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Autosomal Dominant STAT3 Deficiency and Hyper-IgE Syndrome Molecular, Cellular, and Clinical Features From a French National Survey

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Abstract

Autosomal dominant deficiency of signal transducer and activator of transcription 3 (STAT3) is the main genetic etiology of hyper-immunoglobulin (Ig) E syndrome. We documented the molecular, cellular, and clinical features of 60 patients with heterozygous STAT3 mutations from 47 kindreds followed in France. We identified 11 known and 13 new mutations of STAT3. Low levels of interleukin (IL)-6-dependent phosphorylation and nuclear translocation (or accumulation) of STAT3 were observed in Epstein-Barr virus-transformed B lymphocytes (EBV-B cells) from all STAT3-deficient patients tested. The immunologic phenotype was characterized by high serum IgE levels (96% of the patients), memory B-cell lymphopenia (94.5%), and hypereosinophilia (80%). A low proportion of IL-17A-producing circulating T cells was found in 14 of the 15 patients tested. Mucocutaneous infections were the most frequent, typically caused by *Staphylococcus aureus* (all patients) and *Candida albicans* (85%). Up to 90% of the patients had pneumonia, mostly caused by *Staph. aureus* (31%) or *Streptococcus pneumoniae* (30%). Recurrent pneumonia was associated with secondary bronchiectasis and pneumatocele (67%), as well as secondary aspergillosis (22%). Up to 92% of the patients had dermatitis and connective tissue abnormalities, with facial dysmorphism (95%), retention of deciduous teeth (65%), osteopenia (50%), and hyperextensibility (50%). Four patients developed non-Hodgkin lymphoma. The clinical outcome was favorable, with 56 patients, including 43 adults, still alive at the end of study (mean age, 21 yr; range, 1 mo to 46 yr). Only 4 patients died, 3 from severe bacterial infection (aged 1, 15, and 29 yr, respectively). Antibiotic prophylaxis (90% of patients), antifungal prophylaxis (50%), and IgG infusions (53%) improved patient health, as demonstrated by the large decrease in pneumonia recurrence. Overall, the prognosis of STAT3 deficiency may be considered good, provided that multiple prophylactic measures, including IgG infusions, are implemented.

Introduction

Hyper-immunoglobulin E syndrome (HIES) is a complex primary immunodeficiency first described, to our knowledge, by Davis et al [12] in 1966 as Job syndrome (OMIM #147060) in 2 patients. In 1972, Buckley et al [9] reported the same clinical association in 2 boys with very high plasma immunoglobulin (Ig) E levels, which they thus named HIES. Further studies allowed a more precise phenotypic description of the disease and led to the discovery of autosomal dominant (AD) inheritance in multiplex kindreds. [22] AD-HIES confers a selective immunodeficiency, with susceptibility to skin diseases and pneumonia caused by pyogenic bacteria, chronic mucocutaneous candidiasis, [5, 26, 38] and additional features, including facial dysmorphism, impaired shedding of deciduous teeth, bone abnormalities (osteopenia), craniosynostosis, and hyperextensibility. [6, 10, 18, 21, 22, 27, 39, 50, 64] Patients with AD-HIES often display high serum IgE levels and hypereosinophilia. [8, 22] The molecular basis of AD-HIES was identified in 2007. Heterozygous mutations in the signal transducer and activator of transcription 3 (STAT3) gene were identified, affecting

the DNA-binding domain, with a dominant negative effect. [47] Mutations affecting the DNA-binding domain and Src homology 2 (SH2) domains of STAT3 were described shortly thereafter. [28]

STAT3 is activated by various Janus kinases in response to the stimulation of the cell with various cytokines, hormones, and growth factors, and down-regulated by proteins of the suppressor of cytokine signaling (SOCS) family. [48] STAT3 is a major downstream transducer for the cytokine receptor gp130, which is involved in the signaling pathway involving the members of the IL-6 family (IL-6, -11, -27, -31), ciliary neurotropic factor, oncostatin M, leukemia inhibitory factor (LIF), and, to a lesser extent, IL-12R [beta]1 (IL-12 and IL-23). [45] STAT3 also mediates cellular responses to other families of cytokines, including the IL-2 family (IL-2, -7, -9, -15, -21), the interferon (IFN) family (IFN- [gamma], IFN- [alpha]/[beta]), the IL-10 family (IL-10, -19, -20, -22, -24, -26, IFN-lambdas), Flt3 ligand, M-CSF, G-CSF, leptin, and growth hormone. [40, 48, 51] This suggests that STAT3 plays a major role in a number of physiologic pathways, including immunologic pathways in particular. Further studies of patients heterozygous for loss-of-function STAT3 alleles (hereafter referred to as STAT3-deficient patients), some of which were shown to be dominant-negative, led to a more detailed description of the immunologic phenotype of this primary immunodeficiency, with the demonstration of a deficiency of IL-17A- and IL-22-producing T cells [13, 43, 44] and a lack of circulating memory B cells. [3, 4]

Since 2007, up to 230 STAT3-deficient patients have been reported in individual case reports [2–4, 13, 33, 35, 41, 43, 44, 55, 61, 68, 71] or national or international series, including 8 patients (Japan), [47] 37 (United States and Europe), [60] 12 (Lebanon and Europe), [29] 50 (international), [28] 64 (international), [70] and 48 patients (international). [62] However, most reports have focused on the molecular and cellular defects of the patients, providing little clinical information. The nature and severity of the infectious events, the impact of prophylaxis, age at diagnosis, and clinical outcome remain poorly characterized. We therefore undertook a detailed molecular, cellular, and clinical description of what is to our knowledge the largest national cohort reported to date, comprising 60 patients with STAT3 deficiency living in France.

Patients and Methods

Patients and Clinical Definitions

The patients consulted at various French hospitals and were identified through the Centre de Reference des Deficits Immunitaires Hereditaires (CEREDIH) at Necker Enfants Malades Hospital, Paris, France. A detailed questionnaire was completed by the physicians caring for the patients; clinical and laboratory data were collected for the patients from their birth until February 2011 or their death. Approval for this study was obtained from the institutional review board of Necker Hospital, and informed consent was obtained from all patients, or their families in the case of minors, in accordance with the Helsinki Declaration (Commission Nationale de L'informatique et des Libertés [lsqb] CNIL [rsqb] authorization: no. 908256, October 14, 2008).

We used the National Institutes of Health (NIH) scoring system: each feature was scored separately and all the scores were then added together to give a total point score (scores over 40 points indicate that the subject is likely to carry an AD-HIES phenotype, scores of 20–40 points are inconclusive concerning the presence of AD-HIES, and scores below 20 points indicate that the subject is unlikely to have AD-HIES). [9, 12, 19, 24, 53] The definition of Aspergillus species-related pulmonary invasive fungal disease was based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus definitions. [14] Invasive fungal disease was considered proven if the presence of

fungus was systematically demonstrated in diseased tissues; probable if a host factor, clinical features, and mycologic evidence were present; and possible if there were appropriate host factors and sufficient clinical evidence consistent with invasive fungal disease, but no mycologic confirmation. Bone mineral density was measured by dual-energy X-ray absorptiometry of the lumbar spine and hip. Osteoporosis was defined as a lumbar spine or hip score of -2.5 standard deviations (SD) or less, and osteopenia as a score between -1.0 and -2.5 SD. [32]

Genetic Analysis

Genomic DNA was prepared from the blood samples of patients and controls by the standard phenol-chloroform extraction method. Exons 1–24 and of STAT3 and their flanking intron sequences were amplified by polymerase chain reaction (PCR) with specific oligonucleotide primers (available on request) and sequenced with the Applied Biosystems Big Dye terminator kit v.1.1 (Applied Biosystems, Foster City, CA) and an ABI Prism 3130x1 Analyzer (Applied Biosystems). PolyPhen2 (polymorphism phenotyping) (<http://genetics.bwh.harvard.edu/pph2/>), a bioinformatics method for predicting the possible impact of an amino acid substitution on the structure and function of a human protein on the basis of physical and comparative considerations, was used to estimate the effect of the identified STAT3 mutations.

