Autosomal-dominant hyper-IgE syndrome is associated with appearance of infections early in life and/or neonatal rash: Evidence from the Italian cohort of 61 patients with elevated IgE

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Clinical Implications

- Early onset infections, including pulmonary infections, mucocutaneous candidiasis, and skin abscesses, strongly suggest the diagnosis of signal transducer and activator of transcription 3-hyper-IgE syndrome. Eczema associated with high IgE levels is not discriminatory between patients with signal transducer and activator of transcription 3-hyper-IgE syndrome and those with undetermined hyper-IgE syndrome.

TO THE EDITOR:

The hyper-IgE syndromes are primary immunodeficiencies characterized by elevated serum IgE level, eosinophilia, eczema, and recurrent skin and sinopulmonary infections. Heterozygous dominant-negative mutations of signal transducer and activator of transcription 3 (*STAT3*) constitute the most common cause of the autosomal-dominant form of hyper-IgE syndrome (AD-HIES).[1-4] AD-HIES represents a multisystem disease where the immune disorder is associated with connective tissue and skeletal abnormalities, but other genes, such as *DOCK8*, *TYK2*, *PGM3*, *CARD11*, and *ZNF341*, can lead to HIES-like phenotypes. To identify the distinctive features required for an early diagnosis of AD-HIES,[5] we analyzed the clinical and immunologic features of 61 patients who were referred because of high IgE levels (>2000 IU/mL) and underwent *STAT3* genetic sequencing.

We identified 14 distinct heterozygous mutations in 28 of 61 patients analyzed (46%) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Patients carrying the D371-G380del, N567D, M660A, and V463del mutations have been previously described.[6-8] The 33 patients with *STAT3 wild-type* mutations were classified as suffering from undetermined hyper-IgE syndrome (U-HIES).

The mean age at onset was 0.97 years in patients with AD-HIES (range, birth-6.08 years), whereas it was higher (5.07 years) in subjects with U-HIES (range, birth-24 years) (Figure 1, *A*; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The median age at diagnosis was 14.76 years in the AD-HIES cohort (range, 0.4-46.3 years) and 9.18 years in the U-HIES cohort (range, 1-55 years) (Figure 1, *A*). The detection of increased IgE levels as first manifestation was predictive of negative genetic analysis (0% *vs* 30%; $P < .001$) (Figure 1, *B*).

Most patients presented with eczema as first clinical symptom (43% in patients with AD-HIES *vs* 58% in patients with U-HIES; $P = .474$). Atopic dermatitis—like eczema is one of the main features of AD-HIES but even if common in *STAT3*-mutated patients (88.5%), it also occurred in individuals with U-HIES (60.6%) ($P = .016$). Eczema was classified as persistent, severe, or scattered, but none of these features correlated with an increased risk of *STAT3* mutation. In contrast, a strictly specific feature of *STAT3* deficiency was the appearance of newborn rash (57.7% of patients with AD-HIES *vs* 6.1% of patients with U-HIES; $P < .001$).

Early onset of infections was observed mostly in patients with *STAT3* mutations (57% *vs* 6%; $P < .001$). Overall, infectious diseases were more common in *STAT3*-deficient patients, but some infectious manifestations were more strictly associated with *STAT3* mutation. In particular, mucocutaneous candidiasis (70.1% in AD-HIES *vs* 3% in U-HIES) and skin abscesses (77.8% *vs* 6.1%) were strongly associated with AD-HIES ($P < .001$, respectively), whereas pyodermitis (32% *vs* 18.2%), molluscum contagiosum (8.3% *vs* 0%), and warts (4.2% *vs* 0%) were not specific ($P = .182$, 0.173, and 0.421, respectively).

In AD-HIES, patients presenting with respiratory infections, upper respiratory tract infections (URTIs), and pneumonia were common (77.8% in AD-HIES vs 60% in U-HIES). Nevertheless, URTIs and pneumonia were also frequently observed in patients with U-HIES (27.3% and 24.2%, respectively). Among URTIs, sinusitis was more strictly associated with AD-HIES than was otitis ($P = .003$ and $P = .078$, respectively) (Figure 2).

