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

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1 **Clinical aspects of STAT3 gain-of-function germline mutations: A Systematic Review**

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45 **Abstract**

46

47 **Background:** *STAT3* gain-of-function (GOF) germline mutations have been recently  
48 described. A comprehensive overview of this early-onset multiorgan autoimmune and  
49 lymphoproliferative disease has not yet been compiled.

50

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

53

54 **Methods:** A systematic review including articles published before 10/10/2018 in Pubmed,  
55 WoS and CENTRAL databases was performed. We described cases of patients with *STAT3*  
56 GOF germline mutations with genetic analysis and a concordant phenotype if functional  
57 analyses were not performed for the mutation.

58

59 **Results:** The search identified 18 publications describing 42 unique patients. Twenty-eight  
60 different mutations were described. Onset of disease was very early with an average age of 3  
61 (0.5-5) years old. The most frequent manifestations were: autoimmune cytopenias (28/42),  
62 lymphoproliferation (27/42), enteropathy (24/42), interstitial lung disease (15/42), thyroiditis  
63 (13/42), diabetes (10/42), and post-natal growth failure (15/21). Immunodeficiency was not  
64 always a predominant feature. Most patients required significant immunosuppressive therapy.  
65 Five patients received hematopoietic stem cell transplantation, 4 died from complications.  
66 Improvement of symptoms was observed for 8 out of 9 patients that received targeted  
67 biotherapies.

68

69 **Conclusions:** STAT3 GOF syndrome is a new clinical entity to consider when confronted  
70 with a patient with early-onset poly-autoimmunity, lymphoproliferation, and growth failure.  
71 At this time, precise therapeutic guidelines are lacking, but use of anti-IL-6 receptor and JAK  
72 inhibitor biologics are attractive possibilities.  
73

74 **Highlights box.**

75

76

77 **What is already known about this topic?**

78 *STAT3* gain-of-function (GOF) germline mutations have been recently described. A

79 comprehensive overview of this early-onset multiorgan autoimmune and lymphoproliferative

80 disease has not yet been compiled.

81

82 **What does this article add to our knowledge?**

83 We identified 42 unique patients. Typical disease was early-onset with very early endocrine

84 autoimmunity, then pseudo-celiac enteropathy, followed by lymphoproliferation, autoimmune

85 cytopenias and interstitial lung disease in the context of severe growth failure.

86

87 **How does this study impact current management guidelines ?**

88 *STAT3* GOF syndrome is a new entity to consider when confronted with a patient with early

89 onset poly-autoimmunity, lymphoproliferation and/or short stature. There is emerging

90 evidence for the use of targeted biotherapies in this disorder.

91

92

93

94

95 **Key words:** autoimmunity; lymphoproliferative disease; GOF; Evans syndrome; interstitial

96 lung disease; celiac disease; short stature; early onset diabetes; child

97

98 **Abbreviations:**

- 99 STAT: signal transducer and activator of transcription
- 100 GOF: gain-of-function
- 101 GnomAD: Genome Aggregation Database
- 102 IL: interleukin
- 103 JAK: Janus kinase
- 104 LGL: large granular lymphocytic
- 105 SH2: Src homology 2
- 106 ExAC: Exome Aggregation Consortium
- 107 SOCS: suppressor of cytokine signaling
- 108 EBV: Epstein-Barr virus
- 109 ITP: immune thrombocytopenic purpura
- 110 AIHA: autoimmune hemolytic anemia
- 111 NK: natural killer
- 112 Ig: immunoglobulin
- 113 HLA: human leukocyte antigen
- 114 ILD: interstitial lung disease
- 115 IPF: idiopathic pulmonary fibrosis
- 116 DIP: desquamative interstitial pneumonitis
- 117 LIP: lymphocytic interstitial pneumonitis
- 118 DLCO: diffusing capacity of the lungs for carbon monoxide
- 119 LRTI: lower respiratory tract infections
- 120 TPO: thyroperoxidase
- 121 MRI: magnetic resonance imaging
- 122 GH: growth hormone
- 123 SD: standard deviation

- 124 IGF1: insulin-like growth factor -1
- 125 GVH: graft versus host
- 126 ALPS: autoimmune lymphoproliferative syndrome
- 127 FAS: first apoptosis signal
- 128 IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked
- 129 FOXP3: forkhead box P3
- 130 APDS: activated phosphoinositide 3-kinase delta syndrome
- 131 CHAI: CTLA-4 haploinsufficiency with autoimmune infiltration
- 132 LATAIE: LRBA deficiency with autoantibodies, Treg defects, autoimmune  
133 infiltration and enteropathy
- 134 IBD: inflammatory bowel disease
- 135 COOP: cryptogenic organizing pneumonia
- 136

## 137 **Introduction**

138 The transcription factor signal transducer and activator of transcription 3 (STAT3), one of 7  
139 members of the STAT family of transcription factors, is a critical regulator of multiple  
140 processes, including cellular proliferation, survival, differentiation, and regulation of  
141 autoimmunity and inflammation<sup>1</sup>. Therefore, STAT3 mutations (gain-of-function (GOF) or  
142 dominant negative) can result in immunodeficiency, autoimmunity or malignancy. *STAT3*  
143 dominant negative germline mutations are well known, and lead to a primary immune  
144 deficiency syndrome (known as Buckley or Job Syndrome, or autosomal dominant hyper IgE  
145 syndrome OMIM: 147060)<sup>2</sup>. *STAT3* GOF somatic mutations have been reported in  
146 malignancies such as LGL leukemia and hepatocellular adenoma<sup>3</sup>. *STAT3* GOF germline  
147 mutations were discovered recently and lead to early-onset multiorgan dysfunction (OMIM:  
148 615952), including autoimmune disorders, lymphoproliferation, susceptibility to infection and  
149 severe growth failure<sup>1,3-5</sup>.

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

161

## 162 **Methods**

### 163 **Patients**

164 This systematic review was conducted in accordance with the Preferred Reporting Items for  
165 Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic search was  
166 conducted (10/10/2018) to identify studies reporting cases of patients with STAT3 GOF  
167 germline mutations. The literature search and evaluation were performed in 3 databases,  
168 MEDLINE (Pubmed), Web of Science (WoS) and CENTRAL (Cochrane Central Register of  
169 Controlled Trials), for articles published since 01/01/2014 (the first report of STAT3 GOF  
170 germline mutation is Flannagan *et al.*, 2014). The following research keywords in English  
171 were used: (STAT3 AND "gain of function" or "signal transducer and activator of  
172 transcription 3" and "gain of function"), (STAT3 AND "Activating germline mutations" or  
173 "signal transducer and activator of transcription 3" and "Activating germline mutations") and  
174 (STAT3 AND "activating mutation" or "signal transducer and activator of transcription 3"  
175 and "activating mutation"). Another search was manually performed in Google scholar using  
176 the function cited by for Flannagan *et al.*, 2014, Haapaniemi *et al.*, 2015 and Milner *et al.*,  
177 2015. Abstracts and full-length text were screened for all suitable articles. We excluded  
178 duplicate articles or congress abstracts. To be eligible for inclusion, studies and case reports  
179 were required to describe cases of patients with *STAT3* GOF germline mutations with genetic  
180 analysis and a concordant phenotype if functional analyses were not performed for the  
181 mutation. All types of publications, such as articles, reviews, editorials, letters, and  
182 correspondence, reported in English or in French, published online between January 1, 2014  
183 and October 10, 2018 were included.

