

ORIGINAL ARTICLE

WILEY

Immunodeficiency

The first cohort of Iranian patients with hyper immunoglobulin E syndrome: A long-term follow-up and genetic analysis

Mahmood Tavassoli¹ | Hassan Abolhassani^{2,3} | Reza Yazdani² | Mohsen Ghadami⁴ |
Gholamreza Azizi⁵  | Sina Abdolrahim Poor Heravi⁵ | Tannaz Moeini Shad² |
Mostafa Kokabee² | Masoud Movahedi⁶ | Hormoz Abdshahzadeh² |
Mohammad Gharagozlou⁶ | Nima Rezaei^{2,7} | Hossein Esmaeilzadeh⁸ |
Soheila Aleyasin⁸ | Asghar Aghamohammadi¹ 

¹Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

²Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

³Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

⁴Molecular Immunology Research Center, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁵Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

⁶Department of Allergy and Clinical Immunology, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

⁷Network for Immunology in Infection, Malignancy, and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

⁸Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence

Soheila Aleyasin, Allergy Research Center,
Shiraz University of Medical Sciences,
Shiraz, Iran.

Email: aleyasins@sums.ac.ir

and

Asghar Aghamohammadi, Children's Medical
Center Hospital, Tehran, Iran.

Email: aghamohammadi@tums.ac.ir

Edited by: Philippe Eigenmann

Abstract

Background: Hyper-IgE syndromes (HIES) are distinct diseases characterized by recurrent cutaneous and lung infections, eczema, and elevated serum IgE level.

Methods: In this study, clinical manifestations, immunologic findings, and genetic studies of all patients with HIES in the Iranian national registry database were evaluated.

Results: A total of 129 HIES patients with a median age of 14.0 (9.0–24.0) years were followed up for a total of 307.8 patient-years. Genetic studies showed heterozygous *STAT3* mutations in 19 patients and homozygous *DOCK8* mutation in 16 patients. The mean of National Institutes of Health score in *STAT3*-deficient patients was higher than in patients with *DOCK8* mutation ($P = 0.001$). It was shown that the presence of pneumatocele and hematologic complication were significantly frequent in *STAT3*-deficient cases compared to patients with *DOCK8* deficiency ($P = 0.001$ and $P = 0.002$, respectively). Moreover, the median IgE serum levels were higher in patients with *STAT3* gene mutation than in patients with *DOCK8* gene mutation ($P = 0.02$). The eosinophils' count was enhanced in patients with *DOCK8* deficiency than in patients with *STAT3* gene defects ($P = 0.02$).

Tavassoli and Abolhassani contributed equally to this work.

Conclusion: Specific molecular study of *STAT3* and *DOCK8* mutations in patients with HIES clinical phenotype could help the physician to definitively characterize the disease. Since HIES showed the highest rate of unsolved combined immunodeficiency, investigation of other genetic and environmental factors could also help in understanding the mechanism of remaining patients as well as providing strategy into therapeutic modalities.

KEYWORDS

DOCK8, Hyper-IgE syndrome, Pneumatocele, Primary immunodeficiency, *STAT3*

1 | INTRODUCTION

The hyperimmunoglobulin E (IgE) syndromes (HIES) consist of a group of primary immunodeficiency disorders (PID), exhibiting markedly elevated IgE levels, recurrent staphylococcal skin abscesses, eczema, and pulmonary infections.¹⁻³ Distribution of HIES is equal in both genders and has been documented in different ethnic groups. The first cases of HIES (as a Job's syndrome) are related to two girls who had a triad of eczematous dermatitis, recurrent sinopulmonary infections and staphylococcal cold abscess, that were described in 1966.⁴ With advanced progression in 1972, Buckley et al.⁵ subsequently described this syndrome noting characteristic facial features and an elevation in serum IgE levels. Prior to discovery of underlying genetic causes, in 1999, the National Institutes of Health (NIH) introduced the clinical HIES scoring system for diagnosis of autosomal dominant (AD-HIES) form of the disease based on 19 main clinical and laboratory findings for early diagnosis.⁶ It has been proposed that the NIH point scale for diagnosis of HIES >40 points is suggestive for HIES, NIH score before 20-40 is intermediate, whereas a score below 20 made the diagnosis unlikely.^{6,7}

Most of HIES patients seem to be inherited through AD-HIES pattern or are sporadic. *Signal transducer and activator of transcription 3* genes (*STAT3*; OMIM#147060) have been found to be mutated in the group of patients characterized by recurrent staphylococcal infections of lungs, pneumatocele formation, candidiasis, and eosinophilia. However, a minority of HIES cases have demonstrated mutations in *dedicator of cytokinesis 8* (*DOCK8*; OMIM#243700), and *phosphoglucomutase 3* (*PGM3*; OMIM# 615816) genes, serine protease inhibitor, Kazal-type 5 (*SPINK5*; OMIM#256500), and zinc finger protein 341 (*ZNF341*), which have been identified with an autosomal recessive pattern of inheritance (AR-HIES).^{1,8-12} There are still several attempts to identify the gene defects in other HIES cases that the above-mentioned genes are normal. Patients with AD-HIES also are risk of non-immunological abnormalities, including a distinctive facial appearance, pathological fracture, scoliosis, hyperextensive joints, the retention of primary teeth, and craniosynostosis.^{13,14} In contrast, reduced serum IgM levels, lymphopenia, and severe viral skin infections have been suggested as clues for *DOCK8* deficiency, the main form of AR-HIES.^{7,15} These clinical findings might help physician, but these are not present in all

Key Message

In this study, we reported characteristics of 19 patients with *STAT3* and 16 with *DOCK8* gene defects, among 129 patients with HIES. Although there are few published case reports from our region, no comparative study was performed regarding the frequency and distributions of HIES. This study for the first time presented a prospective cohort of registered Iranian HIES patients in order to show their clinical and immunologic characteristics as well as the result of their genetic analysis. This report illustrates the potential difficulty in the diagnosis of *DOCK8* deficiency when the HIES score is suggestive of *STAT3* deficiency, when skin viral infections have not yet manifested.

patients; therefore, the molecular study is essential for definitive diagnosis.

Although there are few published case reports from our region, no comparative study was performed regarding the frequency and distributions of HIES. This study for the first time presented a prospective cohort of registered Iranian HIES patients in order to show their clinical and immunologic characteristics as well as the result of their genetic analysis.