Viral infections were identified mostly in AD-HIES (26.1% *vs* 3%; $P = .015$). *STAT3*-mutated patients presented with recurrent herpesvirus infection reactivation (n = 3), skin infections caused by *Molluscum contagiosum* and *Papillomavirus* (n = 3), and cytomegalovirus viremia (n = 1). One patient with U-HIES had a systemic *varicella-zoster* viral infection. Two episodes of septic arthritis were reported in the U-HIES cohort.

A single fatal infection occurred in a patient with AD-HIES because of disseminated fungal infection at the age of 46 years. Severe infections, defined as sepsis, meningitis, osteomyelitis, and disseminated fungal and viral infections, occurred more frequently in patients with AD-HIES (23.1%), but were observed sporadically in patients with U-HIES (9.1%) ($P = .132$).

Patients with AD-HIES who presented an infection as first clinical manifestation at onset showed a slightly increased risk to develop a severe infectious complication during lifetime ($P = .034$). Conversely, we observed more allergic manifestations in patients with U-HIES (60.6% *vs* 25%; $P = .008$), particularly the frequency

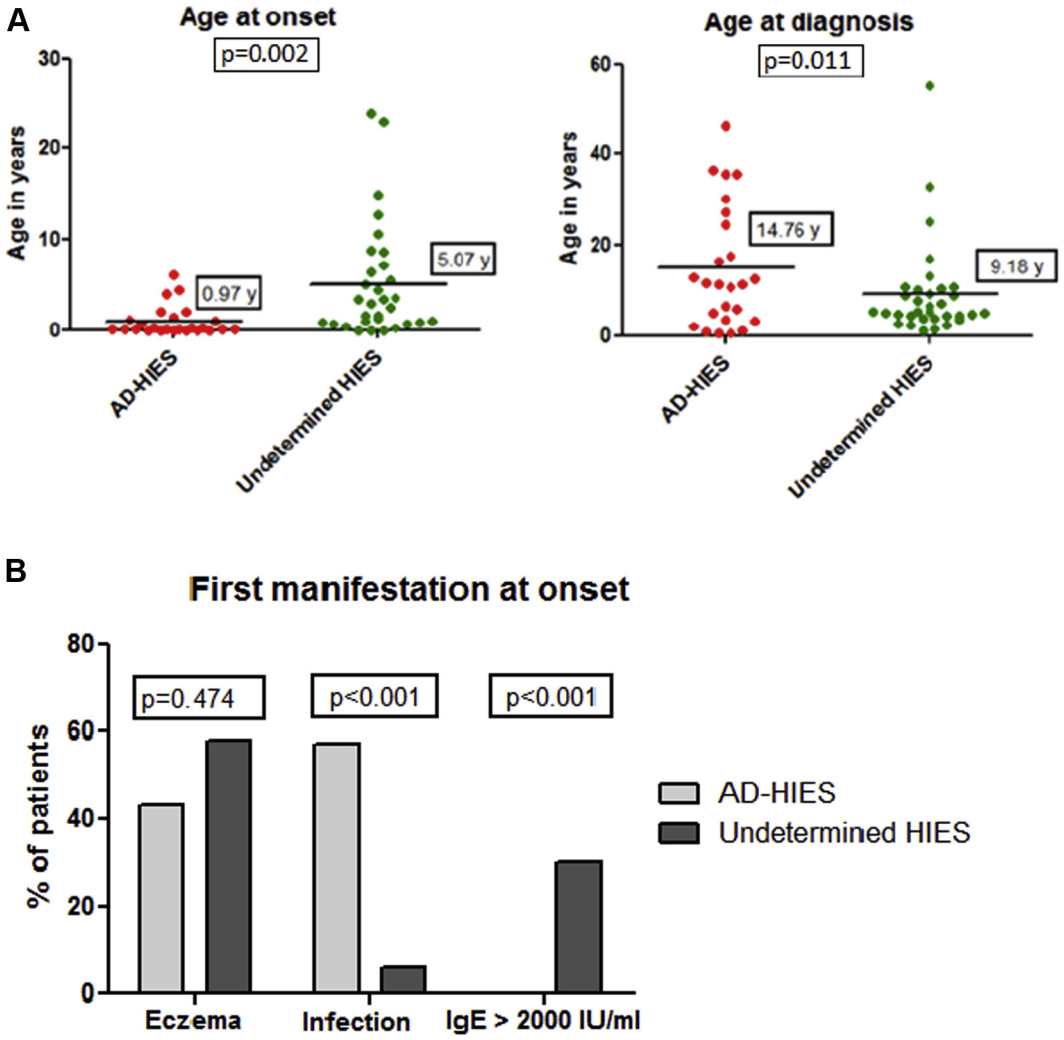

FIGURE 1. A, Mean age at onset and diagnosis in the *STAT3*-mutated cohort, compared with the U-HIES cohort. The mean age at onset was 0.97 years in the *STAT3*-mutated cohort, compared with 5.07 years in the U-HIES cohort. The mean age at diagnosis was 14.76 years in the *STAT3*-mutated cohort and 9.18 years in the *STAT3*-negative cohort. **B,** First clinical manifestation at disease onset in the *STAT3*-mutated cohort, compared with the U-HIES cohort. Most patients presented with eczema as first clinical symptom. Individuals who had an infection as first manifestation had an increased probability to be *STAT3*-mutation carriers. In contrast, the detection of increased IgE levels as first manifestation was predictive of a negative genetic analysis.