Immunologic Investigations

Immunologic investigations were based on those described in previous studies and/or the questionnaires sent to physicians. [54] All antibody determinations were performed before or several months after the end of Ig treatment. Nitroblue tetrazolium reduction tests and chemotaxis were assessed by standard techniques at the various hospitals where the patients were followed. [17]

Statistical Analysis

Survival curves were plotted as a function of age by the Kaplan-Meier method, and, when necessary, were compared in log-rank tests.

Results

Patients and STAT3 Mutations

We studied 60 patients from 47 kindreds (30 female, 30 male) with AD-HIES, diagnosed based on the observation of typical clinical features and the identification of a heterozygous mutation in the STAT3 gene (Table 1). There were no consanguineous families. Twenty-two cases were familial (9 kindreds) (Figure 1); the remaining 38 cases were sporadic. Forty-three kindreds originated from France, 2 from Algeria, 1 from Pakistan, and 1 from Portugal. All patients and their families were living in France at the time of the study. Thirty-six kindreds (55%) carried STAT3 mutations affecting the DNA-binding domain, 15 (32%) carried mutations affecting the SH2 domain, 1 (2%) carried mutations in the linker domain, and 5 (10%) carried mutations affecting the transactivation (TA) domain. We identified 11 known mutations and 13 novel STAT3 mutations (V343F, N472D, I568F, S611G, S614G, G617V, K642E, I665N, S668Y, T708N, K709E, V713M, and T714I) (see Table 1, Figure 2). We sequenced exons 10, 14, 16, and 19–22 from 300 healthy controls, and found none of the new mutations described. Moreover, these mutations were not found in whole-exome sequences from 117 individuals. Most missense mutations (V343F, N472D, G617V, S614G, K642E, I665N, S668Y, T708N, V713M, and T714I) were classified as “probably damaging,” 2 (I568F and S611G) as “possibly damaging,” and only 1 (K709E) as “benign” by polyPhen2. Finally, some mutations were identified in several kindreds:

R382W was found in 10 kindreds, R382Q in 6, V637M in 5, Vdel463 in 3, N472D in 2, Y657C in 2, and K709E in 2 kindreds.

We then investigated the molecular impact of various mutations affecting the STAT3 DNA-binding domain, SH2, or TA domains in Epstein-Barr virus-transformed B lymphocytes (EBV-B cells) stimulated with IL-6, IL-10, IL-21, or IFN-[alpha] (see Supplementary Figure 1a-d). Intracellular flow cytometry analysis of STAT3 tyrosine phosphorylation (pY705) showed that pY705-STAT3 levels in response to stimulation with IL-6, IL-10, and IL-21 were significantly lower in STAT3-deficient patients than in healthy controls (n = 6). This difference was particularly marked in EBV-B cells carrying TA domain mutations. Levels of nuclear translocation and DNA binding by STAT3 in response to stimulation with IL-6, IL-10, IL-21, or IFN- [alpha], evaluated by EMSA ELISA (electrophoretic mobility shift assay/enzyme-linked immunosorbent assay), were significantly lower in STAT3-deficient patients than in healthy controls (n = 8) (see Supplementary Figure 2a-d), but similar amounts of STAT1 DNA-binding complexes were observed in patients and healthy controls upon IFN- [alpha] treatment (data not shown). Finally, levels of mRNA for SOCS3, a STAT3 target gene, in response to stimulation with IL-6, IL-10, IL-21, or IFN- [alpha] were significantly lower in STAT3-deficient cells than in control cells, as shown by reverse transcription PCR (RT-PCR) analysis (see Supplementary Figure 3a-d).

Immunologic and Hematologic Investigations

We analyzed blood leukocyte subsets in 56 patients with STAT3 deficiency (Table 2). Polymorphonuclear neutrophil counts were in normal range for all patients, except during infectious events. Hypereosinophilia ($[mt] 0.5 \times 10^{[sup]9}$ eosinophils/L) was found in 80% of patients (range, 0.5 - $10 \times 10^{[sup]9}$ eosinophils/L). Phagocyte functions (oxidative burst and chemotaxis) were normal in all patients studied. T-cell subsets were present in normal numbers in 98% of patients tested; 1 patient (Patient 3) had persistent global lymphopenia ($0.8 \times 10^{[sup]9}$ lymphocytes/L). We previously showed that IL-17-producing T-lymphocyte levels were low in 14 of the 15 patients tested, [13] with 86% of the tested patients also having low proportions of CCR6+CCR4 -CD4 T cells, CCR6 being a putative marker for Th17 cells. NK cells were present in normal numbers in 92% of patients studied. T cells proliferated normally in response to mitogens and recall antigens in vitro, for all the patients studied. The number of B cells was normal in 98% of patients, but 94.5% of the patients tested had low levels of memory CD19+CD27+ B cells (Figure 3a), and an excess of transitional CD19+IgM+CD38+B cells was found in 4 of the 7 patients tested, consistent with previous reports. [3] The only patient (Patient 3) with a high percentage of CD27+CD19+ cells displayed global lymphopenia, including a lack of B cells. High serum IgE levels were found in 96% of patients, with a median level of $[mt]10,108$ IU/mL (range, 3-93,900 IU/mL). IgE levels were normal in 2 patients (1 at age 2 mo and the other at age 7 yr) (see Table 2, Figure 3b). High serum IgD levels were also found in 8 of the 9 patients tested as previously described. [30] IgG, IgA, and IgM levels were normal to high in most patients, but IgG levels were slightly low in 1 patient, and another patient had low IgG2 levels. The production of antibodies against protein antigens was detected in 78% of the patients tested. Thirteen of the 14 patients tested had detectable IgG antibodies against pneumococcus after infection and/or immunization with nonconjugated vaccine. The production of IgM allohemagglutinins against erythrocyte AB antigens was normal in the 8 patients tested. In conclusion, the immunologic phenotype of patients with STAT3 deficiency is characterized by low levels of circulating IL-17-producing T cells and memory B cells, hypereosinophilia, and high serum IgE and IgD levels.

Demographic Features

The mean age of the cohort at the time of the study was 21 years (range, 1 mo to 46 yr), with a mean age at clinical diagnosis of 6.8 years (range, 0-30 yr). The mean age at the identification of STAT3 mutation was 17 years (range, 1 mo to 46 yr). The observation time was 1214 years for the 60 patients of the cohort, with a mean of 21 years/patient. The mean age at first infection was 10.5 months (range, 0-180 mo; SD, 28 mo). Bacterial and fungal infections were the most prominent clinical feature of the disease. The first clinical signs in most patients were skin rash and lung infections in 70% (42/60) and 38% (23/60) of patients, respectively. An NIH HIES score [mt]40 was found in 82% (47/57) of patients, and half the patients with scores [lt]40 were under the age of 10 years (see Table 1) (mean NIH score, 60). We observed considerable clinical variability in individuals bearing the same heterozygous STAT3 mutation, including those from the same kindred (see Figure 1). Four (7%) patients died (Table 3): 1 in an accident and 3 from uncontrolled bacterial infection (Figure 4). Patient 7 died at age 29 years, from rapidly extensive purulent mediastinitis following esophageal perforation. Patient 19 died at age 15 years from pneumococcal meningitis. Patient 45 died at age 14 months from septic shock and acute respiratory distress syndrome secondary to *Streptococcus pneumoniae* lung infection.

