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ORIGINAL ARTICLE

Clinical Manifestations and Genetic Analysis of 17 Patients with Autosomal Dominant Hyper-IgE Syndrome in Mainland China: New Reports and a Literature Review

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Abstract
Purpose Autosomal dominant hyper-IgE syndrome (AD-HIES) is a rare complicated primary immunodeficiency disease (PID). Signal transducer and activator of transcription 3 (STAT3) gene mutation is found to cause AD-HIES. The distribution of AD-HIES patients with STAT3 deficiency in the Chinese population is not clear. Herein, we retrospectively report 17 AD-HIES patients with STAT3 deficiency and demonstrate their clinical, immunological, and genetic features.
Methods Patients' clinical data were collected from their medical records. Routine laboratory testing results included lymphocyte subset analysis and immunoglobulin quantification. STAT3 mutations were investigated by sequencing of genomic DNA.
Results Among 575 patients with PID, 28 (4.87%) were clinically diagnosed as HIES. Among them, 17 (2.96%) were confirmed as STAT3 mutant AD-HIES. The ratio of male to female patients was 8:9. All of the 17 patients had NIH scores over 40 points. The mean ages at onset and diagnosis were 1.05 and 10.35 years, respectively. Three patients (17.65%, 3/17) died with a mean age of 13.33 years. Eczema, recurrent skin infection, and respiratory tract infection were the most common clinical symptoms and are present in all of the 17 patients in this study. Six patients (37.5%, 6/16) suffered complication from BCG vaccination. Noninfection symptoms are characteristic facial features in 17 patients (100%, 17/17), retention of primary teeth in 10 patients (90.91%, 10/11), and abnormal bone fractures in 7 patients (41.18%, 7/17). Eleven types of STAT3 mutations were identified in 17 patients, including 1 novel mutation.
Conclusions We here retrospectively report the largest Chinese cohort of AD-HIES patients with STAT3 mutation. Unique features, when compared to existing literature reports, include (1) later age of diagnosis, (2) significantly higher rate of BCG complications, and (3) lower rate of candidiasis and chronic otitis media.

Keywords Autosomal dominant · hyper-IgE syndrome · Chinese · STAT3 mutations · infections · noninfection symptoms

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Introduction

The hyperimmunoglobulin E syndromes (HIES; OMIM no. 147060), first described as Job syndrome by Davis et al. [1] in 1966, are rare multisystem primary immunodeficiency diseases (PIDs). In 1972, Buckley et al. [2] reported that two patients with Job syndrome had very high serum IgE levels, which gave rise to the name HIES. Both autosomal dominant and recessive inheritance have been described in HIES

patients [3–7]. Autosomal dominant HIES (AD-HIES), which was characterized by pathologically elevated serum IgE, eczema, hypereosinophilia, recurrent skin and lung infections, distinctive facial features, and skeletal/connective tissue abnormalities, was the most common form of this disease [8–11]. In 2007, Holland et al. [7] firstly reported that AD-HIES was caused by dominant-negative mutations in the signal transducer and activator of transcription factor 3 (*STAT3*) gene.

As a member of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) family proteins, STAT3 mediates responses to multiple cytokines and growth factors and plays an important role in regulating proliferation, differentiation, migration, apoptosis, and cell survival [12–14]. As an "experiment of nature," HIES patients have helped to reveal numerous critical physiological and functional roles of the *STAT3* gene. For instance, several studies revealed that AD-HIES caused by STAT3 mutations had impaired the ability to generate IL-17A- and IL-22-producing T cells and circulating memory B cells [15–18]. Besides, defective response to multiple cytokines, such as IL-6, IL-17, IL-21, and IL-22, was also reported in AD-HIES patients [19–21].

Over 500 AD-HIES cases have been reported worldwide, including many single center studies and some national surveys. Such studies greatly enhanced our understanding of the clinical and immunological features of AD-HIES [22–24]. Understanding the clinical presentations and laboratory and molecular features of genetic disorders among different ethnicities facilitates early diagnosis and management of such diseases. However, no nationwide HIES surveys have been reported in China and only 18 Chinese AD-HIES patients were reported to have STAT3 mutations [25–32] (including two from Taiwan). The largest reported Chinese HIES cohort included nine cases (seven with STAT3 deficiency) and mainly focused on the defects at the molecular and cellular level with minimal clinical and laboratory information of those patients [28]. Almost all others were single case report without statistical information for the clinical and immunological features of AD-HIES patients in Chinese ethnicities.

Shanghai Children's Medical Center (SCMC) of the School of Medicine at Shanghai Jiaotong University is a pediatric tertiary referral teaching hospital in Shanghai, China. It is one of the major PID centers in mainland China. Here, we report 17 AD-HIES patients with STAT3 deficiency from our center from 2008 to 2016. We believe that this is the largest cohort study in China so far. A detailed description of clinical, immunological, and molecular defect is described, in conjunction with literature review of additional 18 Chinese cases, aiming to provide insights to our understanding of STAT3 mutant AD-HIES patients.

Patients and Methods

Patients

From June 2008 to July 2016, a total of 575 patients were diagnosed with PIDs in hospitals affiliated to Shanghai Jiao Tong University, School of Medicine. Among them, 28 unrelated patients (4.87%) were clinically diagnosed as HIES, 17 of whom (60.71%) were confirmed to have STAT3 mutations. The clinical diagnosis of AD-HIES was made based on the following inclusion criteria: (1) characteristics of clinical manifestations of AD-HIES, i.e., eczema, skin and lung bacterial infections (especially pneumatoceles and bronchiectasis), characteristic facial features, abnormal bone fractures, scoliosis, and retention of primary teeth; (2) National Institutes of Health (NIH) scores over 20 points (>40 AD-HIES likely; 20–40 AD-HIES possible; <20 AD-HIES unlikely); and (3) serum IgE levels >2000 IU/mL. This study was approved by the Ethics Committee of SCMC, and written informed consents were obtained from parents or legal guardians of the patients.

Data Collection

Chart review was conducted to collect patients' clinical and laboratory data, such as clinical features, age at onset and diagnosis, family history, vaccination history, laboratory tests (including lymphocyte subpopulations and immunoglobulin levels), treatments, and outcomes. Age of onset was defined as the age when the significant infection symptoms initially emerged. The age of diagnosis was defined as the age when the diagnosis was first considered by an immunologist and serum IgE levels were over 2000 IU/mL. The NIH scoring system was used to evaluate the clinical status of the patients.

Mutation Analysis

STAT3 gene mutation analysis was performed in 28 patients with suspected HIES. Genomic DNA was extracted from the blood samples of patients using blood genomic DNA extraction kit (DP319; Tiangen Biotech Co. Ltd., China). All exons of STAT3 gene and their flanking intron sequences (50 bp or more from the boundary) were amplified by polymerase chain reaction (PCR) with specific primers as previously described (Table 1). The PCR products were then sequenced directly. Sequence alignments were performed using the basic local alignment search tool (BLAST) from the National Center for Biotechnology Information (NCBI). New mutation was confirmed by screening in 100 normal alleles from 50 unrelated, healthy Chinese individuals to rule out the possibility of polymorphism in the Chinese population.

