

Clinical Features, STAT3 Gene Mutations and Th17 Cell Analysis in Nine Children with Hyper-IgE Syndrome in Mainland China

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Abstract

Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency disease characterized by eczema, recurrent staphylococcal aureus skin abscesses, pneumonia with pneumatocele formation, remarkably high serum IgE levels, eosinophilia and involvement of skeleton and connective tissues. Heterozygous signal transducer and activator of transcription 3 (STAT3) mutations were shown to be the cause of autosomal dominant HIES (AD-HIES). In this study, we diagnosed nine patients with HIES from 9 unrelated families on the basis of a National Institutes of Health (NIH) score of ≥ 40 points, sequenced the STAT3 gene of all nine patients, and quantified Th17 cells in peripheral blood of seven patients by flow cytometry in mainland China. All nine patients had characteristic manifestation of HIES with the range of NIH scores 45–77 points. STAT3 hot mutations V637M or R382W/Q were identified in five patients. We identified two novel heterozygous missense mutations (T620S and R609G) located in Src homology 2 (SH2) domain in two patients, respectively. In two other patients, no STAT3 mutations were found. Quantified Th17 cell numbers were markedly decreased or absent (0–0.28% of CD4⁺T cells) in six patients with STAT3 mutations and almost normal (0.53% of CD4⁺T cells) in one wild-type STAT3 patient compared with healthy controls (0.40–2.25% of CD4⁺T cells). These results suggest that not all patients with HIES who had NIH scores over 40 points carry STAT3 mutations, those whose Th17 cell numbers strikingly decreased probably had AD-HIES with STAT3 mutations.

Introduction

Hyper-IgE syndrome (HIES, Job syndrome, OMIM 147060) is a rare primary immunodeficiency disease with the presentation of eczema, recurrent staphylococcal skin abscesses and pneumonia, remarkably high serum IgE levels and eosinophilia. Non-immunological features were recognized as characteristic facial features, retained primary dentition, hyperextension, scoliosis and minimal trauma fractures [1]. Most cases are sporadic or transmitted through an autosomal dominant (AD) pattern [2]. Clinical diagnosis is made based on the National Institutes of Health (NIH) HIES scoring system introduced in 1999 [3]. In 2007, signal transducer and activator of transcription 3 (STAT3) mutations were found to be the cause of the sporadic and autosomal dominant hyper-IgE syndrome (AD-HIES) [4], and patients showed extremely low or absent T helper 17 cells (Th17) in their peripheral blood

[5]. Few Chinese cases of HIES due to STAT3 mutations were reported in Hong Kong, Taiwan and mainland China [6–9]; no investigations have analysed Th17 cell numbers in patients with HIES in mainland China. In this study, we described the phenotypes of Chinese children with HIES, carried out STAT3 gene sequencing in all nine patients and quantified Th17 cell numbers in seven patients.

Materials and methods

Subjects. During 2007–2012, nine patients (5 males, 4 females; age range, 1.7–14.5 years) from nine unrelated Chinese families were enrolled into this study. All patients had the characteristic manifestation of HIES; clinical diagnosis was given to patients with scores that exceeded the threshold (40 points) of the National Institutes of Health (NIH) scoring system. The study was approved by

the ethics committee of Children's Hospital of Chongqing Medical University, and informed consents were obtained.

Mutation analysis of STAT3 gene. Total mRNA of patients and controls was extracted from fresh heparinized venous blood using the RNeasy pure Blood kit (BioTeke, Beijing, China) and subjected to first-strand complementary DNA (cDNA) synthesis using the Prime Script RT Reagent kit (TaKaRa, Dalian, China) according to the manufacturer's protocol. TIANamp DNA Blood Mini kit (Tiangen Biotech, Beijing, China) was utilized according to the manufacturer's protocol. The STAT3 gene was amplified from cDNA and gDNA using specific oligonucleotide primers (Invitrogen, Shanghai, China), and PCR primers of STAT3 were designed according to human STAT3 mRNA and gDNA sequences (NM_139276.2, NC_000017.10), reagents for PCR were purchased from Tiangen Bio-Company. cDNA was sequenced first, followed by confirmatory sequencing of gDNA if a STAT3 mutation was identified. The amplified gene fragments were sequenced using the ABI Big Dye Terminator mixture (Applied Biosystems, Foster City, CA, USA) on an ABI 3100 sequencer (Applied Biosystems). Parents of patients with identified STAT3 mutations were screened for presence of those mutations.

