The clinical, immunological and genetic features of 12 Chinese patients with STAT3 mutation

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Abstract
Background: Loss-of-function (LOF) mutation in signal transducer and activator of transcription 3 (STAT3) was one of the causes of the hyper immunoglobulin E (IgE) syndrome (HIES), while gain-of-function mutation (GOF) in STAT3 leads to immune dysregulation diseases. We retrospectively report 11 LOF STAT3 patients and 1 GOF STAT3 patient and illustrate their onset age, common clinical symptoms, immunologic and molecular manifestation.

Methods: 12 patients were enrolled in our study. Serum immunoglobulins, lymphocyte subset detection and whole-exome sequencing were performed.

Results: The median onset age of STAT3-deficient patients was 1.89 years. Eczema, recurrent respiratory infection, apparent fever, abscesses and Staphylococcus aureus infection was the classical manifestation. Elevated serum IgE level is not entirely unanimous with high eosinophils counts. Moderate viral DNA was also measured in peripheral blood mononuclear cells. We noticed that c.1144C>T was the most common spot, followed by c.1311C>A. Additionally, c.1311C>A and c.1826G>C are two novel mutations. Eight patients obtained a notable improvement after received intravenous immunoglobulin (IVIG).

Conclusion: We believe IVIG may help reduce the opportunity of infection in STAT3-deficient patients. Significant variance at onset age probably is a great challenge for clinicians and urgently needs early diagnosis and treatment.

1. Background
Loss-of-function mutation (LOF) in the signal transducer and activator of transcription 3 (STAT3) gene was one of the underlying causes of the autosomal dominant (AD) hyper immunoglobulin E (IgE) syndrome (HIES) [1]. HIES were first described as Job syndrome in 1966, characterized by eczematous dermatitis, recurrent skin, pulmonary abscesses and elevated serum IgE levels [2-4]. Non-immunological abnormalities consisted of bone abnormalities, retained shedding primary teeth, failure of growth and specific facial features [5]. There was no difference between gender and ethnic [6]. Staphylococcus aureus and candidiasis were the most common pathogen [7]. Meanwhile, STAT3-deficient patients were increasing susceptibility to bacterial and fungal infections and presented a
poor ability to control Epstein-Barr virus (EBV) and Varicella-zoster virus (VZV) [8].
The use of antibiotics and complications prevention was recommended as the treatment strategies for
STAT3-deficient patients, while hematopoietic stem cell transplantation (HSCT) was not valid [9].
On the other hand, gain-of-function mutation (GOF) in STAT3 was associated with multiorgan
autoimmune disorders and immunodeficiency. The immunosuppressive therapy and targeted
biotherapy were recommended to those patients [10].
Herein, we depict a cohort of 12 Chinese patients who carrying STAT3 mutation about their clinical,
immunologic and genetic performance. Our description helps to expand the spectrum of STAT3
mutation diseases in different ethnic groups.
2. Methods
2.1 Patients
We collected 12 patients in Children's Hospital of Fudan University from July 2017 to June 2019.
Written informed consent was obtained from all participant's guardians before enrolling in the study.
The study was approved by the Ethics Committee of the Children's Hospital of Fudan University.
2.2 Serum immunoglobulins and lymphocyte subset detection
As previously reported [11], serum IgG, IgA and IgM were determined by automated clinical chemistry
analyzer (Erba Diagnostics, Mannheim, Germany). IgG (Cat. No.67731), IgA (Cat. No.67746) and IgM
(Cat. No.67732) reagents were all purchased from Orion Diagnostica Oy (Espoo, Finland). IgE reagent
was purchased from Jing yuan Corp (Shanghai, China) and was assessed by UniCAP (Pharmacia,
Uppsala, Sweden).
Flow cytometry is following our previous statement [12]. Briefly, staining for lymphocyte surface
markers was performed after red blood cell lysis. After washing with cold phosphate buffer solution
containing 2% FBS two times, $1 \times 10^4$–$5 \times 10^4$ live cells were analyzed by FACSCalibur flow cytometer
(Becton Dickinson, Franklin Lakes, NJ, USA) using Diva software (BD Biosciences). B cells, Total T cells,
CD4 T cells, CD8 T cells and CD56+/CD16 + natural killer (NK) cells were detected by the BD Multitest
IMK Kit. T-cell subsets was defined by: anti-human CD3 (PerCP-Cy5.5), anti-CD8 (BV510), anti-CD4
(FITC; fluorescein isothiocyanate), anti-CD27 (APC; allophycocyanin), anti-CD45RA (PE-Cy7), anti-
TCRαβ (PE; phycoerythrin) and anti-TCRγδ (BV421). The following were used define B-cell subsets:
anti-CD19 (APC), anti-human CD24 (PE), anti-CD27 (BV450), anti-CD38 (PerCP-Cy5.5) and anti-IgD (BV510) (BD Biosciences).

