
659 paired infection vs. infection-free states. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.
660
661 **Figure 4. Characteristics of lymphocyte subsets in HIES patients with and without**
662 **active infections**
663 (A–F) Graphical representation of $CD3^+$ T cells (A), $CD3^+CD4^+$ T cells (B), $CD3^+CD8^+$

T cells (C), $CD4^+/CD8^+$ ratio (D), $CD19^+$ B cells (E), and $CD16^+CD56^+$ NK cells (F) in HIES patients during infection-free and active infection states. Shaded areas indicate age-adjusted normal ranges. (G–L) Statistical comparisons of $CD3^+$ T cells (G), $CD3^+CD4^+$ T cells (H), $CD3^+CD8^+$ T cells (I), $CD19^+$ B cells (J), $CD16^+CD56^+$ NK cells (K), and $CD4^+/CD8^+$ ratio (L) among healthy controls and STAT3-HIES patients with or without active infections. Group comparisons were performed using the Mann–Whitney U test, and paired analyses were performed using the Wilcoxon signed-rank test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Figure 5. Alterations in immunoglobulin and complement levels in HIES patients with and without active infections

(A–D) Graphical representation of IgE (A), IgM (B), IgG (C), and IgA (D) levels in HIES patients during active infection and infection-free states. Shaded areas indicate age-adjusted normal ranges. (E–F) Statistical comparisons of IgE, IgM, IgG, and IgA (E) as well as C3 and C4 (F) levels among healthy controls and STAT3-HIES patients with or without active infections. (G–I) Longitudinal monitoring of IgE levels in STAT3-HIES patients. Red dots indicate active infection states and blue dots indicate infection-free states. HSCT, hematopoietic stem cell transplantation. The Mann–Whitney U test was used for comparisons between patients and healthy controls, and the Wilcoxon signed-rank test was used for paired comparisons between infectious and infection-free states. *$p < 0.05$.

685 **Table 1.** Clinical features of patients with *STAT3* and *DOCK8* mutations

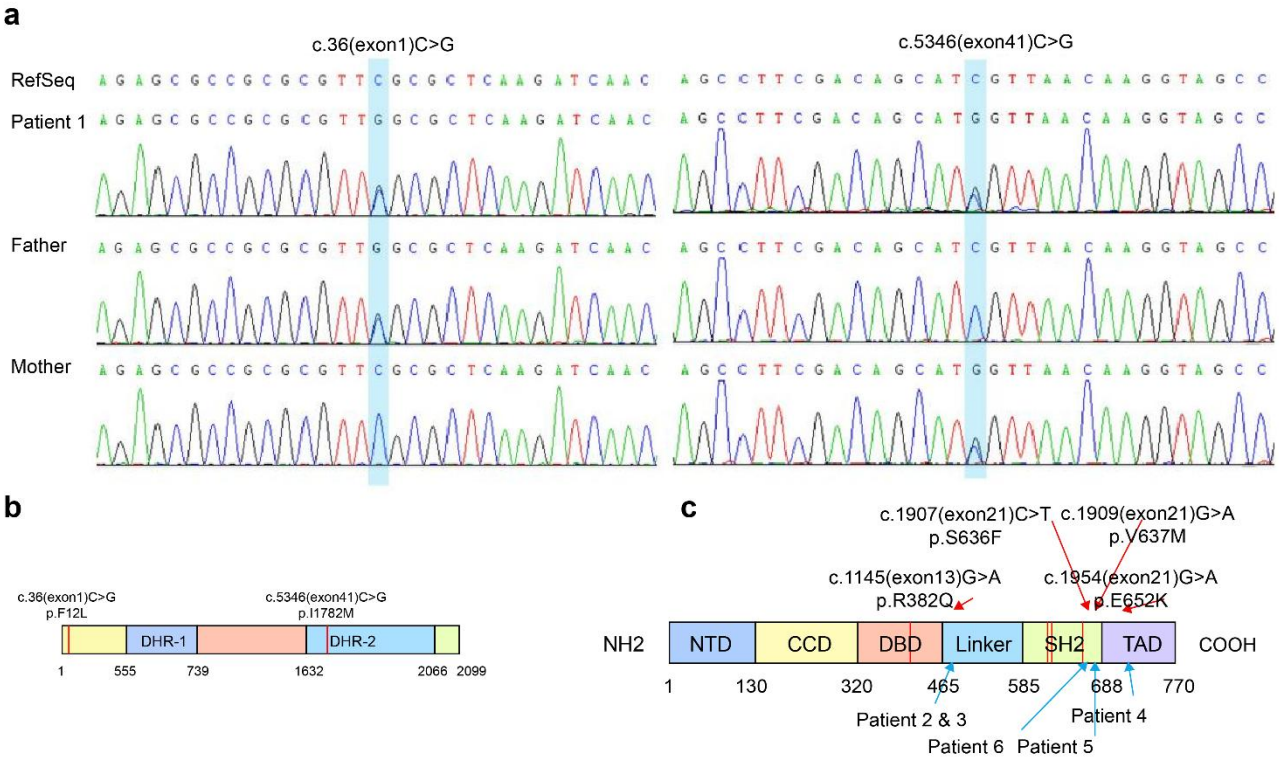
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Type of mutations	**DOCK8 c.36C>G/5346C>G(NM 203447.4)**	**STAT3 (c.1145(exon13) G>A)**	**STAT3 (c.1145(exon13) G>A)**	**STAT3 (c.1954(exon21) G>A)**	**STAT3 (c.1909(exon21) G>A)**	**STAT3 (c.1907(exon21) C>T)**
Age at Genetic Diagnosis	1y4m	10y6m	2y5m	10y5m	1y8m	8y
Age at Sampling (Infectious)	1y3m					
Age at Sampling (Non-infectious)	1y4m					
Sex	Male	Female	Male	Female	Female	Male
Types of	impetigo and abscesses	Trunk and orbital	Suppurative	Suppurative	NA	Left