Table 1 DNA sequences of primers used in this study

Exon	Primer sequence	
2	F-CTTTATCCCTAGTCACAGACC	R-TCAAGACATCCACCACCATA
3	F-GTGTATGCGTCGGCTTCA	R-TCCTCCCACCTCAACCTC
4	F-AAGGTGCCACAGTTCAGT	R-CATTGGGTCTGTTGGATT
5	F-TTAGGGTGGGATGGAAGC	R-GCCTGAGTGGCAGAGCAA
6	F-TGGCATTACAGGCGTGAG	R-TCCTTTGAGGACCCGTAC
7	F-GAGTCAAGGAGGCAAGTGAATATTAG	R-AACCAAGCAAGTTCTGCCAC
8	F-GAAGTTCCTGCTCTGGAGTTG	R-AGTACCAATTCTGTGGGCCTG
9–10	F-TTCAGCATCCACCCAACA	R-TTGGGCAGAAGGAGAAGC
11	F-CCCACAGTGCTGAGATTA	R-CTTTGTGGCTTTGTTCAG
12–14	F-TAAATAACAGGTGGTCAAAG	R-ACAACTCAGCAAGGGACT
15	F-TTTAAGACAGGGTCTCACTC	R-ACAGTAATCATTCCACCTTC
16–17	F-TGGCATGTCCTTTCATTCTG	R-GAAATCTACCTCCCACCTCA
18–19	F-TGTTAGTGAGTGCTGCTGT	R-ATTGCTAACAGGGCATCCATC
20	F-ACGAAGGGTAGGTTGGAC	R-TGAAACAGGGAGTCAAGG
21	F-AGGGTGTTCAGGGTCTCA	R-CGACTACAAATGCGTGCC
22–23	F-ATAAATGAGGGCAGACAACC	R-ATGTTGGATTTAGTGGGTTA
24	F-GAGGGTGGACAACTGAACTA	R-GCAATGCCAGGAGTATGTAG

Flow Cytometric Analysis

Peripheral whole blood was collected using EDTA containing tubes from 7 STAT3 mutant AD-HIES patients and 10 age-matched healthy donors. Peripheral whole blood was stained for 20 min in the dark with 5 μL of the following labeled antibodies: FITC-conjugated CD19, PE-CyTM7 anti-human CD27, and V450 anti-human IgD (BD Bioscience) and PE anti-human IgM (from eBioscience). Samples were analyzed using a BD FACS Canto II (BD), and data were analyzed using FlowJo software (Tree Star, Inc.).

Statistical Analysis

Data are presented as the mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS 17.0 software. Significant differences between the AD-HIES patients and age-matched controls were determined using an unpaired *t* test or nonparametric Mann-Whitney test. Results are presented with 95% confidence intervals, and $P < 0.05$ was considered significant.

Results

Demographic Data

A total of 17 AD-HIES patients with STAT3 deficiency were enrolled in this study. The 17 patients originated from 10 provinces throughout mainland China. The male to female ratio was 8:9. All patients had NIH scores over 40 points (median 61.47 ± 10.59, range 49–88). The mean age at onset of symptoms was 1.05 ± 1.42 years (median 0.42 years, range 0.08–5); 64.29% of the patients had an early onset before 1 year of age and 85.71% before 2 years. The mean age at diagnosis was 10.35 ± 5.75 years (median 12 years, range 3–26) (Fig. 1). The average lag time between onset of symptoms and diagnosis of AD-HIES was 9.30 ± 6.36 years (median 11 years, range 1.00–25.75 years) (Table 2). The first patient who was diagnosed as AD-HIES with STAT3 deficiency was in 2008, while the rest of the patients (88.24%, 15/17) were diagnosed after 2011.

The 17 patients were from 16 unrelated nonconsanguineous families. Three patients had positive

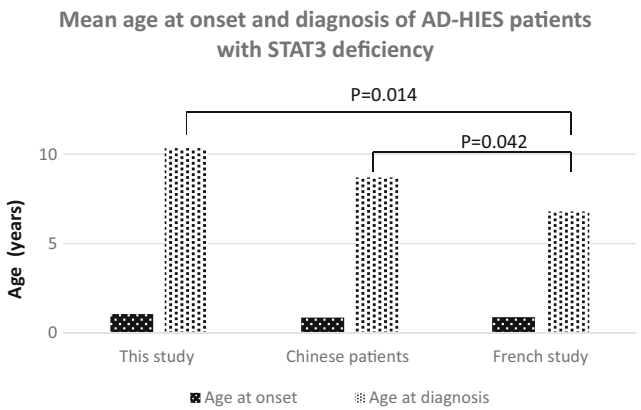

Fig. 1 The mean age at onset and diagnosis of AD-HIES patients with STAT3 deficiency. Seventeen Chinese patients in this study, 35 Chinese patients reported (including 17 in this study), and 60 patients in a French national cohort study are included and compared. The mean diagnosis age in our single center study and all 35 Chinese patients was both significantly later than the French study ($P < 0.05$)