2.3 Whole exome sequencing (WES)
WES and analysis protocols were adapted for genetic analysis. Briefly, genomic DNA samples were extracted from the whole blood of those patients and their parents. Then, genomic DNA fragments were enriched for the target region of the consensus coding sequence exons and subsequently sequenced on the HiSeq2000 sequencer (Illumina, San Diego, CA). The raw data were mapped to the human genome reference sequence (hg19). Nucleotide changes observed in more than 5% of aligned reads were called and reviewed by using NextGENe software (SoftGenetics, State College, PA). Mutations in STAT3 were confirmed by using Sanger sequencing. DNA was extracted from those patients and relatives. Peripheral blood mononuclear cells (PBMCs) were isolated using the RelaxGene Blood DNA System (Tiangen Biotech, Beijing, China) according to the manufacturer's protocol. Primers were designed to span each exon and PCR amplification of STAT3 was carried out at 94 °C for 3 min, followed by 35 cycles of 94 °C for 30 sec, 60 °C for 30 sec and 72 °C for 40 sec. The final extension was performed at 72 °C for 10 min. The PCR product was sequenced in both directions by ABI Prism BigDye terminators.

2.4 Statistical analysis
Data management and statistical analysis were performed by using GraphPad Prism 8 software (GraphPad Software, La Jolla, Calif).

3. Results
3.1 Overview
Table 1 showed the general information of patients. A total of 12 patients, including seven males and five females, were all from nonconsanguineous families. 11 patients were diagnosed with STAT3 LOF mutation and one patient (P12) was STAT3 GOF mutation. 11 STAT3-deficient patients were diagnosed at a median age of 4.74 years (0.5–12 years old) while median onset age was 1.89 years (neonate-11.5 years old), involving in 5 infantile-onset patients (P1, P7, P8, P10 and P11). The onset age of STAT3 GOF patient was 13 years. All the patients were full-term gestation, either cesarean Sect. (2/12) or vaginal delivery (10/12).

3.2 Infectious complications of 11 STAT3 LOF patients
All patients suffered from eczema, especially in facial and scalp areas. More seriously, some of eczema spread from scalp to truncus. Recurrent respiratory infection was most common in our patients (11/11). Moreover, the infection also had been found in other systems, such as otitis media in 5 (P1, P3, P4, P5 and P6), rhinitis in 1 (P10) and diarrhea in 2 (P7 and P8). Rotavirus was detected in P8. *Staphylococcus aureus* infection was one of the noteworthy characteristics in STAT3-deficient patients. Almost half of the patients (P2, P3, P4, P5, P7 and P9) was recognized as *Staphylococcus aureus* pneumonias confirmed by either sputum, blood, or bronchoalveolar lavage fluid (BALF) culture. Abscesses were occurred in 8 patients in a different body part, consisting of the lung in 5 (P2, P3, P7, P9 and P10), the scalp in 4 (P2, P4, P7 and P10), the abdomen in 1(P7) and the buttock in 1(P1). What’s more, P7 and P10 implemented partial lung lobectomy. In our patients, about half of them (5/11. P3, P5, P6, P8 and P9) remarkably accompanied with chronic mucocutaneous candidiasis (CMC) verified by microscopic examination of fungal or fungal culture. Eight patients (8/11. P2, P4, P5, P6, P7, P9, P10 and P11) had a fever. (Figure. 1).