infections	in skin and soft tissues	abscess	otitis media, diarrhea	submandibular adenitis; Multiple soft cluster infections of the torso		maxillofacial and submaxillary soft tissue cellulitis
Pathogens*	*Pseudomonas aeruginosa*, herpes virus	*Aspergillus fumigatus*	*Staphylococcus aureus*, *Streptococcus pneumonia*, Rhinovirus, Adenovirus, Cytomegalovirus	Epstein-Barr virus, Methicillin-resistant *Staphylococcus aureus*, mycoplasma	*Escherichia coli*, *Staphylococcus aureus*	NA
Facial features	-	+	+	+	+	+

Skeletal abnormality	NA	retained primary teeth	NA	retained primary teeth	NA	NA
Chest HRCT	Normal	Consolidation with focal necrosis in the right middle and lower lobes	Double lung pneumonia; Right lower lobe pulmonary consolidation; Right lower lobe pulmonary necrosis; pulmonary cavity	Normal	Mediastinal cyst	Pulmonary cyst
Eczema	NA	+	+	+	+	+

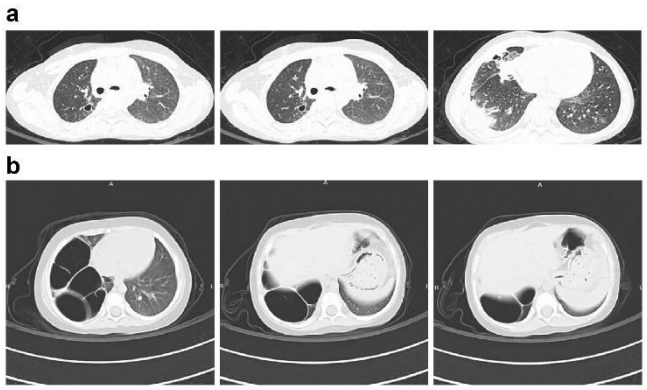
HSCT	-	+	+	-	-	-

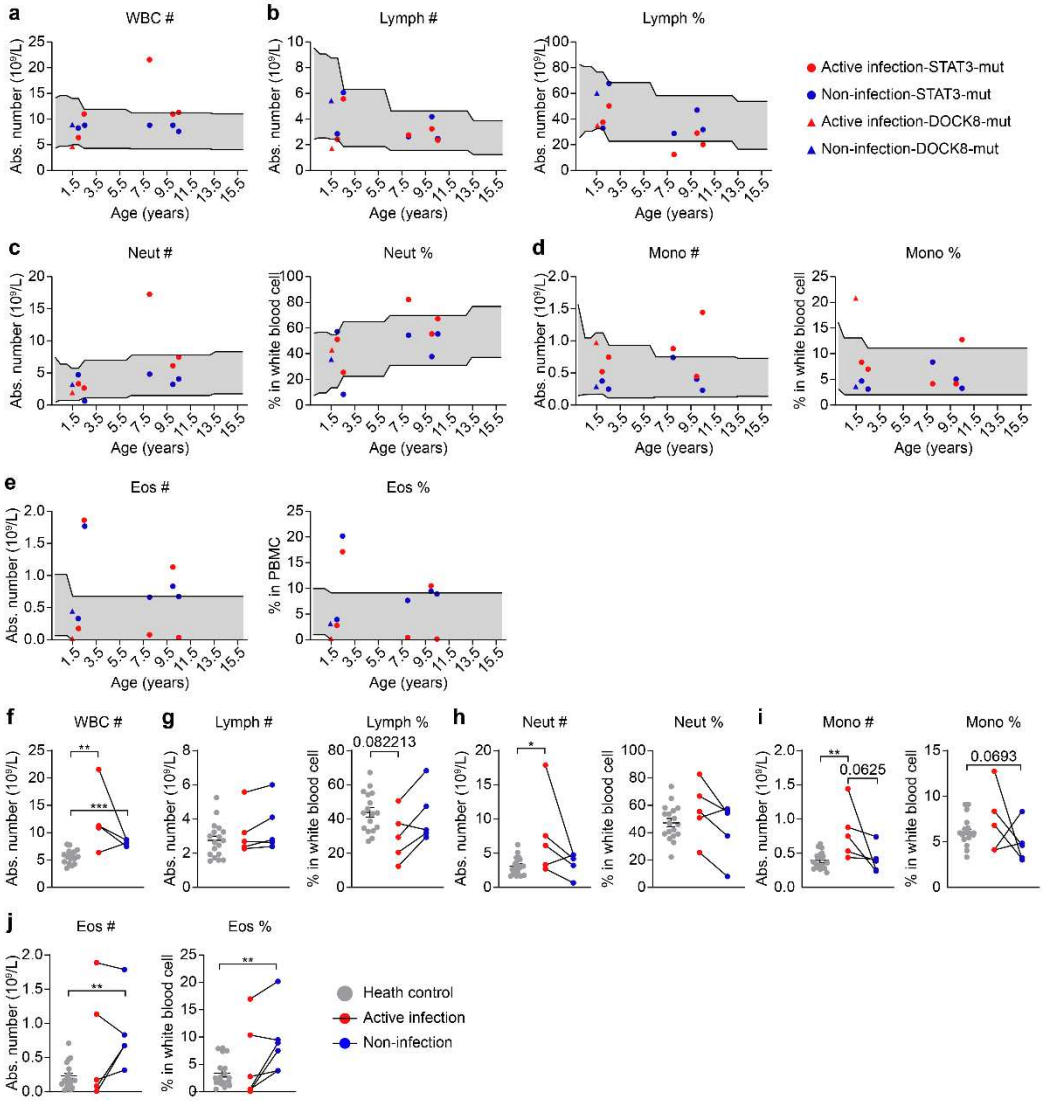
STAT3, signal transducer and activator of transcription 3; DOCK8, dedicator of cytokinesis 8; NA, not available; HRCT, high-resolution computed tomography; y, years; m, months; HSCT, hematopoietic stem cell transplantation; -: No; +: Yes; *, Pathogens listed for infectious episodes correspond to those clinically identified and/or microbiologically confirmed at the time of peripheral blood sampling for immunological assays.