2 | MATERIALS AND METHODS

2.1 | Subjects

All HIES cases who had been referred to the Immunodeficiency Clinic at Children's Medical Center of Tehran University of Medical Sciences (Tehran-Iran) from 1980 to 2017 were enrolled to this study.^{16,17} The patients were recruited according to the guideline approach to severe eczema using SCORing Atopic Dermatitis (SCORAD >40),^{18,19} unsolved recurrent infections, and unsolved immune dysregulation. The clinical diagnosis of HIES was confirmed according to the European Society for Immunodeficiencies (history of infectious diseases, serum IgE >10 times the norm for age, and no evidence

of T-cell and B-cell deficiencies) (<https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria>). All patients with other types of PID associated with allergic diseases were excluded.²¹ The study was approved by the ethics committee of Tehran University of Medical Sciences, and written informed consent was obtained from all participants or their parents before enrolling to the study. Demographic, clinical, immunologic, and mutational analysis data of each patient were documented in a separate datasheet. The phenotypic severity by NIH scoring algorithm was also calculated to predict the probability of AD-HIES.^{6,22,23}

Complete blood count, its differential, serum immunoglobulin, lymphocyte subpopulations, and specific antibody responses were measured, using previously published methods.^{16,17}

2.2 | Genetic study and sequencing analysis

Five milliliters venous blood was collected into ethylenediamine-tetraacetic acid (EDTA) tube and delivered to the laboratory within 24 hours. Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque density gradient centrifugation (Amersham Pharmacia Biotech, Piscataway, NJ) and frozen for further analysis if necessary.

Gene-specific oligonucleotide primers were designed based on human genome sequences and used to amplify all exons and flanking intron sequences of the *STAT3* gene. Polymerase chain reactions (PCRs) were performed according to standard methods. Briefly, 60 ng of each patient's genomic DNA was used as template and amplified using 20 pmol of each primer, 10 mmol/L Tris-HCl at pH 8.3, a $MgCl_2$ concentration depending on the length of exon amplified, 50 mmol/L KCl, 1.5 units of *Thermophilus aquaticus* (Taq) DNA polymerase, and deoxyribonucleotide triphosphates (dNTP). PCR consisted of 30 cycles and was carried out in an automated thermal cycler. The PCR products were subsequently sequenced using the BigDye Terminator Cycle sequencing kit V3.1 on an ABI PRISM 3100 DNA sequencer (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. Direct sequence analysis of the exons (including exon-intron boundaries) was performed using the DNASTAR and BLAST programs.

For patients in which Sanger sequencing failed, targeted gene panel sequencing (TGS, containing four main HIES-associated genes of *STAT3*, *DOCK8*, *PGM3*, and *SPINK5*; Table S1) was carried out using a previously published pipeline.^{24,25} Copy number variation was identified using both read count and paired-end methods on the input BAM data of TGS.^{24,25} The pathogenicity of all disease-attributable gene variants was re-evaluated using the updated guideline for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (ACMG) as described previously.²⁵ Variants in genes with more than five affected patients were selected for the comparative genetic study, enabling statistical analysis between groups. In addition, selected patient groups were analyzed according to mutational scores, affected domains of the mutated protein, and disease severity. Based on the criteria of the ACMG, we considered mutations with strong evidence of computational and

predictive data (PVS1) as severe and the remaining mutations were classified as non-severe (mild).²⁷

2.3 | Statistical analysis

Statistical analysis was performed using a commercially available software package (SPSS Statistics 17.0.0; SPSS, Chicago, Illinois). The one-sample Kolmogorov-Smirnov test is utilized to estimate whether data were normally distributed. Parametric and nonparametric analyses were performed based on the finding of this evaluation. A *p* value of 0.05 or less was considered statistically significant in our study.

3 | RESULTS

A total of 129 HIES patients (73 males, 56 females) with a median (interquartile range, IQR) age of 14.0 (9.0-24.0) years were enrolled in this study. Patients were followed up for a total of 307.8 patient-years with a median follow-up of 2.0 (1.0-4.5) years per patient. The median age at symptom onset was 0.5 (0.01-2.0) years with latest presentation at age 20 years in one patient. HIES patients were diagnosed at a median age of 6.0 (2.0-11.0) years, whereas only 7.7% of patients were diagnosed after age 30 years. The mean $\pm$ standard deviation (SD) of SCORAD at time of enrollment to the study was 68.2 ± 15.6 , and the subsequent measured NIH score showed the mean of 45.3 ± 17.9 (with a wide range of 10-96). Thirty-six patients (~28%) were negative for clinical diagnosis of eczema, and their main clinical presentations were unsolved recurrent infection or immune dysregulation. Demographic and immunological characteristics of all patients are summarized in Table 1.

Molecular analysis revealed that *STAT3* gene (AD-HIES) was mutated in 19 cases and *DOCK8* gene (AR-HIES) in 16 individuals (Table 2). The rest of identified mutations revealed *PGM3* deficiency 3 patients and *SPINK5* deficiency (Comel-Netherton syndrome) in 1 patient, but these 4 patients were excluded from subset analysis due to low sample size and lack of study power. The genetic evaluation failed to find known HIES monogenic cause in 28 patients (41.7% unsolved rate among 68 studied cases). Of note, parental consanguinity and severity of the disease (SCORAD and NIH scores) did not show a significant difference between monogenic HIES patients and remaining unsolved patients. Clinical and immunological features of patients with a mutation in the *STAT3* gene were compared to find the differences between those with *DOCK8* gene mutation (Tables 3-5). It was shown that the presence of pneumatocele, retention of deciduous teeth, and hematologic complication were significantly frequent in *STAT3*-deficient cases compared to those with defects in *DOCK8* gene ($P = 0.001$, $P = 0.001$, and $P = 0.002$, respectively). In contrast, viral cutaneous infections were significantly observed in patients with *DOCK8* deficiency (4 patients with severe papillomavirus, 2 patients with *molluscum contagiosum*, and 2 patients with severe herpes simplex virus infections, $P = 0.004$). Moreover, serum levels of IgG, IgM, and IgE were considerably higher in patients with

STAT3 gene mutation than in patients with DOCK8 gene mutation ($P = 0.002$, $P = 0.002$, and $P = 0.02$, respectively), while the eosinophil cell count was higher in patients with DOCK8 deficiency than in patients with STAT3 gene mutation ($P = 0.02$).

The mean $\pm$ SD of NIH score in STAT3-deficient patients was significantly higher than in patients with DOCK8 mutation (59.7 ± 11.7 vs 40.3 ± 12.8 , $P = 0.001$). Although all STAT3-deficient patients (17/17 evaluated patients) have NIH score > 40 , only half of the patients with DOCK8 deficiency had this condition (5/10 evaluated patients, $P = 0.003$). The frequency of complications in STAT3- and DOCK8-deficient patients with NIH score > 40 was compared. We demonstrated that pneumatocele, failure to shed deciduous teeth, and hyperextensibility were significantly higher in STAT3-deficient patients with NIH score > 40 compared with DOCK8-deficient patients with this condition (Table S2).