Eczema and Staphylococcal Skin Diseases

Most patients (93%, n = 56/60) developed noninfectious dermatitis (see Table 1). A neonatal papulopustular rash was observed in 48% (29/60) of patients, occurring within the first 2 weeks of life in 69% (20/29) of these patients. Skin biopsy revealed eosinophilic spongiotic dermatitis in 4 patients. Chronic eczematiform dermatitis developed in 92% (55/60) of patients before the age of 18 months. The skin features consisted of crusting and extensive papular (prurigo-like) or papulopustular (folliculitis-like) eruptions, initially on face, scalp, chest, and buttocks in particular. Remarkably, subsequent *Staph. aureus* infection was consistently observed and led to chronic impetiginized dermatitis. All STAT3-deficient patients developed bacterial infections of the skin, whether or not they had dermatitis, with a mean age at onset of 11.5 months (range, 0 to 96 mo); such infections were present in 14 (24%) patients at birth. Cold abscesses of the skin, with minor inflammatory symptoms, were observed in 73% (44/60) of patients (ranging from 1 to [mt]60 episodes), most frequently on the neck and trunk, including recurrent cold abscesses on the breast. The other types of bacterial skin infections observed included impetigo, pustulosis, and pyodermitis in 45% of patients (n = 27), folliculitis and/or furunculosis in 35% (n = 21), paronychia in 23% (n = 14), lymph node abscesses in 20% (n = 12), and cellulitis in 16% of patients (n = 10). Evidence for the presence of bacteria was documented for 70% (42/60) of patients. *Staph. aureus* was found in 94% of the documented bacterial episodes (204 of 217 episodes, 0.2 episodes/patient.year), including 1 case of thoracic wall cellulitis due to a Panton-Valentine leukocidin-positive strain of *Staph. aureus*. Other bacteria were isolated more rarely and included gram-negative bacilli for 8 patients and gram-positive bacteria for 4 patients (Figure 5a).

Other Mucocutaneous Infections

Chronic mucocutaneous candidiasis of various mucosal sites and nails was observed in 85% (51/60) of patients, including 64% of patients with oral candidiasis reported in the neonatal period (see Table 1). The affected sites were oral (thrush, glossitis, and/or cheilitis) in 63% of patients (n = 32), chronic onychomycosis in 57% (n = 29), genital in 18% (n = 9), cutaneous in 16% (n = 8), and esophageal in 8% (n = 4) of patients. *Candida albicans* was the most frequently isolated infectious agent and was obtained from 88% (23/26) of samples (see Figure 5a). *C. glabrata* and *C. parapsilosis* were documented in only 1 and 2 children, respectively. Skin infections due to *Trichophyton rubrum*, *T. mentagrophytes*, or *Cryptococcus laurentii* were identified in 1 patient each. Viral skin infections occurred in

only a few patients: 1 patient had a profuse cutaneous herpes simplex virus (HSV)-1 infection during the neonatal period (Kaposi-Juliusberg syndrome), and 7 other patients had HSV infection with the usual clinical presentation (stomatitis, vulvitis, or keratitis). Sixteen patients developed chickenpox; none of them had been immunized with varicella zoster vaccine. Three of the 16 patients received intravenous antiviral treatment: for hemorrhagic chickenpox in 1 case, for chickenpox pneumonia in 1 case, and for a cutaneous *Staph. aureus* superinfection in 1 case. Five patients had zoster virus infection (at 2, 16, 16, 21, and 22 years of age, respectively), including 1 with a multimeric distribution; all these infections resolved favorably with treatment. Nine patients had warts with no unusual extension or outcome. Four other patients had molluscum contagiosum of both infection types, with limited extension and a favorable outcome. Only 1 patient had *Sarcoptes scabiei* pediculosis, with a good outcome once treated.

Pulmonary Infections

In this cohort, 90% (54/60) of patients had bacterial pneumonia, with a mean of 3 episodes per patient (range, 1-30 episodes) (Tables 1 and 4), and a mean age at onset of 39.5 months (range, 0-192 mo). The severity of the infections depended on their extension, and associated pleural effusion was reported in 38% (23/60) of patients. Bacteria were detected in 44% of acute episodes of pneumonia (84/188 episodes, 0.15 episodes/patient.year). *S. pneumoniae* and *Staph. aureus* were the most frequently implicated bacteria, in 30% (25/82) and 29% (24/82) of documented infections, respectively. Other bacteria were also isolated, such as *Haemophilus influenzae* in 13% of cases (n = 11), *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* in 12% of cases (n = 8 and 2, respectively), enterobacteria in 7% of cases, and anaerobic bacteria in 6% of cases (Figure 5b). Finally, 3 cases of *Mycoplasma pneumoniae* infection were reported. Two cases of *Pneumocystis jirovecii* pneumonia were reported, in Patient 51 at age 5 months and Patient 39 at age 30 years, both with a favorable outcome. Two cases of viral pneumonia due to respiratory syncytial virus (RSV) infection in 1 patient and coinfection with RSV, influenza virus, and pneumococcus in another, were identified. This second patient died at the age of 14 months, from associated *S. pneumoniae*-related septic shock, attesting to the higher frequency and severity of bacterial infections in this population. *P. aeruginosa* was isolated almost exclusively from patients with a history of recurrent pneumonia, bronchiectasis, and cystic pulmonary lesions, whereas anaerobic bacteria were isolated from patients with dental and/or ear, nose, and throat (ENT) sources of infection.

Lung Complications

Lung sequelae were reported in 67% (40/60) of patients, taking the form of bronchiectasis in 65% (39/60) of patients or pneumatocele in 52% (31/60) of patients, at a mean age of 21 years (range, 1-45 yr). Other complications also occurred: bronchopleural fistulas, hemoptysis, pneumothorax and/or pneumomediastinum, and tracheal stenosis (see Table 4). As a consequence, 22% (13/60) of patients required at least 1 lung lobectomy (range, 1-3) at a median age of 10 years (range, 1-17 yr), to control a bacterial infection or an invasive pulmonary fungal infection, and/or to cure a lung complication. *Aspergillus* species caused disease in 13 of 60 (22%) patients in the cohort (Table 5), with a favorable outcome in all cases. Eight of the 13 patients were diagnosed with an *Aspergillus* species-related pulmonary invasive fungal infection, based on EORTC/MSG consensus definitions. Invasive fungal infection was considered proven in 4 cases and possible (due to the absence of microbiologic confirmation) in another 4 cases, with a mean age at onset of 11 years (range, 3-16 yr). Four patients developed a pulmonary aspergilloma within pneumatocele cavities, at a mean age at onset of 12.7 years (range, 10-16 yr). Bronchial *Aspergillus* species colonization was observed in 5 patients, and it preceded the onset of invasive aspergillosis in 4 other patients. *A. fumigatus* was isolated in 7 of 9 cases. All of the patients

with *Aspergillus* species-related manifestations had already suffered from at least 3 episodes of recurrent bacterial pneumonia, complicated with secondary bronchiectasis and/or pneumatoceles, suggesting that these complications may be an essential underlying condition for *Aspergillus* colonization.