Table 2 Clinical characteristics in 35 Chinese patients with STAT3 deficiency

Pts	Year of diagnosis/ province	Gender	Age (years)			Family history	BCG	NIH score	cDNA mutation	Types of infection	Types of noninfection	Ref.
			Onset	Diagnosis	Status							
P1	2011/Anhui	F	0.58	13	16	−	+	49	c. 2141C>T	Pneumonia, otitis media, skin infections, lymph node abscesses, sepsis, thrush, onychomycosis	Distinctive facial features, eczema, retained primary teeth	This study
P2	2011/Anhui	F	0.42	9	12	−	N	66	c. 1144C>T	Pneumonia, pulmonary abscess, pneumatocele, skin abscess, hordeolum	Distinctive facial features, eczema, retained primary teeth, fracture, hydropericardium	This study
P3	2013/Hunan	F	2	11	12	−	+	64	c. 1144C>T	Pneumonia, bronchiectasis, skin infections, lymph node abscesses, pneumothorax, pleural thickening	Distinctive facial features, eczema, retained primary teeth, LVFT	This study
P4	2014/Jiangsu	M	1	12	12	−	−	75	c. 1144C>T	Pneumonia, pneumatocele, liver abscess, skin infections, onychomycosis	Distinctive facial features, eczema, retained primary teeth, fracture	This study
P5	2011/Jiangxi	M	1.25	3	6	+	+	53	c. 1144C>T	Pneumonia, pneumatocele, otitis media, sepsis, skin infections, CMV infection, pulmonary atelectasis	Distinctive facial features, eczema, clinodactyly (middle finger)	This study
P6	2013/Gansu	F	0.17	14	15	−	−	64	c. 1970A>C	Pneumonia, liver abscess, skin infections, lymph node abscesses, thrush	Distinctive facial features, eczema, retained primary teeth, fracture	This study
P7	2013/Hunan	F	1.5	4	5	−	−	58	c. 1909G>A	Pneumonia, bronchiectasis, skin infections, thrush, EBV infection	Distinctive facial features, eczema, fracture	This study
P8	2011/Liaoning	M	0.08	12	15	−	+	57	c. 1913A>G	Pneumonia, otitis media, skin infections, lymph node abscesses, onychomycosis	Distinctive facial features, eczema, retained primary teeth	This study
P9	2011/Jiangsu	M	0.08	4	7	−	+	55	c. 1827A>T	Pneumonia, pneumatocele, otitis media, septicopyemia, skin infections, lymph node abscesses, enteritis, pneumothorax	Distinctive facial features, eczema, shoulder dislocation	This study
P10	2012/Jiangsu	M	4	5	7	−	+	56	c. 1909G>A	Pneumonia, bronchiectasis, otitis media, skin infections	Distinctive facial features, eczema	This study
P11	2014/Henan	F	1	12	12	−	−	68	c. 1863C>G	Pneumonia, pneumatocele, otitis media, skin infections, oral ulcer, onychomycosis	Distinctive facial features, eczema	This study
P12	2008/Anhui	F	0.08	15	Dead (17)	−	−	88	c. 1144C>T	Pneumonia, pneumatocele, skin infections	Distinctive facial features, eczema, retained primary teeth, fracture, hip dislocation, mental retardation	This study
P13	2010/Zhejiang	M	0.08	12	Dead (13)	−	−	76	c. 2113T>C	Pneumonia, pneumatocele, pulmonary abscess, skin infections, lymph node abscesses, thrush, enteritis (fungus), hepatitis (HBV)	Distinctive facial features, eczema, retained primary teeth, scoliosis, fracture	This study
P14	2011/Shandong	M	5	8	Dead (10)	−	−	60	c. 2123C>G	Pneumonia, skin infections, genitalia fungal infection	Distinctive facial features, eczema	This study
P15	2016/Zhejiang	M	0.25	13	13	−	−	55	c. 1145G>A	Pneumonia, skin infections, otitis media, lymph node abscesses	Distinctive facial features, eczema, retained primary teeth	This study
P16	2016/Hebei	F	0.23	3	3	+	−	52	c. 1294G>A	Pneumonia, skin infections, thrush, brain abscess	Distinctive facial features, eczema	This study
P17	2016/Hebei	F	0.25	26	26	−	−	49	c. 1294G>A	Pneumonia, skin infections, thrush, otitis media	Distinctive facial features, eczema, retained primary teeth, fracture	This study

Table 2 (continued)

Pts	Year of diagnosis/ province	Gender	Age (years)			Family history	BCG	NIH score	cDNA mutation	Types of infection	Types of noninfection	Ref.
			Onset	Diagnosis	Status							
P18	NA/MC	M	0.12	4.1	Alive[a]	NA	NA	62	c. 1859C>G	Pneumonia, skin infections, thrush, pneumatocele, serious infections	Distinctive facial features, eczema, hyperextensibility	[28]
P19	NA/MC	F	0.24	3	Alive[a]	NA	NA	50	c. 1909G>A	Pneumonia, skin infections, thrush, onychomycosis	Distinctive facial features, eczema, hyperextensibility	[28]
P20	NA/MC	M	0.008	8	Alive[a]	NA	NA	72	c. 1145G>A	Pneumonia, skin infections, thrush, pneumatocele, serious infections	Distinctive facial features, eczema, hyperextensibility, retained primary teeth, scoliosis	[28]
P21	NA/MC	F	0.008	3.1	Alive[a]	NA	NA	62	c. 1909G>A	Pneumonia, skin infections, thrush, bronchiectasis, serious infections	Distinctive facial features, eczema, hyperextensibility	[28]
P22	NA/MC	F	0.008	1.7	Alive[a]	NA	NA	56	c. 1825A>G	Pneumonia, skin infections, thrush, serious infections	Distinctive facial features, eczema	[28]
P23	NA/MC	F	0.003	7	Alive[a]	NA	NA	77	c. 1909G>A	Pneumonia, skin infections, thrush, pneumatocele, serious infections	Distinctive facial features, eczema, hyperextensibility, retained primary teeth, scoliosis, fracture	[28]
P24	NA/MC	M	0.019	1.7	Alive[a]	NA	NA	71	c. 1144C>T	Pneumonia, skin infections, pneumatocele, serious infections	Distinctive facial features, eczema, hyperextensibility	[28]
P25	NA/MC	M	0	8	NA	−	NA	NA	c. 1145G>A	NA	NA	[26]
P26	NA/MC	F	0.16	2	NA	−	NA	NA	c. 1121A>G	NA	NA	[26]
P27	NA/MC	M	5	11	NA	−	NA	NA	c. 2132T>C	NA	NA	[26]
P28	2009/MC	M	10	20	Alive[a] (20)	−	NA	NA	c. 1310A>C	Pneumonia, skin infections, pneumatocele	Distinctive facial features, eczema, retained primary teeth	[25]
P29	2010/MC	M	1.5	3	Alive[a] (3)	−	NA	58	c. 1970A>C	Pneumonia, skin infections	Distinctive facial features, eczema	[27]
P30	2014/MC	M	0	4	Alive[a] (6)	−	NA	49	c. 1144C>T	Pneumonia, skin infections, pneumatocele, thrush	Distinctive facial features, eczema	[32]
P31	2011/MC	F	0	14	Alive[a] (14)	−	NA	68	c. 1843A>G	Pneumonia, skin infections, pneumatocele, bronchiectasis, lymph node abscesses, hepatitis (HBV)	Distinctive facial features, eczema, retained primary teeth, scoliosis	[31]
P32	2014/MC	M	1	17	Alive[a] (17)	−	NA	71	c. 1427C>T	Pneumonia, skin infections, lymph node abscesses, brain abscess	Distinctive facial features, eczema, scoliosis	[29]
P33	2013/MC	M	0	12	Alive[a] (12)	−	NA	NA	c. 1909G>A	Pneumonia, skin infections, lymph node abscesses, hemoptysis	Distinctive facial features, eczema, retained primary teeth	[30]
P34	2009/Taiwan	F	0.047	3	Alive[a] (4)	NA	NA	38	c. 1144C>T	Pneumonia, skin infections	Distinctive facial features, eczema	[33]
P35	2001/Taiwan	M	3.83	6	Alive[a] (16)	NA	NA	46	c. 1406A>G	Pneumonia, skin infections, thrush	Distinctive facial features, eczema, retained primary teeth	[33]

Pts patients, *M* male, *F* female, *LVFT* left ventricular false tendons, *CMV* cytomegalovirus, *EBV* Epstein Barr virus, *N* without vaccination, *NA* not available because of lack of reliable data from the published papers, *MC* mainland China, *DBD* DNA-binding domain, *SH2* Src homology 2, *TAD* transactivation domain

[a] The patient was still alive when the cited paper was published. The number in the braces was the age of the patient when the cited paper was published

family histories (P17 is the mother of P16, and the twin brother of P5 died at 1 year of age). The remaining 14 patients had no positive family history (Table 2).