In patients with the STAT3 gene mutation, the variants are composed of 15 missense, 2 frameshift, and 2 stop-gain mutations (21.0% with severe deleterious PVS1 mutations). We identified that majority of mutations were located in exon 13 due to founder effect of

p.R382Q and p.R382W mutations (68.4% of patients; Table 2). Based on the location of the mutation in STAT3-deficient patients, we classified 18 patients (excluding P17 with mutation in NTD domain) into two different groups according to the damaged domain of the final protein (SH2 group: Src homology 2 domain with 3 cases; and DNA-B group: DNA-binding domain with 15 cases; Table 2). The median (range) of the eosinophils' count in the SH2 group was slightly higher than in the DNA-B group (4483 [2180-6786] vs 980 [158-4968] cell/ μ L, $P = 0.07$). When splitting STAT3-deficient patients based on prediction severity, the median (range) of eosinophil cell count was higher in patients with severe mutation than in patients with mild mutation (2400 [2180-6786] vs 980 [158-4968] cell/ μ L, $P = 0.05$). Moreover, in STAT3-deficient patients with severe mutation, the frequency of gastrointestinal complication (50.0% vs 6.6%, $P = 0.10$; Table S3), endocrine complication (50.0% vs 13.3%, $P = 0.19$; Table S3), malignancy (50.0% vs 6.6%, $P = 0.19$), eosinophilia (100.0% vs 40.0%, $P = 0.08$), and neutropenia (75.0% vs 20.0%, $P = 0.07$) was higher than in the patients with missense mutations; however, there were no statistically significant differences in these parameters.

Parameters	Total (N = 129)	STAT3 (N = 19)	DOCK8 (N = 16)	p-value
Sex ratio; M/F; N (%)	73 (56.6)/56 (43.4)	10 (52.6)/9 (47.4)	6 (37.5)/10 (62.5)	0.56
Consanguinity; N (%)	78 (60.4)	9 (47.3)	13 (81.2)	0.06
Age at study time; median years (IQR)	14.0 (9.0-24.0)	23.0 (11.0-29.0)	9.5 (5.0-12.0)	0.002*
Age at symptom onset; median years (IQR)	0.5 (0.01-2.0)	0.4 (0.1-1.6)	0.7 (0.1-2.0)	0.06
Age at diagnosis; median years (IQR)	6.0 (2.0-11.0)	6.0 (3.0-10.0)	5.0 (2.5-7.0)	0.24
Delay in diagnosis; median years (IQR)	4.5 (1.0-9.0)	5.0 (2.0-10.0)	4.0 (0.6-6.5)	0.12
Course of disease; median years (IQR)	8.5 (4.0-13.0)	10.0 (6.5-18.0)	6.0 (3.0-7.0)	0.23
Follow-up time; median years (IQR)	2.0 (1.0-4.5)	3.0 (1.0-12.5)	1.6 (1.0-2.0)	0.03*
National Institutes of Health Score (SD)	45.3 (17.9)	59.7 (11.7)	40.3 (12.8)	0.001*
First presentation with dermatologic problem; N (%)	99 (76.7)	15 (78.9)	13 (81.2)	1.0
First presentation with non-dermatologic problem; N (%)	28 (21.7)	4 (21.0)	3 (18.7)	0.8
First presentation with upper RTI; N (%)	38 (29.4)	8 (42.1)	9 (56.2)	0.25
First presentation with lower RTI; N (%)	63 (48.8)	14 (73.6)	0 (0)	0.01*
Patients with history of hospitalization; N (%)	45 (34.8)	10 (52.6)	3 (18.7)	0.31

Data were available for one patient. F, female; IQR, range with 75th and 25th percentiles; M, male; N, count; RTI, respiratory tract infection.

*P-value is statistically significant.

TABLE 1 Demographic data of clinically and genetically diagnosed HIES patients at the time of diagnosis

TABLE 2 Mutation analysis of 19 patients with STAT3 gene and 16 patients with DOCK8 gene mutations

No	Gene	Amino acid change	Codon sequence change	Exon	Zygosity	Inheritance	PMID Reported/ New patient	Affected domain	Type of mutation	Prediction Severity
1	STAT3	p.R382Q	c.1145 G > A	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
2	STAT3	p.R382Q	c.1145 G > A	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
3	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
4	STAT3	p.R382Q	c.1145 G > A	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
5	STAT3	p.V637M	c.1909 G > A	EX21	Het	AD	PMID:28916186	SH2	Missense	Mild
6	STAT3	p.N466T	c.1397 A > C	EX21	Het	AD	PMID:28916186	DBD	Missense	Mild
7	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
8	STAT3	p.R382Q	c.1145 G > A	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
9	STAT3	p.R382Q	c.1145 G > A	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
10	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
11	STAT3	p.Y657X	c.1971delT	EX21	Het	AD	PMID:28916186	SH2	Stop-gain	Severe
12	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
13	STAT3	p.Y657X	c.1971delT	EX21	Het	AD	PMID:28916186	SH2	Stop-gain	Severe
14	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
15	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
16	STAT3	p.R382W	c.1144 > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
17	STAT3	p.R18fsX34	c.83 delG	EX2	Het	AD	PMID:28916187	NTD	Frameshift	Severe
18	STAT3	p.F493LfsX508	c.1479delT	EX17	Het	AD	PMID:28916187	DBD	Frameshift	Severe
19	STAT3	p.R382W	c.1144 C > T	EX13	Het	AD	PMID:28916186	DBD	Missense	Mild
20	DOCK8	p.S1711X	c.5132C > A	EX18	Hom	AR	PMID:28916187	DHR2	Stop-gain	Severe
21	DOCK8	Large del	...	EX 1 and EX 27-28	Hom	AR	PMID:28916187	DHR1	Large del	Severe
22	DOCK8	Large del	...	EX7-8	Hom	AR	PMID:28916187	DHR1	Large del	Severe
23	DOCK8	p.S1711X	c.5132C > A	EX40	Hom	AR	PMID:28916187	DHR2	Stop-gain	Severe
24	DOCK8	p.Leu1193Val	c.3577C > G	EX29	Hom	AR	PMID:28916187	DHR2	Missense	Severe
25	DOCK8	Large del	...	EX9 and EX12	Hom	AR	PMID:28916187	DHR2	Large del	Severe
26	DOCK8	p.R1370PfsX1395	c.4106-4107insG	EX32	Hom	AR	PMID:28916187	DHR2	Frameshift	Mild
27	DOCK8	Large del	...	EX25-26	Hom	AR	New	DHR2	Large del	Severe
28	DOCK8	Splice site	c.4682 + 1G>T	EX37	Hom	AR	New	DHR2	Splice site	Severe
29	DOCK8	Large del	...	EX1-10	Hom	AR	New	DHR1	Large del	Severe

