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## Mutation de STAT 3 Gain de Fonction : revue systématique de la littérature

Sarah Marchal

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Sarah Marchal. Mutation de STAT 3 Gain de Fonction : revue systématique de la littérature. Human health and pathology. 2019. dumas-02320090

**HAL Id: dumas-02320090**

**<https://dumas.ccsd.cnrs.fr/dumas-02320090>**

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**UNIVERSITE DE NICE SOPHIA-ANTIPOLIS**

**FACULTE DE MEDECINE DE NICE**

Année 2019

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# **THESE**

Pour l'obtention du

**DIPLOME D'ETAT DE**

**DOCTEUR EN MEDECINE**

**Spécialité : PEDIATRIE**

Présentée et soutenue publiquement le 02 Juillet 2019 à Nice (06)

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**Mutation de STAT 3 Gain de Fonction :  
Revue systématique de la littérature**

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## REMERCIEMENTS

A Madame le Professeur Lisa GIOVANNINI-CHAMI,

Vous m'avez fait l'honneur de diriger cette thèse. Je vous remercie de m'avoir accompagnée avec tant de disponibilité et d'investissement dans ce travail, de m'avoir soutenue et guidée tout au long de mon internat ; vous êtes pour moi un exemple. Veuillez recevoir l'expression de ma profonde gratitude.

A Monsieur le Professeur Etienne BERARD,

Je vous remercie de l'honneur que vous me faites de présider ce jury de thèse et je vous en suis très reconnaissante. Soyez assuré de mon plus profond respect.

A Monsieur le Professeur Pierre-Simon ROHRLICH,

Je vous remercie d'avoir accepté de participer à mon jury de thèse. Je tenais à vous exprimer ma plus grande reconnaissance.

A Madame le Docteur Nathalie TIEULIE,

Vous me faites l'honneur de juger ce travail. Veuillez trouver ici l'expression de mes sentiments respectueux.

My sincere gratitude goes to Dr Tiphany P. VOGEL, for her significant contribution in this work. I sincerely thank you for accepting to be a member of my thesis committee.

I would like to thank Dr Lisa R. FORBES for her participation in this study.

A Monsieur le Docteur Alexandre FABRE,

Je vous remercie d'avoir accepté notre collaboration et d'avoir montré une grande implication dans ce travail.

Aux médecins et aux équipes paramédicales des services qui m'ont accueillie pendant mes semestres d'internat ; à Lenval : Hôpital de jour, Médecine pédiatrique 4<sup>ème</sup>, Urgences pédiatriques, Réanimation pédiatrique, ainsi qu'à l'Archet en Réanimation néonatale et à Antibes en Pédiatrie générale. Vous m'avez toujours reçue avec bienveillance, je vous remercie pour toutes les connaissances que vous avez pu m'inculquer. Je remercie également tous mes co-internes de pédiatrie et autres spécialités avec qui j'ai partagé mon internat.

A ma famille et mes proches, qui m'ont toujours soutenue et encouragée tout au long de mes études médicales. Merci.

A la mémoire de ma Grand-mère, je te dédie ce travail.

## Ce travail a donné lieu aux communications suivantes :

### Communications orales

- **Mutation de STAT3 gain de fonction : revue systématique de la littérature**  
*Journée inter régionale de pneumologie pédiatrique, Nice, Juin 2018*
- **Mutation de STAT3 gain de fonction : apport de l'exome dans notre approche diagnostique.**  
*Journée de la recherche clinique, Nice, Octobre 2017*  
*DES Day, Aix en provence, Mai 2017*

### Communications affichées

- **Mutation de STAT3 gain de fonction : revue systématique de la littérature**  
*Congrès de la Société Française de pédiatrie, Paris, Juin 2019*  
*Congrès de pneumologie et allergologie pédiatrique, Paris, Novembre 2018*  
*Journée de la recherche clinique, Nice, Octobre 2018*  
S. Marchal, A. Fabre, V. Barlogis, B. Mari, P Barbry, P-S. Rohrlich, L. Forbes, T. Vogel, L. Giovannini-Chami
- **Mutation de STAT3 gain de fonction : une nouvelle étiologie de pneumopathie interstitielle diffuse.**  
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# **RESUME**

## **INTRODUCTION**

STAT 3 (Signal transducer and activator of transcription) est un facteur de transcription impliqué dans croissance, différenciation, apoptose de nombreux tissus et dans la régulation de l'inflammation et de l'immunité. Les mutations germinales perte de fonction, déjà bien connues, sont responsables d'un déficit immunitaire primaire (Buckley Syndrome). Les mutations STAT3 germinales gain de fonction (GOF) entraînent une atteinte autoimmune polyviscérale, sévère et précoce ; une atteinte hématologique autoimmune (cytopénies) et non autoimmune (déficit immunitaire, lymphoprolifération) ainsi qu'un retard de croissance staturopondéral sévère. Les premiers cas ont été décrits en 2014, depuis, 42 cas ont été publiés. Il existe une variabilité phénotypique importante, entraînant des difficultés diagnostiques. De ce fait, nous avons réalisé une revue systématique des cas publiés de mutations STAT3 GOF afin de décrire les différents aspects cliniques de cette pathologie et son histoire naturelle.

## **MATERIELS ET METHODES**

Nous avons réalisé une revue systématique des cas publiés avant le 10/10/2018 dans les bases de données Pubmed, WoS, et CENTRAL. Il s'agissait des cas de patients porteurs de la mutation germinale STAT3 GOF.

## **RESULTATS**

42 cas ont été décrits dans 18 articles, 28 différentes mutations étaient mises en évidence. L'âge de début était très précoce avec un âge moyen de 3 ans (0,5-5). Les manifestations les plus fréquentes étaient : cytopénie auto-immune (28/42), lymphoprolifération (27/42), entéropathie (24/42), pneumopathie interstitielle (15/42), thyroïdite (13/42), diabète (10/42), atteinte rhumatologique (9/42) et retard de croissance staturopondéral (15/21). Les atteintes digestives et endocriniennes étaient très précoces, suivies par l'atteinte hématologique. Les atteintes pulmonaires et rhumatologiques étaient quant à elles plus tardives. Des traitements

immunosuppresseurs étaient utilisés dans la plupart des cas. 5 patients ont bénéficié d'une greffe de moelle osseuse, parmi eux, 4 sont décédés des complications de la greffe. Une amélioration des symptômes fut observée chez 8 patients sur 9 ayant reçu une thérapie ciblée.

## **CONCLUSION**

La mutation STAT3 GOF est une nouvelle entité clinique à connaître. Il est judicieux d'y penser devant un patient présentant atteinte autoimmune polyviscérale, lymphoprolifération et retard de croissance. A l'heure actuelle, aucune démarche thérapeutique n'est encore validée mais les thérapies ciblées (anti IL6 et surtout anti JAK) semblent montrer leur efficacité.

## Original Article

# Clinical Aspects of STAT3 Gain-of-Function Germline Mutations: A Systematic Review

Alexandre Fabre, MD, PhD<sup>a,b,\*</sup>, Sarah Marchal, MBBS<sup>c,\*</sup>, Vincent Barlogis, MD, PhD<sup>d</sup>, Bernard Mari, PhD<sup>e</sup>, Pascal Barbry, PhD<sup>e</sup>, Pierre-Simon Rohrlach, MD, PhD<sup>f,g</sup>, Lisa R. Forbes, MD<sup>h</sup>, Tiphonie P. Vogel, MD, PhD<sup>h,†</sup>, and Lisa Giovannini-Chami, MD, PhD<sup>c,g,†</sup> *Marseille, Nice, and Valbonne, France; and Houston, Texas*

**What is already known about this topic?** Signal transducer and activator of transcription 3 (STAT3) gain-of-function (GOF) germline mutations have been recently described. A comprehensive overview of this early-onset multiorgan autoimmune and lymphoproliferative disease has not yet been compiled.

**What does this article add to our knowledge?** We identified 42 unique patients. Typical disease was early-onset with very early endocrine autoimmunity, then pseudo-coeliac enteropathy, followed by lymphoproliferation, autoimmune cytopenias, and interstitial lung disease in the context of severe growth failure.

**How does this study impact current management guidelines?** STAT3 GOF syndrome is a new entity to consider when confronted with a patient with early-onset polyautoimmunity, lymphoproliferation, and/or short stature. There is emerging evidence for the use of targeted biotherapies in this disorder.

**BACKGROUND:** Signal transducer and activator of transcription 3 (STAT3) gain-of-function (GOF) germline mutations have been recently described. A comprehensive overview of this early-onset multiorgan autoimmune and lymphoproliferative disease has not yet been compiled.

**OBJECTIVE:** We have conducted a systematic review of published STAT3 GOF cases to describe clinical, diagnostic, and therapeutic aspects of the disease.

**METHODS:** A systematic review including articles published before October 10, 2018, in PubMed, Web of Science, and Cochrane Central Register of Controlled Trials databases was

performed. We described cases of patients with STAT3 GOF germline mutations with genetic analysis and a concordant phenotype if functional analyses were not performed for the mutation.

**RESULTS:** The search identified 18 publications describing 42 unique patients. Twenty-eight different mutations were described. Onset of disease was very early with an average age of 3 (0.5-5) years. The most frequent manifestations were autoimmune cytopenias (28 of 42), lymphoproliferation (27 of 42), enteropathy (24 of 42), interstitial lung disease (15 of 42), thyroiditis (13 of 42), diabetes (10 of 42), and postnatal growth failure (15 of 21). Immunodeficiency was not always a predominant feature. Most patients required significant immunosuppressive therapy. Five patients received hematopoietic stem cell transplantation, and 4 died from complications. Improvement of symptoms was observed for 8 of 9 patients who received targeted biotherapies.