EBV-DNA was measured in PBMCs for 2 out of 11 patients (P7 and P10) and the viral load was 9.00E + 03 and 2.60E + 03, respectively. Cytomegalovirus (CMV)-DNA was also detected in blood, urine and BALF for two patients (P6 and P10) with the virus load in 8.69E + 04 and 2.00E + 05, respectively.

### 3.3 Immunological presentation of 11 STAT3 LOF patients

Eosinophil count increased in different degrees (470 ~ 5860 cells/µL, reference range: 30–500 cells/µL). (Table 1). Elevated serum IgE concentration was considered as one of the most prominent characteristics in STAT3-deficient patients. Apart from P8 (67.2 KU/L) and P11 (43.87 KU/L), other patients encountered high serum IgE levels range from 1841.29 KU/L to 17310.4 KU/L (the average value range was < 100 KU/L). IgG, IgA and IgM level approximately remained normal. (Table 2).

Lymphocytes roughly remained normal in patients, although the absolute number of Total T cells (in P1 and P4), CD4 T cells (in P4 and P7) and Total B cells (in P5 and P7) slightly increased. Four patients (P3, P7, P9, P10) had decreased NK cells. (Table 2). At the same time, we performed T cells and B lymphocytes subpopulation for three patients who had will to draw blood. All of them presented with ascended double-negative T cells and decreased memory B cells. P8 had two-fold higher effector
memory cytotoxic T cells while P9 presented two-fold higher terminally differentiated effector memory cytotoxic T cells. P4 showed dramatic decline in γδ T cells. (Table 3).

### 3.4 Non-immunological abnormalities of 11 STAT3 LOF patients

Two patients (2/11. P5 and P7) suffered from growth retardation. Retention of primary teeth also happened in three patients (3/11. P1, P2 and P7). Three patients (3/11. P1, P5 and P7) experienced facial features. Broad nose and high-arched palate were displayed in P1. Meanwhile, P5 showed coarse facies and prominent forehead, the same with P7. Skeletal abnormality, principally pigeon chest, only occurred in P7. Furthermore, enlarged lymph nodes, particularly in the cervical and inguinal region could be observed in 4 patients (P2, P4, P6 and P7). Splenomegaly was detected in P5 and P7, and the former also suffered from enlargement of the liver. Furthermore, P5 and P10 appeared food allergy. (Figure. 1).

As previously reported [13], the National Institutes of Health (NIH) scores were the most common accepted clinical STAT3-deficient diseases scoring system. In our study, 5 out of 11 patients reached or exceeded 40 points and two patients (P8 and P11. They had been evaluated 27 and 21 scores, respectively) were below the diagnostic standard.

### 3.5 The patient harboring STAT3 GOF mutation

P3 suffered from repeated cough, nasitis, diarrhea and CMC. Diffusely enlarged lymph node and hepatosplenomegaly was found in this patient. She also presented autoimmune hemolytic anemia, reduced white blood cells and platelet, acratia, diabetes, alopecia and delayed pubertal development. IgE level was 221.65 KU/L. For the lymphocyte subsets, the patient suffered from a severe reduction of all kinds of lymphocytes. EBV-DNA viral load was 4.05E + 04 in PBMCs and mycoplasma viral load was 2.42E + 08.

### 3.6 Mutation of STAT3 gene

WES suggested those patients had heterozygous mutations in STAT3. (Figure. 2). As shown in Table 1 that other variants were all de novo mutation type except for P11 whose variants derived from his father (c.994C > A; p.H332N). We noticed that c. 1144C > T(R382W) was the most common spot in our study, which was identified in 3 patients (27.27%), followed by c. 1311C > A(H437Q) in 2 patients (18.18%). H437Q and R609T were two novel mutations that could not be found in OMIM and clinvar.
databases. Moreover, H437Q and R609T were supposed as disease-causing in Mutationtaster; meanwhile they were also predicated as a deleterious mutation by software PopViz [14]. (Figure. 3). What's more, the mutation for the GOF STAT3 patient was a known mutation (1261G > A; p.G421R) and proven to be GOF by Milner [15].