of asthma (36.4% *vs* 4%; $P = .003$). A single episode of anaphylaxis by nuts occurred in a patient with AD-HIES at the age of 30 years.[6]

Skeletal and connective tissue abnormalities were observed only in the cohort of patients with *STAT3* mutations and included typical facial appearance (84%), retained primary teeth (65.4%), scoliosis (42.3%), high-arched palate (40%), and joint hyperextensibility (32%). Craniosynostostosis was observed in a single patient with AD-HIES. Notably, not all the typical facial abnormalities appeared early in life.

Lung complications, such as bronchiectasis (53.4%), pneumatoceles (39.4%), fibrosis (3.6%), and emphysema (3.6%), were detected by chest computed tomography (CT) scan in half the patients with AD-HIES and only in a single individual with U-HIES ($P < .001$) (Figure 2). Five patients with AD-HIES with severe lung disease (35.7%) underwent lung resection.

However, early diagnosis of AD-HIES was associated with a better pulmonary outcome, as the median age at diagnosis was 19.6 ± 10.4 years in the group of patients with AD-HIES with lung disease, as compared with 7.3 ± 10.5 years in the group of patients with AD-HIES without lung damage. In patients with *STAT3* mutations, lung disease was associated with recurrent pneumonia ($P < .001$).

Malignancies occurred only in *STAT3*-mutated patients: 2 of them developed non-Hodgkin lymphoma, whereas another one had a thyroid carcinoma. However, the limited number of cases was not sufficient to prove an increased risk of malignancies in patients with AD-HIES ($P = .080$). Fractures appearing after minor trauma were observed only in patients with AD-HIES ($P = .001$), whereas no cardiovascular, neurological, and autoimmune manifestations were recognized in both groups of patients.