To date, three patients (17.65%, 3/17) have died. P14 died due to *Pneumocystis jiroveci* pneumonia (PCP); P12 and P13 had unknown causes of death. The mean age at death was 13.33 ± 3.51 years. The remaining 14 patients are still alive, with an average age of 11.5 ± 5.84 years (range 3–26 years) (Table 2).

Related Skin Symptoms

All of the 17 patients displayed eczema as initial symptom, which was mainly located on the face and limbs (76.47 and 52.94%, respectively) (Table 2). Fifteen patients (88.24%) presented with eczema during the neonate stage and eight patients within the first 2 weeks of life. Severity of eczema was assessed by the SCORAD index: nine patients (52.94%) had moderate eczema (SCORAD, 16–40) and eight (47.06%) had severe eczema (SCORAD, >40). The eczema was subsided in 13 patients (76.47%) as they were getting older, and symptoms had no change in 4 patients (23.53%) over time. All of the 17 patients underwent allergen testing. Six of them had positive skin prick tests to inhalant allergens. Food allergies were identified in two patients: milk protein allergy in P1 and egg, soy, and peanut protein allergy in P7. P1 was negative on testing for seafood and egg, although these foods did aggravate his eczema.

Recurrent skin infections were also observed in all 17 patients, 13 (76.47%) of whom showed initial infection within the first 2 years of life (Table 2). The scalp and face were the most common sites of infection (100%, 17/17), followed by the hip (35.29%, 6/17). Cold abscesses of the skin were observed in nine patients (52.94%) with a mean age of onset at 5.04 ± 3.1 years (range 1.25–10), eight of whom underwent surgical incision, drainage, and syringe irrigation of the abscesses. Wound cultures were done in four of the patients, and *Staphylococcus aureus* was isolated from three patients and *Streptococcus* from the other patient. Other types of bacterial skin infections observed included pustulosis in 14 patients (82.35%) and folliculitis in 7 patients (41.18%).

Symptoms of Respiratory Tract and Soft Tissue Infection

All 17 patients (100%) had respiratory tract infections (RTIs). Upper respiratory tract infections (URTIs) were most common among AD-HIES patients in our study, with an average of 17.80 episodes per person per year (range 0–36 episodes). Eleven patients (64.70%) had URTIs more than 5 times per year. All 17 patients (100%) had history of lower respiratory tract infections (LRTIs), with a mean of 2.2 episodes per patient per year (range 0–8 episodes). Pneumonia occurred in all 17 patients (100%) in this cohort, 7 of whom had pneumonia more than 2 times per year (Table 2). Bacteria were detected in six patients by sputum culture, and *S. aureus*, *Streptococcus constellatus*, and *Aspergillus* were isolated from P4, P13, and P7, respectively. The other three patients were culture-negative. In addition, three cases (P2, P3, and P7) of *Mycoplasma pneumoniae* infections and one case (P14) of *P. jiroveci* infection were diagnosed. Recurrent pneumonia was mostly associated with secondary pneumatocele in seven patients (41.18%) and bronchiectasis in three patients (17.65%). Four patients (57.14%, 4/7) with pneumatocele underwent lung lobectomy. Other complications include pneumothorax in P2 and P9, pleural thickening in P2, and pulmonary atelectasis in P5 (Table 2).

Other infections include recurrent and chronic otitis media in eight (47.06%) and lymph node abscesses in seven patients (41.18%). Two patients with lymph node abscesses required surgical excision to control infection. Recurrent liver abscesses were observed in two patients (11.76%), one of whom underwent hepatectomy to control bacterial infection. Sepsis was found in two patients (11.76%) with unknown pathogenic bacteria, and septicopyemia due to *S. aureus* was noticed in one patient (P9) (Table 2).

Beside bacterial infections, virus infections were found in three patients (17.65%): cytomegalovirus (CMV) infection in P5 with abnormal liver function and hepatomegaly, Epstein Barr virus (EBV) infection in P7, and hepatitis B virus (HBV) infection in P13. Furthermore, AD-HIES patients with STAT3 deficiency were prone to fungal infections, with thrush in 35.29% of the patients (6/17), chronic onychomycosis in 23.53% of the patients (4/17), and genitalia infection in 5.88% of the patients (1/17) (Table 2).

Noninfection Symptoms

Characteristic facial features were observed in all patients (100%, 17/17), which was more remarkable with increase of age. The retention of primary teeth was the second most common noninfection symptom. The standard age of finishing shedding primary teeth in Chinese children is 12 years. Ten of the 11 patients (90.91%) over the age of 12 were found to have retained primary teeth.

Seven of the 17 patients (41.18%) experienced abnormal bone fractures, which were located at the femoral head (P13), anklebone (P13), tibiofibular (P2 and P4), foot bone (P2 and P17), radioulna (P6), clavicle (P7), and femur (P12). Multiple fracture sites were recorded in two of seven patients (28.57%), of whom P13 suffered repeated femoral head fractures. Some other skeletal abnormalities were observed in four patients (23.53%), including shoulder dislocation in P9, hip dislocation in P12, scoliosis in P13, and clinodactyly in P5.

Two patients (11.76%) presented with cardiovascular abnormality, including left ventricular false tendons (LVFT) complicated with mild tricuspid regurgitation in P3 and

hydropericardium in P2. One patient (P12) had mental retardation, who had delayed speech skill at the age of 2 and delayed walking skill at the age of 4 (Table 2).

BCG Complications

A total of 16 patients (94.12%) received BCG vaccination according to the National Vaccination Program. Six (37.5%) cases suffered from BCG complications, including local ulceration and abscess formation at the site of vaccination in 25% of the patients (4/16, P3, P5, P8, and P10), and disseminated BCG infections in 12.5% of the patients (2/16, P1 and P9). The site of disseminated BCG infections was the lung (Table 2).

Immunological Characteristics

Table 3 shows immunological characteristics of the 17 patients. All of them had high serum IgE levels (>2000 IU/mL), with an average level of 17,054 ± 16,778.53 IU/mL. Sixteen patients had peripheral eosinophil counts over 0.3×10^9/L and 2 over 1.5×10^9/L (Table 3).

B cell immunotyping was performed in seven patients who agreed to have blood drawn. As is known to us, CD19+ B cells can be subgrouped into different B cell subsets according to the expression of CD27 and IgD on their surface: CD27−IgD+ (naive B cells), CD27+IgD− (switched memory B cells), CD27+IgD+ (nonswitched memory B cells), and CD27−IgD− (double negative B cells). AD-HIES patients with positive STAT3 mutation had significantly decreased memory B cells (CD19+CD27+) than age-matched healthy controls, 16.44 ± 3.11% ($P = 0.000$) of the total CD19+ B cell, including both unswitched memory B cells (average 12.26 ± 3.29%; $P = 0.005$) and switched memory B cells (average 4.18 ± 1.84%; $P = 0.000$). The IgM− only memory B cells were also significantly decreased in STAT3 mutated patients (average 0.59 ± 0.37%; $P = 0.014$) compared to controls. However, naive B cells were significantly increased in patients with STAT3 mutation (average 79.45 ± 4.93%; $P = 0.002$) when compared to healthy controls (Table 3).