**CONCLUSIONS:** STAT3 GOF syndrome is a new clinical entity to consider when confronted with a patient with early-onset polyautoimmunity, lymphoproliferation, and growth failure. At this time, precise therapeutic guidelines are lacking, but use of anti-IL-6 receptor and JAK inhibitor biologics is an attractive possibility. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

**Key words:** Autoimmunity; Lymphoproliferative disease; GOF; Evans syndrome; Interstitial lung disease; Celiac disease; Short stature; Early-onset diabetes; Child

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 14, 2018; revised February 10, 2019; accepted for publication February 11, 2019.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.02.018>

The transcription factor signal transducer and activator of transcription 3 (STAT3), one of 7 members of the STAT family of transcription factors, is a critical regulator of multiple processes, including cellular proliferation, survival, differentiation,



**Abbreviations used**

<i>AIHA</i> - Autoimmune hemolytic anemia
<i>COOP</i> - Cryptogenic organizing pneumonia
<i>DIP</i> - Desquamative interstitial pneumonitis
<i>E</i> - Endomysium
<i>G</i> - Gliadin
<i>GH</i> - Growth hormone
<i>GOF</i> - Gain-of-function
<i>HLA</i> - Human leukocyte antigen
<i>IBD</i> - Inflammatory bowel disease
<i>IGF1</i> - Insulin-like growth factor-1
<i>ILD</i> - Interstitial lung disease
<i>IPF</i> - Idiopathic pulmonary fibrosis
<i>ITP</i> - Immune thrombocytopenic purpura
<i>LGL</i> - Large granular lymphocytic
<i>LIP</i> - Lymphocytic interstitial pneumonitis
<i>LRTI</i> - Lower respiratory tract infection
<i>NK</i> - Natural killer
<i>PRISMA</i> - Preferred Reporting Items for Systematic Reviews and Meta-analyses
<i>SD</i> - Standard deviation
<i>SOCS</i> - Suppressor of cytokine signaling
<i>STAT</i> - Signal transducer and activator of transcription
<i>TTG</i> - Anti-tissue transglutaminase

and regulation of autoimmunity and inflammation.<sup>1</sup> Therefore, *STAT3* mutations (gain-of-function [GOF] or dominant negative) can result in immunodeficiency, autoimmunity, or malignancy. *STAT3*-dominant negative germline mutations are well known and lead to a primary immune deficiency syndrome (known as Buckley or Job syndrome, or autosomal-dominant hyper IgE syndrome; OMIM: 147060).<sup>2</sup> *STAT3* GOF somatic mutations have been reported in malignancies such as large granular lymphocytic (LGL) leukemia and hepatocellular adenoma.<sup>3</sup> *STAT3* GOF germline mutations were discovered recently and lead to early-onset multiorgan dysfunction (OMIM: 615952), including autoimmune disorders, lymphoproliferation, susceptibility to infection, and severe growth failure.<sup>1,3-5</sup>

In 2014 and 2015, 3 major studies reported the first 19 patients with *STAT3* GOF, describing genetics, clinical features, and basic immunophenotyping.<sup>1,4,6</sup> Only case reports have been published thereafter without a comprehensive overview of clinical aspects and natural history of the disease. Recently, a study on management with targeted biotherapies reported 4 additional patients.<sup>7</sup> The phenotype of *STAT3* GOF is diverse, which makes its clinical definition and diagnosis difficult. The first manifestations of *STAT3* GOF can be nonspecific inflammation and/or lymphoproliferation involving varied organ systems and, therefore, a *STAT3* GOF patient could be first seen by a clinician of any subspecialty not yet familiar with this new immune dysregulation syndrome. Herein we have compiled a systematic review of published *STAT3* GOF cases to describe the genetics, functional studies, and clinical aspects of the disease.

**METHODS****Patients**

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic search was conducted (October

10, 2018) to identify studies reporting cases of patients with *STAT3* GOF germline mutations. The literature search and evaluation were performed in 3 databases, MEDLINE (PubMed), Web of Science, and Cochrane Central Register of Controlled Trials, for articles published since January 1, 2014 (the first report of *STAT3* GOF germline mutation is Flanagan et al, 2014). The following research keywords in English were used: (*STAT3* AND “gain of function” or “signal transducer and activator of transcription 3” and “gain of function”), (*STAT3* AND “Activating germline mutations” or “signal transducer and activator of transcription 3” and “Activating germline mutations”), and (*STAT3* AND “activating mutation” or “signal transducer and activator of transcription 3” and “activating mutation”). Another search was manually performed in Google Scholar using the function cited by Flanagan et al (2014), Haapaniemi et al (2015), and Milner et al (2015). Abstracts and full-length text were screened for all suitable articles. We excluded duplicate articles or congress abstracts. To be eligible for inclusion, studies and case reports were required to describe cases of patients with *STAT3* GOF germline mutations with genetic analysis and a concordant phenotype if functional analyses were not performed for the mutation. All types of publications, such as articles, reviews, editorials, letters, and correspondence, reported in English or in French, published online between January 1, 2014, and October 10, 2018, were included.

**Genetic evaluation**

Frequency of variants was determined using the gnomAD database (<http://gnomad.broadinstitute.org/>). Prediction of pathogenicity was performed in UMD predictor (<http://umd-predictor.eu/>) and Mutation Taster (<http://www.mutationtaster.org/>).

**Statistical analysis**

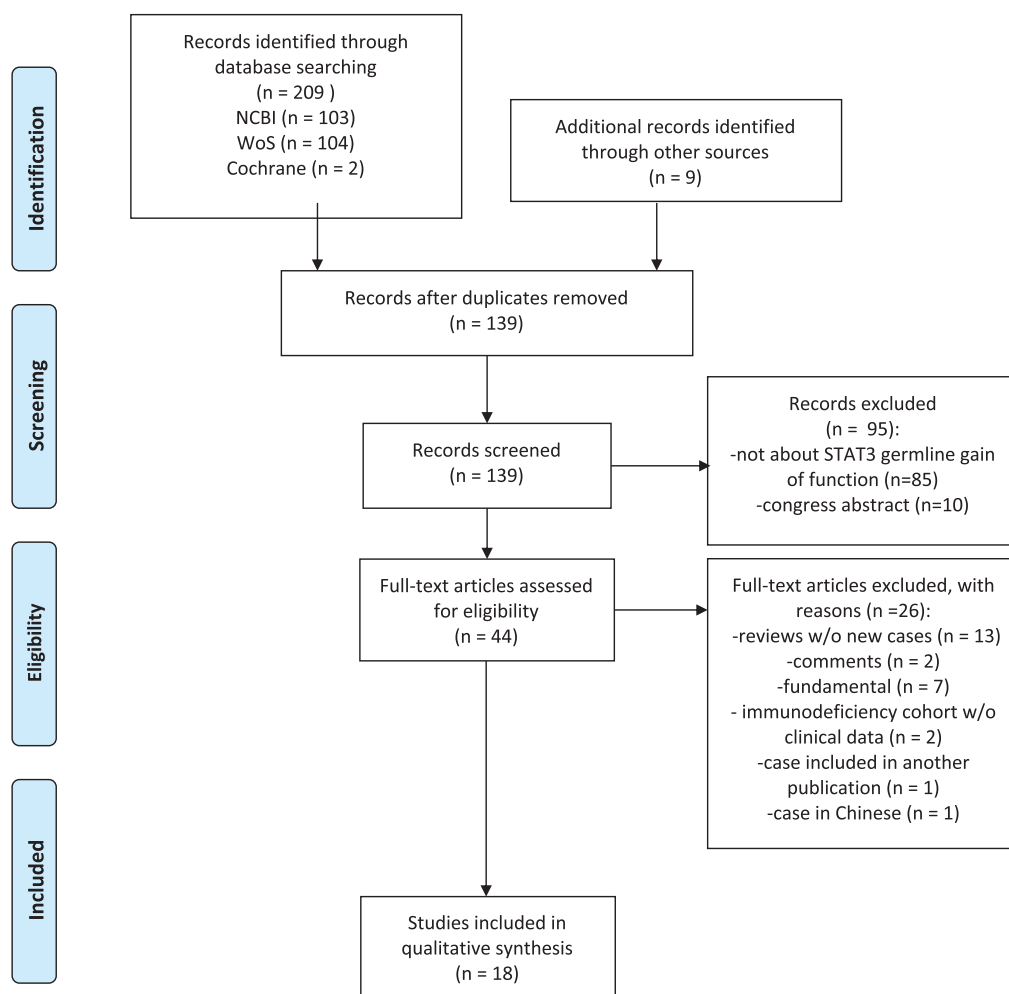
Data were collected and organized using Microsoft Excel (Microsoft, Redmond, Wash), and statistical analysis was performed using R. Data were presented as median and (first, third) quartiles.

**RESULTS**

The search identified 18 publications describing 42 unique patients. The list of included articles is presented in Table E1 (available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)), sorted by date of publication. Figure 1 summarizes the PRISMA diagram.

**Genetics and functional analysis**

At this time, 28 different mutations from 42 cases have been described, located mostly in the DNA-binding domain (Figure 2 and Table E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). All patients were heterozygous for the mutation, 21 were *de novo* mutations, and 7 were inherited in an autosomal-dominant manner within 5 different families. Six unaffected members were described within 4 of these 5 families. Penetrance is thus incomplete. Analysis of described *STAT3* variants in the gnomAD database showed only 1 mutation as already reported (p.R246Q with a frequency of 1/246408 alleles); all the others are not reported. All mutations reported but one (an in-frame amino acid deletion) are missense. All variants were predicted pathogenic or probably pathogenic by UMD predictor and disease causing by Mutation Taster. According to ExAC data, *STAT3* is a constrained gene with a pLI (an indicator of intolerance to loss of function) of 1 (the least tolerant),<sup>8</sup> and



**FIGURE 1.** PRISMA flow diagram. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-analyses; *STAT3*, signal transducer and activator of transcription 3; *WoS*, Web of Science.

indeed all the mutations reported are very rare. These features support autosomal dominant inheritance.<sup>9</sup>

Functional studies were reported for all mutations except 4,<sup>10,11</sup> and confirmed GOF of *STAT3* (Table E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The functional tests developed were (1) an *in vitro* *STAT3* reporter luciferase assay under basal or stimulated conditions (IL-6/growth hormone [GH]) in A4, HEK293 or INS-1E cells, and (2) suppressor of cytokine signaling 3 (SOCS3) expression levels under basal or stimulated (IL-21) conditions in Epstein-Barr virus–transformed patient cell lines or primary cells. Of note, under basal conditions, the luciferase reporter assay was normal for 2 patients (but abnormal in stimulated conditions), and under stimulated conditions, the assay was normal for 2 other patients (but abnormal in basal conditions). GOF mutations resulted in at least a 10-fold increase of luciferase reporter assays for 7 patients. The absence of obvious genotype-phenotype correlations and the fact that *STAT3* hyperactivity does not appear to correlate with the severity of the phenotype suggest that environmental and other genetics factors may contribute to this syndrome.<sup>12</sup>

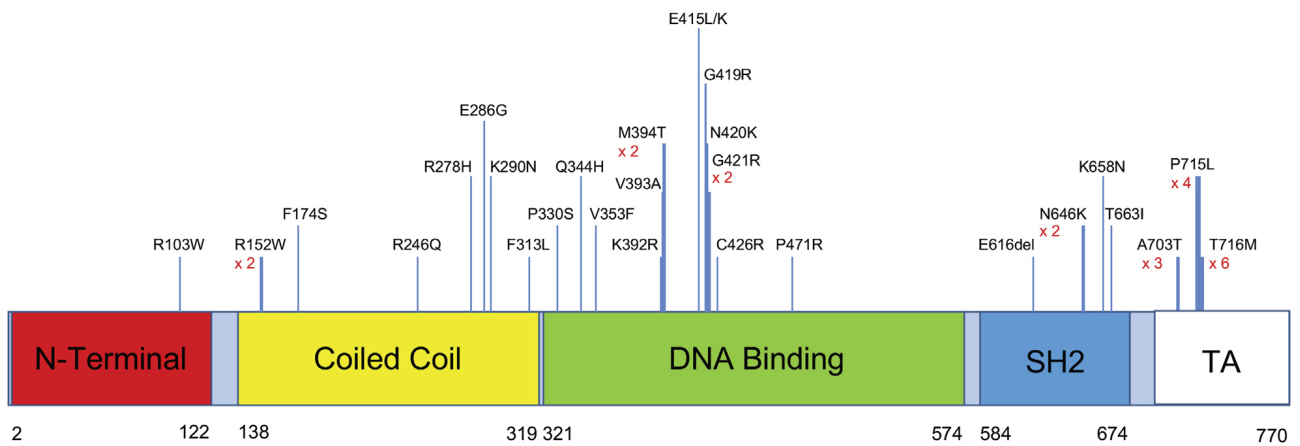
### Clinical aspects

Clinical expression phenotypes of *STAT3* GOF syndrome are very diverse. Among the 42 cases (sex ratio [M/F] = 18/22 = 0.82),<sup>1,4,6,7,10,11,13-25</sup> the most frequent features were hematologic disease, failure to thrive/short stature, and multiorgan autoimmune disorders.