Ear, Nose, and Throat Infections

ENT infections had occurred since very early childhood but were also frequently reported in adults. They affected 90% (54/60) of patients and consisted of recurrent otitis media in 73% (44/60) of patients (ranging from 0 to 10 episodes), usually complicated with chronic otorrhea, external otitis in 27% (16/60) of patients, and cholesteatoma in 1 patient at age 17 years (see Table 1). Recurrent and chronic sinusitis were observed in 40% (24/60) of patients; severe pharyngitis, laryngitis, and/or rhinitis in 20% (12/60); mastoiditis in 10% (6/60); and tonsillitis and parapharyngeal abscesses in 10% (6/60) of patients. The bacteria most frequently isolated were *P. aeruginosa* in 40% (14/35) of episodes and *Staph. aureus* in 37% (13/35) of episodes, mostly corresponding to recurrent and/or chronic ENT infections. Other bacteria (8/34 documented episodes) were less frequently isolated due to the lack of systematic microbiologic documentation in ENT infections: *S. pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*. *P. aeruginosa* bacteria were detected in all cases of external otitis. No case of ENT infections with filamentous fungi was documented for this cohort.

Other Infections

Septicemia was reported in 8 patients, with a median age at onset of 5.5 years (range, 1 mo to 39 yr). It was caused by *Staph. aureus* in 5 cases and *S. pneumoniae* in 3 cases, with the lung identified as the source of infection in half the cases. Two patients had central nervous system infections: *Staph. aureus* meningitis occurred secondary to a neurosurgical procedure in 1 patient at age 26 years, and pneumococcal meningitis occurred at age 15 years in 1 patient who had undergone surgery in early childhood for craniosynostosis. Deep-seated abscesses occurred in 7 patients, at a median age at onset of 9.5 years (range, 1-32 yr): liver abscesses (n = 5) with *Staph. aureus* isolated in 1 and *S. pneumoniae* in another case, purulent mediastinitis (n = 2), and pararectal abscess caused by *Staph. aureus* (n = 1). Osteoarticular infections were reported, with a median age at onset of 14.5 years (range, 1-39 yr), in 22% (13/59) of patients, with a total of 18 episodes of osteitis (n = 7), osteomyelitis (n = 3), spondylodiscitis (n = 3), osteoarthritis (n = 2), arthritis (n = 1), and subperiosteal abscess (n = 1). *Staph. aureus* was isolated from 76% (10/13) of osteoarticular infections. There were 3 cases of acute *E. coli* pyelonephritis, 5 patients had recurrent bacterial conjunctivitis, 3 had blepharitis, and 4 had recurrent chalazion (due to *Streptococcus agalactiae* in 1 case). Finally, bacillus Calmette-Guerin vaccination was performed in 60.5% (20/33) of informative patients, with no adverse effects.

Prophylaxis to Prevent Infections

Antibacterial prophylaxis was administered to 90% (54/60) of patients of this cohort after diagnosis of the primary immunodeficiency, 50% (30/60) of patients received antifungal prophylaxis, and 53% (32/60) of patients underwent polyvalent IgG infusions (Table 6). Preventive treatment included antibiotic prophylaxis with oral cotrimoxazole, penicillin, macrolides, and/or cephalosporin in most cases. Antibiotic prophylaxis began at a mean age of 7.8 years (range, 2 mo to 39 yr). Cotrimoxazole was replaced by cloxacillin, with a high degree of efficacy, in 6 of 7 adult patients with recurrent bacterial infections despite prophylactic cotrimoxazole treatment. Azithromycin was added to the pre-existing prophylactic regimen in 3 patients, for the purposes of immune modulation. Antibiotic prophylaxis was discontinued in 5 patients with chronic infections. Four patients did not receive antibiotic prophylaxis, 1 patient (Patient 45) died from septic shock due to *S.*

pneumoniae and a second (Patient 47) had bilateral chronic otorrhea and chronic obstructive pulmonary disease with bronchiectasis and pulmonary cyst lesions. The remaining 2 patients had few infections.

Preventive treatment included antifungal prophylaxis in 50% of patients, with a mean age at initiation of 12 years (range, 2 mo to 28 yr). Twenty patients received primary antifungal prophylaxis in the form of itraconazole or voriconazole, and 10 patients received secondary antifungal prophylaxis in the form of itraconazole, voriconazole, and/or caspofungin (see Table 6). Four of these patients developed invasive pulmonary aspergillosis despite appropriate antifungal prophylaxis.

Thirty-two (54%) patients received IgG treatment (400-500 mg/kg every 3 or 4 wk by the intravenous route, or 100 mg/kg per week by the subcutaneous route); all but 2 young patients under the age of 4 years had an NIH score above 40. The mean age for the initiation of IgG infusions was 14 years (range, 1-39 yr) (Table 7). We evaluated the impact of IgG infusions on the incidence of bacterial pneumonia in the 32 patients who received IgG. We had access to data for 449 years and 140 years of follow-up without and with IgG treatment, respectively. The incidence of bacterial pneumonia was 27.8/100 patients per year in the absence of IgG treatment and 9.3/100 patients per year with IgG treatment; this difference was highly significant, with a $[\chi^2]$ value of 20.47 ($p = 6 \times 10^{-6}$). Thus, prophylaxis combining oral antibiotics and IgG injections seems to be particularly beneficial in patients with recurrent pulmonary infections, and antifungal prophylaxis should be offered to patients with pneumatocele or bronchiectasis.

Dysmorphia and Abnormalities of Connective Tissue and Skeleton

Dysmorphia was observed in 95% of patients, with a high and prominent forehead in 85% (51/60), prognathism or retrognathism in 53% (32/60), enlargement of the interalar distance in 85% (51/60), thickening of the soft tissues of the ear or nose in 73% (44/60), and high arched palate in 53% (32/60) of patients (see Table 1). Dysmorphia clearly tended to increase with age. The retention of deciduous teeth was observed in 65% (34/52) of informative patients over the age of 8 years. Abnormal bone fractures had occurred in 42% of patients (25/60; 56 fractures were registered) with a median of 2 fractures per patient (range, 1-10). Half the patients had undergone bone mineral density explorations, and osteopenia was observed in 59% (17/29) of these patients. Joint hyperextensibility was found in 50% (30/60) of patients, including genu valgum, varum or recurvatum and/or varus foot; episodes of unusual joint dislocation and scoliosis were found in 38% (23/60) of patients. Some other skeletal abnormalities were reported, including craniosynostosis ($n = 2$), retracted tendons ($n = 2$), spondylolisthesis L5-S1 ($n = 1$), and spina bifida occulta ($n = 1$). We also noted neurologic features, consisting of syringomyelia in Patient 11 treated by surgery at age 5 years and a posterior fossa arachnoid cyst in Patient 35 treated by surgery at age 26 years.

Neoplasia

Four of the 60 (7%) patients (Patients 12, 20, 25, 26) had a history of hematologic malignancy (Table 8). All 4 had suffered from non-Hodgkin lymphoma (NHL), with a mean age at onset of 21 years (range, 8-34 yr): 2 cases of Burkitt lymphoma (1 disseminated and 1 localized), 1 case of disseminated anaplastic lymphoma kinase (ALK)-negative anaplastic NHL, and 1 case of localized diffuse large B-cell lymphoma (DLBCL). No association with EBV was observed. All patients were successfully treated by chemotherapy, with a CHOP (prednisone + vincristine + cyclophosphamide + adriamycin)-type regimen used in 3 patients (Patients 12, 20, 26). Patient 26 also received high-dose methotrexate and cytarabine, followed by autologous stem cell transplantation. Burkitt lymphoma in Patient

25 was treated by an intensified version of the LMB protocol. No serious side effects were observed during treatment, with no exacerbation of infection, fatal sepsis, or unusual toxic side effects in particular. None of these patients underwent radiotherapy, and all remained in complete remission after a median follow-up period of 4 years (range, 1.5-13.5 yr).