184

### 185 **Genetic evaluation**

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

189

### 190 **Statistical analysis**

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

194

### 195 **Results**

196 The search identified 18 publications describing 42 unique patients. The list of included  
197 articles is presented in **Table E1**, sorted by date of publication. **Figure 1** summarizes the  
198 PRISMA diagram.

199

### 200 **Genetics and functional analysis**

201 At this time, 28 different mutations from 42 cases have been described, located mostly in the  
202 DNA binding domain (**Figure 2 and Table E2**). All patients were heterozygous for the  
203 mutation, 21 were *de novo* mutations and 7 were inherited in an autosomal dominant manner  
204 within 5 different families. Six unaffected members were described within 4 out of these 5  
205 families. Penetrance is thus incomplete. Analysis of described STAT3 variants in the  
206 gnomAD database showed only one mutation as already reported (p.R246Q with a frequency  
207 of 1/246408 alleles), all the others are not reported. All mutations reported but one (an in  
208 frame amino acid deletion) are missense. All variants were predicted pathogenic or probably  
209 pathogenic by UMD-predictor and disease causing by Mutation Taster. According to ExAC  
210 data, *STAT3* is a constrained gene with a pLI (a indicator of intolerance to loss of function) of

211 1 (the least tolerant),<sup>8</sup> and indeed all the mutations reported are very rare. These features  
212 support autosomal dominant inheritance<sup>9</sup>.

213         Functional studies were reported for all mutations except 4<sup>10,11</sup>, and confirmed gain of  
214 function of STAT3 (**Table E2**). The functional tests developed were (i) an *in vitro* STAT3  
215 reporter luciferase assay under basal or stimulated conditions (IL-6/growth hormone) in A4,  
216 HEK293 or INS-1E cells, and (ii) SOCS3 expression levels under basal or stimulated (IL-21)  
217 conditions in EBV-transformed patient cell-lines or primary cells. Of note, under basal  
218 conditions, luciferase reporter assay was normal for two patients (but abnormal in stimulated  
219 conditions) and under stimulated conditions the assay was normal for two other patients (but  
220 abnormal in basal conditions). GOF mutations resulted in at least ten-fold increase of  
221 luciferase reporter assays for seven patients. The absence of obvious genotype-phenotype  
222 correlations and the fact that STAT3 hyperactivity does not appear to correlate with the  
223 severity of the phenotype suggest that environmental and other genetics factors may  
224 contribute to this syndrome.<sup>12</sup>

225

### 226         **Clinical aspects**

227 Clinical expression phenotypes of STAT3 GOF syndrome are very diverse. Among the 42  
228 cases (sex ratio (M/F) = 18/22 = 0.82)<sup>1,4,6,7,13-18,10,19-22,11,23-25</sup>, the most frequent features were  
229 hematologic disease, failure to thrive/short stature and multi-organ autoimmune disorders.  
230 Onset of disease was very early with an average age of onset of 3 (0.5-5) years old (**Figure 3**),  
231 including 17 cases occurring before one year. Eight patients died, at a median age of 12.5  
232 years (5.5-18.25), including 4 from complications of stem cell transplantation.

233         The following description is based on the 42 reported cases.

234

235

236 *Hematologic manifestations*

237 Hematologic disease was the most frequent finding (35/42), especially autoimmune  
 238 cytopenias (28/42), including immune thrombocytopenia (ITP)<sup>4,6,11,15-17,19,22,23</sup> (24/28),  
 239 autoimmune hemolytic anemia (AIHA)<sup>1,4,11,15-17,19,22,23</sup> (19/28) and neutropenia<sup>4,16,17</sup> (9/28)  
 240 (**Table E3**). AIHA and ITP were observed concurrently in 15 cases<sup>4,7,11,15-17,19,22,23</sup>. There was  
 241 an autoimmune pancytopenia in 4 cases<sup>4</sup>. Age of onset was specified in 8 cases; median age  
 242 of onset was 3.5 years old (**Figure 3**).

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

254 Lymphoproliferation (27/42) was described mainly with adenopathy<sup>1,4,7,11,15-17,19,20</sup>  
 255 (23/27) and hepatosplenomegaly<sup>1,4,7,14-17,19,20,23</sup> (23/27), which was concomitant in 19 cases.  
 256 There was mediastinal adenopathy in 3 cases. Age of onset of lymphoproliferation was  
 257 specified in 8 cases, the median age was 2.5 (1.9-3.5) years old for adenopathy and 3 (1.9-8)  
 258 years old for hepatosplenomegaly (**Figure 3**). Hemophagocytic lymphohistiocytosis was  
 259 described in 1 case<sup>7</sup>. Malignancy was described in 2 cases. One adult patient had Hodgkin  
 260 lymphoma<sup>4</sup> and 1 patient developed LGL leukemia<sup>1</sup> at the age of 14. IgA level was reported

261 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  
 262 invariantly associated with enteropathy.

263

264 *Gastrointestinal manifestations*

265 Hepatic and digestive diseases were described in 26 cases (**Table E4**). Enteropathy was found  
 266 in 24/42 patients (**Table E5**). Average age of onset, reported for 11 patients, was 1 (0.5-1.02)  
 267 year, and most (9/11) before the second year (**Figure 3**). The clinical signs were diarrhea (17  
 268 patients), abdominal pain (4) and vomiting (2), associated with growth failure in 12 cases.  
 269 The disease was initially classified as celiac disease in 9 cases. Response to gluten free diet  
 270 was reported for 7 patients: 1 patient responded<sup>1</sup>, 1 patient responded partially<sup>1</sup>, 1 patient  
 271 responded in combination with azathioprine and tacrolimus<sup>10</sup>, and there was no response for 4  
 272 patients<sup>1,14,20,24</sup>. For the 5 patients with reported HLA, 3 were DQ2 or DQ8 positive. Both  
 273 DQ2 positive patients were responsive to a gluten free diet. Of the 11/42 patients for which  
 274 celiac antibodies (anti-gliadin (G), anti-tissue transglutaminase (TTG) or anti-endomysium  
 275 (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  
 276 celiac antibodies had no clinical signs of enteropathy. Among the 9 patients with positive  
 277 celiac antibodies, 7 had positive anti-G (5 isolated anti-G, 1 anti-G/E, 1 anti-G/TTG) and 1  
 278 had isolated anti-TTG. Antibody specificity was not reported for the last patient.