Flow cytometric analysis of Th17 cells. Peripheral blood mononuclear cells (PBMCs) from patients suspected with HIES and from 12 healthy controls were isolated using a Ficoll gradient (TBD, Tianjin, China). Cells were suspended at a density of 2×10^6 cells/ml and maintained in RPMI 1640 medium (1 ml) supplemented with 10% heat-inactivated foetal bovine serum (FBS) (TBD) and cultured in the 24-well plate. For intracellular IL-17A staining, cells were stimulated with 50 ng/ml phorbol-myristate acetate (PMA) and 750 ng/ml ionomycin (Sigma-Aldrich, St. Louis, MO, USA) in the presence of GolgiPlug (BD Biosciences Pharmingen, San Diego, CA, USA) for 4 h at 37 °C and 5% CO₂, cells were then harvested and stained with phycoerythrin-Cy5 (PE-Cy5) anti-human CD3 and fluorescein isothiocyanate (FITC) anti-human-CD8 in a dark place at room temperature for 20 min, followed by fixation and cytoplasmic staining (Th17 cytofix/cytoperm, perm/wash were purchased from BD Biosciences Pharmingen) with anti-human-IL-17A-PE-conjugated murine monoclonal antibodies (mAbs). An irrelevant PE-conjugated IgG1 mAb was used as the isotype-matched control. Th17 cells were analysed as CD3⁺CD8⁻ IL-17⁺/CD3⁺CD8⁻ cells (CD4⁺T cells) (CD4⁺T cells were markedly decreased after stimulated by PMA, so CD3⁺CD8⁻ cells were chosen to stand for CD4⁺T cells) by flow cytometry (BD FACSCalibur, San Jose, CA, USA). CellQuest software (BD Bioscience Pharmingen) was used for analysis. All the mAbs (anti-CD3-PECy5, anti-CD8-FITC, anti-IL-17A-PE, IgG1) were purchased from eBioscience (San Diego, CA, USA). The normal Th17 cell range was defined by evaluating 12 healthy control subjects.

Statistical analysis

Differences in the percentage of CD4⁺IL-17⁺ T cells in patients and healthy controls were statistically tested using an unpaired *t*-test.

Results

Clinical characteristics

All nine patients were not from consanguineous families and did not have family histories of the disease. The patients all had recurrent eczema and pneumonia, particularly high serum IgE levels (757.4–38,900 IU/ml) and eosinophilia (700–10,045 cells/ μ l), and their NIH scores were over 40 points (range, 45–77 points) (Fig. 1, Table 1). Five patients with lung abscesses required emergency treatment after the development of pneumatoceles and pneumothorax. Two of the five patients received pulmonary lobectomy for the treatment of pneumatoceles. Lung biopsy of patient 1 showed damaged lung tissue, thinner or fractured alveolar septa and eosinophilic infiltrates in the alveolar septa and alveolar cavities (Fig. 2A). Every patient had a history of recurrent skin abscesses. 'Cold' abscesses were more regularly observed in patient 2. Three patients had internal abscesses [liver (*n* = 3), epiploon (patient 5) and deep inguinal region (patient 5)]. Patient 9 suffered from sepsis caused by *acinetobacter baumannii*. Six patients had recurrent oral thrush beyond infancy. Patient 2 had a history of chronic hyperkeratotic fingernails. All patients with the exception of patient 5 had characteristic facial features such as coarse facial skin, ocular hypertelorism and wide-fleshy nasal tip. Bone abnormalities such as osteoporosis, delayed shedding of deciduous teeth, hyperextensibility of joints and scoliosis were also present in the studied patients. Clavicle fractures with minor trauma happened in patient 8. None of our patients had midline anomaly or developed lymphomas. Patient 5 died of life-threatening hemoptysis.

Basic immunological assessments

We analysed immunoglobulins and lymphocyte subsets in the nine studied patients (Table 2). IgG level was slightly low in patient 4, but high in patient 5 before intravenous immunoglobulin (IVIG) treatment was administered. IgA levels were low in patients 3 and 5. Patients 4 and 5 had low IgM levels. Patient 4 had low level of CD4⁺ T cells. NK cells were present in low numbers in patients 1, 2 and 8. Nitroblue tetrazolium (NBT) tests showed normal in seven detected patients.