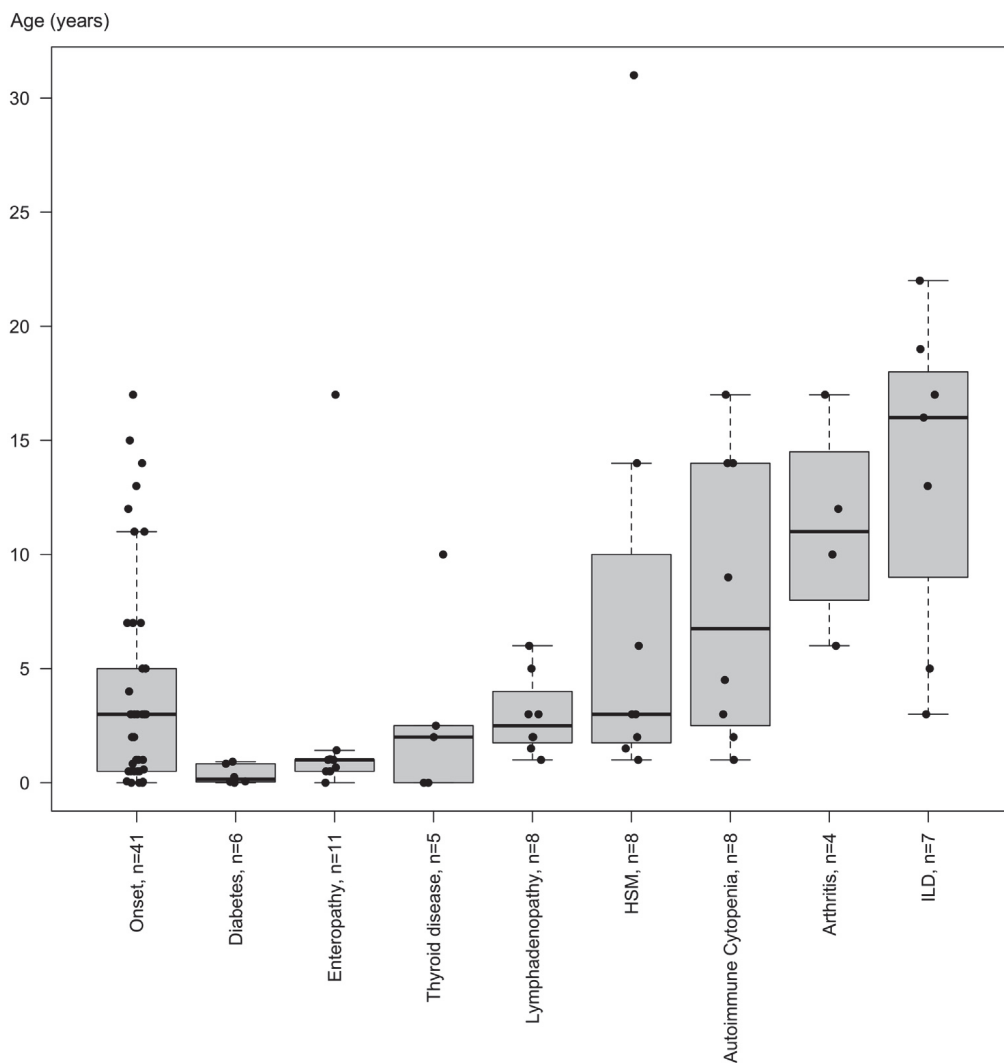
Onset of disease was very early with an average age of onset of 3 (0.5-5) years (Figure 3), including 17 cases occurring before 1 year. Eight patients died at a median age of 12.5 (5.5-18.25) years, including 4 from complications of stem cell transplantation.

The following description is based on the 42 reported cases.

**Hematologic manifestations.** Hematologic disease was the most frequent finding (35 of 42), especially autoimmune cytopenias (28 of 42), including immune thrombocytopenic purpura (ITP)<sup>4,6,11,15-17,19,22,23</sup> (24 of 28), autoimmune hemolytic anemia (AIHA)<sup>1,4,11,15-17,19,22,23</sup> (19 of 28), and neutropenia<sup>4,16,17</sup> (9 of 28) (Table E3, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). AIHA and ITP were observed concurrently in 15 cases.<sup>4,7,11,15-17,19,22,23</sup> There was an autoimmune pancytopenia in 4 cases.<sup>4</sup> Age of onset was



**FIGURE 2.** Schematic of the STAT3 protein showing the location of mutations reported to cause STAT3 GOF. STAT3 is divided into 6 domains: the N-terminal domain, coiled-coil domain, DNA-binding domain, linker domain, Src-homology 2 (SH2) domain, and trans-activation domain (TA). Mutations shown represent mainly missense mutations and the resulting amino acid changes, but there is also 1 deletion. Mutations replicated in several patients are indicated in red by the number of patients reported and using bold lines. *GOF*, Gain-of-function; *STAT3*, signal transducer and activator of transcription 3.



**FIGURE 3.** Age at onset of the disease and at onset of different clinical manifestations. *HSM*, Hepatosplenomegaly; *ILD*, interstitial lung disease.

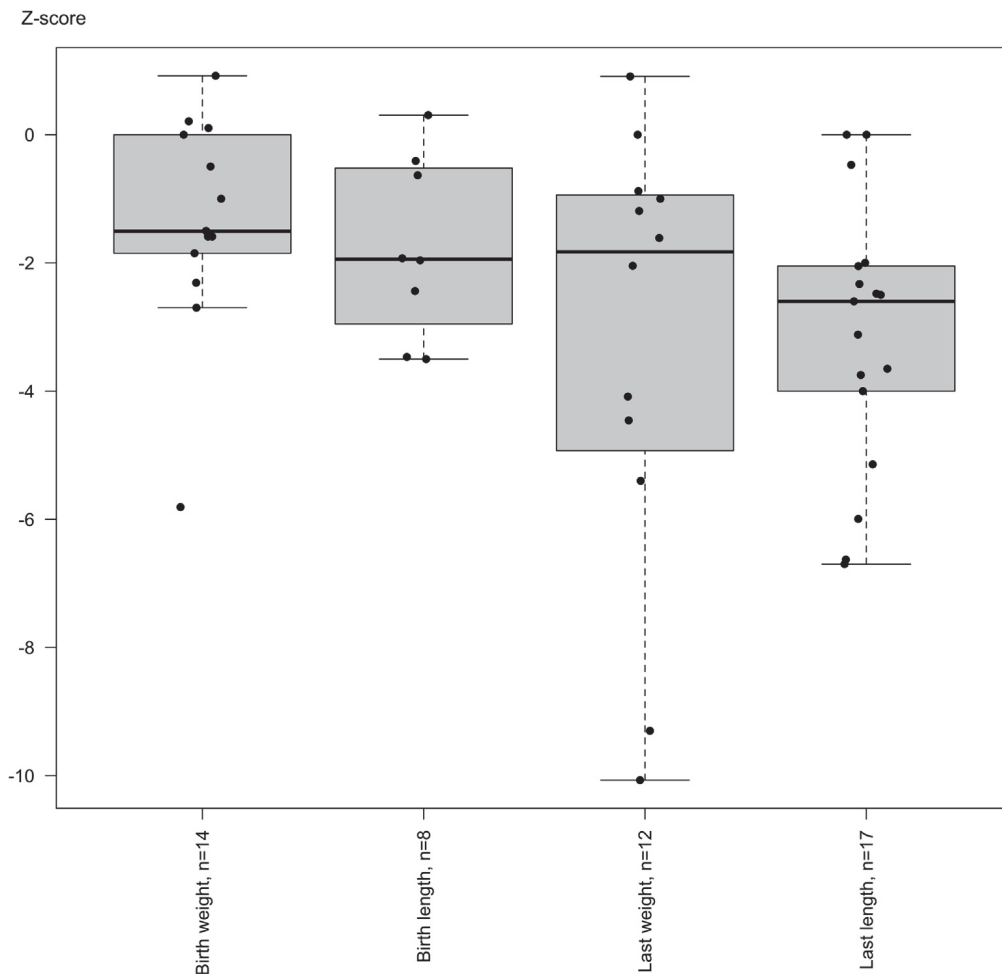


FIGURE 4. Weight and height z-scores at birth and last visit.