Other Clinical Features

Cardiovascular manifestations consisted of hypertension complicated with left ventricular hypertrophy in Patient 18, a case of anoxic brain hemorrhagic necrosis consecutive to septic shock (Patient 10), and a history of incidental deep venous thrombosis in 3 patients, with leg phlebitis (Patients 3, 40, 43; 6 episodes) and pulmonary embolism in 2 patients (Patients 3, 40; 3 episodes). Only 1 patient (Patient 42) had brain magnetic resonance imaging at the time of this retrospective study, and she had asymptomatic linear periventricular hyperintensities with white matter hyperintensity at age 7 years. In other patients, neurologic signs were observed including postinfectious myelitis-related spastic tetraparesis in Patient 44 and unexplained ataxia with acute exacerbations in Patient 50. Asthma and allergic manifestations were observed in 8% (5/60) and 22% (13/60) of patients, respectively, and consisted of food allergies (n = 5), respiratory allergies to agents such as pollen and dust mites (n = 4), and 1 case of iodinated contrast agent-related urticaria. Finally, allergies to antibiotics (sulfamethoxazole, penicillins) were found in 8 patients, including 3 who had had sulfamethoxazole-induced Quincke edema early in life (Patients 6, 21, 58) and 1 patient who had tetracycline-induced drug rash with hypereosinophilia and systemic symptoms (DRESS) syndrome. No particular association with autoimmune signs was observed, although specific searches were not performed systematically in all patients.

Discussion

We provide here a detailed description of the clinical, immunologic, and genetic features and outcome of 60 patients with STAT3 deficiency followed in France. We report the functional impact of various heterozygous STAT3 mutations. STAT3 deficiency is a primary immunodeficiency with heterogeneous clinical and laboratory features, and STAT3 mutation screening should be undertaken if clinical and laboratory signs are present, such as atypical eczematiform dermatitis, recurrent cutaneous cold abscesses due to bacteria, chronic mucocutaneous candidiasis, recurrent pneumonia caused by pyogenic bacteria complicated with bronchiectasis and pneumatoctyst formation, the development of aspergillosis in these lung lesions, and connective tissue and/or bone abnormalities. [45,62,70] These clinical signs are associated with the following laboratory features: hyper-IgE, eosinophilia, and Th17 lymphopenia. In the current study, as previously reported, [3,65] we found a low percentage of memory B cells, contrasting with a normal total B-cell population in almost all patients. Indeed, 94.5% of the STAT3-deficient patients of this cohort displayed CD27+CD19+ lymphopenia. This evaluation is easier for laboratories to carry out in routine practice than Th17 lymphocyte counts, which requires intracellular staining due to the presence of very small T-cell populations ([It]2%). [13,43,44,62,70] We suggest that CD19+CD27+ cell counts should be included in recommendations for the diagnosis of patients with AD-HIES, before STAT3 genetic analysis is carried out.

The results obtained for the current series of patients enlarges the spectrum of heterozygous STAT3 mutations. We identified 13 new mutations and confirmed the existence of 11 previously reported mutations, including the 4 recurrent mutations R382W, R382Q, V463del, and V637M (found in 17%, 15.5%, 12%, and 8.6% of patients from this cohort, respectively). These heterozygous STAT3 mutations---R382W, R382Q, V463del, and V637M---have been found in STAT3-deficient patients described in previous studies (21%, 11%, 7%, and 14.5% of patients, respectively, accounting for more than 53% of the mutations identified to date). We have confirmed that these mutations are located at

mutation hotspots. [28,29,33,47,55,60,62,70,71] Exons 13, 16, and 21---in which these mutations are located---could thus be sequenced first, in cases of suspected STAT3 deficiency. An impairment of STAT3 phosphorylation and STAT3 translocation to the nucleus and DNA-binding were found in EBV-B cell lines from 9 patients bearing 5 previously identified heterozygous mutations (R382W, R382Q, T412S, Vdel463, and V637M) and from 7 patients bearing 6 previously unidentified heterozygous mutations (N472D, S614G, T708N, K709E, V713M, and T714I). One of these 6 new mutations, K709E, was considered by the Polyphen2 algorithm to have a benign impact in STAT3 functions. However, we showed that this mutation has an important impact on STAT3 phosphorylation and STAT3 nuclear translocation or accumulation in functional experiments. These results indicate that the Polyphen2 algorithm provides an indication, but additional functional assays are required to determine the true impact of each of the new mutations on STAT3 phosphorylation and nuclear translocation.

The 3 hallmarks of the clinical infectious phenotype of STAT3-deficient patients are recurrent “cold” staphylococcal skin abscesses, recurrent bacterial pneumonia, and chronic mucocutaneous candidiasis. All patients in the current cohort had developed staphylococcal skin infections. This frequency of staphylococcal skin infections is similar to that reported for other large cohorts. [29,60,62,70] The blood cells of STAT3-deficient patients display defective responses to IL-6, [47] because STAT3 plays a major role in the signaling pathway downstream from IL-6Rs. [45] Evidence suggesting a specific role of IL-6 in the pathogenesis of staphylococcal disease has been provided by the description of neutralizing circulating anti-IL-6 autoantibodies in a child with recurrent staphylococcal skin disease. [59]

Up to 95% of the patients in the current cohort had recurrent bacterial pneumonia. A similar frequency has been reported for other large cohorts of STAT3-deficient patients (Table 9). [29,60,62,70] After these infections, the major complication is pneumatocele, which was found in up to half the patients in our cohort. Evidence suggestive of a specific role for STAT3 in the pathogenesis of lung infections was provided by the demonstration of STAT3 involvement in the production of antibacterial factors by keratinocytes and bronchial epithelial cells. [46]

About 85% of the patients in this cohort developed chronic candidiasis infection. In the other large cohorts of STAT3-deficient patients previously studied, chronic mucocutaneous candidiasis was reported in 43%, 56% and 64% of patients (see Table 9). [29,62,70] Based on the finding that mouse IL-17-producing T cells play a role in immunity to both systemic and mucosal *C. albicans* infection, [16] several groups have shown that IL-17-producing T-cell lymphopenia occurs in STAT3-deficient patients. [13,43,44,46,60] Evidence for a specific role of IL-17-producing T cells in the pathogenesis of mucosal *C. albicans* infection was recently provided by the description, in patients with isolated chronic mucocutaneous candidiasis, of autosomal recessive IL-17RA deficiency or AD-IL-17F deficiency, indicating that human IL-17A and IL-17F are essential for protective immunity to *C. albicans* and, to a lesser extent, *Staph. aureus* in mucosae, but that they are otherwise redundant. [56-58] Moreover, we recently found gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis. [42] Mutations in the same domain of STAT1 were found independently by another group. [67] The mechanism involves loss-of-STAT1 dephosphorylation, and the gain-of-function results in enhanced cellular responses to STAT1-dependent IL-17 inhibitors IL-27, IFN[alpha]/[beta], and IFN[gamma], as well as STAT3-dependent IL-17 inducers IL-6, IL-21, and possibly IL-23. [42] These experiments of nature neatly illustrate how the genetic dissection of infectious diseases will illuminate the pathogenesis of the various infections seen in AD-HIES patients. [1] The pathogenesis

of staphylococcal disease in HIES patients, atleast the cutaneous lesions, might result from impaired IL-6 immunity. [59]

Clinical presentation tended to improve with time, probably due to correct diagnosis and more appropriate care, except in patients with progressive pulmonary insufficiency and chronic bronchial suppuration. [20] Preventive treatment included antibiotic prophylaxis, mostly with cotrimoxazole. [66] However, antibiotics specifically targeting *Staph. aureus*, such as cloxacillin, are a good alternative (C. Aguilar, personal communication). The documentation of bacterial infections also facilitated the adaptation of antibiotic treatment to the microbiologic ecology of each patient. Such antibiotic prophylaxis was clearly of benefit for skin infections and external otitis. However, it was difficult to evaluate the effect of antibiotic prophylaxis, because almost all the patients in our cohort had been on such prophylaxis since childhood.