279

280 Gastrointestinal biopsy results were reported in multiple STAT3 GOF patients.  
 281 Pathology of the esophagus showed normal<sup>18</sup> or mild changes, such as basal cell  
 282 hyperplasia<sup>4,21</sup>. Pathology of the stomach showed moderate gastritis in 9 patients<sup>1,4,14,18,20,21,24</sup>,  
 283 with lymphocytic infiltration noted in 4. In 14 patients<sup>1,4,6,10,14,18,20-22,24</sup>, abnormalities of the  
 284 duodenum were reported. This was predominantly villous atrophy (11 patients<sup>1,4,10,14,18,20</sup>) as  
 285 well as inflammation (12 patients<sup>1,4,6,10,14,18,20,21,24</sup>) with intraepithelial lymphocyte infiltration

286 in 9 patients<sup>1,6,10,14,18,20,21,24</sup>. For 5 patients with sequential biopsies, 2 had a normalization of  
287 the biopsy<sup>1,18</sup>, 1 patient's was initially normal followed by a second abnormal one<sup>1</sup>, and 2 no  
288 improvement<sup>20,24</sup>. Colonic biopsies were normal in only 1 case<sup>14</sup> and showed colitis in 5  
289 cases<sup>4,6,11,18</sup>.

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

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

300

### 301 *Pulmonary manifestations*

302 Twenty-two patients developed lung disease with a predominance of interstitial lung disease  
303 and recurrent lower respiratory tract infection (**Table E6**). 15/42 patients developed  
304 interstitial lung disease<sup>1,4,7,10,11,15,20,21,24</sup>. The median age of onset, specified in 7 cases, was 16  
305 (9-18) years old and was substantially delayed in regards to hematologic, endocrine and  
306 gastrointestinal features (**Figure 3**). Among these 15 patients, 7 had lymphocytic interstitial  
307 pneumonitis (LIP)<sup>4,7,15,20,21</sup>, 2 granulomatous lung disease<sup>11,21</sup>, 2 desquamative interstitial  
308 pneumonitis (DIP)<sup>1,24</sup>, 1 idiopathic pulmonary fibrosis (IPF)<sup>4</sup> and 1 cryptogenic organizing  
309 pneumonia (COOP)<sup>1</sup>. With regard to the clinical presentation, asthma-like symptoms in early  
310 infancy were described in 3 patients who presented later with ILD. A lung biopsy was

311 performed in 3 cases<sup>1,4,15</sup>. The first case showed diffuse interstitial fibrosis (IPF)<sup>4</sup>. The second  
312 displayed a diffuse interstitial fibrosis that was associated with alveolar thickening and  
313 macrophages (DIP)<sup>1</sup>. The third case displayed atypical interstitial lymphoblastic infiltrate  
314 (LIP)<sup>15</sup>.

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

324 11/42 patients had recurrent lower respiratory tract infections<sup>1,4,6,14,16,19,21,22,24</sup> (LRTI).  
325 There was 1 case of *Mycobacterium avium* lung infection<sup>6</sup>. Among patients with LRTIs, 6 had  
326 hypogammaglobulinemia, 4 T-cell lymphopenia, 4 decreased NK-cells and 1 pan-  
327 lymphopenia. Seven of these patients were treated with immunosuppressive treatment and the  
328 chronology of lung infection with regard to treatment onset was not detailed.

329

### 330 *Endocrinopathies*

331 Endocrine diseases were also a frequent feature, reported in 21/42 patients (**Table E7**). Type I  
332 diabetes was the earliest endocrine manifestation in STAT3 GOF syndrome (10/42)<sup>1,4,11,16-18</sup>.  
333 It appeared before 1 month of life in 3 cases and between 1 month and 12 months in 3 cases.  
334 The median age of onset of type I diabetes was 8 weeks (2.3-35.5) (**Figure 3**). HLA  
335 genotyping was high risk in 3 cases<sup>1,16</sup> and low risk in 2 cases.

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

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

342

#### 343 *Growth failure*

344 Weight and/or height at birth were recorded in 14 cases, intrauterine growth restriction  
 345 (weight and/or height at birth < -2SD) was present in 5 cases (35%)<sup>1,16,20,21</sup> (**Figure 4**). Post-  
 346 natal growth failure (height and/or weight < -2SD) was presented in 15 cases among 21 where  
 347 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>.  
 348 Growth failure was associated with intrauterine growth restriction in 3 cases. IGF1 was low in  
 349 7 of 10 patients tested, however, 5 also had enteropathy which could have affected nutritional  
 350 status and so the IGF1 level. GH stimulation was performed in 4 cases<sup>1,4,16</sup>, there was a  
 351 positive response in 3 cases<sup>1,4,16</sup>. 7 patients benefited from GH treatment, it was effective in  
 352 3<sup>4,21</sup> and showed a partial response in 4<sup>1,20,21,24</sup>.

353

#### 354 *Other features*

355 Dysmorphic features are not a predominant feature of STAT3 GOF syndrome (2/37).  
 356 Cutaneous disease (16/42) was mainly atopic dermatitis (12/16)<sup>1,4,6,7,10,11,20,21</sup> and alopecia  
 357 (4/16)<sup>4,10,14</sup> (**Table E8**). The age of onset of cutaneous disease was reported in 4 cases all  
 358 under the age of 2 years.

359 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  
 360 severe arthritis<sup>11</sup> and 1 case of oligoarthritis<sup>20</sup>. In 1 case, polyarthritis regressed with systemic

361 treatment with tocilizumab<sup>4</sup>. The age of onset was specified in 4 cases, with a median of 11  
362 (9-13.25) years of age.

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

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

373 Ocular affects were reported in 5/42 patients<sup>1,19,20,22</sup>, including 2 patients with uveitis  
374 and keratoconjunctivitis sicca in 2 cases. Neurological disease was not predominant, with 1  
375 case of ocular myasthenia gravis<sup>4</sup>, 1 case of cerebral atrophy that led to abnormal  
376 psychomotor development<sup>4</sup>, and 1 patient with cerebral palsy<sup>4</sup>. Three patients<sup>1,4</sup> developed  
377 thrombosis (1 internal carotid and 2 vena cava), but additional details were not provided.  
378 Finally 1 patient developed disseminated intra-vascular coagulation<sup>7</sup>.