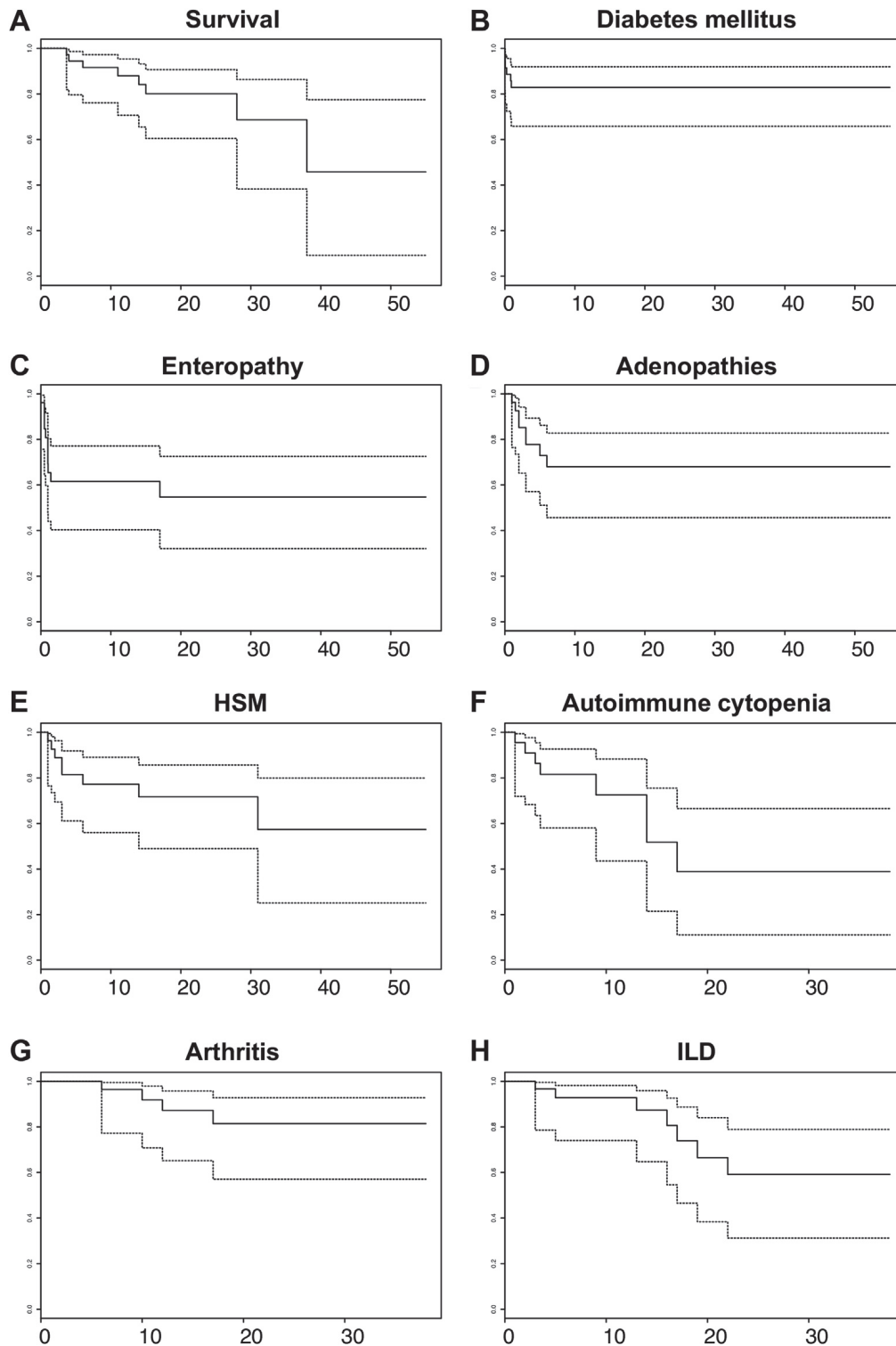
specified in 8 cases; median age of onset was 3.5 years (Figure 3).

Immunodeficiency (hypogammaglobulinemia or lymphopenia or recurrent infections) was not as severe as could be expected from the phenotype of *STAT3*-dominant negative mutations, but it was described in many cases (28 of 42). Infection susceptibility was described in most *STAT3* GOF patients (23 of 28), mainly recurrent upper and lower respiratory tract infections (LRTIs) (11 of 23)<sup>1,4,6,14,16,19,21,24</sup> leading to bronchiectasis in 2 cases. Hypogammaglobulinemia was reported in about half of patients<sup>1,4,6,11,14,15,17,21,22,24</sup> (18 of 28); it was associated with clinical infection in 16 cases. A decrease of immune cells to varying degrees was noticed for T cells<sup>4,6,11,19,20</sup> (8 of 28), natural killer (NK) cells<sup>1,6,11,16,19,24</sup> (9 of 28), and B cells, particularly memory B cells<sup>4,19,20</sup> (4 of 28). Furthermore, T regulatory cell levels were reported in 11 patients, and were decreased in 10 of 11 cases, all with multiorgan autoimmunity. Th17 cells levels were also reported in 4 cases, but were high in only one case.

Lymphoproliferation (27 of 42) was described mainly with adenopathy<sup>1,4,7,11,15-17,19,20</sup> (23 of 27) and hepatosplenomegaly<sup>1,4,7,14-17,19,20,23</sup> (23 of 27), which was concomitant in 19 cases. There was mediastinal adenopathy in 3 cases. Age of onset of lymphoproliferation was specified in 8 cases, the median age was 2.5 (1.9-3.5) years for adenopathy and 3 (1.9-8) years for hepatosplenomegaly (Figure 3).

Hemophagocytic lymphohistiocytosis was described in 1 case.<sup>7</sup> Malignancy was described in 2 cases. One adult patient had Hodgkin lymphoma<sup>4</sup> and 1 patient developed LGL leukemia<sup>1</sup> at the age of 14. The IgA level was reported in 16 cases, being elevated in 5 cases<sup>10,14,20,21</sup> and low in 8 cases.<sup>1,11,15,17,22</sup> Hyper IgA was invariably associated with enteropathy.

**Gastrointestinal manifestations.** Hepatic and digestive diseases were described in 26 cases (Table E4, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Enteropathy was found in 24 of 42 patients (Table E5, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Average age of onset, reported for 11 patients, was 1 (0.5-1.02) year, and most (9 of 11) before the second year (Figure 3). The clinical signs were diarrhea (17 patients), abdominal pain (4), and vomiting (2), associated with growth failure in 12 cases. The disease was initially classified as celiac disease in 9 cases. Response to gluten-free diet was reported for 7 patients: 1 patient responded,<sup>1</sup> 1 patient responded partially,<sup>1</sup> 1 patient responded in combination with azathioprine and tacrolimus,<sup>10</sup> and there was no response for 4 patients.<sup>1,14,20,24</sup> For the 5 patients with reported human leukocyte antigen (HLA), 3 were DQ2 or DQ8 positive. Both DQ2 positive patients were responsive to a gluten-free diet. Of the 11 of 42 patients for whom celiac antibodies (anti-gliadin [G], anti-tissue transglutaminase [TTG], or anti-



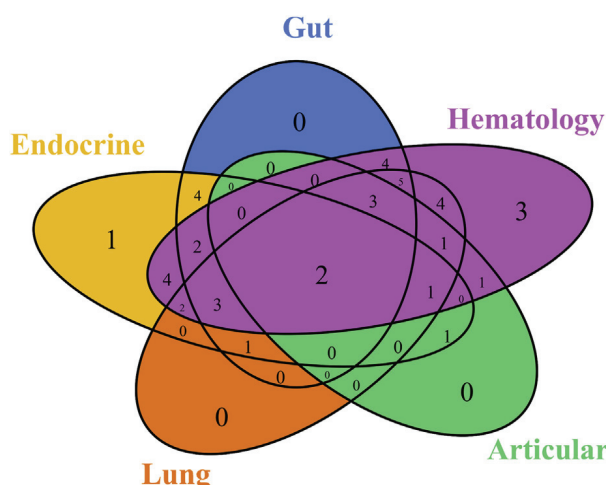
**FIGURE 5.** Kaplan-Meier survival curves. Kaplan-Meier survival curves of (A) overall survival, (B) diabetes mellitus, (C) enteropathy, (D) lymphadenopathy, (E) hepatosplenomegaly (HSM), (F) autoimmune cytopenias, (G) arthritis, and (H) interstitial lung disease (ILD). On the X axes, time is expressed in years. The Y axes represent either the percentage of survival (in A) or the number of patients free of the disease (B-H). Solid lines represent survival curves and dotted lines the confidence intervals.

endomysium [E]) were tested,<sup>1,6,10,18,20</sup> 9 were positive and 2 were negative.<sup>1</sup> The 2 patients with negative celiac antibodies had no clinical signs of enteropathy. Among the 9 patients with positive celiac antibodies, 7 had positive anti-G (5 isolated anti-

G, 1 anti-G/E, 1 anti-G/TTG) and 1 had isolated anti-TTG. Antibody specificity was not reported for the last patient.

Gastrointestinal biopsy results were reported in multiple STAT3 GOF patients. Pathology of the esophagus showed





**FIGURE 6.** Venn diagram of endocrine, gut, hematologic, articular, and pulmonary clinical manifestations.

normal<sup>18</sup> or mild changes, such as basal cell hyperplasia.<sup>4,21</sup> Pathology of the stomach showed moderate gastritis in 9 patients,<sup>1,4,14,18,20,21,24</sup> with lymphocytic infiltration noted in 4. In 14 patients,<sup>1,4,6,10,14,18,20-22,24</sup> abnormalities of the duodenum were reported. This was predominantly villous atrophy (11 patients<sup>1,4,10,14,18,20</sup>) as well as inflammation (12 patients<sup>1,4,6,10,14,18,20,21,24</sup>) with intraepithelial lymphocyte infiltration in 9 patients.<sup>1,6,10,14,18,20,21,24</sup> For 5 patients with sequential biopsies, 2 had a normalization of the biopsy,<sup>1,18</sup> 1 patient was initially normal followed by a second abnormal one,<sup>1</sup> and 2 no improvement.<sup>20,24</sup> Colonic biopsies were normal in only 1 case<sup>14</sup> and showed colitis in 5 cases.<sup>4,6,11,18</sup>

In addition, 9 patients were reported with liver disease,<sup>4,7,10,11,20,22</sup> 4 with autoimmune hepatitis (with anti-DNA and anti-smooth muscle antibodies) requiring liver transplant in 2 of them. One patient had achalasia.<sup>4</sup> Three patients developed pancreatic exocrine insufficiency,<sup>1,20</sup> 2 of whom also had diabetes.<sup>1</sup>

Seven patients affected by enteropathy were treated with targeted biotherapies (tocilizumab and ruxolitinib or tofacitinib) that improved their symptoms, need for TPN or NG tube feeds, and nutrition status. One patient who benefited from stem cell transplantation had improvement in his gastrointestinal symptoms, especially diarrhea.<sup>4</sup> One patient gained control of her diarrhea with immunosuppressive treatment (azathioprine and tacrolimus) in association with a gluten-free diet.<sup>10</sup>