Mutations of STAT3

With PCR-direct sequencing analysis, seven STAT3 heterozygous mutations were identified (Fig. 3, Table 2):

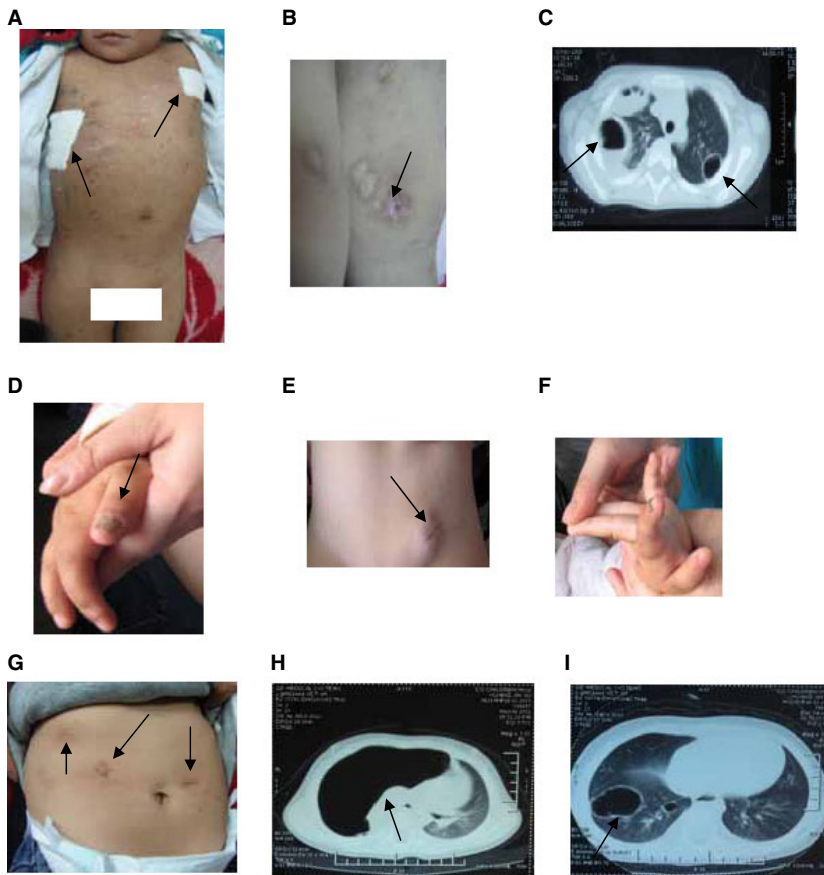


Figure 1 Clinical features of HIES children. Patient 1: 4-year-2-month-old boy. (A) Multiple scars of *S. aureus* skin infections and the sites of thoracic drainage. (B) Scars of pyogenic gonarthrititis. (C) Multiple lung abscesses in 2008. Patient 2: 3-year-old girl. (D) Onychomycosis. (E) Cold abscesses in left inguinal region. (F) Hyperextensibility of metacarpophalangeal joints. Patient 7: 1-year-9-month-old girl. (G) Scars of multiple *S. aureus* skin abscesses in abdominal wall. Patient 9: 1-year-9-month-old boy. (H) Pneumatothorax in 2012. (I) Pneumatocele in 2012.

The missense mutation in patient 1 (c.1859 C>G, T620S) and the missense mutation in patient 7 (c.1825A>G, R609G) both were not previously described in the STAT3 mutation database (<http://bioinf.uta.fi/STAT3base/>) or in the literature and not present in the single nucleotide polymorphism database (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). We detected that the nucleotide 1859 and 1825 site variations did not occur in 100 alleles from 50 healthy individuals (frequency 0%). So, these are two novel missense mutations located in the Src homology 2 (SH2) domain of the protein. Three hotspot mutations were revealed in patients 2, 6, 8 (c.1909 G>A, V637M), patient 3 (c.1145 G>A, R382Q) and patient 9 (c.1144 C>T, R382W). Parents of patients with STAT3 mutations did not have the same mutations (parents of patient 3 were not available for analysis). No STAT3 mutations were found in patients 4 and 5.