STAT3 Mutation

STAT3 gene mutation analysis by genomic DNA sequencing was performed in 28 patients who were clinically diagnosed as AD-HIES, and 11 distinct mutations were identified in 17 patients, including 10 reported mutations and 1 novel mutation (Y705H). Eight patients (47.06%) carried STAT3 mutations affecting the DNA-binding domain (DBD), six (35.29%) affecting the SH2 domain, and three (17.65%) affecting the transactivation domain (TAD). All were missense heterozygous mutations, located in exon 13 (6/17, 35.29%), exon 21 (4/17, 23.53%), exon 22 (3/17, 17.65%), exon 15 (2/17, 11.76%), and exon 20 (2/17, 11.76%), respectively. Three (R382W, V637M, and R382Q) are considered as hotspot mutations in other countries, accounting for 29.41% (5/17), 11.76% (2/17), and 5.88% (1/17) of our patients, respectively (Table 5 and Fig. 2). Y705H is a novel mutation identified in the present study that was not found in 100 normal alleles from 50 unrelated, healthy individuals. Three online bioinformatics tools, namely PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/), and combined annotation dependent depletion (CADD) (http://cadd.gs.washington.edu/), were used to predict the functional effect of the new mutation. Results from all three indicated that the mutation is deleterious (with a score of 0.979, 0.020, and 25.300, respectively). A mutation significance cutoff (MSC) study showed that with a 99% confidence interval (CI), STAT3-specific cutoffs for PolyPhen2, SIFT, and CADD are 0.003, 0.051, and 15.290, respectively, predicting high impact of this variation. Furthermore, an allele frequency of 0 was obtained from the 1000 genomes database (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/).

Discussion

Currently, worldwide population-based PID prevalence data are still scarce. Most published PID prevalence data were the result of estimation based on country-based registry cohort studies, which could not be considered as a standard to evaluate the disease prevalence throughout the world. Even less is known as for the prevalence of HIES due to the extremely low incidence plus the need for exploring disease-causing genes. Previous studies indicate the incidence of HIES among PIDs being 1.46–4.65%, which varies among different countries. For instance, estimates from statistical analysis have shown that HIES affect about 0.64/1,000,000 individuals in France [34], 1.04/1,000,000 live births in Japan [35], and 1.00/1,000,000 live births in Taiwan [36]. Currently, there is no national PID registry in China, meaning no accurate prevalence data on HIES. By using HIES incidence in Japan [35] and with a population of 1.36 billion, mainland China is estimated to have 1414 HIES cases. However, only 60 HIES patients from mainland China have been reported in English or Chinese literature (including 17 in this study) [25–32, 37, 38]. The lack of a nationwide HIES survey and the lack of recognition of PID and HIES may contribute to the low case finding rate in mainland China. The proportion of HIES accounting for PIDs was 1.46, 4.65, and 4.52% in France, Taiwan, and Japan, respectively [34–36]. We have 4.87% of the 575 PIDs in our center with suspected HIES, which is similar to Taiwan and Japan. Furthermore, 2.96% (17/575) patients were confirmed to have STAT3 mutation, consistent with that reported from another PID center in China (2.17%) [26]. Up to this date, a total of 35 Chinese HIES patients with

Table 3 Immunologic investigations in 17 AD-HIES patients with STAT3 deficiency in this study

Patients	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	Normal range
Immunoglobulins																		
IgG (g/L)	15.1	11.6	13.5	16.93	20	40	15.2	14.2	7.99	12.3	23.9	21.1	30.3	12.7	14.1	15.4	22.29	7.0–16.0
IgA (g/L)	1.51	3.21	1.13	1.18	0.26	0.86	2.01	1.21	0.74	0.5	1	2.6	3.08	0.9	2.1	1.03	1.62	0.7–4.0
IgM (g/L)	1.6	2.93	2.19	1.7	1.91	1.8	2.41	1.39	1.29	1.72	1.86	2.45	4.35	1.19	0.86	1.42	1.15	0.4–2.3
IgE (IU/mL)	22000	2500	2000	5000	7390	2000	10,000	11,128	19,600	29,000	3000	23,500	60,600	18,800	22,900	48,000	2500	5.0–165.3
Lymphocyte counts (10^9/L)	3.9	4.0	3.0	1.9	4.5	4.1	2.3	3.3	4.2	2.2	3.0	2.2	4.5	6.6	3.6	4.0	3.0	1.2–3.4
CD3+ T cell counts (10^9/L)	3.17	2.91	2.33	1.63	3.50	3.06	1.99	2.54	3.24	1.634	2.41	1.77	2.90	5.35	3.16	2.71	2.56	0.7–2.10
CD3+ T cell (%)	81.17	72.9	77.6	85.93	77.8	74.7	86.4	77	77.2	74.36	80.4	80.5	64.5	81.1	87.76	67.61	85.4	55.0–83.0
CD3+CD4+ (%)	41.66	34.4	35.2	53.66	45.1	37.4	49.9	34	42.2	37.3	40.2	38.9	23.7	40.2	43.59	42.05	59.5	28.0–57.0
CD3+CD8+ (%)	36.59	34.1	33.6	27.88	25.7	35.8	27.1	39	26.2	35.8	30.4	27.9	29.5	32.4	40.3	20.51	17.2	10.0–39.0
CD19+ B cell counts (10^9/L)	0.47	0.28	0.24	0.18	0.86	0.81	0.21	0.56	0.86	0.44	0.57	0.34	1.11	1.04	0.32	1.13	0.33	0.10–0.50
CD19+ B cell (%)	12.07	7.1	8.1	9.42	19	19.8	9.2	17	20.4	20.18	19.1	15.6	24.7	15.8	8.96	28.35	11.0	6.0–19.0
CD19+CD27−IgD+ (%)	ND	83.11	ND	86.23	ND	ND	83.73	78.89	ND	70.89	75.36	77.97	ND	ND	ND	ND	ND	60.09 (51.91–71.01)[a]
CD19+CD27+IgD+ (%)	ND	14.19	ND	8.78	ND	ND	11.86	16.50	ND	12.62	7.25	14.63	ND	ND	ND	ND	ND	18.03 (11.34–24.59)[a]
CD19+CD27+IgD− (%)	ND	2.01	ND	3.11	ND	ND	3.01	3.13	ND	6.65	6.49	4.88	ND	ND	ND	ND	ND	15.46 (8.46–24.45)[a]
CD19+CD27−IgD− (%)	ND	0.69	ND	1.88	ND	ND	1.41	1.38	ND	9.84	10.90	2.51	ND	ND	ND	ND	ND	6.42 (2.95–16.68)[a]
CD19+CD27+IgM+IgD− (%)	ND	0.13	ND	0.18	ND	ND	0.54	0.46	ND	1.09	0.70	1.00	ND	ND	ND	ND	ND	2.12 (0.70–4.63)[a]
CD16+CD56+ counts (10^9/L)	0.10	0.14	0.14	0.06	0.12	0.23	0.01	0.13	0.08	0.10	0.07	0.06	0.49	0.20	0.08	0.08	0.11	0.09–0.60
CD16+CD56+ (%)	2.51	3.5	4.5	3.25	2.6	5.5	0.3	4	2	4.39	2.34	2.5	10.8	3	2.32	2.11	3.5	7.0–31.0
Eosinophils (10^9/L)	0.67	0.46	0	5.50	1.00	2.35	0.28	1.04	0.62	0.57	1.40	1.22	0.45	0.43	1.49	0.87	0.93	0.02–0.52