**Pulmonary manifestations.** Twenty-two patients developed lung disease with a predominance of interstitial lung disease (ILD) and recurrent LRTI (Table E6, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Of 42 patients, 15 developed ILD.<sup>1,4,7,10,11,15,20,21,24</sup> The median age of onset, specified in 7 cases, was 16 (9-18) years and was substantially delayed in regard to hematologic, endocrine, and gastrointestinal features (Figure 3). Among these 15 patients, 7 had lymphocytic interstitial pneumonitis (LIP),<sup>4,7,15,20,21</sup> 2 granulomatous lung disease,<sup>11,21</sup> 2 desquamative interstitial pneumonitis (DIP),<sup>1,24</sup> 1 idiopathic pulmonary fibrosis (IPF),<sup>4</sup> and 1 cryptogenic organizing pneumonia (COOP).<sup>1</sup> With regard to the clinical presentation, asthma-like symptoms in early infancy were described

in 3 patients who presented later with ILD. A lung biopsy was performed in 3 cases.<sup>1,4,15</sup> The first case showed diffuse interstitial fibrosis (IPF).<sup>4</sup> The second displayed a diffuse interstitial fibrosis that was associated with alveolar thickening and macrophages (DIP).<sup>1</sup> The third case displayed atypical interstitial lymphoblastic infiltrate (LIP).<sup>15</sup>

Three patients required long-term oxygen therapy and 1 invasive ventilation. Immunosuppressive treatment of pulmonary manifestations was detailed in 8 cases (steroids in 6 cases, tacrolimus in 2 cases, mycophenolate mofetil in 2 cases, azathioprine in 1 case, sirolimus in 1 case, cyclosporine in 1 case, and tocilizumab combined with ruxolitinib in 2 cases, tocilizumab combined with tofacitinib in 1 case). Immune suppression had a positive effect in 2 cases: 1 patient who benefited from tocilizumab associated with ruxolitinib required less oxygen;<sup>20</sup> 1 patient who was treated with mycophenolate mofetil had improvement in diffusing capacity of the lungs for carbon monoxide.<sup>4</sup> One pulmonary patient had a bone marrow transplant, but died from multiple organ failure.<sup>21</sup>

Of 42 patients, 11 had recurrent LRTIs.<sup>1,4,6,14,16,19,21,22,24</sup> There was 1 case of *Mycobacterium avium* lung infection.<sup>6</sup> Among patients with LRTIs, 6 had hypogammaglobulinemia, 4 T-cell lymphopenia, 4 decreased NK cells, and 1 pan-lymphopenia. Seven of these patients were treated with immunosuppressive therapy, and the chronology of lung infection with regard to treatment onset was not detailed.

**Endocrinopathies.** Endocrine diseases were also a frequent feature, reported in 21 of 42 patients (Table E7, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Type I diabetes was the earliest endocrine manifestation in STAT3 GOF syndrome (10 of 42).<sup>1,4,11,16-18</sup> It appeared before 1 month of life in 3 cases and between 1 month and 12 months in 3 cases. The median age of onset of type I diabetes was 8 (2.3-35.5) weeks (Figure 3). HLA genotyping was high risk in 3 cases<sup>1,16</sup> and low risk in 2 cases.

Hypothyroidism was found in 13 of 42<sup>1,4,7,10,11,16-18,21</sup> STAT3 GOF patients. It appeared before 1 month of life in 2 cases. The median age of onset of thyroid disease was 2 (0-2.5) years. Hypothyroidism and diabetes were comorbid in 4 cases.<sup>1,11,16,18</sup>

To a lesser extent, the pituitary gland was affected. One patient was described with isolated central corticotropin deficiency.<sup>20</sup> There was 1 case of presumed pituitary dysfunction that responded well to GH treatment.<sup>4</sup> Finally, 1 patient was reported with GH insensitivity.<sup>16</sup>

**Growth failure.** Weight and/or height at birth were recorded in 14 cases, intrauterine growth restriction (weight and/or height at birth < -2 standard deviation [SD]) was present in 5 cases (35%)<sup>1,16,20,21</sup> (Figure 4). Postnatal growth failure (height and/or weight < -2SD) was presented in 15 cases among 21 where it was reported (75%).<sup>1,4,7,10,16,18,20,21,24</sup> Height was less than or equal to -4SD in 5 cases.<sup>1,4,16,20</sup> Growth failure was associated with intrauterine growth restriction in 3 cases. Insulin-like growth factor-1 (IGF1) was low in 7 of 10 patients tested; however, 5 also had enteropathy that could have affected nutritional status and so the IGF1 level. GH stimulation was performed in 4 cases;<sup>1,4,16</sup> there was a positive response in 3 cases.<sup>1,4,16</sup> Seven patients benefited from GH treatment; it was effective in 3<sup>4,21</sup> and showed a partial response in 4.<sup>1,20,21,24</sup>

**TABLE 1.** Treatments reported in STAT3 GOF patients

Treatments	Total	Positive effect	Negative effect/no effect	Not determined
<b>Nontargeted therapies</b>				
Systemic steroids	17 <sup>1,6,7,10,14,16,17,21,22,24</sup>	3 <sup>14,16,17</sup>	6 <sup>1,16,22,24</sup>	8 <sup>6,7,10,21</sup>
Inhaled steroids	2 <sup>1,21</sup>	—	2 <sup>1,21</sup>	—
Mycophenolate mofetil	5 <sup>1,4,7,17,22</sup>	2 <sup>4,17</sup>	1 <sup>7</sup>	2 <sup>1,22</sup>
Tacrolimus	4 <sup>1,7,10</sup>	1 <sup>1</sup>	2 <sup>7,10</sup>	1 <sup>1</sup>
Azathioprine	4 <sup>7,19,24</sup>	—	4 <sup>7,19,24</sup>	—
Rituximab	3 <sup>7,15,19</sup>	1 <sup>15</sup>	1 <sup>7</sup>	1 <sup>19</sup>
Sirolimus	3 <sup>7,21</sup>	—	3 <sup>7,21</sup>	—
Anti TNF-alpha	3 <sup>7,24</sup>	—	3 <sup>7,24</sup>	—
Infliximab	1 <sup>24</sup>	—	1 <sup>24</sup>	—
Adalimumab	1 <sup>24</sup>	—	1 <sup>24</sup>	—
Methotrexate	2 <sup>7,24</sup>	—	2 <sup>7,24</sup>	—
Cyclophosphamide	2 <sup>7</sup>	—	2 <sup>7</sup>	—
Cyclosporine	1 <sup>21</sup>	—	1 <sup>21</sup>	—
Abatacept	1 <sup>21</sup>	—	1 <sup>21</sup>	—
Alemtuzumab	1 <sup>7</sup>	—	1 <sup>7</sup>	—
Anti-IL1	1 <sup>7</sup>	—	1 <sup>7</sup>	—
HSCT	5 <sup>4,7,16,21</sup>	1 <sup>4</sup>	4 <sup>7,16,21</sup>	—
<b>Targeted therapies</b>				
Tocilizumab	9 <sup>4,7,14,20,24</sup>	8 <sup>4,7,14,20,24</sup>	1 <sup>7</sup>	—
Addition of jakinib	8 <sup>4,7,20,24</sup>	5 <sup>7,20,24</sup>	3 <sup>4,7</sup>	—

HSCT, Hematopoietic stem cell transplantation; GOF, gain-of-function; STAT3, signal transducer and activator of transcription 3.

**Other features.** Dysmorphic features are not a predominant feature of STAT3 GOF syndrome (2 of 37). Cutaneous disease (16 of 42) was mainly atopic dermatitis (12 of 16)<sup>1,4,6,7,10,11,20,21</sup> and alopecia (4 of 16)<sup>4,10,14</sup> (Table E8, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The age of onset of cutaneous disease was reported in 4 cases all under the age of 2 years.

Arthritis was described in 9 cases,<sup>1,4,6,11,20,22,24</sup> including 3 cases of polyarthritis,<sup>4,24</sup> 1 severe arthritis,<sup>11</sup> and 1 case of oligoarthritis.<sup>20</sup> In 1 case, polyarthritis regressed with systemic treatment with tocilizumab.<sup>4</sup> The age of onset was specified in 4 cases, with a median of 11 (9-13.25) years of age.

Six patients suffered from osteoporosis<sup>1,4,14,20,24</sup> and 2 from osteopenia;<sup>4</sup> among them, 2 had received corticosteroid treatment. There was 1 case of acroosteolysis,<sup>4</sup> resorption of the distal bony phalanges. Delayed bone age was noted in 6 cases.<sup>4,16,24</sup> Two patients presented with joint laxity.<sup>4</sup> Dental abnormalities such as decay or delayed teeth eruption (a common feature of STAT3-dominant negative mutations) were noted in 5 cases.<sup>1,4,16,20</sup>

Renal disease was reported in 3 cases.<sup>14,20,22</sup> One patient presented with nephrolithiasis at an adult age. There was 1 case of proximal tubulopathy with severe hypercalciuria at 5 years, associated with cortical renal hyperechogenicities compatible with microcysts, but without renal impairment. Finally, 1 patient had a chronic renal impairment and died from end stage renal failure.

Ocular affects were reported in 5 of 42 patients,<sup>1,19,20,22</sup> including 2 patients with uveitis and keratoconjunctivitis sicca in 2 cases. Neurological disease was not predominant, with 1 case of ocular myasthenia gravis,<sup>4</sup> 1 case of cerebral atrophy that led to

abnormal psychomotor development,<sup>4</sup> and 1 patient with cerebral palsy.<sup>4</sup> Three patients<sup>1,4</sup> developed thrombosis (1 internal carotid and 2 vena cava), but additional details were not provided. Finally, 1 patient developed disseminated intravascular coagulation.<sup>7</sup>

### Clinical progression

STAT3 GOF syndrome encompasses many target organ diseases with a sequential median age of onset (Figures 3 and 5). Endocrine and gastrointestinal disease is very early onset and appears clearly before the onset of hematologic disease. Polyautoimmunity with  $\geq 2$  autoimmune diseases was frequent (29 of 42);  $\geq 3$  autoimmune diseases was reported in 16 of 42 patients. Single-organ autoimmune disease was reported in 10 patients and 3 patients had no obvious autoimmunity. Although hematologic disease was also predominant, it was not invariant as 7 patients did not have any hematologic disease (Figure 6). Finally, 4 patients had neither polyautoimmunity nor hematologic disease.

### Therapeutic options

Most of the symptomatic patients with STAT3 GOF syndrome required significant immunosuppressive therapy. Treatment was outlined in 23 cases and is presented in Table 1.

Nontargeted immunosuppressive therapies were overall ineffective.