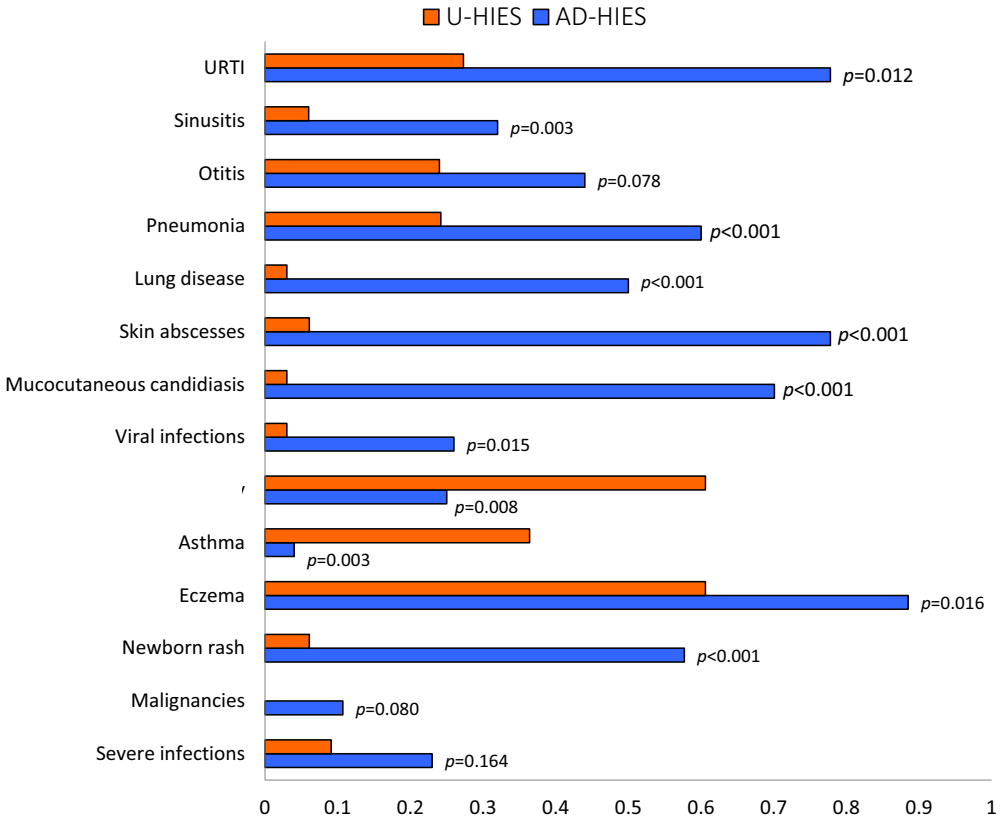

FIGURE 2. Clinical manifestations and disease complications of patients with AD-HIES as compared with patients with U-HIES. Pneumonia with lung disease, skin abscesses, mucocutaneous candidiasis, and newborn rash were highly specific of AD-HIES ($P < .001$), whereas allergic manifestations and asthma were more common in patients with U-HIES ($P = .008$ and $P = .003$, respectively).

Elevated specific IgE levels against food and aeroallergens were found with a similar distribution in both cohort of patients. The detection of elevated specific IgE levels did not correlate with an increased frequency of allergic manifestations or asthma in both cohorts ($P = .051$ and $P = .315$, respectively).

Staphylococcus aureus and *Pseudomonas aeruginosa* isolates were detected only in patients with AD-HIES, whereas *S aureus* colonization of skin and nasal mucosa and respiratory airways colonization by *Haemophilus influenzae* and *Streptococcus pneumoniae* were seen in both groups.

Overall, our study reveals that early appearance of rash, mucocutaneous candidiasis, skin abscesses, or pneumonia is highly specific of AD-HIES, whereas allergic manifestations were also common in patients with U-HIES.

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METHODS

Patients

Sixty-one individuals with IgE levels of greater than 2000 IU/mL have been retrospectively analyzed. Twenty-eight patients with diagnosis of AD-HIES entered the Italian Primary Immunodeficiency Network (IPINet) registry. In each of the IPINet center, patients with AD-HIES are managed according to the HIES IPINet protocol. Thirty-three individuals from different Italian hospitals were referred to our department with the clinical suspicion of HIES because of their clinical presentation and the detection of high serum IgE levels (>2000 IU/mL), but their molecular sequencing of STAT3 was negative. In these patients, secondary causes of elevated serum IgE levels (ie, parasitic and other infectious diseases, malignancies, inflammatory disorders, other primary immunodeficiencies) had been previously ruled out. Clinical and laboratory data were retrospectively collected by the referring physicians throughout a specific questionnaire. Patients, or their parents in the case of minors, gave written informed consent. Approval for this study was obtained by the institutional review board of Spedali Civili of Brescia (NP 2834).