TABLE 2 (Continued)

No	Gene	Amino acid change	Codon sequence change	Exon	Zygosity	Inheritance	PMID Reported/ New patient	Affected domain	Type of mutation	Prediction Severity
30	DOCK8	p.R482X	c.C1648T	EX14	Hom	AR	New	DHR1	Stop-gain	Severe
31	DOCK8	p.R482X	c.C1648T	EX14	Hom	AR	New	DHR1	Stop-gain	Severe
32	DOCK8	p.E1301X	c.G3901T	EX31	Hom	AR	New	DHR2	Stop-gain	Severe
33	DOCK8	p.E1301X	c.G3901T	EX31	Hom	AR	New	DHR2	Stop-gain	Severe
34	DOCK8	p.E1301X	c.G3901T	EX31	Hom	AR	New	DHR2	Stop-gain	Severe
35	DOCK8	Large del	...	EX1-48	Hom	AR	New	DHR2	Large del	Severe

AD, autosomal dominant; AR, autosomal recessive; DBD, DNA-binding domain; DHR1, DOCK-homology region 1 domain; DHR2, DOCK-homology region 2 domain; Het, heterozygous; Hom, homozygous; Large del, large deletion; NTD, N-terminal domain; SH2, Src Homology 2 domain.

In patients with *DOCK8* gene defects, all mutations were homozygous (100% parental consanguinity), without any obvious hotspots for mutation. Only 1 missense was identified, and the remaining pathogenic variants were composed of 7 stop-gain, 1 splice site, 1 frameshift mutations, and 6 large deletions (93.7% with severe deleterious PVS1 mutations). Based on the location of the mutation in *DOCK8* gene, we classified 16 patients into two different groups according to the damaged domain of the final protein (DHR1 group: DOCK-homology region 1 with 5 cases; and DHR2 group: DOCK-homology region 2 with 11 cases; Table 2). The frequency of hepatomegaly in DHR1 group (60.0%) was higher than in the DHR2 group (10.0%); however, the differences were not statistically significant ($P = 0.07$).

4 | DISCUSSION

In this study, we reported characteristics of 19 patients with *STAT3* and 16 with *DOCK8* gene defects, among 129 patients with HIES. Although stepwise genetic evaluation using Sanger sequencing and TGS showed 58.3% diagnostic yield in the evaluated HIES patients (compared to 87.1% in other syndromic combined immunodeficiency),²⁶ the recently discovered autosomal recessive gene *ZNF34* was not included in our gene panel. Moreover, due to the possibility of the presence of novel gene defects in this group, they should undergo whole exome or whole genome sequencing. Since the rate of consanguinity was not different between patients with known monogenic defects and unsolved patients, both autosomal recessive and autosomal dominant models could be expected in former group. Based on the previous reports, nearly 60%-70% of patients with HIES have dominant mutations in *STAT3* and 10%-15% have autosomal recessive mutations in *DOCK8*.²⁸ These percentages are completely different from our observation in this survey, which was 36.5% and 30.7% for *STAT3* and *DOCK8* genes, respectively.

The NIH score sensitively identifies patients with AD-HIES (Job's syndrome). It has been proposed that NIH clinical score >40 (with points coming from both immune and non-immune categories) can predict more than 95% of patients with *STAT3* mutation.²⁹ The sensitivity of this clinical scoring system was supported for diagnosis of *STAT3* deficiency by our findings, as all of our evaluated patients with *STAT3* mutations had to score >40, while its specificity is questionable because 50% of patients with mutations in *DOCK8* had also NIH clinical score >40. However, some manifestations especially pneumatocele, failure to shed deciduous teeth, and hyperextensibility can help to distinguish between two diseases. Moreover, we observed similar NIH score between monogenic defects and unsolved HIES patients and, therefore, would suggest to prioritized next-generation sequencing on those with NIH score >40.

In this study, recurrent staphylococcal skin abscess and pneumonia were found in all *STAT3* mutant patients that have been indicated by previous reports.^{7,30} Susceptibility to staphylococcal disease has been explained by defective signaling cascades of IL-6 receptors, because of the role of *STAT3* in this pathway.³¹ Moreover, excessive

TABLE 3 Laboratory features of HIES patients at the time of diagnosis

Parameters	Total (N = 129)	Normal range	STAT3 (N = 19)	DOCK8 (N = 16)	p-value
IgG; mg/dL (IQR)	1254 (854-1753)	700-1600	1578 (1360-2378)	942 (728-1342)	0.002*
IgA; mg/dL (IQR)	144 (73-237)	70-400	139 (65-216)	193 (95-264)	0.46
IgM; mg/dL (IQR)	82 (40-150)	40-230	133 (105-191)	33 (37-115)	0.002*
IgE; IU/mL (IQR)	2526 (1250-5820)	0-100	3383 (1552-12430)	1436 (517-2644)	0.02*
IgE > 2000; N (%)	68 (52.7)	...	12 (63.1)	6 (37.5)	0.18
WBC; cell/ μ L (IQR)	11540 (8750-15830)	4000-11000	14560 (11540-18570)	13308 (11410-14420)	0.48
Neutrophils; cell/ μ L (IQR)	4774 (3010-8902)	1800-8000	7617 (2300-12349)	10125 (7120-11074)	0.37
Neutropenia; N (%)	46 (35.6)	20-70	6 (31.5)	4 (25.0)	0.72
Eosinophils; cell/ μ L (IQR)	1169 (451-3447)	50-800	1117 (602-2593)	4122 (1845-9818)	0.02*
Eosinophilia; N (%)	63 (48.8)	...	15 (78.9)	9 (56.2)	0.27
Lymphocytes; cell/ μ L (IQR)	2833 (1841-4729)	1500-6500	4883 (2811-7084)	2074 (1270-3942)	0.08
CD3 ⁺ T cell; cell/ μ L (IQR)	1982 (951-3570)	1000-1700	3372 (2041-4763)	927 (428-2551)	0.09
CD4 ⁺ T cells; cell/ μ L (IQR)	887 (519-1720)	400-1200	1623 (840-3092)	568 (314-8932)	0.29
CD8 ⁺ T cells; cell/ μ L (range)	763 (256-6873)	350-800	1320 (247-4082)	1236 (875-5342)	0.55
CD19 ⁺ lymphocytes; cell/ μ L (range)	510 (31-6648)	150-300	918 (352-3927)	723 (53-1328)	0.40
Platelet $\times 10^3$; cell/ μ L (IQR)	327 (243-457)	150-450	381 (253-460)	420 (216-650)	0.42

IQR, range with 75th and 25th percentiles; N, count; WBC, white blood cells.