Five patients<sup>4,7,16,21</sup> received hematopoietic stem cell transplantation; 4 died from complications (graft versus host disease and systemic adenovirus in 1 case, multiple organ failure in 1 case, systemic adenovirus infection in 1 case, and adenovirus pneumonia and post-transplant hemophagocytic lymphohistiocytosis in 1 case), and the other had improved growth and a complete remission of his autoimmune disease.<sup>4</sup>

TABLE II. Clinical features of single-gene defects with immune dysregulation<sup>3,4,7,26-32</sup>

Gene	STAT3 GOF		STAT3 DN (AD-HIES)		STAT1 GOF		STAT5b deficiency		APDS		ALPS		IPEX		LATAIE		CHAI	
	STAT3 AD	STAT3 CH	STAT3 AD	STAT3 CH	STAT1 AD	STAT1 CH	STAT5b AD	STAT5b CH	PIK3CD AD	PIK3CD CH	TNFRSF6 AD	TNFRSF6 CH	FOXP3 AD	FOXP3 CH	LRBA AD	LRBA CH	CTLA-4 AD	CTLA-4 CH
Transmission																		
Onset of symptoms	Childhood	Childhood	Early infancy	Childhood	Childhood	Childhood	Childhood	Childhood	1-3 years	1-3 years	1-3 years	1-3 years	Early infancy	Childhood	Childhood	Childhood	Childhood	Childhood
Lymphoproliferation	SM, HM	SM, HM	—	SM, HM	SM, HM	SM, HM	—	—	LAD, SM, ENT lymphoid hyperplasia	LAD, SM, ENT lymphoid hyperplasia	80% chronic lymphoproliferation (>6 mo); LAD, SM, HM	70% AD (some somatic mutations)	—	LAD, SM, HM	LAD, SM, HM	LAD, SM, HM	LAD, SM	LAD, SM
Autoimmune disorder (immune dysregulation)	AIHA, ITP	Thyroiditis	—	Thyroiditis	Alopecia, psoriasis, scleroderma, lupus	ITP	Interstitial lung disease	Interstitial lung disease	30% cytopenias	Insulin-dependent diabetes	Rare other autoimmune manifestations: nephritis, hepatitis, biliary cirrhosis, colitis, arthritis, vasculitis	70% cytopenias: AIHA, ITP or neutropenia	Early-onset enteritis with villous atrophy and lymphocytic infiltrates	Enteropathy	Enteropathy	Enteropathy	>50% enteropathy	>50% interstitial lung disease
Other	Interstitial lung disease	Pseudo-ceeliac enteropathy, colitis, autoimmune hepatitis, autoimmune cytopenia	Thyroiditis	Pseudo-ceeliac enteropathy, colitis, autoimmune hepatitis, autoimmune cytopenia	Arthritis	Arthritis	Thyroiditis	Thyroiditis	Arthritis	Hemolytic anemia	Interstitial lung disease	AIHA, ITP	Hemolytic anemia	Interstitial lung disease	AIHA, ITP	AIHA, ITP	AIHA, ITP	AIHA, ITP
	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis	Arthritis
	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia	Alopecia
	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections	Herpesvirus infections
	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections	Fungal infections
	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections	Bacterial infections
	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections	Respiratory infections
	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature	Short stature

(continued)



TABLE II. (Continued)

Increased risk of malignancy Laboratory parameters	STAT3 DN (AD-HIES)		STAT1 GOF		STAT5b deficiency		APDS		ALPS		IPEX		LATAIE		CHAI	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Hypogammaglobulinemia	Elevated IgE	Reduced switched memory B cells	Treg deficiency and dysfunction	Reduced T cells and NK cells, hypogammaglobulinemia	Decreased IgM/IgG ± increased IgM	Direct combs positive, hypergamma globulinemia	Elevated IgE	Elevated DNT cells	50% hypogammaglobulinemia	Hypogammaglobulinemia						
Reduced switched memory B cells and Tregs	Eosinophilia	Decreased Th17 cells, low IgG2 and IgG4	Reduced T cells and NK cells, hypogammaglobulinemia	Naive CD4 T-cell and memory B-cell lymphopenia with elevated transitional B cells		Elevated plasma sFASL	Eosinophilia	Reduced Tregs	Anti-enterocyte antibodies	Reduced switched memory B cells						
Decreased Th17 cells and T memory lymphopenia	Decreased Th17 cells					Elevated plasma IL-10										
References	Milner et al, 2015 <sup>4</sup>	Vogel et al, 2015 <sup>3</sup>	Forbes et al, 2018 <sup>7</sup>	Hwa, 2016 <sup>31</sup>	Coutler et al, 2016 <sup>28</sup>	Neven et al, 2011 <sup>29</sup>	Barzagli et al, 2018 <sup>30</sup>	Gómez-Díaz et al, 2016 <sup>27</sup>	Schubert et al, 2014 <sup>26</sup>							

Toubiana et al, 2016<sup>32</sup>

AD, Autosomal dominant; AD-HIES, autosomal-dominant hyper-immunoglobulin E syndrome; AHA, autoimmune hemolytic anemia; ALPS, autoimmune lymphoproliferative syndrome; APDS, activated phosphoinositide 3-kinase delta syndrome; AR, autosomal recessive; CHAI, CTLA-4 haploinsufficiency with autoimmune infiltration; DN, dominant negative; DNT, double-negative T cells (CD3+TCRβ+CD4-CD8-); ENT, Ear nose throat; GOF, gain-of-function; HM, hepatomegaly; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; ITP, immune thrombocytopenic purpura; LAD, lymphadenopathy; LATAIE, LRBA deficiency with autoantibodies, Treg defects, autoimmune infiltration, and enteropathy; LRBA, LPS-responsive beige-like anchor; sFASL, soluble Fas ligand; SM, splenomegaly.

Other therapeutic options consisted of targeting molecules that play an important role in the STAT3 pathway. Nine patients<sup>4,7,14,20,24</sup> received anti-IL6 receptor monoclonal antibody therapy (tocilizumab), with a positive effect on autoimmune disease except in 1 patient.<sup>7</sup> The effect nevertheless seems to plateau. In 1 case it was used in monotherapy<sup>4</sup> and it resulted in improvement of the general condition, alleviation of diarrhea, and increased Treg cells.<sup>14</sup> In the 8 other patients, tocilizumab was given with a Jak inhibitor (ruxolitinib or tofacitinib), and this showed clear improvement in 5 patients, most notably for their enteropathy and oxygen support.

DISCUSSION

In recent years, multiple monogenic causes of early-onset autoimmunity and lymphoproliferation have been identified, now including STAT3 GOF syndrome.<sup>3,4,7,26-32</sup> These disorders have overlapping clinical and immunologic features (Table II). In addition to these early-onset monogenic autoimmune syndromes, the differential diagnoses for the symptoms of STAT3 GOF syndrome are plentiful due to multiple features within each organ system. Therefore, several differential diagnoses can be considered. Our systematic review summarizes current knowledge about specific characteristics of the disease. Average onset of organ systems appears to occur sequentially (Figure 3), with early-onset diabetes and enteropathy preceding hematologic manifestations and lung disease.

The enteropathy was frequently initially diagnosed as pseudo-celiac, with villous atrophy, but without the usual serologic signature. Only half of the patients tested had the high-risk HLA (compared with more than 95% in classic celiac disease). Gluten-free diet had no effect in most patients. STAT3 GOF patients presenting with early-onset inflammatory bowel disease (IBD)-like phenotypes lacked the classical histologic findings of IBD and lymphocyte infiltration.

Early-onset endocrinopathies including neonatal diabetes and early-onset thyroiditis were among the first symptoms occurring during infancy. Polyautoimmunity (encountered in 29 of 42 patients) included arthritis, autoimmune hepatitis, alopecia areata, and autoimmune cytopenias notably later in life. Intra-uterine growth retardation was encountered in 1 of 3 of patients and postgrowth failure in 3 of 4, with 5 patients < -4SD. Growth failure is a predominant feature of STAT3 GOF syndrome. This could be the consequence of digestive disease (malabsorption), diabetes, hypothyroidism, respiratory insufficiency, frequent infections, or corticosteroid treatment. However, it could also be inherent to the STAT3 GOF mutations. Indeed, STAT5b is the major transcription factor downstream of GH signaling,<sup>31,33</sup> and STAT3 activation can inhibit STAT5 phosphorylation.<sup>16</sup>

STAT3 GOF appears as a new etiology of ILD, mainly LIP as well as other forms of ILD such as COOP or DIP. Pathology showed fibrosis in 2 patients. LIP results from pulmonary interstitial accumulation of lymphocytes. Several publications have suggested that STAT3 plays a role in regulating fibroblast function in fibrotic lung diseases and that aberrant STAT3 signaling plays a critical role in usual interstitial pneumonia and IPF pathogenesis.<sup>34</sup>

Hematologic disease was frequent, onset after infancy, and included lymphoproliferation, immunodeficiency with infection susceptibility (mainly recurrent LRTI and rare opportunistic

infections), and autoimmune cytopenias. Despite the well-known association of somatic STAT3 GOF mutations with malignancy, cancer was reported in only 2 patients. Given the young average age of STAT3 GOF patients, long-term follow-up will be critical to fully understand the risk of malignancy in STAT3 GOF syndrome.

The immunologic consequences of *STAT3* GOF mutations would be predicted to result in expansion of Th17 cells and inhibition of Treg cells, which plays a critical role in the development of autoimmunity.<sup>5,10</sup> This is because, among other triggers, STAT3 is activated by IL-6 and plays an important role in differentiation of CD4 T cells.<sup>5</sup> We hypothesize that because of the severity of disease in most symptomatic STAT3 GOF patients, the reported T-cell subsets were not performed in treatment naïve patients and that therapy with immunosuppression impacted Th17 development.

STAT3 interacts with other STATs mainly via SOCS3, which is a downstream target of STAT3 and negative regulator of STAT3 signaling.<sup>3-5</sup> Through this mechanism, STAT3 is believed to inhibit STAT1 and STAT5 phosphorylation. Disruption of STAT5 activation leads to inhibition of Treg development. In fact, most STAT3 GOF patients with reported T-cell subsets did have decreased Treg cells counts, but, to date, the majority of the few patients examined have been found to have normal levels of Th17 cells.

Nontargeted immunosuppressive treatments were disappointing in this cohort. Available biotherapies and bone marrow transplant constitute a real hope for these patients. Use of targeted therapy with tocilizumab and ruxolitinib or other JAK inhibitors may change the natural course of the disease. Bone marrow transplant could be a curative option when life-threatening complications occur, but available data are insufficient to determine safety or optimal conditions for this therapeutic option.<sup>7</sup>

This systematic review has some limitations. Four patients did not have any functional tests and many papers did not include specific details of clinical aspects, most notably the timing of onset of the different clinical features. A study reporting the complete natural history of the disease with timing of the onset of the different manifestations would be worth investigating. Nevertheless, the clinical summaries of STAT3 GOF made in this systematic review will be a useful tool to select among patients with early-onset autoimmunity and lymphoproliferation to direct specific testing for STAT3.