379

### 380 **Clinical Progression**

381 STAT3 GOF syndrome encompasses many target organ diseases with a sequential median  
382 age of onset (**Figure 3 and Figure 5**). Endocrine and gastrointestinal disease is very early-  
383 onset and appears clearly before the onset of hematologic disease. Poly-autoimmunity with  $\geq$   
384 2 autoimmune diseases was frequent (29/42);  $\geq 3$  autoimmune diseases was reported in 16/42  
385 patients. Single organ autoimmune disease was reported in 10 patients and 3 patients had no

386 obvious autoimmunity. Although hematologic disease was also predominant, it was not  
387 invariant as 7 patients did not have any hematologic disease (**Figure 6**). Finally, 4 patients  
388 had neither poly-autoimmunity nor hematologic disease.

389

### 390 **Therapeutic options**

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

393 Non targeted immunosuppressive therapies were overall ineffective.

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

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

407

### 408 **Discussion**

409 In recent years, multiple monogenic causes of early-onset autoimmunity and  
410 lymphoproliferation have been identified, now including STAT3 GOF syndrome<sup>3,4,7,26-32</sup>.

411 These disorders have overlapping clinical and immunologic features (**Table 2**). In addition to  
412 these early-onset, monogenic autoimmune syndromes, the differential diagnoses for the  
413 symptoms of STAT3 GOF syndrome are plentiful due to multiple features within each organ  
414 system. Therefore, several differential diagnoses can be considered. Our systematic review  
415 summarizes current knowledge about specific characteristics of the disease. Average onset of  
416 organ systems appears to occur sequentially (**Figure 3**), with early-onset diabetes and  
417 enteropathy preceding hematologic manifestations and lung disease.

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

423 Early-onset endocrinopathies including neonatal diabetes and early onset thyroiditis  
424 were among the first symptoms occurring during infancy. Polyautoimmunity (encountered in  
425 29/42 patients) included arthritis, autoimmune hepatitis, alopecia areata and autoimmune  
426 cytopenias notably later in life. Intra-uterine growth retardation was encountered in 1/3 of  
427 patients and post-growth failure in 3/4, with 5 patients < -4SD. Growth failure is a  
428 predominant feature of STAT3 GOF syndrome. This could be the consequence of digestive  
429 disease (malabsorption), diabetes, hypothyroidism, respiratory insufficiency, frequent  
430 infections or corticosteroid treatment. However, it could also be inherent to the *STAT3* GOF  
431 mutations. Indeed, *STAT5b*, is the major transcription factor downstream of GH  
432 signaling<sup>31,33</sup>, and *STAT3* activation can inhibit *STAT5* phosphorylation<sup>16</sup>.

433 *STAT3* GOF appears as a new etiology of ILD, mainly LIP as well as other forms of  
434 ILD such as COOP or DIP. Pathology showed fibrosis in 2 patients. LIP results from  
435 pulmonary interstitial accumulation of lymphocytes. Several

436 publications have suggested that STAT3 plays a role in regulating  
437 fibroblast function in fibrotic lung diseases and that aberrant STAT3  
438 signaling plays a critical role in usual interstitial pneumonia and idiopathic pulmonary  
439 fibrosis pathogenesis<sup>34</sup>.

440 Hematologic disease was frequent, onset after infancy and included lymphoproliferation,  
441 immunodeficiency with infection susceptibility (mainly recurrent LRTI and rare opportunistic  
442 infections), and autoimmune cytopenias. Despite the well-known association of somatic  
443 STAT3 GOF mutations with malignancy, cancer was only reported in 2 patients. Given the  
444 young average age of STAT3 GOF patients, long term followup will be critical to fully  
445 understand the risk of malignancy in STAT3 GOF syndrome.

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

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

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

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

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

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

484

**485 Conclusion**

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

494

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599

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602

603 **Figure legends**

604

605

606

607 **Figure 1. PRISMA flow diagram.**

608

609 **Fig. 2 Schematic of the STAT3 protein showing the location of mutations reported to**  
610 **cause STAT3 GOF.**

611 STAT3 is divided into 6 domains: the N-terminal domain, coiled-coil domain, DNA binding  
612 domain, linker domain, Src-homology 2 (SH2) domain and transactivation domain (TA).  
613 Mutations shown represent mainly missense mutations and the resulting amino acid changes,  
614 but there is also one deletion. Mutations replicated in several patients are indicated in red by  
615 the number of patients reported and using bold lines.