*p-value is statistically significant.

inflammation in mucosal spaces of STAT3-deficient cases, in response to bacterial lipopolysaccharide, may predispose AD-HIES patients to more bacterial pneumonia and pneumatocele formation.³²

Biallelic null mutations in 93.7% of DOCK8-deficient patients compared to mono-allelic null mutation in only 21.0% of STAT3-deficient patients conferred gene damage index prediction of both genes (18.2 in DOCK8 and 1.5 in STAT3).³³ Similarly, collection of pathogenic mutation in the Human Gene Mutation Database indicates predominance of missense mutations in STAT3 (86 out of 104, 82.6%) and null mutations in DOCK8 (46 out of 59, 77.9%, <http://www.hgmd.cf.ac.uk>). We identified 6 recurrent mutations from which p.R382W and p.R382Q STAT3 mutations in 8 (42.1%) and 5 (26.3%) of patients of this cohort, respectively, confirming that these defects are at hotspots location.^{23,34,35} Moreover, based on our findings we suggest that exons which could thus be sequenced first in suspected STAT3-deficient cases are 13 and 21, in national clinical setting. Severe mutations in STAT3 presented slightly higher frequency of gastrointestinal and endocrine manifestations. Although the presence of these complications was reported before in AD-HIES,^{36,37} special attention should be paid to differing them from presentation of STAT3 gain-of-function variants associated with hypogammaglobulinemia and lymphoproliferative disorders.^{38,39} Diminished T helper 17 (Th17) could be helpful for immunologic diagnosis of HIES patients; however, these data were only available in 6 STAT3-deficient patients (all <0.5% of total CD4⁺ T cells) and none of DOCK8-deficient patients limiting the subcohort analysis.

Importance of clinical evaluation has been defined for AD-HIES differential diagnosis.¹¹ However, special features of AD-HIES (including diminished memory T and B cells, near absence of Th17 cell differentiation, pneumatoceles or bronchiectasis, scoliosis, reduced

bone density, and Chiari malformations) may be absent and the diagnosis should be considered in approach to patients with severe atopic dermatitis.²² Similarly, the presence of neurologic complication (eg, encephalitis, meningitis, central nervous system vasculitis, brain abscess, brain infarct/stroke, hemiparesis, and diplegia) and recurrent cutaneous viral infections (eg, *molluscum contagiosum* virus, human papillomavirus, *herpes simplex* virus, severe primary varicella, and *herpes zoster*) may help the physician to suspect for defects in DOCK8.³⁰ Furthermore, thrombocytopenia with small platelets (in males with Wiskott-Aldrich syndrome),⁴⁰ trichorrhexis invaginata, and enteropathy leading to failure to thrive (in cases with Netherton syndrome),⁴¹ congenital ichthyosis and bamboo hair (in patients with Comel-Netherton syndrome), short stature, brachydactyly, cognitive impairment and hypomyelination (PGM3-deficient patients), and lymphadenopathy, hepatosplenomegaly, and opportunistic infections (in patients with Omenn syndrome) should be considered for confirmation of the diagnosis.⁴² However, recently emerged syndrome due to ZNF-341 deficiency likely has less determining parameters to AD-HIES, due to the tight dependence of STAT3 activity on ZNF341 in lymphocytes.¹¹

DOCK8 is involved in cytoskeletal rearrangement required for cellular adhesion and development,⁴³ and its function is important for T cell homeostasis. It is also critical for dendritic cells (DCs) migration which accelerates priming of naïve CD4⁺ T cells. The survival and function of viral-specific CD8⁺ T cells, as well as long-term memory of Th17 cells, is impaired in DOCK8 deficiency, which may explain the susceptibility to persistent cutaneous viral infections.^{44,45} Moreover, the absence of DOCK8 impairs B-cell proliferation and immunoglobulin production driven by Toll-like receptor 9 (TLR9).⁴⁵ DOCK8 has also an important role in NK cell function, and its

Parameters, N (%)	Total (N = 129)	STAT3 (N = 19)	DOCK8 (N = 16)	p-value
Recurrent infection	79 (61.2)	14 (73.6)	9 (56.2)	0.31
Otitis	33 (25.5)	7 (36.8)	7 (43.7)	0.73
Pneumonia	85 (65.8)	16 (84.2)	8 (50.0)	0.06
Sinusitis	21 (16.2)	5 (26.3)	6 (37.5)	0.71
Bronchiectasis	15 (11.6)	4 (21.1)	3 (18.7)	1.0
Splenomegaly	3 (2.3)	1 (5.2)	0 (0)	1.0
Hepatomegaly	18 (13.9)	3 (15.7)	4 (25.0)	0.67
Lymphadenopathy	21 (16.52)	4 (21.0)	0 (0)	0.10
Allergy	39 (30.2)	8 (42.1)	10 (62.5)	0.31
Oral ulcer	15 (11.6)	5 (26.3)	1 (6.2)	0.18
Recurrent diarrhea	18 (13.9)	3 (15.7)	4 (25.0)	0.67
Malignancy	16 (12.4)	3 (15.7)	1 (6.2)	0.60
BCGosis	5 (3.8)	3 (15.7)	0 (0)	0.23
Conjunctivitis	10 (7.7)	1 (5.2)	2 (12.5)	0.58
Candidacies	39 (30.2)	8 (42.1)	6 (37.5)	1.0
Meningitis	5 (3.8)	0 (0)	1 (6.2)	0.45
Eczema	93 (72.0)	17 (89.4)	13 (81.2)	0.64
Skin abscesses/infection	105 (81.3)	16 (84.2)	13 (81.2)	1.0
Skin viral infections	18 (13.9)	1 (5.2)	8 (50.0)	0.004*
Pneumatocele	19 (14.7)	13 (68.4)	1 (6.2)	0.001*
Retention of deciduous teeth	15 (11.6)	13 (68.4)	1 (6.2)	0.001*
Scoliosis	14 (10.8)	8 (42.1)	2 (12.5)	0.07
Clubbing	6 (4.6)	4 (21.1)	0 (0)	0.10

BCG, bacillus Calmette-Guérin; N, count.