STAT3 GOF syndrome is heterogeneous and patients do not universally present with hematologic autoimmunity, or obvious lymphoproliferation, immunodeficiency, or short stature. They can also have a wide variety of solid organ manifestations such as pseudo-celiac disease, pseudo-juvenile arthritis, endocrinopathies, ILD, and cutaneous disease. However, notably, very early-onset diabetes or atypical celiac disease are clues to this syndrome and can be for a long time the only manifestation.

Current diagnostic methods for STAT3 GOF syndrome include genetic testing paired with functional analysis of new mutations. This process is available only in expert centers, using mainly luciferase reporter assays. The SOCS3 level of expression has also been used as a functional assay. Levels of GOF determined by the luciferase reporter assay seem to be the best assessment to potentially delineate genotype-phenotype correlations in the future.

## CONCLUSIONS

STAT3 GOF syndrome caused by heterozygous, germline *STAT3* GOF mutations is a new clinical entity to think about when confronted with early-onset polyautoimmunity with lymphoproliferation, enteropathy, ILD, and associated with severe growth failure. Heterogeneity of the phenotype makes a precise clinical definition difficult. Currently, genetic analysis is the only valid diagnostic method. At this time, defined therapeutic guidelines are still lacking, but use of anti-IL-6 receptor and JAK inhibitor biologics is an attractive possibility while other future options, such as anti-STAT3 therapeutics, are being developed.

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## ONLINE REPOSITORY

TABLE E1. Publications selected for systematic review

Title	Journal	First author	Year
Activating germline mutations in STAT3 cause early-onset multiorgan autoimmune disease	<i>Nat Genet</i>	Flanagan et al <sup>E1</sup>	2014
Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 GOF mutations	<i>Blood</i>	Milner et al <sup>E2</sup>	2015
Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3	<i>Blood</i>	Haapaniemi et al <sup>E3</sup>	2015
A novel human STAT3 mutation presents with autoimmunity involving Th17 hyperactivation	<i>Oncotarget</i>	Wienke et al <sup>E4</sup>	2015
Genetic diagnosis using whole exome sequencing in common variable immunodeficiency	<i>Front Immunol</i>	Maffucci et al <sup>E5</sup>	2016
Pulmonary manifestations of the autoimmune lymphoproliferative syndrome. A retrospective study of a unique patient cohort	<i>Annals ATS</i>	Lau et al <sup>E6</sup>	2016
A novel <i>de novo</i> activating mutation in STAT3 identified in a patient with common variable immunodeficiency (CVID)	<i>Clin Immunol</i>	Russell et al <sup>E7</sup>	2017
An activating mutation in STAT3 results in neonatal diabetes through reduced insulin synthesis	<i>Diabetes</i>	Velayos et al <sup>E8</sup>	2017
Short stature in a boy with multiple early-onset autoimmune conditions due to a STAT3 activating mutation: could intracellular growth hormone signaling be compromised?	<i>Horm Res Paediatr</i>	Sediva et al <sup>E9</sup>	2017
STAT3 GOF mutations associated with autoimmune lymphoproliferative syndrome like disease deregulate lymphocyte apoptosis and can be targeted by BH3 mimetic compounds	<i>Clin Immunol</i>	Nabhani et al <sup>E10</sup>	2017
Tocilizumab promotes regulatory T-cell alleviation in STAT3 GOF-associated multiorgan autoimmune syndrome	<i>Clin Ther</i>	Khoury et al <sup>E11</sup>	2017
Up, down, and all around: diagnosis and treatment of novel STAT3 variant	<i>Front Pediatr</i>	Weinreich et al <sup>E12</sup>	2017
Partial growth hormone insensitivity and dysregulatory immune disease associated with <i>de novo</i> germline activating STAT3 mutations	<i>Mol Cell Endocrinol</i>	Gutiérrez et al <sup>E13</sup>	2018
Pediatric-onset Evans syndrome: heterogeneous presentation and high frequency of monogenic disorders including LRBA and CTLA4 mutations	<i>Clin Immunol</i>	Besnard et al <sup>E14</sup>	2018
STAT3 GOF: a new kid on the block in interstitial lung diseases	<i>Am J Respir Crit Care Med</i>	Fabre et al <sup>E15</sup>	2018
Genetic heterogeneity of uncharacterized childhood autoimmune diseases with lymphoproliferation	<i>Pediatr Blood Cancer</i>	Takagi et al <sup>E16</sup>	2018
Jakinibs for the treatment of immune dysregulation in patients with GOF STAT1 or STAT3 mutations	<i>J Allergy Clin Immunol</i>	Forbes et al <sup>E17</sup>	2018
STAT3 GOF: a new etiology of severe rheumatic disease	<i>Rheumatology</i>	Giovannini-Chami et al <sup>E18</sup>	2018

GOF, Gain-of-function; LRBA, LPS-responsive beige-like anchor; STAT, signal transducer and activator of transcription.

**TABLE E2.** Mutations described and functional tests

Age (onset)	Mutation	Domain	Functional test	Publication
4 y	<b>G421R</b>	DBD	STAT3 luciferase	Milner et al <sup>E2</sup>
7 y	T663I	SH2	STAT3 luciferase	Milner et al <sup>E2</sup>
3 y	<b>R152W</b>	CC	STAT3 luciferase	Milner et al <sup>E2</sup> and Lau et al <sup>E6</sup>
13 y	V353F	DBD	STAT3 luciferase	Milner et al <sup>E2</sup>
3 y	Q344H	DBD	STAT3 luciferase	Milner et al <sup>E2</sup>
5 y	E415K	DBD	STAT3 luciferase	Milner et al <sup>E2</sup>
<1 y	<b>T716M</b>	TA	STAT3 luciferase	Milner et al <sup>E2</sup>
3 y	N420K	DBD	STAT3 luciferase	Milner et al <sup>E2</sup>
<1 y	<b>A703T</b>	TA	STAT3 luciferase	Milner et al <sup>E2</sup>
15 y	<b>A703T</b>	TA	STAT3 luciferase	Milner et al <sup>E2</sup>
12 y	<b>A703T</b>	TA	STAT3 luciferase	Milner et al <sup>E2</sup>
<1 y	<b>T716M</b>	TA	STAT3 luciferase	Milner et al <sup>E2</sup>
eo	<b>T716M</b>	TA	STAT3 luciferase	Milner et al <sup>E2</sup>
2 wk	<b>T716M</b>	TA	STAT3 luciferase	Flanagan et al <sup>E1</sup>
Birth	K392R	DBD	STAT3 luciferase	Flanagan et al <sup>E1</sup>
3 wk	<b>N646K</b>	SH2	STAT3 luciferase	Flanagan et al <sup>E1</sup>
43 wk	<b>N646K</b>	SH2	STAT3 luciferase	Flanagan et al <sup>E1</sup>
<1 y	K658N	SH2	STAT3 luciferase	Flanagan et al <sup>E1</sup>
17 y	<b>M394T</b>	DBD	STAT3 luciferase	Haapaniemi et al <sup>E3</sup>
6 mo	<b>G421R</b>	DBD	Milner et al <sup>E2</sup>	Khoury et al <sup>E11</sup>
3 y	G419R	DBD	STAT3 luciferase	Weinreich et al <sup>E12</sup>
11 mo	<b>P715L</b>	TA	SOCS3	Sediva et al <sup>E9</sup>
1 y	<b>P715L</b>	TA	SOCS3	Sediva et al <sup>E9</sup>
3 y	R278H	CC	STAT3 luciferase	Nabhani et al <sup>E10</sup>
2 y	<b>M394T</b>	DBD	STAT3 luciferase	Nabhani et al <sup>E10</sup>
Birth	P330S	DBD	STAT3 luciferase	Velayos et al <sup>E8</sup> and Camarero et al <sup>E19</sup>
6 mo	P471R	Linker	Nd	Wienke et al <sup>E4</sup>
3 y	<b>T716M</b>	TA	Flanagan et al <sup>E1</sup>	Besnard et al <sup>E14</sup>
2 y	<b>P715L</b>	SH2	Sediva et al <sup>E9</sup>	Besnard et al <sup>E14</sup>
1 y	E415L	DBD	STAT3 luciferase	Fabre et al <sup>E15</sup>
Birth	E616del	SH2	STAT3 luciferase	Gutiérrez et al <sup>E13</sup>
<2 y	C426R	DBD	STAT3 luciferase	Gutiérrez et al <sup>E13</sup>
14 y	K290N	CC	STAT3 luciferase	Russell et al <sup>E7</sup>
11 y	R246Q	CC	Nd	Maffucci et al <sup>E5</sup>
3 y	F313L	CC	Nd	Maffucci et al <sup>E5</sup>
5 y	R103W	NH2	Nd	Maffucci et al <sup>E5</sup>
3 y	<b>T716M</b>	TA	Milner et al <sup>E2</sup>	Takagi et al <sup>E16</sup>
7 y	<b>R152W</b>	CC	Milner et al <sup>E2</sup>	Forbes et al <sup>E17</sup>
3 y	F174S	CC	STAT3 luciferase	Forbes et al <sup>E17</sup>
7 mo	E286G	CC	STAT3 luciferase	Forbes et al <sup>E17</sup>
7 y	<b>P715L</b>	SH2	STAT3 luciferase	Forbes et al <sup>E17</sup>
1 y	V393A	DBD	STAT3 luciferase	Giovannini-Chami et al <sup>E18</sup>

eo, Early-onset; nd, not determined; STAT, signal transducer and activator of transcription.

Mutations in bold are those described in more than 1 patient.

**TABLE E3.** Hematologic presentation

Hematologic disease	35/42 (83%)
<i>Immunodeficiency</i>	28/42 (67%)
Infection susceptibility	23/28
Viral	10/23
Herpes virus	7/10
Pox virus (molluscum contagiosum)	3/10
West Nile virus	1/10
HPV	1/10
Fungal	5/23
Bacterial	7/23
Nontuberculous mycobacteria	1/23
Unspecified	8/23
Hypogammaglobulinemia	18/28
NK-cell lymphopenia	9/28
T-cell lymphopenia	8/28
B-cell (memory) lymphopenia	4/28
<i>Autoimmune cytopenia</i>	28/42 (67%)
ITP	24/28
AIHA	19/28
Neutropenia	9/28
<i>Lymphoproliferation</i>	27/42 (64%)
Adenopathy	23/27
Hepato and/or splenomegaly	23/27
<i>Malignant process</i>	2/42 (4.8%)
Hodgkin lymphoma	1/2
Large granular leukemia	1/2

AIHA, Autoimmune hemolytic anemia; HPV, human papillomavirus infection; ITP, immune thrombocytopenic purpura; NK, natural killer.