3.7 Therapy
All the 11 STAT3 LOF patients were given prophylactic antimicrobials and symptomatic treatment. Eight patients (P1, P2, P3, P4, P5, P6, P8 and P11) obtained a notable improvement of their eczema, respiratory infection and candida infections after received intravenous immunoglobulin (IVIG) in the dose of 400–600 mg/kg/m. The GOF STAT3 patient received treatment with the anti-IL6R monoclonal antibody tocilizumab and got a stable condition with less alopecia, normal blood glucose and less infection.

4. Discussion
In this study, we retrospectively report 12 patients caused by STAT3 mutation, all from unrelated patients. Most STAT3-deficient patients develop clinical presentations at an average age of 1.89 years. Our patients have a wide range of differences in onset age from neonates to adolescence. Furthermore, the most common clinical symptoms are respiratory tract, cutaneous infection, especially in recurrent eczema, abscess and fever. Likewise, consistent with previous reports [16, 17], we identify that the high incidence of recurrent Candida albicans infections, which is correlated with damaged IL-17 and IL-22 response. However, limited by actual situation, we do not do a related functional experiment in five patients who suffered from CMC. Additionally, there is no patient faced with Aspergillus infection, different from that 17.5% of STAT3-deficient patients occurred aspergillosis in lung cavities [18]. More than half of the patients go through otitis media so that we also should pay attention to the auricular region in STAT3-deficient patients, as previously reported [19]. It had been described previously that gastrointestinal inflammation developed as a part of the manifestations of STAT3 LOF mutation disease [20]. However, diarrhea only occurred in 2 patients in our study. Different from two large-scale STAT3-deficient cohort studies in China [21–23], a few patients emerge classical non-immunological features, including special faces, dental and developmental abnormality.
Because this is a retrospective analysis and doctors are likely to neglect some slight facial changes especially numerous patients was young when they first visited our hospital. The lesser incidence of primary teeth retention maybe because they are young and not at an age at which their teeth should fall out. Lack of scoliosis in our patients can be explained by many are young, and not at adolescence when this emerges.

We find that the increased IgE level is not entirely unanimous with high eosinophils counts. STAT3 mutation was reported to lead to impaired memory B cells [22, 23]. This is consistent with our finding that three patients show mildly damaged in memory B cells. STAT3 plays a pivotal role in the development, differentiation and maintenance of T cell memory and central memory T cell was fewer in patients with HIES [8, 24]. The ability of CD8 T cells to control herpes viruses is problematic in STAT3-deficient patients, which may partly explain why a portion of our STAT3-deficient patients show EBV and CMV viraemia [25]. Naïve CD8 T cells was increased while effector memory, central memory and terminally differentiated effector memory cytotoxic T cells was decreased in STAT3-deficient patients [26]. Different from the previous report, one patient in our study shows the normal central memory T cell but increased effector memory T cells. Considering that STAT3 deficiency have the ability to generate memory CD8 T cells [25], we speculate that the number of memory CD8 T cells is increased in the study, but their function may be impaired. Inconsistent with that STAT3 deficiency had the normal number of γδT cells [27], three of our patients have obvious reduction in γδT cells. Not all patients have high NIH scores.

Molecular study finds that HIES is caused by a variation of STAT3, Dedicator of cytokinesis 8 (DOCK8) [28], phosphoglucomutase 3 gene (PGM3) [9] and ZNF341 [29]. Simultaneously, the STAT3 deficiency disease is categorized into two types: STAT3 LOF mutation is generalized to combined immunodeficiencies with syndromic features, while STAT3 GOF mutation is a disease of immune dysregulation, especially regulatory T cell defects according to International Union of Immunological Societies in 2019 [30]. Our patients overwhelmingly perform STAT3 LOF mutation. As for the different clinical representations between STAT3 LOF and GOF in our cohort, that patient mainly behaves autoimmune diseases as mentioned in previous papers [15]. She also performs most of the traditional
AD STAT3-deficient manifestations except eczema and highly elevated serum IgE levels.