*p-value is statistically significant

absence results in defective NK-target cell immunologic synapse.⁴⁹ This may contribute to the unusual susceptibility of DOCK8-deficient patients to viral infections.⁵⁰ Finally, DOCK8-deficient patients may have decreased number and function of T regulatory cells,⁵¹ which may contribute to autoimmunity and elevated IgE levels. In

this study, five DOCK8-deficient patients initially presented with an NIH score >40 without recognized cutaneous manifestations of viral infections. This led to a presumptive diagnosis of AD-HIES, possibly STAT3 deficiency, in these patients at initial evaluation. In these patients, laboratory features may differentiate DOCK8

TABLE 4 Clinical manifestation of clinically and genetically diagnosed HIES patients

Parameters; N (%)	Total (N = 129)	STAT3 (N = 19)	DOCK8 (N = 16)	p-value
Respiratory tract	89 (68.9)	14 (73.6)	10 (62.5)	0.71
Lower respiratory tract	86 (66.6)	13 (68.4)	8 (50.0)	0.31
Upper respiratory tract	41 (31.7)	8 (42.1)	10 (62.5)	0.31
Hematologic	68 (52.7)	15 (78.9)	4 (25.0)	0.002*
Gastrointestinal	34 (26.3)	3 (15.7)	5 (31.2)	0.42
Rheumatologic	4 (3.1)	0 (0)	0 (0)	1.0
Neurologic	13 (10.0)	0 (0)	3 (18.7)	0.08
Dermatologic	121 (93.7)	18 (94.7)	13 (81.5)	0.31
Ophthalmologic	10 (7.7)	1 (5.2)	2 (12.5)	0.58
Cardiovascular	7 (5.4)	0 (0)	2 (12.5)	0.20
Endocrine	13 (10.0)	4 (21.0)	0 (0)	0.10
Multiple sites	115 (89.1)	17 (94.4)	12 (75.0)	0.37

N, Count.

*p-value is statistically significant.

TABLE 5 Affected organs of clinically and genetically diagnosed HIES patients

deficiency from STAT3 deficiency include serum Ig levels and eosinophil counts.⁵² Approximately 95% of reported DOCK8-deficient patients have suffered from cutaneous viral infections, and MCV could be isolated from 50% of these cases. Mucocutaneous viral infections are difficult to control in DOCK8 cases and often occur concurrently.⁵³ Majority of our DOCK8-deficient patients did not respond to imiquimod and cidofovir (intralesional in 3 and systemic in 1 patient, respectively). Widespread MCV infection is difficult to treat with standard therapies including salicylic acid, cryotherapy, and imiquimod (add reference). Interferon- α has been used sporadically with mixed results.⁵⁴ Hematopoietic stem cell transplantation (HSCT) has been suggested to be curative in a growing number of patients with DOCK8 deficiency, with a resolution of eczema and recurrent infections including viral skin infections.⁵⁵ Thus, it is of supreme importance to document the diagnosis of DOCK8 deficiency molecularly as early as possible.

This report illustrates the potential difficulty in the diagnosis of DOCK8 deficiency when the HIES score is suggestive of STAT3 deficiency, when skin viral infections have not yet manifested. An early genetic diagnosis of DOCK8 deficiency and differentiation from AD-HIES with the minimum possible delay could provide an insight to requirement of HSCT for this disease associated with high morbidity and mortality.⁵⁶ Unbiased next-generation sequencing in HIES patients would certainly increase the value especially in verification of diagnosis and providing larger sample size for specification of subcohorts and analysis of patients according to mutation severity. Moreover, specific molecular study of not only STAT3 and DOCK8 mutations, but also other monogenic forms of the HIES could help the physician to definitively characterize the disease, while it could also help in understanding the mechanism of clinical phenotypes as well as provide strategy into therapeutic modalities.

CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTION

MT, NR, and AA conceived of the presented idea. MT, RY, H.A, GA, S.APH, and MG participated in the collection of information. GA and TM performed the analytic calculations and performed the numerical simulations. SA, MK, and HE contributed to the writing of the manuscript. HA, N.R, and RY contributed to the final version of the manuscript. AA supervised the project.

ORCID

Gholamreza Azizi  <https://orcid.org/0000-0001-5658-2511>

Asghar Aghamohammadi  <https://orcid.org/0000-0002-9454-1603>

REFERENCES

1. Minegishi Y, Saito M. Molecular mechanisms of the immunological abnormalities in hyper-IgE syndrome. *Ann N Y Acad Sci*. 2011;1246:34-40.
2. Freeman AF, Holland SM. Hyper IgE syndrome: review and future directions. *Exp Rev Clin Immunol*. 2005;1:645-651.
3. Joh K. Hyper-IgE syndrome. *Nihon rinsho Jpn J Clin Med*. 2005;63(Suppl 5):479-483.
4. Davis SD, Schaller J, Wedgwood RJ, Harvard MD. Syndrome. Recurrent, "cold", staphylococcal abscesses. *Lancet*. 1966;1:1013-1015.
5. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics*. 1972;49:59-70.
6. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med*. 1999;340:692-702.
7. Woellner C, Gertz EM, Schaffer AA, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J Allergy Clin Immunol*. 2010;125(424–32):e8.
8. Sowerwine KJ, Holland SM, Freeman AF. Hyper-IgE syndrome update. *Ann N Y Acad Sci*. 2012;1250:25-32.
9. Heimall J, Freeman A, Holland SM. Pathogenesis of hyper IgE syndrome. *Clin Rev Allergy Immunol*. 2010;38:32-38.
10. Minegishi Y. Hyper-IgE syndrome. *Curr Opin Immunol*. 2009;21:487-492.
11. Beziat V, Li J, Lin JX, et al. A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. *Sci Immunol*. 2018;3.
12. Picard C, Bobby Gaspar H, Al-Herz W, et al. International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. *J Clin Immunol*. 2018;38:96-128.
13. Takada H, Minegishi Y. [Recent advances in the pathogenesis of hyper IgE syndrome]. *Nihon Rinsho Meneki Gakkai Kaishi*. 2010;33:15-19.
14. Orozco CV, Velasquez LH, Mendez NH, Augusto B, Salazar T. [Hyper IgE syndrome. Opportune diagnosis and management]. *Rev Alerg Mex*. 2008;55:38-45.
15. Su HC. Combined immunodeficiency associated with DOCK8 mutations and related immunodeficiencies. *Dis Markers*. 2010;29:121-122.
16. Aghamohammadi A, Mohammadinejad P, Abolhassani H, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. *J Clin Immunol*. 2014;34:478-490.
17. Abolhassani H, Kiaee F, Tavakoli M, et al. Fourth Update on the Iranian National Registry of Primary Immunodeficiencies: Integration of Molecular Diagnosis. *J Clin Immunol*. 2018;38:816-832.
18. Celakovska J, Bukac J. SCORAD reflects the duration of atopic dermatitis lesions. *Indian J Dermatol*. 2013;58:247.
19. Gelmetti C, Colonna C. The value of SCORAD and beyond. Towards a standardized evaluation of severity? *Allergy*. 2004;59(Suppl 78):61-65.
20. Harari M, Dreier J, Czarnowicki T, Ruzicka T, Ingber A. SCORAD 75: a new metric for assessing treatment outcomes in atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2012;26:1510-1515.
21. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID. (European Society for Immunodeficiencies). *Clinical Immunol*. 1999;93:190-197.
22. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. *Immunol Rev*. 2005;203:244-250.

23. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007;357:1608-1619.
24. Feng Y, Chen D, Wang GL, Zhang VW, Wong LJ. Improved molecular diagnosis by the detection of exonic deletions with target gene capture and deep sequencing. *Genet Med*. 2015;17:99-107.
25. Abolhassani H, Aghamohammadi A, Fang M, et al. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. *Genetics Med*. 2019;21:243-251.
26. Abolhassani H, Chou J, Bainter W, et al. Clinical, immunologic, and genetic spectrum of 696 patients with combined immunodeficiency. *J Allergy Clin Immunol*. 2018;141:1450-1458.
27. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-424.
28. Engelhardt KR, McGhee S, Winkler S, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol*. 2009;124(1289-302):e4.
29. Hsu AP, Sowerwine KJ, Lawrence MG, et al. Intermediate phenotypes in patients with autosomal dominant hyper-IgE syndrome caused by somatic mosaicism. *J Allergy Clin Immunol*. 2013;131:1586-1593.
30. Renner ED, Rylaarsdam S, Añover-Sombke S, et al. Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced T (H)17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. *J Allergy Clin Immunol*. 2008;122:181-187.
31. Minegishi Y, Saito M, Tsuchiya S, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007;448:1058-1062.
32. Anolik R, Elmariah S, Lehrhoff S, Votava HJ, Martiniuk FT, Levis W. Hyperimmunoglobulin E syndrome with a novel STAT3 mutation. *Dermatol Online J*. 2009;15:16.
33. Itan Y, Shang L, Boisson B, et al. The human gene damage index as a gene-level approach to prioritizing exome variants. *Proc Natl Acad Sci*. 2015;112(44):13615-13620.
34. Jiao H, Tóth B, Erdős M, et al. Novel and recurrent STAT3 mutations in hyper-IgE syndrome patients from different ethnic groups. *Mol Immunol*. 2008;46:202-206.
35. Kim HJ, Kim JH, Shin YK, Lee SI, Ahn KM. A novel mutation in the linker domain of the signal transducer and activator of transcription 3 gene, p.Lys531Glu, in hyper-IgE syndrome. *J Allergy Clin Immunol*. 2009;123:956-958.
36. Arora M, Bagi P, Strongin A, et al. Gastrointestinal manifestations of STAT3-deficient hyper-IgE syndrome. *J Clin Immunol*. 2017;37:695-700.
37. Yamazaki-Nakashimada M, Zaltzman-Girshevich S, Garcia de la Puente S, et al. Hyper-IgE syndrome and autoimmunity in Mexican children. *Pediatric Nephrol*. 2006;21:1200-1205.
38. Haapaniemi Em, Kaustio M, Rajala HL, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. *Blood*. 2015;125:639-648.
39. Chandrasekaran P, Zimmerman O, Paulson M, et al. Distinct mutations at the same positions of STAT3 cause either loss or gain of function. *J Allergy Clin Immunol*. 2016;138(1222-24):e2.
40. Ariga T. Wiskott-Aldrich syndrome; an x-linked primary immunodeficiency disease with unique and characteristic features. *Allergol Int*. 2012;61:183-189.
41. Sun JD, Linden KG. Netherton syndrome: a case report and review of the literature. *Int J Dermatol*. 2006;45:693-697.
42. Kato M, Kimura H, Seki M, et al. Omenn syndrome—review of several phenotypes of Omenn syndrome and RAG1/RAG2 mutations in Japan. *Allergol Int*. 2006;55:115-119.
43. Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. *Arthritis Res Ther*. 2012;14:228.
44. Harada Y, Tanaka Y, Terasawa M, et al. DOCK8 is a Cdc42 activator critical for interstitial dendritic cell migration during immune responses. *Blood*. 2012;119:4451-4461.
45. Jabara HH, McDonald DR, Janssen E, et al. DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. *Nat Immunol*. 2012;13:612-620.
46. Randall KL, Chan S-Y, Ma CS, et al. DOCK8 deficiency impairs CD8 T cell survival and function in humans and mice. *J Exp Med*. 2011;208:2305-2320.
47. Randall KL, Lambe T, Goodnow CC, Cornall RJ. The essential role of DOCK8 in humoral immunity. *Dis Markers*. 2010;29:141-150.
48. Lambe T, Crawford G, Johnson AL, et al. DOCK8 is essential for T-cell survival and the maintenance of CD8+ T-cell memory. *Eur J Immunol*. 2011;41:3423-3435.
49. Crawford G, Enders A, Gileadi U, et al. DOCK8 is critical for the survival and function of NKT cells. *Blood*. 2013;122:2052-2061.
50. Mizesko MC, Banerjee PP, Monaco-Shawver L, et al. Defective actin accumulation impairs human natural killer cell function in patients with dedicator of cytokinesis 8 deficiency. *J Allergy Clin Immunol*. 2013;131:840-848.
51. Janssen E, Henner M, Ullas S, et al. DOCK8 deficient patients have a breakdown in peripheral B cell tolerance and defective regulatory T cells. *J Allergy Clin Immunol*. 2014.
52. Sanal O, Jing H, Ozgur T, et al. Additional diverse findings expand the clinical presentation of DOCK8 deficiency. *J Clin Immunol*. 2012;32:698-708.
53. Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. *Arch Dermatol*. 2012;148:79-84.
54. Papan C, Hagl B, Heinz V, et al. Beneficial IFN- α treatment of tumorous herpes simplex blepharoconjunctivitis in dedicator of cytokinesis 8 deficiency. *J Allergy Clin Immunol*. 2014;133:1456-1458.
55. Aydin SE, Freeman AF, Al-Herz W, et al. Hematopoietic stem cell transplantation as treatment for patients with DOCK8 deficiency. *J Allergy Clin Immunol Pract*. 2018; S2213-2198(18)30706-2. <https://doi.org/10.1016/j.jaip.2018.10.035>
56. Metin A, Tavit B, Azik F, et al. Successful bone marrow transplantation for DOCK8 deficient hyper IgE syndrome. *Pediatr Transplant*. 2012;16:398-399.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Tavassoli M, Abolhassani H, Yazdani R, et al. The first cohort of Iranian patients with hyper immunoglobulin E syndrome: A long-term follow-up and genetic analysis. *Pediatr Allergy Immunol*. 2019;30:469-478. <https://doi.org/10.1111/pai.13043>

Supplementary data

The First Cohort of Iranian Patients with Hyper Immunoglobulin E Syndrome: A Long-Term Follow-up and Genetic Analysis

Tavassoli et al.