A positive impact of prophylaxis for bacterial infections was also observed with IgG treatment in this study. The rationale for IgG treatment was based on the recurrence of pyogenic bacterial infections with a particular lung and ENT tropism and the occurrence of memory B-cell lymphopenia with an accelerated decline of specific antibody titers after initially normal primary Antibody responses and the lower than normal secondary Antibody responses observed in STAT3-deficient patients in the present report and previous studies. [3,4,63,65] The duration of follow-up from the initiation of IgG treatment in the current cohort is short, but a decrease in the frequency of bacterial pneumonia was observed, with the occurrence of atleast 1 episode of bacterial pneumonia in 27.8% of years without IgG treatment and 9.3% of years with IgG treatment. These encouraging results are preliminary and require confirmation and validation in prospective studies to evaluate the precise impact of IgG treatment on the prevention of lung abnormalities. An *in vivo* study of the kinetics of antibody production in STAT3-deficient patients is also now required.

Antifungal prophylaxis should be offered to patients with structural airway abnormalities. The mechanism responsible for invasive fungal infections in STAT3-deficient patients is probably related to local epithelial impairment due to structural injuries following recurrent bacterial pneumonia, rather than myeloid dysfunction. [22,46,68] The prevention and treatment of these destructive pulmonary lesions by prophylactic surgery to exclude pneumatocele formation may constitute a valuable way of preventing filamentous fungal infections in STAT3-deficient patients.

Characteristic facial features in STAT3-deficient patients include dysmorphism, with a prominent forehead, broad nasal bridge, and abnormally large interalar distance. [22] STAT3-deficient patients also have bone abnormalities, including recurrent pathologic fractures with osteoporosis, delayed shedding of deciduous teeth, hyperextensibility of joints, scoliosis, and craniosynostosis. [23] The percentages of patients with dysmorphism, delayed shedding of the deciduous teeth, and skeletal features in the current cohort were similar to those reported for other cohorts of STAT3-deficient patients. [29,60,62,70] It is noteworthy that in Shprintzen-Wiedemann syndrome, a severe autosomal recessive condition caused by a null mutation in the leukemia inhibitory factor receptor gene (LIFR), [11,31] LIFR-deficient patients had several clinical features in common with STAT3-deficient patients, including osteoporosis, spontaneous fractures, joint hyperextensibility, and scoliosis. Several studies in mice have confirmed the role of LIFR in the control of osteoclastogenesis, [7] and STAT3 has been implicated in the signaling pathway of LIFR, which is associated with gp130. [25] The skeletal features reported in STAT3-deficient patients probably result from impairment of the LIFR signaling pathway. Other features, such as the retention of primary teeth, result from abnormal IL-11 responses, as suggested by the recent identification of IL-11R deficiency in patients with cranial dysostosis and

dental anomalies (49). It is probable that the genetic dissection of the various phenotypes associated with the HIES will proceed along these lines, not only for the infectious and tumoral features (IL-17F, IL-17RA), but also for the developmental features (LIFR, IL11R).

However, the noninfectious features of STAT3-deficient patients were of less importance than the frequency and severity of infections, with the exception of lymphoma. We confirm the association of STAT3 deficiency and lymphoma in this series, as already reported. [35,37] All the lymphoma cases reported in this cohort were unrelated to EBV. [69] The 22 previously reported cases included 6 of T-cell origin; 12 of B-cell origin, NHL; and 4 cases of Hodgkin lymphoma. Half were nodal and most were unrelated to EBV. [35] The median age at presentation of lymphoma was 21 years in the current cohort (range, 8-34 yr), and 19 years in previous studies (range, 4-69 yr). [35] All patients with lymphoma in the current report were alive at the end of follow-up, with persistent complete remission of the lymphoma, whereas 9 of the patients described in previous studies died. Gain-of-function somatic mutations in the STAT3 gene are known to be associated with carcinoma and hematologic malignancies including multiple myeloma, leukemia, and lymphoma. [15,34,72] By contrast, no such association has been reported for loss-of-function mutations of the STAT3 gene. As STAT3 is an oncogene, the occurrence of lymphomas in these patients is paradoxical and unexplained. Further investigations are required to improve our understanding of the mechanism of tumorigenesis in patients with germline loss-of-function STAT3 mutations.

In conclusion, recurrent bacterial skin and/or respiratory tract infections were consistently observed in the STAT3-deficient patients of the current cohort. *Staph. aureus* was the most commonly isolated pathogen by far, documented in all informative patients and in 72% (250/345 episodes) of all documented bacterial episodes. Most patients experienced their first infection very early in life, with neonatal infection reported in 39% of patients and infections during the first year of life in 81% (48/59) of patients. Fungal infections were also frequent: 85% of patients had chronic mucocutaneous candidiasis, and 22% had aspergillosis infection and/or colonization. STAT3-deficient patients clearly benefit from stringent clinical follow-up, with appropriate continuous antibiotic prophylaxis, IgG therapy in patients with recurrent lung infections, antifungal prophylaxis in patients with lung abnormalities, and good compliance with treatment and follow-up, which should be monitored with particular attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	autosomal dominant
CEREDIH	Centre de Reference des Deficits Immunitaires Hereditaires
DRESS	drug rash with hypereosinophilia and systemic symptoms
EBV-B cells	Epstein-Barr virus-transformed B lymphocytes
EMSA ELISA	electrophoretic mobility shift assay/enzyme-linked immunosorbent assay
ENT	ear, nose, and throat
EORTC/MSG	European Organization for Research and Treatment of Cancer/Mycoses Study Group
HIES	hyper-immunoglobulin E syndrome

HSV	herpes simplex virus
IFN	interferon
Ig	immunoglobulin
IL	interleukin
LIF	leukemia inhibitory factor
LIFR	leukemia inhibitory factor receptor
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health, PCR, polymerase chain reaction
RSV	respiratory syncytial virus
RT	reverse transcription
SD	standard deviation
SH2	Src homology 2
SOCS	suppressor of cytokine signaling
STAT3	signal transducer and activator of transcription 3
TA	transactivation

Figure 1.

Pedigrees of the 9 kindreds with STAT3 deficiency (familial cases) identified. Each kindred with STAT3 deficiency is designated by a capital letter (K), each generation is designated by a Roman numeral (I) and each individual is designated by an Arabic numeral (from left to right). Patients with a clinical phenotype are indicated by closed symbols. In each family, the proband is indicated by an arrow. Individuals whose genetic status could not be evaluated are indicated by "E?". Patient age at last follow-up and NIH score are also provided.

Figure 2.