**TABLE E4.** Gastrointestinal manifestations

Gastrointestinal manifestations	26/42 (62%)
<i>Clinical presentation</i>	
Diarrhea	17/26
Failure to thrive	12/26
Abdominal pain	4/26
Vomiting	2/26
<i>Enteropathy</i>	24/42 (57%)
Histopathology	16/24
Villous atrophy	11/16
Intraepithelial lymphocyte infiltration	9/16
Biology	
Celiac disease antibodies	11/24
Negative celiac disease autoantibodies	2/11
Positive celiac disease autoantibodies	9/11
Anti-gliadin	7/9
Anti-transglutaminase	2/9
Anti-endomysium	1/9
Unspecified enterocyte antibodies	1/9
HLA	5/24
DQ2 and/or DQ8 positive	3/5
DQ2 and DQ8 negative	2/5
<i>Other digestive disease</i>	
Gastritis	9/42 (21%)
Lymphocytic	3/9
Collagenic	1/9
Nodular	1/9
Unspecified	4/9
Colitis	5/42 (12%)
Lymphocytic	1/5
Collagenic	1/5
Unspecified	3/5
Esophagitis	2/42 (5%)
Proctitis	1/42 (2%)
Achalasia	1/42 (2%)
Hepatopathy	9/42 (21%)
Hepatitis	4/9
Liver granuloma	1/9
Other	4/9
Exocrine pancreatic insufficiency	3/42 (7%)

HLA, Human leukocyte antigen.



TABLE E5. Clinical, biological, and pathological characteristics of patients with enteropathy

Publication	Reference	Age of onset (y)	Celiac disease	HLA	Anti-TTG	Anti-gliadin	Anti-endomysium	Pathology	Response to gluten-free diet
Patients with enteropathy 24/42									
<i>Patients with enteropathy initially classified as celiac disease (9/24)</i>									
Flanagan et al <sup>E1</sup>	Patient 1	1.42	Yes	DQ2+	Positive	Nd	Nd	Nd	Responsive to gluten-free diet
Flanagan et al <sup>E1</sup> and Haapaniemi et al <sup>E3</sup>	Patient 2/2	0.5	Yes	DQ2+ DQ8+	Nd	Positive	Positive	EGD 1 y: subtotal villous atrophy with intraepithelial lymphocyte infiltration EGD 14 y: normal	Moderately responsive to gluten-free diet
Flanagan et al <sup>E1</sup> and Haapaniemi et al <sup>E3</sup>	Patient 5/1	0.5	Yes	DQ2- DQ8-	Negative	Positive	Negative	EGD 3 y: unremarkable	Not responsive to gluten-free diet
Khoury et al <sup>E11</sup>	Patient 1	0.5	Yes	Nd	Positive	Positive	Negative	EGD 11 y: subtotal villous atrophy with intraepithelial lymphocyte infiltration EGD 6 mo: consistent with celiac disease EGD 17 y: moderate gastritis, colonoscopy: normal	Not responsive to gluten-free diet
Velayos et al <sup>E8</sup> and Camarero et al <sup>E19</sup>	Patient 1/1	1.03	Yes	DQ2- DQ8-	Negative	Positive	Negative	EGD 13 mo: partial duodenal atrophy, <sup>E8</sup> mild increase of intraepithelial lymphocytes <sup>E19</sup> EGD 10 y: normal aspect upper endoscopy, lymphocytic gastritis, esophagus normal	Nd
Wienke et al <sup>E4</sup>	Patient 1	0.67	Yes	Nd	Ns (positive anti-enterocyte antibody)	Ns (positive anti-enterocyte antibody)	Ns (positive anti-enterocyte antibody)	EGD 15 y: duodenal biopsy normal, collagenous gastritis + colonoscopy: rectal and colonic biopsy showed collagenous colitis EGD 8 y: Marsh 3b*c	Improved with gluten-free diet plus azathioprine and tacrolimus
Besnard et al <sup>E14</sup>	Patient 1	Nd	Yes	Nd	Nd	Nd	Nd	Nd	Nd
Fabre et al <sup>E15</sup>	Patient 1	0.5	Yes	DQ8+	Negative	Positive	Negative	EGD 1 y: villous atrophy with elevated intra epithelial lymphocytes, nodular gastritis	Not responsive to gluten-free diet

Giovanini-Chami et al <sup>E18</sup>	Patient 1	1	Yes	Nd	Negative	Positive	Nd	Biopsy proven heterogeneous villous atrophy and marked intraepithelial lymphocytic infiltration with chronic antral and fundic gastritis	Not responsive to gluten-free diet
<i>Patients with enteropathy and without celiac disease classification (15/24)</i>									
Haapaniemi et al <sup>E3</sup>	Patient 3	17	No	Nd	Nd	Positive	Negative	EGD 17 y: lymphatic hyperplasia, duodenal polyposis, mild chronic antral gastritis + colonoscopy: lymphocytic colitis	Nd
Milner et al <sup>E2</sup> and Forbes et al <sup>E17</sup>	Patient 5/15	Nd	No	Nd	Nd	Nd	Nd	Esophagus with reactive epithelial changes, stomach with mild reactive lymphoid aggregates, and mild mucosal edema, duodenum with villous blunting and crypt hyperplasia with increased eosinophils and mild inflammatory infiltrate with extensive degranulation	Nd
Milner et al <sup>E2</sup>	Patient 6	Nd	No	Nd	Nd	Nd	Nd	Duodenum with subtotal atrophy and chronic inflammation in the lamina propria	Nd
Milner et al <sup>E2</sup>	Patient 7	Nd	No	Nd	Nd	Nd	Nd	Increased intraepithelial and lamina propria lymphocytes and plasma cells with abundant apoptotic bodies throughout the gastrointestinal tract consistent with autoimmune enteropathy	Nd
Milner et al <sup>E2</sup>	Patient 9	Nd	No	Nd	Nd	Nd	Nd	Stomach with mild chronic gastritis, duodenum with severe chronic duodenitis with cryptitis and with villous atrophy, colon with focal active colitis, rectum with focal cryptitis and increased apoptosis	Nd
Milner et al <sup>E2</sup>	Patient 12	Nd	No	Nd	Nd	Nd	Nd		Nd

(continued)



TABLE E5. (Continued)

Publication	Reference	Age of onset (y)	Celiac disease	HLA	Anti-TTG	Anti-gliadin	Anti-endomysium	Pathology	Response to gluten-free diet
Milner et al <sup>E2</sup>	Patient 13	Nd	No	Nd	Nd	Nd	Nd	Small bowel with total villous destruction and severe acute and chronic inflammation, colon with severe inflammatory changes and chronicity	Nd
Gutiérrez et al <sup>E13</sup>	Patient 1	1	Nd	Nd	Nd	Nd	Nd	EGD 2 y: lymphocytic gastritis, basal cell hyperplasia of the esophagus; stomach consistent with gastritis; mild lymphoid nodularity was observed in the duodenum	Nd
Gutiérrez et al <sup>E13</sup>	Patient 2	1	Nd	Nd	Nd	Nd	Nd		Nd
Russell et al <sup>E7</sup>	Patient 1	Nd	Nd	Nd	Nd	Nd	Nd	34 y, duodenum: almost devoid of surface glandular epithelium. Intact villi are of normal architecture with no villous blunting or increase in intraepithelial lymphocytes. No nodular lymphoid hyperplasia, granuloma, active inflammation or ulceration. No giardia, cryptosporidia or CMV. Absent CD138+ plasma cells within lamina propria	Nd
								34 y, ileum: mild villous distortion, edema and patchy neutrophilic infiltrate within the lamina propria with focal cryptitis. Absent plasma cells. No granuloma formation. No luminal organisms or CMV-like viral inclusions	

35 y, colon: preserved crypt architecture showing paucicellular lamina propria with no plasma cells. No active inflammation or granulomata

Maffucci et al <sup>ES</sup>	Patient 3	Nd	Nd	Nd	Nd	Nd	Nd	Microscopic colitis	Nd
Forbes et al <sup>E17</sup>	Patient 12	Nd	Nd	Nd	Nd	Nd	Nd		Nd
Forbes et al <sup>E17</sup>	Patient 13	Nd	Nd	Nd	Nd	Nd	Nd		Nd
Forbes et al <sup>E17</sup>	Patient 14	Nd	Nd	Nd	Nd	Nd	Nd		Nd
Forbes et al <sup>E17</sup>	Patient 17	Nd	Nd	Nd	Nd	Nd	Nd		Nd

EGD, Esophagogastroduodenoscopy; HLA, human leukocyte antigen; Nd, not determined; Ms, nonspecified; TTG, tissue transglutaminase.

**TABLE E6.** Lung disease

Lung disease	22/42 (52%)
Interstitial lung disease	15/42 (36%)
LIP	7/15
DIP	2/15
COOP	1/15
IPF	1/15
Inflammatory lung disease	1/15
Granulomatous lung disease	2/15
Unspecified	1/15
Infection	11/42 (26%)
Viral	2/11
Nontuberculous mycobacteria	1/11
Recurrent LRTI	8/11
Bronchiectasis	2/11
Asthma-like symptoms	4/42 (9%)
Chest CT specified	6/22
Histology specified	3/22

COOP, Cryptogenic organizing pneumonia; CT, computed tomography; DIP, desquamative interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LIP, lymphoid interstitial pneumonia; LRTI, lower respiratory tract infection.

**TABLE E7.** Endocrinopathies

Endocrinopathies	21/42 (50%)
Type 1 diabetes	10/42 (24%)
Anti-GAD antibodies	4/10
Anti-IAA antibodies	2/10
Anti-IA2 antibodies	2/10
Anti-ICA antibodies	1/10
Negative antibodies	1/10
nd	5/10
Hypothyroidism	13/42 (31%)
Unspecified thyroid antibodies	3/13
Anti-TPO	2/13
Nd	8/13
Presumed hypophysitis	1/42 (2%)
GH insensitivity	1/42 (2%)
Central corticotropin deficit	1/42 (2%)

GAD, Glutamic acid decarboxylase; IA2, insulinoma-associated antigen-2; IAA, insulin autoantibodies; ICA, islet cell autoantibodies; Nd, not determined; TPO, thyroperoxidase.

**TABLE E8.** Other autoimmune diseases

Cutaneous disease	16/42 (38%)
Atopic dermatitis	12/16
Alopecia	4/16
Other dermatitis	2/16
Scleroderma	1/16
Arthritis	9/42 (22%)
Polyarthritis or severe	4/9
Oligoarthritis	1/9
Unspecified	4/9
Ocular disease	5/42 (14%)
Keratoconjunctivitis	3/5
Posterior uveitis with cystic macular edema	1/5
Uveitis	1/5
Pigmentary retinitis	1/5

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## **SERMENT D'HIPPOCRATE**

« Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. »