Sequencing

Patients with elevated IgE levels were analyzed for STAT3 mutations at the Institute of Molecular Medicine "Angelo Nocivelli" of Brescia, or were previously reported.[E1,E2] Genomic DNA was isolated from 200 μL of blood samples by the DNeasy kit (Qiagen, Hilden, Germany) purification method. By PCR, with specific primers, exons 1 to 24 of STAT3 and their flanking introns were amplified. Then, they were sequenced using the Big Dye Terminator kit (Applied Biosystems, Waltham, Mass) and the ABI Prism 310 Analyzer (Applied Biosystems). Finally, the sequences were analyzed by using the BioEdit sequence software (Carlsbad, Calif). Computational analysis with PoliPhen-2 was used to predict the possible impact of *STAT3* mutations on the structure and the function of the protein. Among the patients *with STAT3 wild-type* mutations, only the ones with a suggestive clinical presentation were further analyzed for *DOCK8*, TYK2, or *PGM3*. Individuals found to harbor mutations in other HIES-causing genes (ie, *DOCK8*) were excluded from the analysis.

Clinical and immunologic investigations

Data collection included investigation of the past medical history focusing on the familiarity for immunologic diseases, infections (site and etiology, if available), autoimmune manifestations, allergies, and malignancies. In details, allergic disease was defined by the report of allergic rhinitis, asthma, food allergy, or anaphylaxis. The physical examination explored signs of infection or infective complications (ie, signs of sinusitis, pulmonary disease, and cutaneous manifestations), characteristic face, skeletal, and dental abnormalities, and vascular and neurological anomalies. Analysis of specific IgE panels (ImmunoCAP) was used to measure the levels of specific allergen-reactive IgE. Microbiological analysis included serological screening for viruses (ie, human simplex virus, varicella-zoster virus, hepatitis C virus, hepatitis B virus, cytomegalovirus, and EBV) and microbial culture. Radiologic examinations (skeletal or chest X-ray and thoracic computed tomography scan) and spirometry were performed according to the clinical history.

Statistical analysis

The analysis was processed using the software STATA14 (StataCorp, College Station, Texas). Qualitative variables were analyzed using Fisher exact test, whereas continuous variables were compared by Student *t* test or Wilcoxon signed-rank test. The relative *P* value was considered significant when found less than .05.

TABLE E1. Clinical features and laboratory data of 61 individuals with elevated IgE levels referred for genetic analysis of *STAT3*