Schematic representation of the STAT3 gene. Positions of the STAT3 mutations in the DNA binding (DNA) domain, the Src homology 2 (SH2) domain, the transactivation (TA) domain, amino-terminal (AT) domain, or coiled-coil (CC) domain. Underlined mutations were identified in patients from the current study; mutations not underlined were identified in previous studies. [2–4,28,29,33,35,36,41,47,52,55,60–62,70,71] The positions of all known mutations are indicated in amino acid nomenclature, with the exception of mutations starting with c. at the bottom, which are shown in nucleotide nomenclature.

Figure 3.

A, B-cell immunophenotyping in 55 STAT3-deficient patients. Percentage of CD27+CD19+ B cells in STAT3-deficient patients, with the gray area representing the normal values for these cells according to age. In the gray circle, the only patient (Patient 3) with a high percentage of CD27+CD19+ cells displayed global lymphopenia, including B-cell lymphopenia. B, IgE levels in 56 STAT3-deficient patients (KU/L). The gray area indicates the normal values of IgE as a function of age.

Figure 4.
Survival curve of the 60 STAT3-deficient patients.

Figure 5.

A, Documented skin infections. Skin bacterial infections were caused by *Staph. aureus* in 204 episodes and by other bacteria in 13 episodes (*E. coli* in 3, *Proteus mirabilis* in 2, *P. aeruginosa* in 2, *Enterobacter aerogenes* in 1, *Serratia marcescens* in 1, [alpha] or [beta]-hemolytic *Streptococcus* in 3, and *Propionibacterium acnes* in 1). Skin fungal infections were caused by *C. albicans* in 23 episodes and by other fungi in 6 episodes (*C. parapsilosis* in 2, *C. glabrata* in 1, *T. rubrum* in 1, *T. mentagrophytes* in 1, and *Cryptococcus laurentii* in 1). Skin viral infections were caused by varicella zoster virus in 16, herpes simplex virus in 8, human papillomavirus in 9, and the Molluscum contagiosum poxvirus in 4 episodes. Isolated *Sarcoptes scabiei* pediculosis was reported in 1 episode. B, Documented lung infections. *S. pneumoniae* and *Staph. aureus* were the most frequently involved, in 25 and 24 episodes of documented infections, respectively. Three cases of *M. pneumoniae* infections were also reported. The other bacteria isolated were *H. influenzae* isolated in 11, *P. aeruginosa* in 8, *Stenotrophomonas maltophilia* in 2, *E. coli* in 2, *K. pneumoniae* in 2, *Serratia marcescens* in 2, *Fusobacterium* species in 1, *Bacteroides fragilis* in 1, *Prevotella oralis* in 1, and *Moraxella catarrhalis* in 2 episodes. Lung fungal infections were secondary aspergillosis in 13 episodes, and 2 cases of pneumocystosis were also identified. Two patients also presented respiratory infections caused by respiratory syncytial virus (RSV), and 1 displayed a respiratory infection caused by varicella zoster virus (VZV).

Table 1

Characteristics and Outcome in the French Cohort of 60 STAT3-Deficient Patients

K	Pt	Age #/Sex (yr)	Country of Origin	Status	STAT3 Mutation	Domain	NIH Score	Age at 1st Sign (yr)	Age at Diagnosis (yr)	Infection				Dermatitis		Connective Tissue Sign				NHL
										Skin	Lung	Severe Bacterial	ENT	CMC	Aspergillus	Dysmorphia	Teeth	Osteopenia	Fracture	
K1	P1	15/F	France	Alive	V637M	SH2	57	1	2	+	+	+	+	+	+	+				
K2	P2	11/M	France	Alive	R382W	DNA	50	<1	3	+	+	+		+	+	+				
K3	P3	39/M	France	Alive	F384L	DNA	72	<1	7	+	+	+		+	+	+	+		+	
K3	P4	4/F	France	Alive	F384L	DNA	56	1	3	+	+	+		+	+			+	+	
K4	P5	15/F	France	Alive	T708N	TA	62	>5	9	+	+	+		+	+	+	+	+	+	
K5	P6	19/F	France	Alive	R382Q	DNA	73	<1	2	+	+	+	+	+	+	+	+	+	+	
K6	P7	29/F	France	Dead	nd	nd	85	<1	?	+	+	+	+	+	+	+	+	+	+	
K6	P8	29/M	France	Dead	T622I	SH2	68	<1	3	+	+	+	+	+	+	+	+	+	+	
K7	P9	12/F	France	Alive	R382Q	DNA	51	<1	9	+	+	+	+	+	+	+	+	+	+	
K8	P10	24/F	France	Alive	R382W	DNA	73	<1	?	+	+	+	+	+	+	+	+	+	+	
K9	P11	18/M	Algeria	Alive	R382W	DNA	74	<1	5	+	+	+	+	+	+	+	+	+	+	
K10	P12	38/M	France	Alive	K642E	SH2	66	<1	7	+	+	+	+	+	+	+	+	+	+	+
K11	P13	19/F	France/Morocco	Alive	T714I	TA	78	Birth	Birth	+	+	+	+	+	+	+	+	+	+	+
K12	P14	36/F	France	Alive	Vdel463	DNA	63	Birth	30	+	+	+	+	+	+	+	+	+	+	
K12	P15	11/F	France	Alive	Vdel463	DNA	14	<1	7	+	+	+	+	+	+	+	+	+	+	
K12	P16	10/M	France	Alive	Vdel463	DNA	59	<1	7	+	+	+	+	+	+	+	+	+	+	
K13	P17	17/F	France	Alive	T620A	SH2	52	<1	<1	+	+	+	+	+	+	+	+	+	+	
K14	P18	25/M	French West Indies	Alive	R382W	DNA	84	<1	10	+	+	+	+	+	+	+	+	+	+	
K15	P19	15/F	France	Alive	S611G	SH2	70	<1	4	+	+	+	+	+	+	+	+	+	+	
K16	P20	23/M	France	Alive	R382W	DNA	68	<1	2	+	+	+	+	+	+	+	+	+	+	+
K17	P21	20/F	French West Indies	Alive	S668Y	SH2	74	<1	9	+	+	+	+	+	+	+	+	+	+	
K18	P22	33/F	France	Alive	R382Q	DNA	68	<1	15	+	+	+	+	+	+	+	+	+	+	
K18	P23	10/M	France	Alive	R382Q	DNA	19	<1	<1	+	+	+	+	+	+	+	+	+	+	
K19	P24	16/M	France	Dead	V343F	DNA	70	<1	5y	+	+	+	+	+	+	+	+	+	+	
K20	P25	22/F	France	Alive	R382W	DNA	86	?	?	+	+	+	+	+	+	+	+	+	+	+