616

617 **Figure 3. Age at onset.**

618 Age at onset of the disease and at onset of different clinical manifestations.

619

620 **Figure 4. Weight and height z-scores at birth and last visit.**

621 Weight and height z-scores at birth and last visit.

622

623 **Figure 5. Kaplan-Meier survival curves.**

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

629

630 **Figure 6. Venn diagram of clinical manifestations.**

631 Venn diagram of endocrine, gut, hematologic, articular and pulmonary clinical  
632 manifestations.

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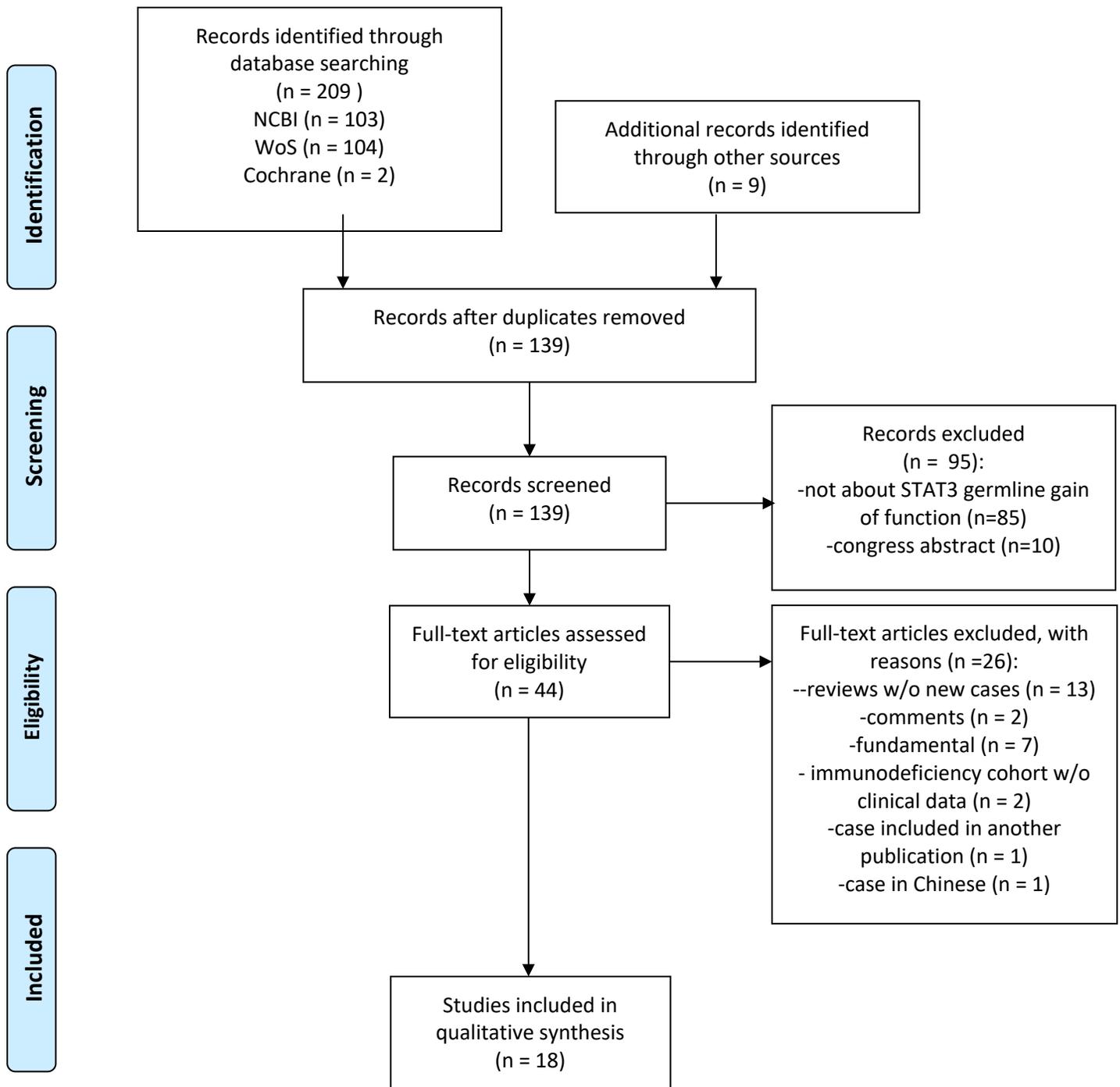
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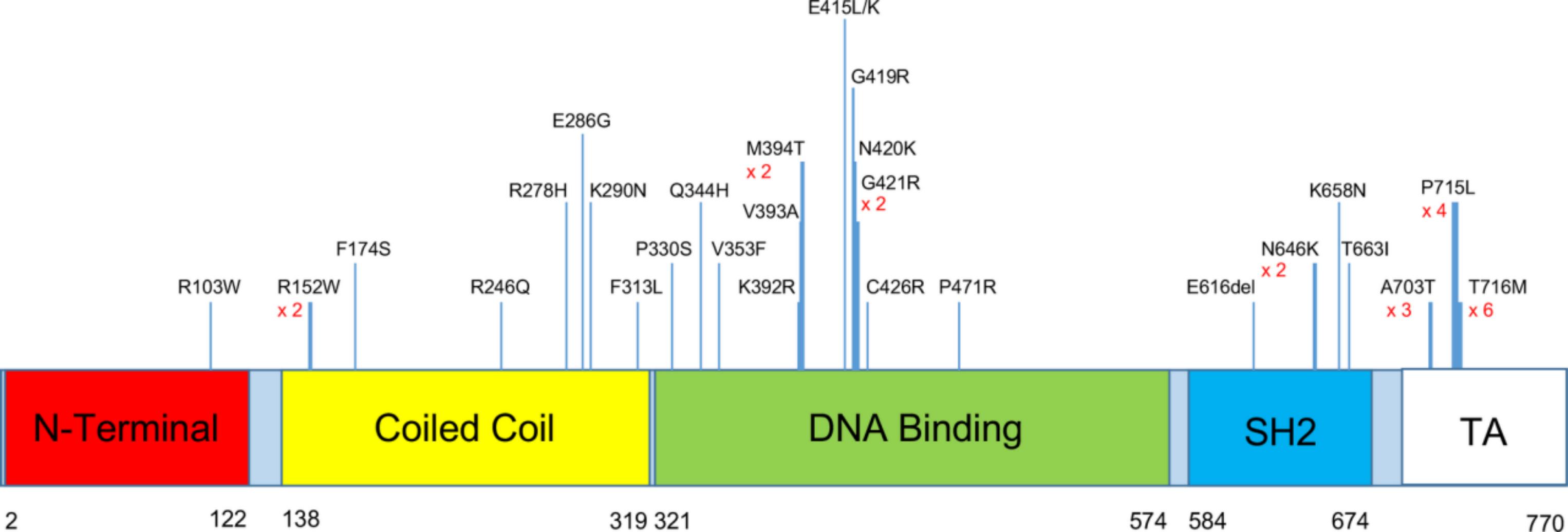
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**Figure 1. PRISMA Flow diagram**