Percentages of peripheral blood T cells (CD3+), CD4+ T cells (CD3+CD4+), CD8+ T cells (CD3+CD8+), and B cells (CD19+) were referred to total lymphocytes. Percentages of naive (IgD+CD27−), unswitched memory (IgD+CD27+), switched memory (IgD−CD27+), double negative B (IgD−CD27−), and IgM− only memory (CD19+CD27+IgM+IgD−) were referred to total CD19+ B cells

ND not determined

[a] Data was obtained from 10 age-matched healthy donors in this study

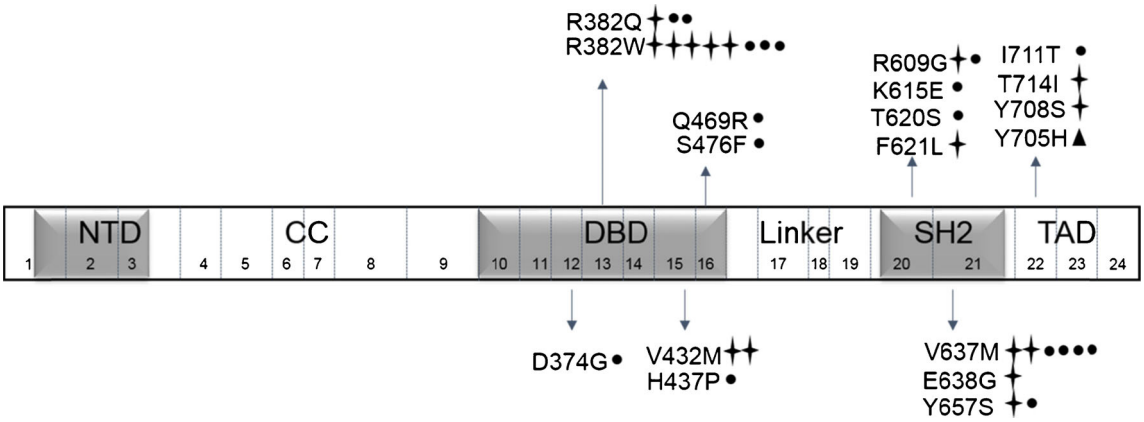

Fig. 2 STAT3 gene mutations found in Chinese HIES patients. All of the mutations were located in the DNA-binding domain (*DBD*), the Src homology 2 (*SH2*) domain, and the transactivation domain (*TAD*). No mutation was found in the N-terminal domain (*NTD*), coiled-coil (*CC*) domain, or linker domain. Mutations marked by *asterisk* represent mutations identified in this cohort study, and mutations marked by *circle* represent mutations identified in previous studies. Mutation marked by *triangle* is the novel mutation identified in this study

STAT3 deficiency have been reported in English and Chinese literature (including the 17 patients in this study and 2 patients from Taiwan) [25–33, 37, 38]. The ratio of male to female was 19:16, similar with our single center study.

The NIH clinical HIES scoring system is an important evaluation system for HIES: scores ≥40 points suggest HIES [22]. In our single center study, all 17 HIES patients had NIH scores above 40. Among the other 13 Chinese patients reported (5 patients excluded due to lack of clinical data), all but 1 (score of 38) had NIH scores over 40. The mean NIH score in all of the 30 Chinese patients (including this study) was 61.47 ± 10.59 (range 38–88). However, studies from other countries showed that some HIES patients with STAT3 mutation had NIH scores under 40 [22, 24] (Table 4). Moreover, all of the non-STAT3 mutated HIES patients had NIH scores under 40 in this study, although some patients from China showed NIH scores over 40 [28, 33]. It is important to pinpoint here that our sequencing does not exclude mutants located in introns or the promoter of *STAT3* gene. Moreover, it does not exclude copy number variations (CNVs). This may contribute to the specific NIH scores in our group.

With regard to the mean onset age of STAT3 mutant AD-HIES, there was little reliable information from large cohort reports around the world. In the present study, the mean age of onset is 1.05 years old considering the first infectious episode, consistent with all of the 35 Chinese patients (mean age 0.85 ± 1.42 years; range 0–10; $P = 0.567$). The mean onset age in a French national cohort study was 0.875 years old (range 0–15 years old) [24], which seemed to be similar with our single center study and all of the Chinese patients reported (statistical analysis could not be done because of the lack of individual data in the French cohort). In addition, the mean age at diagnosis is 10.35 years, which is similar to all 35 Chinese patients (mean age 8.70 ± 5.80 years; range 1.7–20; $P = 0.254$). However, the mean diagnosis age in our single center study and all 35 Chinese patients was both significantly later than the French study (mean age 6.8 years; range 0 month to 30 years; $P = 0.014$ and 0.042, respectively). In addition, for the diagnostic delay, there was no significant difference between our study and all of the Chinese patients (mean lag 7.85 ± 5.72 years; range 1.0–25.75 years; $P = 0.362$). Although statistical analysis could not be done because of the lack of available data, it seemed that the diagnostic delay in Chinese patients was longer than in French patients (mean lag 5.925 years) (Table 4 and Fig. 1). The later diagnosis implies the lack of recognition of this immunodeficiency disease in China.

Seventeen percent of patients had positive family history, in contrast to the other 18 Chinese patients previously reported. Positive family history is often reported by other countries [15, 24]. In the present study, 17.65% of the patients died at a mean age of 13.33 years, while 5% of the patients of the French study died at the age of 15.06 years (except one patient who died in an accident) [24]. The insufficient pediatric immunologists and the lack of recognition of PIDs by primary-care physicians might explain the low quality of life and short survival of HIES patients in China. However, the other 15 Chinese patients reported (3 were excluded because of lack of available information from the published paper) were all alive when the papers were published (Table 2).