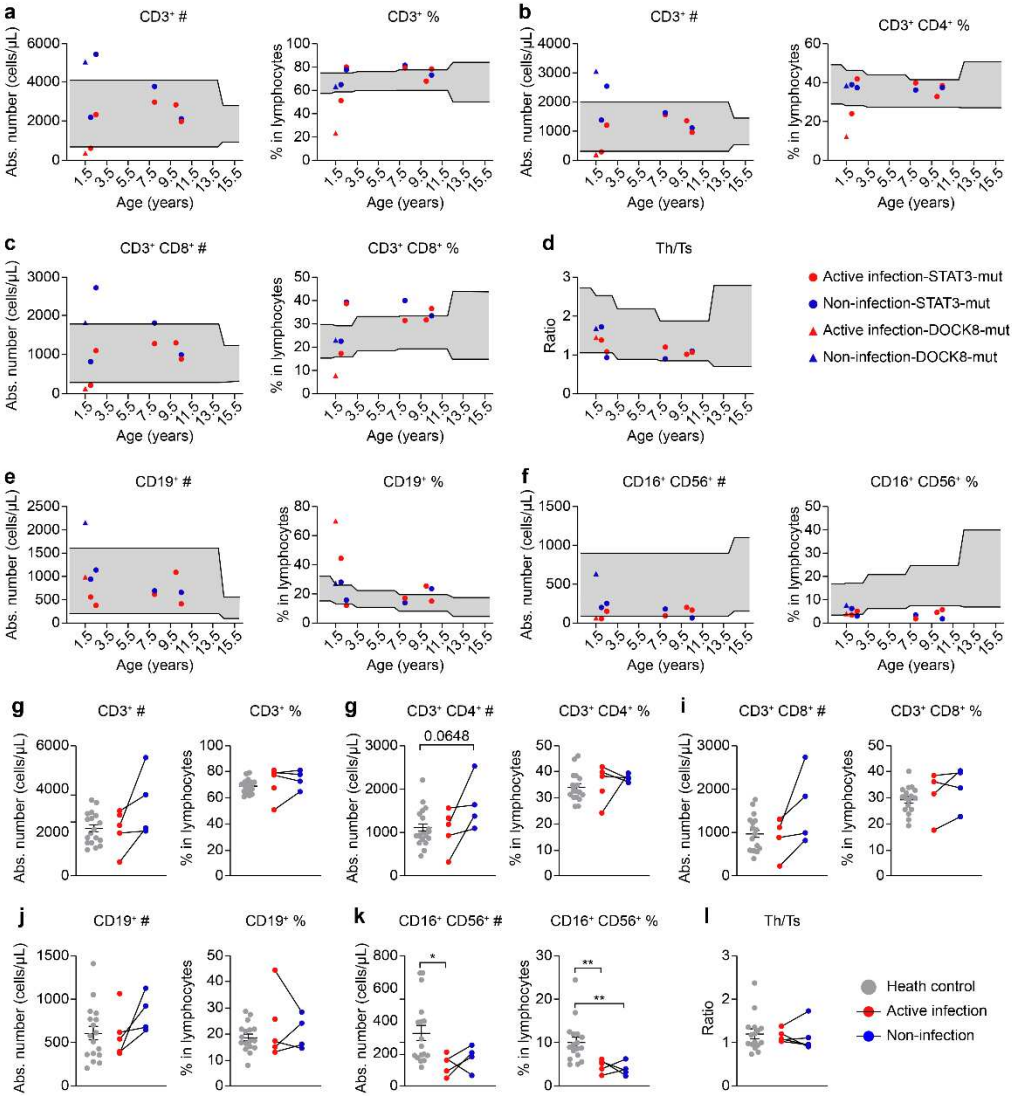

a
c.36(exon1)C>G
c.5346(exon41)C>G
RefSeq
Patient 1
Father
Mother
b
c.36(exon1)C>G
p.F12L
c.5346(exon41)C>G
p.I1782M
DHR-1
DHR-2
1
555
739
1632
2066
2099
c
c.1907(exon21)C>T
p.S636F
c.1909(exon21)G>A
p.V637M
c.1145(exon13)G>A
p.R382Q
c.1954(exon21)G>A
p.E652K
NH2
NTD
CCD
DBD
Linker
SH2
TAD
COOH
1
130
320
465
585
688
770
Patient 2 & 3
Patient 6
Patient 5
Patient 4