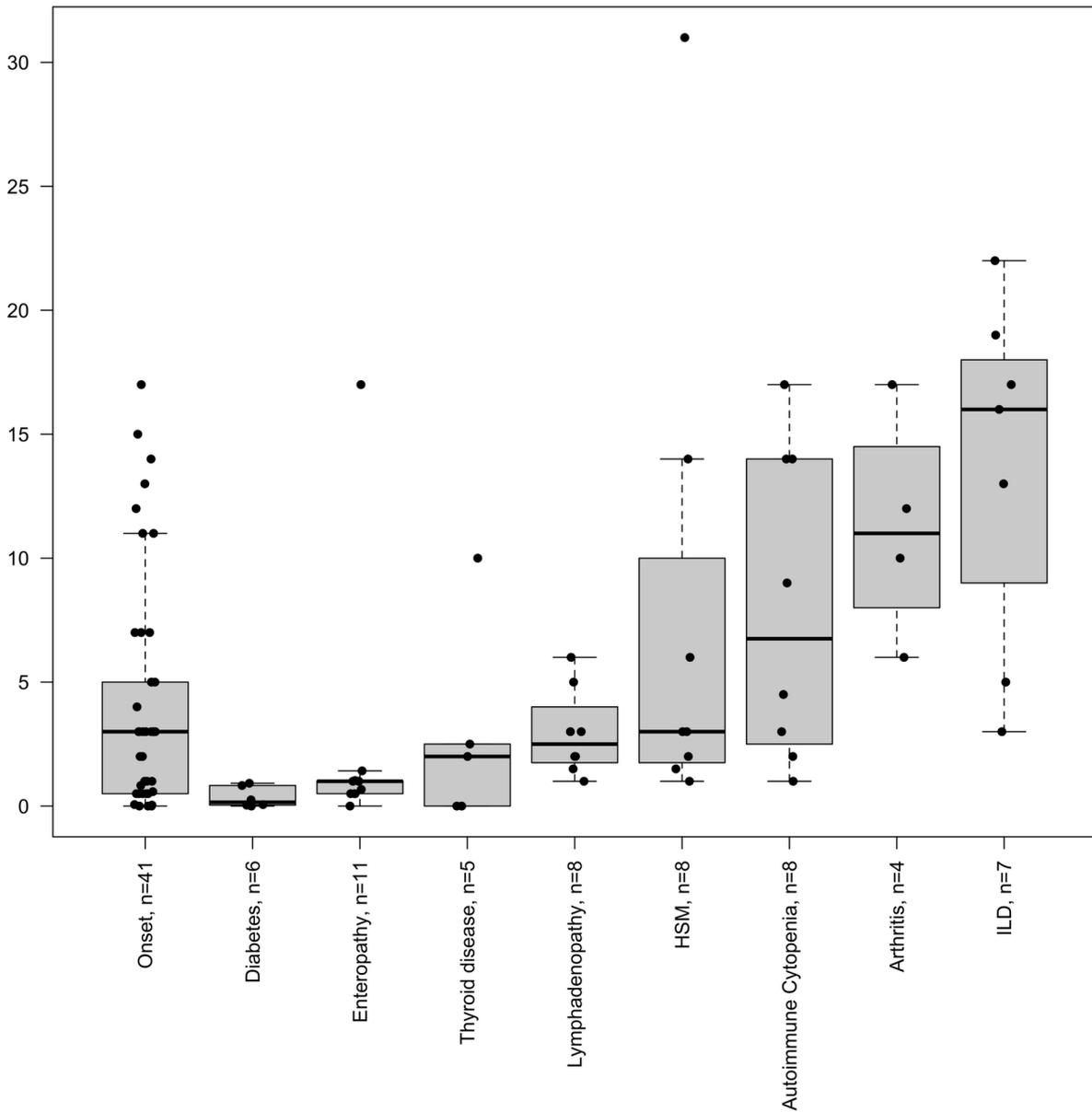


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

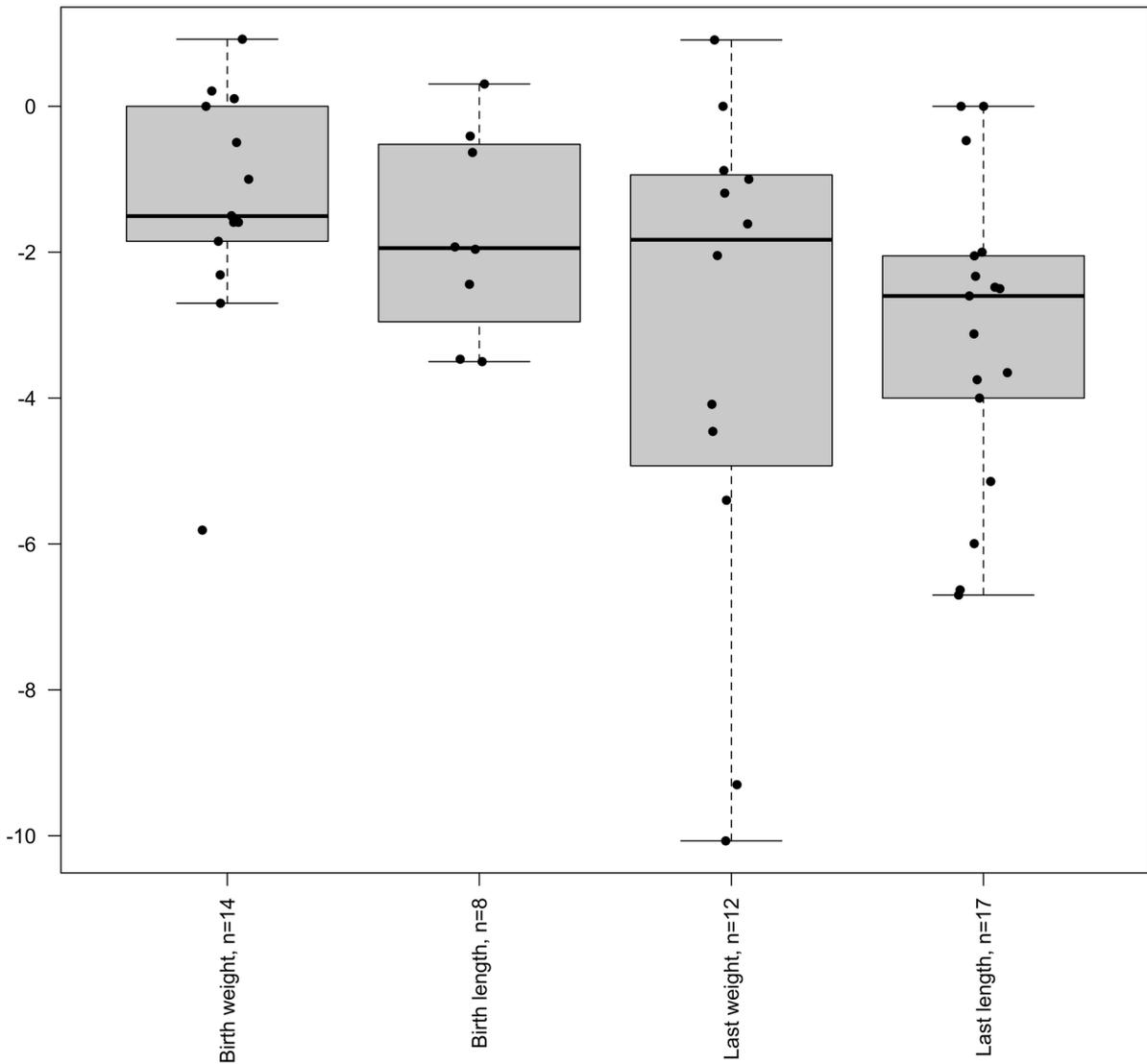
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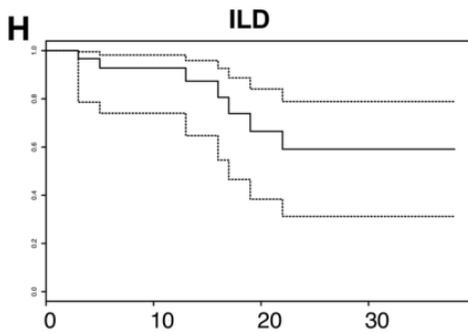
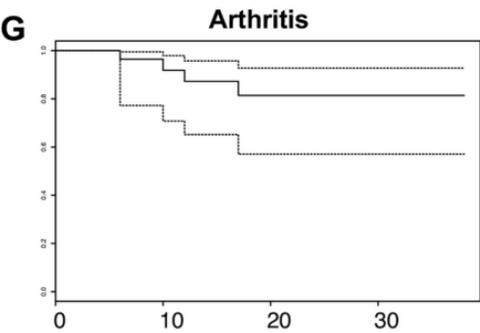
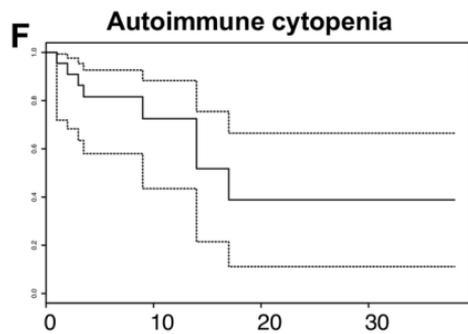
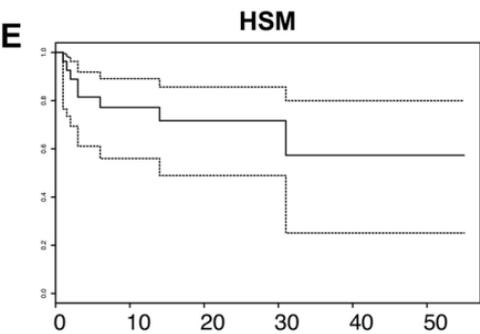
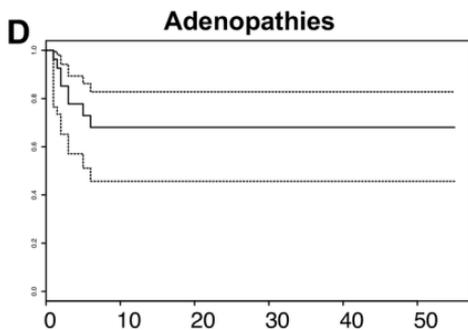
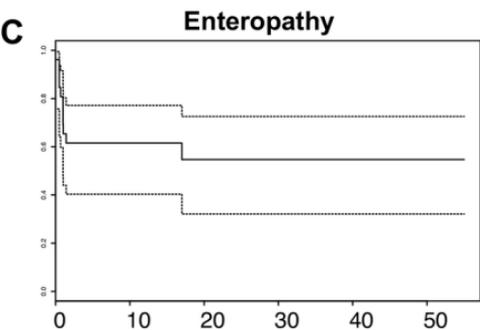
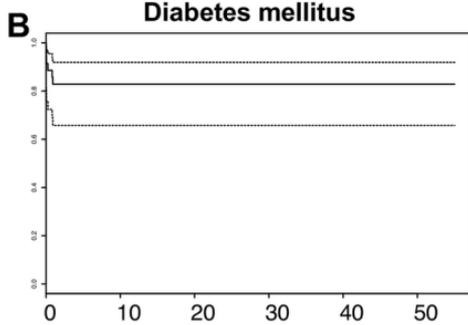
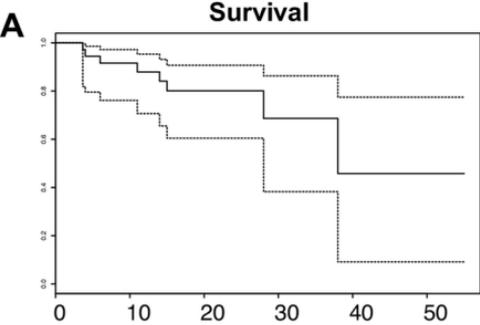