Patients' features						Immunologic analyses							
Pt	Group	Sex	Age at onset (y)	Age at diagnosis (y)	First symptom	WBC (cells/μL)	L (cells/μL)	E (%)	E (cells/μL)	IgE (UI/mL)	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)
1	STAT3 AD-HIES	F	4	35	Infection	4,320	1,092	3.2	138	1,251	1,060	135	62
2	STAT3 AD-HIES	F	Newborn	1	Eczema	6,280	3,564	4.9	307	5,000	1,047	102	99
3	STAT3 AD-HIES	F	0.2	36	Infection	5,210	NA	7.7	401	5,000	1,100	135	91
4	STAT3 AD-HIES	M	Newborn	0.4	Eczema	31,010	5,750	60	18,606	961	201	52	76
5	STAT3 AD-HIES	M	Newborn	2	Eczema	21,150	4,575	11.9	2,516	5,000	819	44	86
6	STAT3 AD-HIES	M	1.4	12	Infection	6,510	3,211	5	325	5,299	1,077	235	119
7	STAT3 AD-HIES	M	0.2	11	Infection	10,600	NA	11	1,166	43,320	1,603	8	210
8	STAT3 AD-HIES	M	2	27	Infection	7,900	NA	14	1,106	3,211	1,176	228	192
9	STAT3 AD-HIES	F	0.2	11	Infection	12,940	2,588	14	1,811	54,805	3,299	339	140
10	STAT3 AD-HIES	M	0.1	3	Eczema	10,700	2,511	17	181	5,380	1,361	102	123
11	STAT3 AD-HIES	M	0.1	35	Eczema	8,200	NA	3.7	303	5,040	NA	NA	NA
12	STAT3 AD-HIES	M	2	16	Infection	5,480	1,554	15	822	8,117	1,083	224	186
13	STAT3 AD-HIES	F	4	12	Infection	12,800	2,560	1	128	13,000	3,135	156	854
14	STAT3 AD-HIES	F	Newborn	5	Eczema	12,040	2,640	5	602	22,610	1,560	79	249
15	STAT3 AD-HIES	M	Newborn	24	Infection	6,700	1,860	6	402	12,743	1,450	159	68
16	STAT3 AD-HIES	M	0.2	0.6	Eczema	NA	NA	NA	NA	NA	NA	NA	NA
17	STAT3 AD-HIES	F	0.7	3	Eczema	5,730	2,750	3	170	5,000	1,059	198	67
18	STAT3 AD-HIES	F	0.1	11	Infection	6,700	2,650	NA	NA	5,000	1,160	306	140
19	STAT3 AD-HIES	M	1	46	Eczema	NA	NA	NA	NA	NA	NA	NA	NA
20	STAT3 AD-HIES	M	0.1	6	Infection	17,900	3,225	13	2,300	4,118	1,560	42	76
21	STAT3 AD-HIES	M	Newborn	0.7	Eczema	22,510	4,970	16.6	4,430	1,034	1,034	64	72
22	STAT3 AD-HIES	F	6	17	Infection	9,650	2,490	2.4	230	1,370	1,400	166	124
23	STAT3 AD-HIES	F	0.2	10	Eczema	4,900	2,580	4	196	2,000	1,400	68	52
24	STAT3 AD-HIES	M	0.2	5	Infection	8,280	4,730	9	720	5,000	9,970	801	995
25	STAT3 AD-HIES	M	1	30	Eczema	3,100	1,176	5	155	12,464	839	106	163
26	STAT3 AD-HIES	F	NA	NA	Infection	NA	NA	NA	NA	NA	NA	NA	NA
27	STAT3 AD-HIES	M	NA	NA	Infection	NA	NA	NA	NA	13,600	NA	NA	NA
28	STAT3 AD-HIES	F	NA	NA	Infection	NA	3,570	NA	200	3,130	NA	NA	NA
29	U-HIES	M	15	17	High IgE	5,710	2,166	0.5	NA	5,000	3,333	308	159
30	U-HIES	M	NA	5	Eczema	10,610	4,000	22.1	NA	5,000	1,415	169	89
31	U-HIES	M	12	13	High IgE	8,710	2,900	26	2,200	915	1,242	138	87
32	U-HIES	F	5	5	High IgE	9,160	3,900	NA	1,050	3,046	923	95	46
33	U-HIES	M	3	7	Infection	5,660	2,470	4.2	237	4,456	1,660	187	62
34	U-HIES	F	5	6	Eczema	6,740	2,010	NA	900	3,997	670	129	52
35	U-HIES	F	6	10	High IgE	4,950	2,240	2	240	659	1,030	165	85
36	U-HIES	M	4	4	High IgE	6,720	2,400	2.6	174	3,898	NA	NA	NA
37	U-HIES	M	1	4	Eczema	10,010	3,670	NA	680	3,856	993	92	62

(continued)