Table S1- The 269 genes included in the panel for targeted next generation sequencing of HIES patients (* main genes)

Genes symbols					
ACP5	CD81	GFI1	MAP3K14	RNASEH2C	TRAF3IP2
ACTB	CD8A	GUCY2C	MASP1	RNF168	TREX1
ADA	CEBPE	HAX1	MASP2	RORC	TRNT1
ADAM17	CFB	HPS1	MCM4	RNF31	TPP1
ADAR	CFD	HPS4	MEFV	RPSA	TPP2
AICDA	CFH	HPS6	MRE11A	RTEL1	TTC37
AIRE	CFHR1	ICOS	MSH6	SAMHD1	TTC7A
AK2	CFHR2	IFIH1	MS4A1	SBDS	TYK2
AP3B1	CFHR3	IFNG	MTHFD1	SEMA3E	UNC119
APOL1	CFHR4	IFNGR1	MVK	SERPING1	UNC13D
ATM	CFHR5	IFNGR2	MYD88	SH2D1A	UNC93B1
B2M	CFI	IGLL1	NBN	SH3BP2	UNG
BLM	CFP	IKBKB	NCF1	SKIV2L	USB1
BLNK	CHD7	IKBKG	NCF2	SCL29A3	VPS13B
BTK	CIITA	IKZF1	NCF4	SLC35C1	VPS45
C1R	CLPB	IL10	NFAT5	SLC37A4	WIPF1
C1QA	CLEC7A	IL10RA	NFKBIA	SLC46A1	XIAP
C1QB	COLEC11	IL10RB	NFKB2	SMARCA1	ZAP70
C1QC	CORO1A	IL12B	NHP2	SP110	ZBTB24
C1S	CR2	IL12RB1	NLRC4	STAT1	
C2	CSF2RA	IL17F	NLRP3	STAT2	
C3	CSF3R	IL17RA	NLRP12	STAT3*	
C4A	COH1	IL17RC	NOD2	STAT5B	
C4B	COPA	IL1RN	NOD10	STIM1	
C5	CORO1A	IL21	NRAS	STK4	
C6	CTLA4	IL21R	ORAI1	STX11	
C7	CTPS1	IL2RA	PARN	SPINK5*	
C8A	CTSC	IL2RG	PIK3CD	STXBP2	
C8B	CXCR4	IL36RN	PIK3R1	TAP1	
C8G	CYBA	IL6	PLCG2	TAP2	
C9	CYBB	IL7R	PGM3*	TAPBP	
CARD9	DCLRE1B	INO80	PNP	TAZ	
CARD11	DCLRE1C	IRAK4	POLE	TBK1	
CARD14	DKC1	IRF7	PRF1	TBX1	
CASP10	DNMT3B	IRF8	PRKCD	TCF3	
CASP8	DOCK8*	ISG15	PRKDC	TCN2	
CCBE1	ELANE	ITCH	PSMB8	TERT	
CD17	EPG5	ITGB2	PSTPIP1	THBD	
CD19	FADD	ITK	PTPRC	TICAM1	
CD27	FAS	JAGN1	RAB27A	TINF2	
CD247	FASLG	JAK3	RAC2	TLR3	
CD3D	FCGR3A	KRAS	RAG1	TMC6	
CD3E	FCN3	LAMTOR2	RAG2	TMC8	
CD3G	FERMT1	LCK	RBCK1	TMEM173	
CD40	FERMT3	LIG4	RFX5	TNFRSF13B	
CD40LG	FOXN1	LPIN2	RFXANK	TNFRSF13C	

<i>CD46</i>	<i>FOXP3</i>	<i>LRBA</i>	<i>RFXAP</i>	<i>TNFRSF1A</i>	
<i>CD59</i>	<i>FPR1</i>	<i>LYST</i>	<i>RHOH</i>	<i>TNFRSF4</i>	
<i>CD79A</i>	<i>G6PC3</i>	<i>MAGT1</i>	<i>RNASEH2A</i>	<i>TNFSF12</i>	
<i>CD79B</i>	<i>GATA2</i>	<i>MALT1</i>	<i>RNASEH2B</i>	<i>TRAF3</i>	

0

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

Table S2- The frequency of complications in patients with NIH score>40.

Parameters	HIES STAT3 (Details available on 17 patients, 100% of total patients>40)		HIES DOCK8 (Details available on 10 patients, 50% of total patients>40)		p-value
	NO	%	NO	%	
IgE IU/ml>2000	11/17	64.7	5/5	100.0	0.26
Recurrent skin abscess	16/17	94.1	4/5	80.0	0.41
Recurrent pneumonia	16/17	94.1	4/5	80.0	0.41
Pneumatocele	13/15**	86.7	1/5	20.0	0.01*
Failure to shed deciduous teeth	13/13**	100.0	1/5	20.0	0.001*
Scoliosis	8/17	47.0	0/5	0.0	0.11
Pathologic bone fracture	5/17	29.4	0/5	0.0	0.28
Eosinophilia	15/17	88.2	5/5	100.0	1.0
Characteristic face	14/17	82.3	4/5	80	1.0
Midline anomaly	3/17	17.6	0/5	0.0	1.0
Newborn rash	13/14**	92.9	4/5	80.0	0.46
Eczema	17/17	100.0	5/5	100.0	1.0
Recurrent upper respiratory infections	14/17	82.3	5/5	100.0	1.0
Candidiasis	8/17	47.0	2/5	40.0	1.0
Other unusual infection	4/17	23.5	5/5	100.0	0.004*
Hyperextensibility	14/17	82.3	0/5	0.0	0.002*
Lymphoma	0/17	0.0	1/5	20.0	0.22
Increased interalar distance	15/17	88.2	3/5	60.0	0.21
Cathedral palate	13/17	76.4	3/5	60.0	0.10
* The difference was statistically significant ($p<0.05$)					
** Data missing since cannot be extracted from medical records or were not medically indicated.					

16
17
18
19
20
21
22
23
24
25
26
27
28
29

Table S3- The frequency of gastrointestinal and endocrine complications in AD-HIES patients.					
Parameters	HIES STAT3 Severity (n=4)		HIES STAT3 Mild (n=15)		p-value
	NO	%	NO	%	
Gastrointestinal complication	2	50.0	1	6.6	0.10
Gastroesophageal reflux disease	1	25.0	0	0	0.21
Dysphagia	1	50.0	0	0	0.21
Chronic diarrhea	2	50.0	1	6.6	0.10
Endocrine complication	2	50.0	2	13.3	0.19
Autoimmune hypothyroiditis	1	25.0	2	13.3	0.53
Autoimmune hyperthyroiditis	1	25.0	0	0	0.21
<i>* The difference was statistically significant ($p<0.05$)</i>					