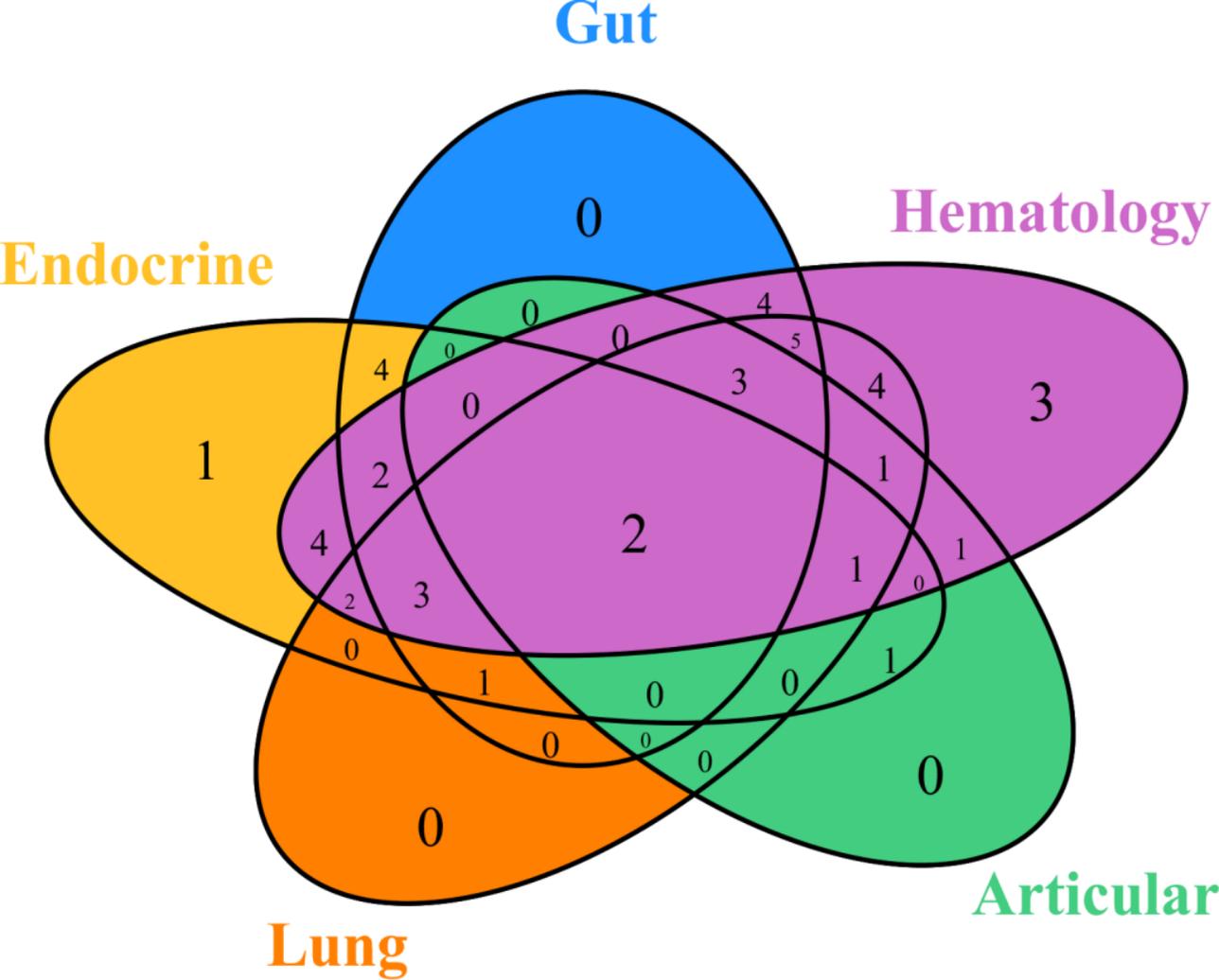
Age (years)