691

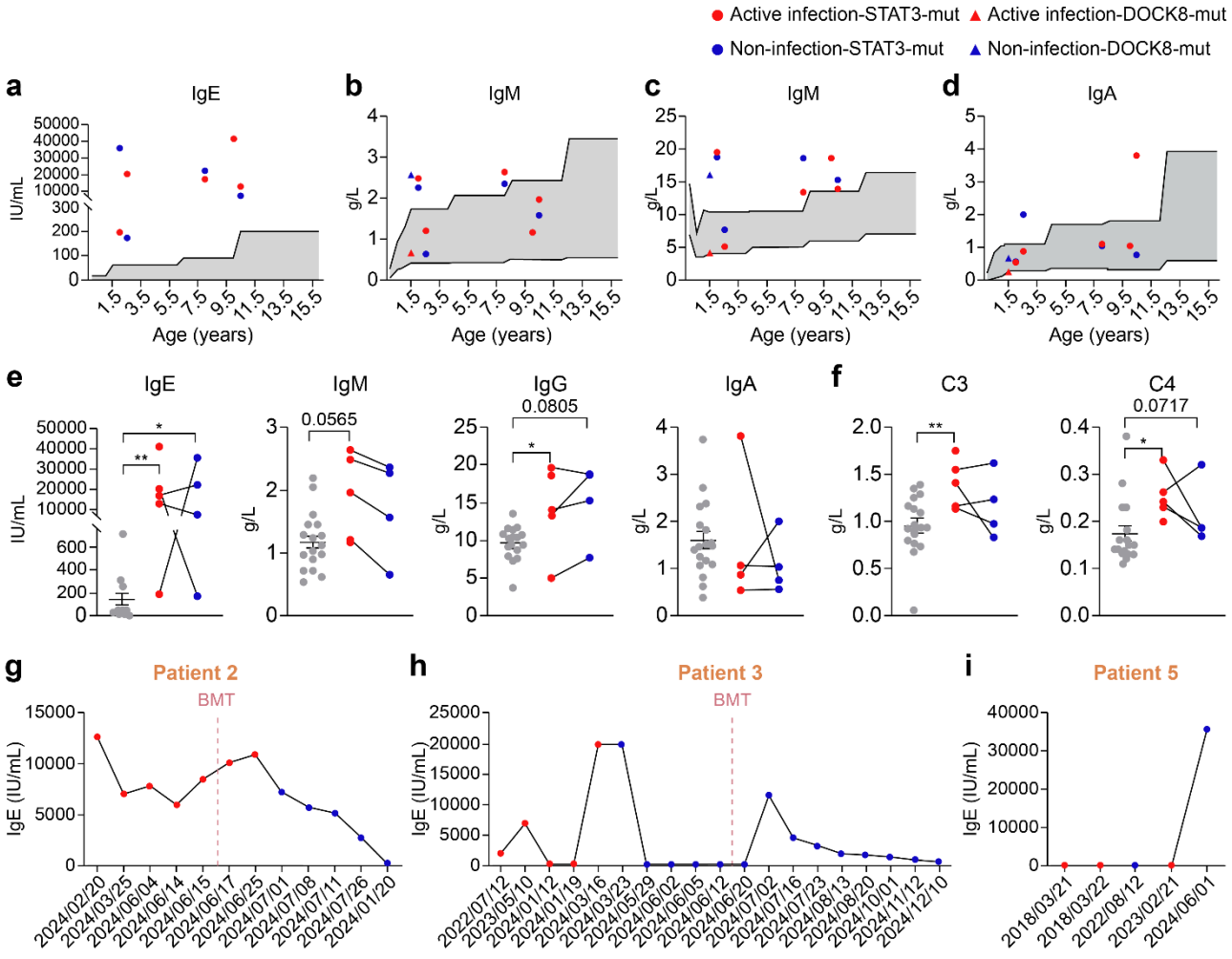
692




a
WBC #
b
Lymph #
Lymph %
Abs. number (10⁹/L)
Age (years)
Active infection-STAT3-mut
Non-infection-STAT3-mut
Active infection-DOCK8-mut
Non-infection-DOCK8-mut
c
Neut #
Neut %
% in white blood cell
d
Mono #
Mono %
e
Eos #
Eos %
% in PBMC
f
g
h
i
j
0.082213
0.0625
0.0693
Heath control
Active infection
Non-infection


a
CD3+ #
CD3+ %
b
CD3+ #
CD3+ CD4+ %
c
CD3+ CD8+ #
CD3+ CD8+ %
d
Th/Ts
e
CD19+ #
CD19+ %
f
CD16+ CD56+ #
CD16+ CD56+ %
g
CD3+ #
CD3+ %
g
CD3+ CD4+ #
0.0648
CD3+ CD4+ %
i
CD3+ CD8+ #
CD3+ CD8+ %
j
CD19+ #
CD19+ %
k
CD16+ CD56+ #
*
CD16+ CD56+ %
**
**
l
Th/Ts
Abs. number (cells/μL)
% in lymphocytes
Ratio
Age (years)
Active infection-STAT3-mut
Non-infection-STAT3-mut
Active infection-DOCK8-mut
Non-infection-DOCK8-mut
Heath control
Active infection
Non-infection

694


Active infection-STAT3-mut
Active infection-DOCK8-mut
Non-infection-STAT3-mut
Non-infection-DOCK8-mut
a
IgE
IU/mL
Age (years)
b
IgM
g/L
Age (years)
c
IgM
g/L
Age (years)
d
IgA
g/L
Age (years)
e
IgE
IgM
IgG
IgA
0.0565
0.0805
f
C3
C4
0.0717
g
Patient 2
BMT
IgE (IU/mL)
h
Patient 3
BMT
IgE (IU/mL)
i
Patient 5
IgE (IU/mL)