Decreased number of circulating TH17 cells

The proportion of Th17 cells in CD4⁺ T cells (CD3⁺CD8⁻IL-17A⁺/CD3⁺CD8⁻ cells) was tested in seven patients (Fig. 4, Table 2). In six patients (patient 1, 2, 6, 7, 8 and 9), Th17 cell numbers were extremely low or absent (0.03%, 0.13%, 0%, 0%, 0.28%, 0.16% of CD4⁺T cells, respectively; average, 0.12% of CD4⁺T cells)

compared with healthy controls (average, 0.83% of CD4⁺T cells; range, 0.40–2.25%). Patient 4 who had no STAT3 mutation had Th17 cell numbers of 0.53%, which is almost normal compared with healthy controls.

Discussion

We report here the detailed clinical features, STAT3 mutation analyses of 9 sporadic HIES cases in mainland China. All patients excluding patient 5 demonstrated an early onset before 6 months. The first manifestation in six cases was a newborn rash. Recurrent and mild to severe eczema occurred in all cases. Unlike atopic dermatitis, eczema in HIES cases affects atypical areas like scalp, limb and trunk [2, 10] and typically the affected patients do not have a family history of atopy [11]. Eosinophilic infiltrates were seen when performing a skin biopsy on patient 8 (Fig. 2B). All patients developed recurrent skin and lung infections. The pathogen was restricted mainly to *Staphylococcus aureus*. A similar frequency has been reported in other large cohorts of patients with STAT3-mutations [12–14]. Skin ‘cold’ abscesses, which are pathognomonic to HIES, were seen in the studied patients, but more readily observed in patient 2. The abscess is filled with pus that always permits the growth of *S. aureus* [11]. Five patients suffered from dangerous staphylococcal pulmonary

Table 1 Clinical findings in nine patients with HIES by NIH scoring system.

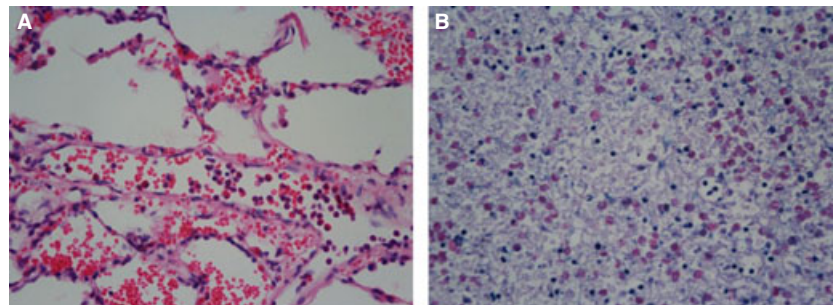
Patient/Sex	P1/M	P2/F	P3/M	P4/M	P5/M	P6/F	P7/F	P8/F	P9/M
Age of scoring (years)	4.1	3	8	11	14.5	3.1	1.7	7	1.7
Age of onset	3 months	6 months	3 days	3 days	2 years	3 days	3 days	1 days	7 days
Status	Alive	Alive	Alive	Alive	Dead	Alive	Alive	Alive	Alive
Highest serum-IgE level (IU/ml)	1008.4	5106	38,900	>5000	757.4	11,300	11,300	1181.2	>3000
Skin abscess (Pathogen)	3–4	>4 (Sa)	>4 (Sa)	1–2	>4	3–4 (Sa)	>4 (Sa)	>4 (Sa)	>4 (Sa)
Pneumonia (episodes over lifetime) (Pathogen)	>3 (Sa)	3	>3 (MRSA)	2	>3	>3 (Sa)	1	>3	>3 (Sa)
Parenchymal lung anomalies	Pneuma	No	Pneuma	No	Bronchi	Pneuma	No	Pneuma	Pneuma
Retained primary teeth	NA	NA	>3	>3	NA	NA	NA	>3	NA
Scoliosis, maximum curvature ^a	No	No	10°(L)	6°(L)	No	No	No	No	No
Fractures with minor trauma	No	No	No	No	No	No	No	Yes	No
Highest eosinophil count (cells/ μ l)	2610	2175	3930	10,045	1515	700	2260	1920	3980
Characteristic face	Mildly	Mildly	Mildly	Mildly	No	Mildly	Mildly	Mildly	Mildly
Newborn rash	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Eczema (worst stage)	Severe	Severe	Severe	Severe	Mild	Mild	Severe	Severe	Severe
Upper respiratory infections per year	>6	>6	3	>6	>6	>6	>6	>6	>6
Candidiasis	Oral (Ca)	Oral Fingernails	Oral (Ca)	No	No	Oral	Oral	Oral (Ca)	No
Other serious infections	Severe	No	Severe	No	Severe	Severe	Severe	Severe	Severe
Fatal infection	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Hyperextensibility	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes
High palate	Yes	No	No	No	NA	Yes	Yes	No	No
Young-age correction	2–5 years	2–5 years	>5 years	>5 years	>5 years	2–5 years	1–2 years	>5 years	1–2 years
NIH score (points) ^b	62	50	72	48	45	62	56	77	71