Z-score







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

<b>Treatments</b>	<b>Total</b>	<b>Positive effect</b>	<b>Negative effect / no effect</b>	<b>Not determined</b>
<b>Non targeted 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>	-
<b>HSCT</b>	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>	-

**Table 2. Clinical features of single-gene defects with immune dysregulation**<sup>3,4,7,26-32</sup>

	STAT3 GOF	STAT3 DN (AD-HIES)	STAT1 GOF	STAT5b deficiency	APDS	ALPS	IPEX	LATAIE	CHAI
Gene	STAT3	STAT3	STAT1	STAT5b	PIK3CD	TNFRSF6	FOXP3	LRBA	CTLA-4
Transmission	AD	AD	AD	AR	AD	70% AD (some somatic mutations)	X-linked	AR	AD
Onset of Symptoms	Childhood	Early infancy	Childhood	Childhood	1-3 years	1-3 years	Early infancy	Childhood	Childhood
Lymphoproliferation	SM, HM	-	SM, HM	-	LAD, SM, ENT lymphoid hyperplasia	80% chronic lymphoproliferation (>6 months): LAD, SM, HM	-	LAD, SM, HM	LAD, SM
Autoimmune disorder (immune dysregulation)	AIHA, ITP Early-onset pseudo-coeliac enteropathy, Interstitial lung disease, Early-onset diabetes and thyroiditis, Arthritis, Alopecia	-	Thyroiditis, Alopecia, Psoriasis, Scleroderma, Lupus, Pseudo-coeliac enteropathy, Colitis, Autoimmune hepatitis, Autoimmune cytopenia	Interstitial lung disease, ITP, Thyroiditis, Arthritis	30% Cytopenias, Insulin-dependent diabetes, Arthritis	70% Cytopenias: AIHA, ITP or neutropenia, Rare other autoimmune manifestations: nephritis, hepatitis, biliary cirrhosis, colitis, arthritis, vasculitis	Early-onset enteritis with villous atrophy & lymphocytic infiltrates, Endocrinopathy: diabetes (sometimes neonatal) & thyroiditis, Hemolytic anemia	Enteropathy, AIHA, ITP, Interstitial lung disease, Diabetes, Hepatitis, Psoriasis	>50% Enteropathy >50% Interstitial lung disease, AIHA, ITP
Other	Herpesvirus infections, Fungal infections, Bacterial infections,	Dermatitis, Neonatal rash, Skin abscesses,	Fungal infections (especially chronic mucocutaneous	Growth failure, Dysmorphic features, Eczema,	Upper & lower respiratory infections,	Rare recurrent infections	Early-onset failure to thrive, Neonatal	Upper & lower respiratory infections, Bronchiectasis,	Upper & lower respiratory infections

	Respiratory infections,  Short stature	Pneumonias, Bronchiectasis, Pneumatocele, Fungal infections, Bacterial infections, Herpes virus infections, Dysmorphic features, Vascular abnormalities	candidiasis), Severe viral infections, Bacterial infections, Mycobacterial infections, Bronchiectasis, Asthma, Eczema, Dysphagia, Failure to thrive	Severe herpesvirus infections, Recurrent infections	Pneumonia, Bronchiectasis, Chronic rhinosinusitis, Severe or recurrent herpesvirus infections		erythema, Eczema, Psoriasiform dermatitis, Alopecia	Viral infections, Fungal infections, Bacterial infections	
Increased risk of malignancy	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Laboratory parameters	Hypogammaglobulinemia,  Reduced switched memory B-cells & Tregs	Elevated IgE, Eosinophilia, Decreased Th17 cells, B and T memory lymphopenia	Reduced switched memory B cells, Decreased Th17 cells, Low IgG2 and IgG4,	Treg deficiency and dysfunction, Reduced T cells and NK cells, Hypergammaglobulinemia	Decreased IgA/IgG +/- increased IgM, Naive CD4 T-cell & Memory B-cell lymphopenia with elevated transitional B- cells	Direct Coombs positive, Hypergammaglobulinemia, Elevated DNT cells, Elevated plasma sFASL, Elevated plasma IL-10, Elevated plasma vitamin B12	Elevated IgE, Eosinophilia, Anti-enterocyte antibodies	50% Hypogammaglobulinemia, Reduced Tregs, Reduced switched memory B-cells	Hypogammaglobulinemia

References	Milner, Blood 2015 <sup>4</sup>	Vogel, J Clin Immunol 2015 <sup>3</sup>	Forbes, JACI 2018 <sup>7</sup> ; Toubiana, 2016 <sup>32</sup> Blood 2016 <sup>32</sup>	Hwa, Growth Horm IGF Res 2016 <sup>31</sup>	Coulter, JACI 2016 <sup>28</sup>	Neven, Blood 2011 <sup>29</sup>	Barzagli, JACI 2018 <sup>30</sup>	Gamez-Diaz, JACI 2016 <sup>27</sup>	Schubert, Nat Med 2014 <sup>26</sup>
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Footnotes: ALPS: Autoimmune Lymphoproliferative Syndrome; LAD: lymphadenopathy; SM: splenomegaly; HM: hepatomegaly; AIHA: autoimmune hemolytic anemia; ITP: Immune thrombocytopenia; DNT: double-negative T-cells (CD3+TCR $\alpha\beta$ +CD4<sup>-</sup>CD8<sup>-</sup>); LATAIE: LRBA deficiency with autoantibodies, Treg defects, autoimmune infiltration, and enteropathy; CHAI: CTLA-4 haploinsufficiency with autoimmune infiltration ; AD-HIES : autosomal-dominant hyper-immunoglobulin E syndrome, GOF : gain-of-function ; DN : dominant negative, AD : autosomal dominant, AR : autosomal recessive.