Skin symptoms (eczema and skin infection), the characteristic clinical features of HIES, were found in all 17 AD-HIES patients in this study and the other 15 Chinese patients reported (3 were excluded due to lack of data) (Table 2). Eczema was the initial presentation in all 17 patients. However, most patients experienced improvement of the skin condition with age, which was different from previous reports [24]. In this study, bacteria were the leading pathogens of skin infection. Fungal mucocutaneous infections (thrush, onychomycosis, and genital infections) were also found in the current group as well as patients from previously reported Chinese literature, although in a much low incidence. For example, the incidence

Table 4 Laboratory and clinical phenotypes of STAT3 mutant HIES patients reported in this study compared to other cohort studies

Laboratory and clinical phenotypes	China This study $n = 17$	France Chandesris et al. [24] $n = 60$	International Woellner et al. [22] $n = 64$	USA and Central Europe Renner et al. [39] $n = 38$
Age of onset (years)	1.05	0.875	NA	NA
Age of diagnosis (years)	10.35	6.8	NA	NA
Diagnosis lag (years)	9.30	5.925	NA	NA
NIH score >40	100% (17/17)	82% (47/57)	92.2% (59/64)	97.4% (37/38)
Hyperserum IgE level	100% (17/17)	96% (54/56)	100% (64/64)	94.7% (36/38)
BCG complications (a)	37.5% (6/16)	0% (0/20)	NA	NA
Allergy	35.29% (6/17)	22% (13/60)	NA	NA
Eczema	100% (17/17)	92% (55/60)	90.6% (58/64)	100% (38/38)
Skin infection	100% (17/17)	100% (60/60)	90.6% (58/64)	100% (38/38)
Cold abscess	52.94% (9/17)	73% (44/60)	NA	NA
Pneumonia	100% (17/17)	90% (54/60)	95.3% (61/64)	92% (35/38)
Pneumatocele	41.18% (7/17)	52% (31/60)	74.6% (47/63)	72% (27/38)
Bronchiectasis (b)	17.65% (3/17)	65% (39/60)	NA	NA
Chronic otitis media (c)	47.06% (8/17)	73% (44/60)	NA	NA
Lymph node abscesses	41.18% (7/17)	20% (12/60)	NA	NA
Liver abscess	11.76% (2/17)	8.3% (5/60)	NA	NA
Candidiasis (d)	58.82% (10/17)	85% (51/60)	43.1% (25/58)	81% (31/38)
Distinctive facial features	100% (17/17)	95% (57/60)	90.6% (58/64)	89.4% (34/38)
Retained primary teeth	90.91% (10/11)	65% (39/60)	80% (44/55)	
Abnormal bone fractures	41.18% (7/17)	42% (25/60)	45.8% (27/59)	
Hyperextensibility	NA	50% (30/60)	52.7% (29/55)	
Scoliosis (e)	1/17 (5.88%)	38% (23/60)	26% (13/55)	
Symptomatic vascular abnormalities	0% (0/17)	8.3% (5/60)	NA	NA
Lymphoma	0% (0/17)	11.67% (7/60)	NA	NA

Taking $P < 0.05$ as a cutoff, there are statistically significant difference between our cohort and the French cohort on some clinical manifestations, including BCG complications (a), bronchiectasis (b), chronic otitis media (c), candidiasis (d), and scoliosis (e). The P values are 0.000 (a), 0.001 (b), 0.041 (c), 0.041 (d), and 0.011 (e), respectively

NA not available

of chronic mucocutaneous candidiasis (CMC) is significantly higher in the French study (85%) compared to our experience ($P = 0.041$) [24]. This difference may be attributed to a diagnosis bias, and French physicians may be more sensitive to diagnosing CMC. Cold abscesses, another typical skin infection in HIES patients, were found in 52.94% of the patients in this study, very similar to that of the French study (73%, $P = 0.109$) [24] (Table 4). Besides, there was a substantial risk of bacterial superinfection presenting as impetigo and folliculitis, probably due to the defective skin barrier. Studies have shown that *S. aureus* infection is prominent at the site of infection [40, 41], which is consistent with our study.

RTIs have a great impact on the quality of life of HIES patients. The spectrum of RTIs in this study is similar to previous studies in other countries [8, 23, 24] (Table 4). All patients have a history of RTIs, with URTIs being the most common. The same is true for other cases reported in China. For 35 Chinese patients, 3 were excluded because of lack of available information from the published papers. All of the other 32 patients (100%) had pneumonia, and the majority of them (56.25%) developed pneumatocele and/or bronchiectasis, which was similar with our single center study ($P = 0.862$) and French reports ($P = 0.324$) [24] (Table 4). Previous studies revealed *Streptococcus pneumoniae*, *S. aureus*, and *Haemophilus influenzae* being the most common pathogens involved in respiratory infection of HIES [8, 24]. Bacteria were only isolated from 33.33% (two of six) of the patients in the present study and 57.14% (four of seven) of the patients reported from another Chinese study [28]. Fungal pneumonia (typically *Aspergillus*), often reported in AD-HIES patients, was less observed (5.88%) in this study. The lower identified pathogen rate may be, in part, attributed to delaying or lacking of detection and low-threshold use of antibiotics in the primary hospital in mainland China. However, we do notice a higher rate of *M. pneumoniae* infections (17.65%) than that reported in France (5%, $P = 0.086$) [24].

P. jiroveci, an opportunistic pathogen often leading to severe pulmonary infection, is often identified in HIV-infected and immunocompromised patients, that is also reported in AD-HIES patients [24, 42]. We have one patient who died due to *Pneumocystis* pneumonia.

In addition to RTIs, other infections found in our patients mainly included recurrent and chronic otitis media, lymph node abscesses, and liver abscess. The French national AD-HIES survey [24] showed that up to 73% of the patients suffered from recurrent otitis media, which was significantly higher than what we found ($P = 0.041$). Patients with lymph node abscesses (20%) and liver abscess (8%) were similar to what we saw in our patients ($P = 0.074$ and 0.837, respectively). The rate of severe infection (sepsis and septicopyemia, 17.65%) in our study is similar to the French study (13.3%, $P = 0.654$) [24]. Viral infections, commonly reported in AD-HIES patients, were noticed much less often in this study. Of note, although BCG complications were reported to be less common in AD-HIES patients, up to 37.5% of the cases suffered from BCG complications in this study. There was a significant difference between our study and the French study ($P = 0.000$). However, the reason for the high incidence is still unknown.