Sa, *Staphylococcus aureus*; MRSA, *methicillin-resistant staphylococcus aureus*; Pneuma, Pneumatocele; Bronchi, Bronchiectasis; NA, not available; ND, not determined; Ca, *Candida albicans*.

^aThe degrees show maximal spinal curvature; Spinal locations are denoted by L (lumbar).

^bNIH scoring system was recommended by Grimbacher *et al.* [3].

Figure 2 (A) Lung biopsy of patient 1: damaged lung tissues, thinner or fractured alveolar septa and eosinophilic infiltrates in the alveolar septa and alveolar cavities (Haematoxylin-eosin [HE] staining, 400 $\times$); (B) Skin biopsy of patient 8: a lot of eosinophilic infiltrates in subcutaneous tissues (HE staining, 400 $\times$).



complications such as lung abscess, pyothorax, pneumothorax or hydropneumothorax which are all conditions that should be closely monitored. Pneumothorax in particular may become life-threatening if emergency treatment is not given. The pulmonary cyst formation after pneumonia is a distinguishing feature of AD-HIES, which was observed in these five patients. There were no significant differences in NIH scores or ages of onset observed between the patients.

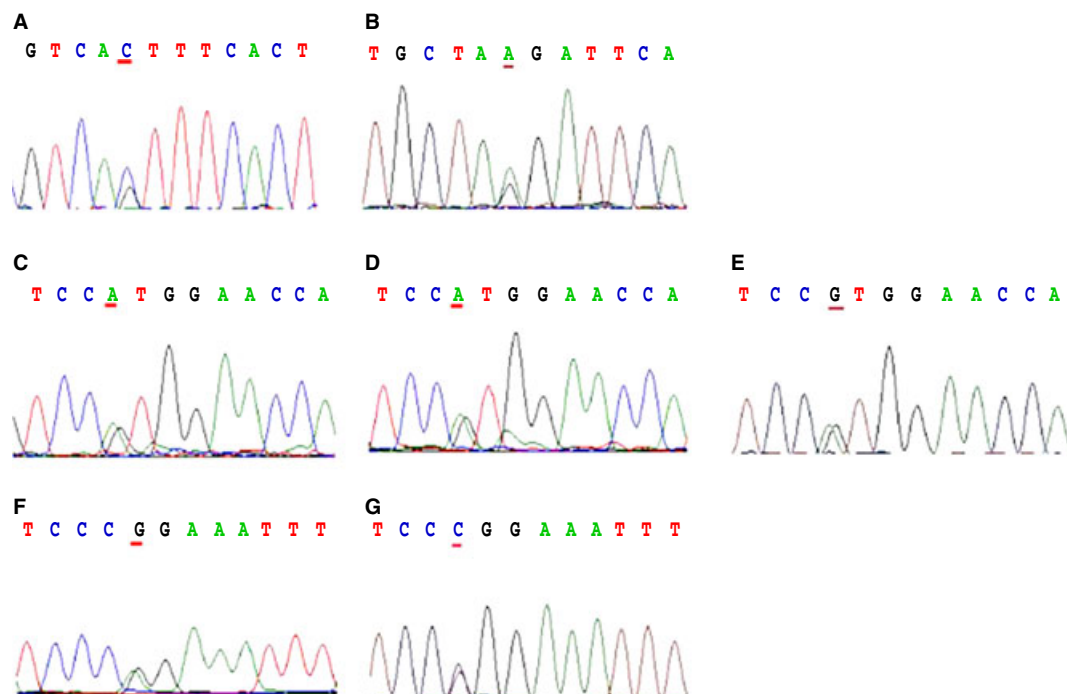
To date, about 230 unique STAT3 mutations have been identified in patients with AD-HIES [15]. Most were missense mutations located in the DNA-binding and SH2 domain of STAT3 protein; The most common hotspot mutations are R382W/Q and V637M, respectively [4]. In