TABLE E1. *(Continued)*

Patients' features						Immunologic analyses							
Pt	Group	Sex	Age at onset (y)	Age at diagnosis (y)	First symptom	WBC (cells/μL)	L (cells/μL)	E (%)	E (cells/μL)	IgE (UI/mL)	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)
38	U-HIES	M	3	3	Eczema	8,590	4,300	3	NA	680	1,070	90	148
39	U-HIES	M	3	5	Eczema	10,840	6,400	5.1	552	5,000	NA	NA	NA
40	U-HIES	M	0.9	1	Eczema	16,790	12,390	NA	690	4,338	829	57	80
41	U-HIES	F	NA	10	Eczema	6,140	2,200	2.4	150	5,000	1,242	109	73
42	U-HIES	M	3	3	Eczema	8,470	5,150	13	1,030	5,000	NA	NA	NA
43	U-HIES	M	1	4	Eczema	6,310	2,700	13.4	840	3,600	840	86	64
44	U-HIES	F	24	32	Eczema	12,440	2,400	NA	1,200	5,000	619	160	43
45	U-HIES	M	Newborn	2	Eczema	9,870	4,600	25	2,000	5,000	660	32	88
46	U-HIES	M	1	3	High IgE	13,570	7,000	9.1	1,230	2,229	1,190	79	55
47	U-HIES	F	7	7	Diarrhea	8,400	3,800	7.6	630	2,245	1,320	152	112
48	U-HIES	M	2	2	High IgE	8,870	3,900	18.8	1,670	4,434	942	54	118
49	U-HIES	M	1	4	Eczema	8,690	3,000	NA	1,300	4,689	1,103	149	121
50	U-HIES	M	0.8	2	Infection	13,470	4,300	4.9	600	5,000	1,080	111	118
51	U-HIES	M	0.6	1	Eczema	11,720	6,000	NA	NA	5,805	705	133	64
52	U-HIES	M	0.4	5	Eczema	11,990	4,790	NA	790	4,465	1,073	187	117
53	U-HIES	M	1	5	Eczema	9,230	4,330	NA	NA	5,000	1,170	126	57
54	U-HIES	F	0.7	4	High IgE	11,230	5,020	13.9	1,560	92	1,380	128	97
55	U-HIES	F	10	10	High IgE	8,470	3,770	20.4	1,727	776	1,021	129	188
56	U-HIES	F	8	8	High IgE	7,300	3,200	11.6	846	2,716	NA	NA	NA
57	U-HIES	M	Newborn	10	Eczema	7,460	3,680	9.1	678	3,130	724	103	29
58	U-HIES	M	0.2	25	Eczema	10,030	2,100	10.8	1,083	5,000	1,340	380	1,143
59	U-HIES	F	23	55	Aphthosis	8,150	3,000	6.5	529	1,533	950	207	92
60	U-HIES	F	Newborn	9	Eczema	8,210	3,000	16.4	1,346	5,000	993	157	83
61	U-HIES	F	8	8	Eczema	4,970	2,880	NA	430	4,149	892	133	92

E, Eosinophils; *F*, female; *L*, lymphocytes; *M*, male; *NA*, not available; Pt, patient; *WBC*, white blood cell.

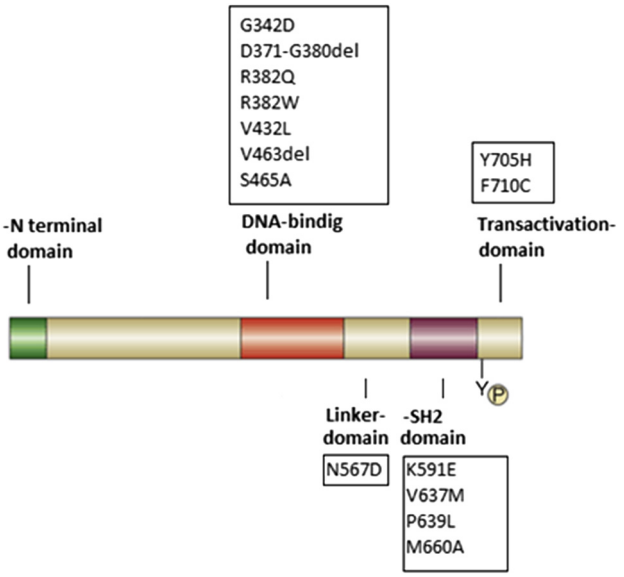

FIGURE E1. Schematic representation of the human STAT3 protein structure. We identified 14 distinct heterozygous mutations localizing to the DNA-binding domain (7), the −SH2 domain (4), the transactivation domain (2), and the linker domain (1), respectively.