The noninfectious pathological changes, although less important than infection, occurred very frequently in AD-HIES patients with STAT3 mutation (Table 4). Similar to previous reports, characteristic facial features are the most frequent noninfectious features in all Chinese patients including the 17 of our study. Retention of primary teeth, another typical feature for AD-HIES, was found in 87.5% of the Chinese patients (10 of 11 in this study and 4 of 5 in other published Chinese studies). Other oral cavity abnormalities, such as ectopic eruption, noneruption of permanent teeth, palatal lesions, and tongue lesions, were also reported in STAT3 mutant HIES patients [43]. Though not statistically different, outpatients showed a slightly higher rate of retention of primary teeth (90.91%) when compared to the French national study ($P = 0.088$) [24]. HIES patients with STAT3 mutation also have bone abnormalities [23, 24], such as reduced bone mineral density, chronic inflammation of bone, and osteoclast hyperfunction, which often lead to bone fracture. The incidence of abnormal bone fractures in our studies was similar to that reported from other countries. Again, the 35 Chinese patients showed slightly lower incidence of bone abnormalities (25%, 8/32) than the French study, although not statistically significant ($P = 0.112$). Such low incidence might be partially explained by the different styles of physical activity seen in different countries. In China, children's physical activities are usually under close supervision of their parents, which may reduce the incidence of bone fractures. On the other hand, long bone fracture is found to be most common in our group, which includes the tibia, fibula, ulna, radius, and clavicle. In contract, fractures of the rib and pelvic are most common in other countries [24]. We hypothesize that the different fracture patterns may be attributed to the different styles of physical activity in different countries. Other skeletal abnormalities, such as dislocations, scoliosis, hyperextensibility, and clinodactyly, are noticed in our patient group and other Chinese patients reported [24, 36]. However, genu valgum, spondylolisthesis, and spina bifida occulta, which were reported previously, are not observed in Chinese patients. Although a high incidence of peripheral or cerebral artery disease (84%) and coronary artery anomalies (50%) [44] was reported in STAT3 mutant patients, we did not find vascular abnormalities in the present study. In fact, we did not do further examinations, such as imaging and ultrasound scans, unless some clinical symptoms of vascular disease occurred. This may have contributed to the underdiagnosis of vascular abnormalities. One patient with mental retardation was reported in this study. However, there was no evidence to show that loss-of-function and dominant-negative effect of the STAT3 mutants were related with mental retardation, and further studies are warranted. Notably, some of the clinical symptoms were developmental and the patients in our study were a younger patient population, so it is possible that some of the phenotypes were underrepresented in this study. Further long-term follow-up study is still needed.

STAT3 is the only gene known to cause AD-HIES [45]. In our cohort of 28 patients suspected to have HIES, 17 carried 11 distinct heterozygous STAT3 mutations, including 16 patients with 10 previously identified mutations and 1 patient with novel mutation (Y705H). Tyr-705 is the most important phosphorylation site of STAT3 and is critical for optimal induction of STAT3 transcriptional activation [12]. Therefore, it is obvious that replacing Tyr with His at position 705 would impact the physiological function of STAT3. Unfortunately, the pathogenic effect of the mutation was not proven by a functional assay in this study.

At this point, a total of 35 Chinese HIES patients with STAT3 mutations were reported, including 18 patients in the previous studies and 17 patients in this study [25–32, 37, 38] (Table 5 and Fig. 2). R382W, identified in 8 of 35 patients (22.86%), was the most common mutation in Chinese patients, followed by V637M in 6 patients (17.14%). All are missense heterozygous mutations, affecting exon 13 (11/35, 31.43%), exon 21 (9/35, 25.71%), exon 20 (5/35, 14.29%), exon 22 (4/35, 11.43%), exon 15 (3/35, 8.57%), exon 16 (2/35, 5.71%), and exon 12 (1/35, 2.86%). Most of the patients (31/35, 88.57%) carry STAT3 mutations affecting DBD (17/35, 48.57%) and SH2 domains (14/35, 40.00%). Fewer patients (4/35, 11.43%) carry mutations affecting TAD (Fig. 2). Similarly, the French national AD-HIES survey showed that 87% of patients carried STAT3 mutations affecting the DBD (55%) and SH2 domains (32%) and only 10% of patients carried mutations affecting the TAD [24]. In addition to the affected functional domains mentioned above, STAT3

Table 5 Summary of the *STAT3* gene mutations in 35 Chinese patients with AD-HIES

Pts	cDNA mutation	Exon	Predicted effect on protein	Affected domain	Ref.
P1	c. 2141C>T	22	T714I	Transactivation	This study
P2	c. 1144C>T	13	R382W	DNA binding	This study
P3	c. 1144C>T	13	R382W	DNA binding	This study
P4	c. 1144C>T	13	R382W	DNA binding	This study
P5	c. 1144C>T	13	R382W	DNA binding	This study
P6	c. 1970A>C	21	Y657S	SH2	This study
P7	c. 1909G>A	21	V637M	SH2	This study
P8	c. 1913A>G	21	E638G	SH2	This study
P9	c. 1827A>T	20	R609S	SH2	This study
P10	c. 1909G>A	21	V637M	SH2	This study
P11	c. 1863C>G	20	F621L	SH2	This study
P12	c. 1144C>T	13	R382W	DNA binding	This study
P13	c. 2113T>C[a]	22	Y705H	Transactivation	This study
P14	c. 2123C>G	22	T708S	Transactivation	This study
P15	c. 1145G>A	13	R382Q	DNA binding	This study
P16	c. 1294G>A	15	V432M	DNA binding	This study
P17	c. 1294G>A	15	V432M	DNA binding	This study
P18	c. 1859C>G	20	T620S	SH2	[28]
P19	c. 1909G>A	21	V637M	SH2	[28]
P20	c. 1145G>A	13	R382Q	DNA binding	[28]
P21	c. 1909G>A	21	V637M	SH2	[28]
P22	c. 1825A>G	20	R609G	SH2	[28]
P23	c. 1909G>A	21	V637M	SH2	[28]
P24	c. 1144C>T	13	R382W	DNA binding	[28]
P25	c. 1145G>A	13	R382Q	DNA binding	[26]
P26	c. 1121A>G	12	D374G	DNA binding	[26]
P27	c. 2132T>C	22	I711T	Transactivation	[26]
P28	c. 1310A>C	15	H437P	DNA binding	[25]
P29	c. 1970A>C	21	Y657S	SH2	[27]
P30	c. 1144C>T	13	R382W	DNA binding	[32]
P31	c. 1843A>G	20	K615E	SH2	[31]
P32	c. 1427C>T	16	S476F	DNA binding	[29]
P33	c. 1909G>A	21	V637M	SH2	[30]
P34	c. 1144C>T	13	R382W	DNA binding	[33]
P35	c. 1406A>G	16	Q469R	DNA binding	[33]

Pts patients, *SH2* Src homology 2

[a] Novel STAT3 mutations

loss-of-function mutations were also reported to be in the N-terminal domain, coil-coiled domain, and linker domain [46]. However, such mutations have not been found in the Chinese population.

Studies have shown that STAT3 mutant HIES patients have significantly reduced numbers of IL-17-producing CD4+ T (Th17) cells, suggesting the key role of STAT3 in the development of Th17 cells. The reduced Th17 cell numbers were also reported in Chinese patients. Besides, dominant-negative mutations in STAT3 were reported to cause impaired memory B cell generation. The latter plays an important role in secondary humoral immune responses and other immune functions [18]. As previously reported, we also found decreased memory B cells (including unswitched, switched, and IgM− only memory B cells) in STAT3 mutant AD-HIES patients compared to normal healthy controls, implying the importance of STAT3 in memory B cell development.

In summary, we present the largest AD-HIES cohort from mainland China with a detailed description of their clinical, laboratory, and molecular features. We also reviewed all of the Chinese HIES patients known to have STAT3 mutation. The information presented here included the incidence, severity,

and constellation of features of STAT3 mutations causing AD-HIES in Chinese individuals.

Conclusions

We here retrospectively report the largest Chinese cohort study of AD-HIES patients with STAT3 mutation. Unique features, when compared to existing literature reports, include (1) later age of diagnosis, (2) significantly higher rate of BCG complications, and (3) lower rate of candidiasis and chronic otitis media.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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