this article, in addition to confirming three previously reported hotspot mutations, we have identified two novel mutations (T620S and R609G), both of which were located in the SH2 domain. We did not observe significant differences in the clinical features between the patients bearing the two novel mutations and those bearing hotspot mutations. It has been reported that increased non-immunological features, including a high palate and increased interalar distance, as well as increased scoliosis in younger patients was observed in the SH2 domain mutation group [16]. However, in our patients, there were no significant differences between the DNA-binding domain (DBD) and SH2 domain (SH2D) mutation group.

Table 2 Basic immunologic assessments and STAT3 gene analysis in nine HIES patients.

Patient/Sex	P1/M	P2/F	P3/M	P4/M	P5/M	P6/F	P7/F	P8/F	P9/M
Immunoglobulins (g/l)									
IgG	12.962	10	9.37	7.601↓	24.88↑	15.007	9.1	12.3	11.3
IgA	0.623	1.02	0.56	1.515	0.54↓	0.935	0.426	0.813	0.404
IgM	1.456	0.96	1.18	0.109↓	1.16↓	1.765	2.330	1.72	2.14
Highest IgE (IU/ml)	1008.4↑	5106↑	38,900↑	>5000↑	757.4↑	11,300↑	11,300↑	1181.2↑	>3000↑
C3	1.27	0.79↓	1.16	1.32	0.82	1.10	1.74	1.15	1.16
C4	0.21	NA	0.318	0.55	0.47	0.36	0.37	0.11	0.38
Lymphocyte subsets									
CD3 (%)	74.9	69	64	62	64	71	64	86	69
CD4 (%)	30.2	37	28.7	14↓	35	41	31	46	28
CD8 (%)	31.8	28	31	42	28	28	26	38	36
CD4/CD8	0.95	1.32	0.93	0.33↓	1.25	1.46	1.21	1.22	0.78
CD19 (%)	14	24	21.7	13	23	19	23	9	23
CD16CD56 (%)	2.10↓	6↓	14.2	21	15	8	12	3↓	7
Nitroblue tetrazolium test	Normal	Normal	NA	Normal	Normal	Normal	NA	Normal	Normal
Th17 (% of CD4)	0.03	0.13	NA	0.53	NA	0	0	0.28	0.16
STAT3 analysis	T620S	V637M	R382Q	Wild type	Wild type	V637M	R609G	V637M	R382W

NA, not available.

**Figure 3** STAT3 gene mutation analysis. (A) Patient 1: c.1859 C>G, T620S; (B) Patient 7: c.1825 A>G, R609G; (C–E) Patients 2, 6 and 8: c.1909 G>A, V637M; (F) Patient 3: c.1145 G>A, R382Q; (G) Patient 9: c.1144 C>T, R382W. Nucleotide with underline indicates the mutant site.

All five patients with SH2D mutations and one patient with DBD mutation had sinusitis or otitis, which seems to be in line with the previous study [16]. We did not identify STAT3 mutations in patients 4 and 5 even though they had scores that exceeded the NIH score of 40 points. Both of them did not form pneumatocele after recurrent pneumonia. Patient 5 also lacked somatic features such as

characteristic facial features, scoliosis and failure of baby teeth to exfoliate. We suspect that the two patients carry autosomal recessive (AR) patterns of inheritance, which has been associated with tyrosine kinase 2 (TYK2) gene mutations or the dedicator of cytokinesis 8 (DOCK8) gene mutations. We did not find TYK2 gene mutations in patient 4 as well; however, we noticed that the patient