We find c. 1311C > A(H437Q) and c. 1826G > C(R609T) are two novel STAT3 mutations in STAT3-deficient patients. The three patients carrying novel mutations have apparent clinical and immunologic features of STAT3 deficiency even though we did not perform function experiments of those new mutation sites. Notably, one patients’ variant is derived from his father, who has de novo mutation in STAT3 and clinical symptom has appeared when he was young. In keeping with numerous reports [21–23] that c. 1144C > T (R382W) is a hotspot mutation in patients carrying STAT3 gene mutation in China. On the other hand, different from that literature, secondary common mutation c. 1909G > A (V637M) only exhibit in one patient of this study (9.09%).

5. Conclusion

In summary, this study is limited by the absence of long-term follow-up study and related experimental validation. However, our research emphatically illustrates the clinical, immunologic and genetic manifestation of STAT3-deficient disease in Han Chinese people and extends the spectrum of STAT3 deficiency diseases in different ethnic groups. Furthermore, this study implicates that IVIG may help reduce the opportunity of infection and STAT3 deficiency needs early diagnosis and treatment for a better prognosis.

Abbreviations
AD
Autosomal Dominant
BALF
Bronchoalveolar Lavage Fluid
CCDS
Consensus Coding Sequence
CMC
Chronic Mucocutaneous Candidiasis
CMV
Cytomegalovirus
DOCK8
Dedicator of Cytokinesis 8
EBV
Epstein-Barr Virus
GOF
Gain of Function
HIES
Hyper IgE Syndrome
HSCT
Hematopoietic Stem Cell Transplantation
IgE
Immunoglobulin E
IVIG
Intravenous Immunoglobulin
LOF
Loss of Function
MRI
Magnetic Resonance Imaging
NIH
National Institutes of Health
NK
Natural Killer
PBMC
Peripheral Blood Mononuclear Cells
PBS
Phosphate Buffer Solution
PGM3
Phosphoglucomutase 3 Gene
STAT3
Signal Transducer and Activator of Transcription 3
VZV
Varicella-Zoster Virus
WES
Whole Genome Sequencing
Declarations
**Ethics approval and consent to participate**
Written informed consent was obtained from all participant’s guardians before enrolling in the study. The study was approved by the Ethics Committee of the Children’s Hospital of Fudan University.

**Consent for publication**

The participant has consented to the submission of the case report to the journal.

**Availability of data and materials**

Not applicable

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

All authors contributed to the study conception and design. Material preparation was performed by Li Lin, Ying Wang, Bijun Sun and Luyao Liu. Data collection and analysis were performed by Li Lin, Wenjing Ying, Wenjie Wang, Qinhua Zhou, Jia Hou, Haili Yao, Jinqiao Sun and Xiaoquhuang Wang. The first draft of the manuscript was written by Li Lin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Tables**
Due to technical limitations, Tables 1-3 are only available as a download in the supplemental files section.

**Figures**

![Figure 1](image)

A variety of clinical manifestations of 11 patients carrying loss-of-function (LOF) mutation in STAT3. The right number presents the number of LOF STAT3 patients and Y-axis shows the different disease symptoms.
Figure 2

Schematic structure of STAT3 and mutation information of this study. STAT3 is a protein consist of 770 amino acids. Six squares present its protein domains and all the alteration of the base in this article was marked by the arrow. Black arrow shows the mutation which had been reported. Red arrow shows the novel mutation in this study.
CADD vs. MAF plot of STAT3 by PopViz. The horizontal axis shows MAF scores and the vertical axis presents the scores of CADD. The nine mutations of our patients (G421R, R382W, R382P, R609T, H332N, V637M, F621L, R609S and H437Q) are malignant and highlighted in red. All the MAF is -7 and the CADD scores are 35, 35, 35, 31, 31, 27, 26.6, 25.8 and 25.6, respectively. * shows the novel mutation in this study.

Supplementary Files
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Table 2-ACC-0407.xlsx
Table 3-ACC-0407.xlsx