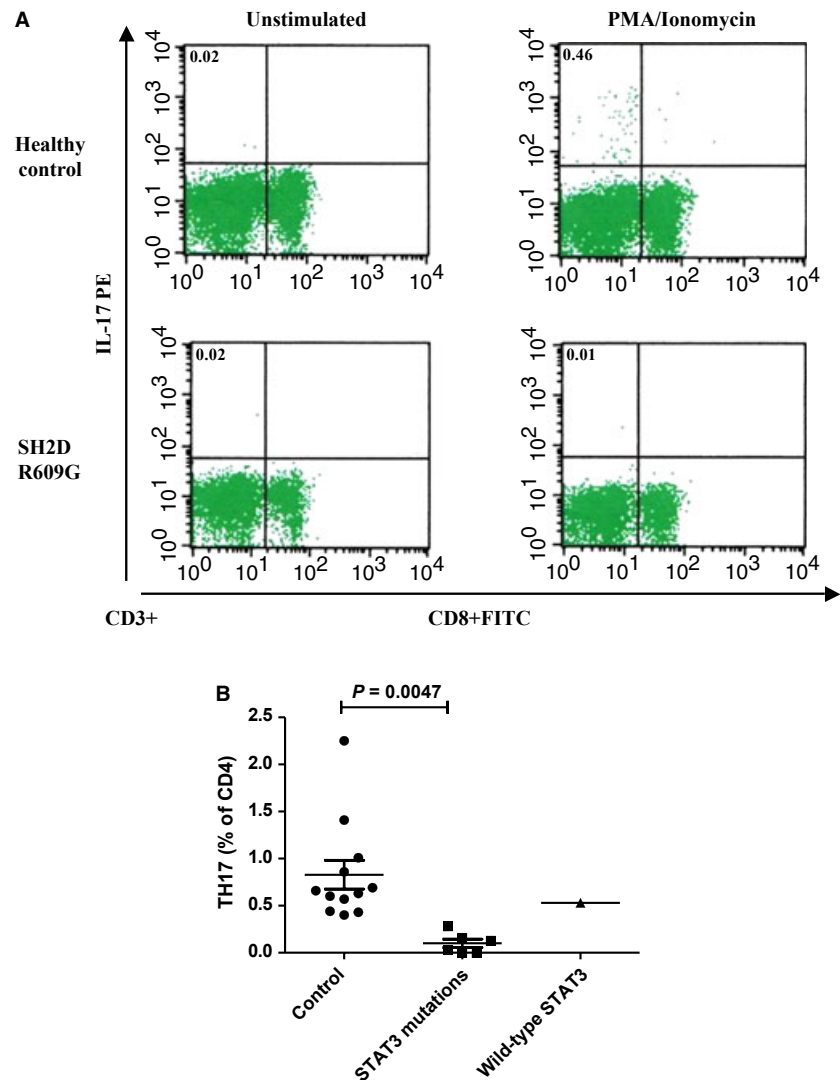


Figure 4 (A) Intracellular staining for IL-17 production in PMA/ionomycin-activated CD4⁺ T cells. The patient with HIES with a SH2D (R609G) mutation has fewer circulating TH17 cells compared with the healthy control. (B) Percentage of TH17 cells in PBMCs is significant low compared with healthy controls ($P < 0.05$) in six patients with STAT3 mutations, normal in patient with wild-type STAT3 compared with healthy controls.

suffered from herpes simplex virus (HSV) infections in his mucous membrane of lips and oral cavity, he also had low levels of IgM and CD4⁺ T cells, which is consistent with immunological features of patients with DOCK8 mutations reported [17, 18]. We found that exon 4–12 and exon 26–33 of DOCK8 gene in this patient could not be amplified from cDNA samples. Next-generation sequencing will be performed to determine whether the patient is DOCK8 deficient HIES. We observed low levels of IgA and IgM in patient 5. No evidence of any viral infections was found in the patient. However, we did not extract enough blood samples from the patient to sequence the TYK2 gene and DOCK8 gene because he died of life-threatening hemoptysis early in the study.

STAT3 was initially recognized as a signal transducer for IL-6 and epidermal growth factor (EGF) [19]. After receptor binding by cytokines, STAT3 protein is phosphorylated by the receptor-associated JAK enzymes, which then forms homo- or heterodimers that translocate to the

cell nucleus where they bind to target DNA and act as transcription activators. Mutant STAT3 protein functioned as dominant-negative, reduced protein activity in binding to target DNA, leading to malfunction of the immune system [20]. Expression of dominant-negative STAT3 inhibits airway epithelial cell migration during repair [21]. STAT3 involves the production of antibacterial factors by keratinocytes and bronchial epithelial cells [22]. It also regulates the expression of matrix metalloproteinases (MMPs), which are involved in tissue response to injury and are aberrant in HIES [23]. These factors may explain the pathologic changes of lung tissue and pneumatocele after *S. aureus* pneumonia. Evidence suggesting a specific role for STAT3 in human central memory T cell formation, and the control of certain chronic viruses has been provided by the description of a cell-intrinsic defect in the number of central memory CD4⁺ and CD8⁺ T cells in patients with AD-HIES and compromised T cell memory to varicella zoster virus (VZV) and Epstein–Barr

virus (EBV) [24]. However, our patients lacked the viruses infections mentioned above. Whether STAT3 is associated with the production of *S. aureus*-specific memory T cells needs to be further studied. Patients with AD-HIES have dramatically lower numbers of antigen-specific memory B cells [25–27], but no correlation between the percentage of memory B cells and the infection history has been revealed yet. It has been shown in mice that immature B cells preferentially switch to IgE versus IgG1 [28]. Whether or not the IgE elevation in patients with AD-HIES is related to impaired B cell maturation still needs to be clarified.

Dominant-negative mutations in STAT3 lead to impaired generation of Th17 cells, which is a newly described T helper cell subgroup with specificities against extracellular bacteria [29, 30] and fungal antigens [31, 32]. STAT3 mutations result in decreased expression of regulator retinoid-related orphan receptor γ t (ROR γ t), the transcription factor necessary for the development of Th17 cells. Th17 cells subsequently induce a set of effector molecules, including IL-17, IL-21, IL-22, and IL-23R plus several chemokines and other defence molecules [33]. Keratinocytes and bronchial epithelial cells, unlike fibroblasts and endothelial cells, show a much higher dependence on Th17 cytokines for their production of antistaphylococcal factors, including neutrophil-recruiting chemokines and antimicrobial peptides. This likely accounts for recurrent staphylococcal infections confined to the skin and lung in patients with AD-HIES [22]. Human IL-17A and IL-17F are essential for mucocutaneous immunity against *Candida albicans* [34], which suggests that the development of chronic mucocutaneous candidiasis (CMC) in patients with AD-HIES results from impaired IL-17 immunity. It has been proved in several studies that patients who carry STAT3 mutations always presented impaired Th17 cell development [5, 12, 13, 22, 33]. After evaluating clinical status according to the NIH scoring system, analysis of Th17 cell numbers preceding STAT3 sequencing was recommended by diagnostic guidelines for STAT3 deficiency HIES patients in 2010 [13]. It was shown in our data that six STAT3-mutant patients had significant decreased Th17 cell numbers (Th17 cell numbers of patients 3 and 5 were not available to be analysed). Among the six, three patients (patients 1, 6 and 7) who carried STAT3 mutations in SH2 domain had nearly absent Th17 cells, but their infections did not seem to be more severe than the other three patients. Patient 4, who had wild-type STAT3, had no decrease in Th17 cell numbers. Compared with the other patients, infections were milder in patient 4 and pathogens such as *S. aureus* and *C. albicans* were absent in his medical history; recurrent pneumonia might result from other pathogens. Normal Th17 cells may explain his milder infections.

For AD-HIES, the major goal of treatment focuses on control of skin and lung infections. Our patients benefit from prophylactic antibiotics including oral administration

of sulfamethoxazole+trimethoprim (SMZco) and IVIG as well as itraconazole for prevention of bacterial and fungal infection. Because AD-HIES is a multisystem disorder and infections in patients are usually well controlled by conservative therapies, hematopoietic stem cell transplantation (HCT) is not recommended unless hematopoietic malignancy occurs [35].

In conclusion, we identified heterozygous STAT3 mutations, including two novel missense mutations in seven of nine patients suspected HIES in mainland China. Not all patients with HIES whose NIH scores above 40 points carried STAT3 mutations. Patients with STAT3 mutations showed a remarkably decreased number of circulating Th17 cells. Currently, the correlation between genotype and phenotype in patients with AD-HIES is not fully elucidated. A better understanding of pathogenesis will lead to new treatment modalities for AD-HIES.

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