K	Pt	Age */Sex (yr)	Country of Origin	Status	S/TAT3 Mutation	Domain	NIH Score	Age at 1st Sign (yr)	Age at Diagnosis (yr)	Infection					Dermatitis		Connective Tissue Sign				NHL			
										Skin			Severe Bacterial		ENT	CMC	Aspergillus	Dysmorphia		Teeth		Osteopenia	Fracture	Hyperextensibility
										Lung														
K21	P26	23/F	France	Alive	V713M	TA	69	<1	3	+	+	+	+	+	+	+	+	+	+	+				
K22	P27	10/F	France	Alive	S614G	SH2	53	<1	6	+	+	+	+	+	+	+	+	+	+	+				
K23	P28	29/M	France	Alive	R382Q	DNA	67	<1	1	+	+	+	+	+	+	+	+	+	+	+				
K23	P29	4/M	France	Alive	R382Q	DNA	33	<1	1	+	+	+	+	+	+	+	+	+	+	+				
K23	P30	2/M	France	Alive	R382Q	DNA	25	Birth		+	+	+	+	+	+	+	+	+	+	+				
K24	P31	7/F	France	Alive	K709E	TA	64	<1	4	+	+	+	+	+	+	+	+	+	+	+				
K25	P32	15/M	Algeria	Alive	R382W	DNA	54	<1	<1	+	+	+	+	+	+	+	+	+	+	+				
K26	P33	26/F	France	Alive	V637M	SH2	73	<1	2y	+	+	+	+	+	+	+	+	+	+	+				
K27	P34	18/M	France	Alive	V637M	SH2	64	<1	<1	+	+	+	+	+	+	+	+	+	+	+				
K28	P35	30/M	France	Alive	Vdel463	DNA	64	<1	3	+	+	+	+	+	+	+	+	+	+	+				
K29	P36	21/F	France	Alive	T412S	DNA	44	>5	15	+	+	+	+	+	+	+	+	+	+	+				
K30	P37	43/M	France	Alive	nd	nd	nd	<1	?	+	+	+	+	+	+	+	+	+	+	+				
K30	P38	13/F	France	Alive	N472D	DNA	nd	<1	?	+	+	+	+	+	+	+	+	+	+	+				
K31	P39	30/F	France	Alive	R382W	DNA	74	<1	17	+	+	+	+	+	+	+	+	+	+	+				
K32	P40	28/F	France	Alive	R382W	DNA	73	<1	4	+	+	+	+	+	+	+	+	+	+	+				
K33	P41	16/M	France	Alive	Y657C	SH2	45	<1	?	+	+	+	+	+	+	+	+	+	+	+				
K34	P42	11/F	France	Alive	R382Q	DNA	59	<1	7	+	+	+	+	+	+	+	+	+	+	+				
K35	P43	38/F	Pakistan	Alive	Vdel463	DNA	79	<1	24	+	+	+	+	+	+	+	+	+	+	+				
K35	P44	11/M	Pakistan	Alive	Vdel463	DNA	55	<1	1	+	+	+	+	+	+	+	+	+	+	+				
K35	P45	1/F	Pakistan	Dead	Vdel463	DNA	33	Birth		+	+	+	+	+	+	+	+	+	+	+				
K36	P46	19/M	France	Alive	N472D	DNA	55	<1	14	+	+	+	+	+	+	+	+	+	+	+				
K37	P47	37/M	France	Alive	V637M	SH2	74	<1	?	+	+	+	+	+	+	+	+	+	+	+				
K38	P48	45/F	France	Alive	I665N	SH2	65	<1	?	+	+	+	+	+	+	+	+	+	+	+				
K38	P49	17/F	France	Alive	I665N	SH2	26	>5	18	+	+	+	+	+	+	+	+	+	+	+				
K39	P50	19/M	France	Alive	K709E	TA	77	<1	<1	+	+	+	+	+	+	+	+	+	+	+				
K40	P51	19/M	France	Alive	R382W	DNA	37	<1	2	+	+	+	+	+	+	+	+	+	+	+				
K41	P52	8/F	France	Alive	P639S	SH2	51	1	6	+	+	+	+	+	+	+	+	+	+	+				
K42	P53	30/M	France	Alive	I568F	Linker	41	<1	1	+	+	+	+	+	+	+	+	+	+	+				

K	Pt	Age */Sex (yr)	Country of Origin	Status	57A73 Mutation	Domain	NIH Score	Age at 1st Sign (yr)	Age at Diagnosis (yr)	Infection			Dermatitis		Connective Tissue Sign				NHL
										Severe Bacterial	ENT	CMC	Aspergillus	Dysmorphia	Teeth	Osteopenia	Fracture	Hyperextensibility	
K43	P54	25/F	France	Alive	G617V	SH2	67	<1	8	+	+	+	+	+	+	+	+	+	
K44	P55	0.3/M	France	Alive	R382Q	DNA	32	Birth	Birth	+	+	+	+	+	+	+	+	+	
K45	P56	38/M	France	Alive	Y657C	SH2	68	<1	?	+	+	+	+	+	+	+	+	+	
K46	P57	27/M	Portugal	Alive	V637M	SH2	79	<1	?	+	+	+	+	+	+	+	+	+	
K47	P58	46/M	France	Alive	Q469H	DNA	44	<1	?	+	+	+	+	+	+	+	+	+	
K28	P59	0.1/M	France	Alive	Vdel463	DNA	nd	Birth	Birth	+									
K3	P60	7/M	France	Alive	F384L	DNA	14	5	7										

Abbreviations: ? = unknown, *Aspergillus* = *Aspergillus* species-related disease, CMC = chronic mucocutaneous candidiasis, K = kindred, nd = not determined, Pt = patient, severe bacterial infection = septicemia, meningitis, deep inner abscess, arthritis, osteomyelitis, Teeth = retention of deciduous teeth.

* Age at time of study .

Table 2

Immunologic Investigations in 55 STAT3-Deficient Patients

	Patients Tested (n)	Normal (%)	Low (%)	High (%)
Lymphocytes (10^9 lymphocytes/L)	54	98	2	-
CD4 T lymphocytes (%)	54	98	2	-
CD8 T lymphocytes (%)	54	96	4	-
CD4 CCR4-CCR6+ T lymphocytes (N >2%)	35	14	86	-
Th17 lymphocytes (%)	15	7	93	-
B lymphocytes (%)	55	98	2	-
CD27+CD19+ memory B lymphocytes (%)	55	5.5	94.5	-
NK lymphocytes (%)	26	92	8	-
T-cell proliferation (cpm)	18	100	-	-
IgG levels (g/L)	45	71	2	27
IgG1 levels (g/L)	14	100	-	-
IgG2,3,4 levels (g/L)	14	86	14	-
IgA levels (g/L)	45	69	13	18
IgM levels (g/L)	45	69	-	31
IgD levels	9	11	-	89
IgE levels (KU/L)	56	4	-	96
Antibodies against protein antigens (tetanus, diphtheria, or polio)	24	79	21	-
Antibody against <i>H. influenzae</i> type b	5	100	-	-
Antibody against <i>S. pneumoniae</i>	14	93	7	-
Allohemagglutinin	8	100	-	-
Nitroblue tetrazolium or dihydrorhodamine test	23	100	-	-
Neutrophil chemotaxis	16	100	-	-

Table 3
Causes and Age of Death in the French Cohort of STAT3-Deficient Patients

K	Pt	NIH Score	STAT3 Mutation	Age at Death	Cause of Death
K6	P7	85	T622I	29 yr	Purulent mediastinitis after esophageal perforation and paravertebral abscess caused pyogenic bacteria
K6	P8	68	T622I	29 yr	Accident
K15	P19	70	S611G	15 yr	Meningitis caused by <i>S. pneumoniae</i>
K35	P45	33	Vdel463	14 mo	Septic shock and acute respiratory distress syndrome caused by <i>S. pneumoniae</i>

Abbreviations: See Table 1.

Table 4
Documented Bacterial Pneumonia in the French Cohort of STAT3-Deficient Patients

Pt	Age at Time of Study (yr)	STAT3 Mutation	Age at Time of Pneumonia (yr)	No.	Bacteria Detected	Complications				Other Complications	Lobectomy
						Pleural Effusions	Bronchiectasis	Pneumatocyst			
P1	15	V637M	1, 3, 5, 6, 7, 10, 14	6	<i>S. aureus</i> , <i>S. pneumoniae</i>	+	+	+	+		+
P2	11	R382W	0.7, 2, 7	>3	<i>S. pneumoniae</i>	+	+	+	+	Bronchial fistula	
P3	39	F384L	* 27, 28, 33	>4	<i>S. aureus</i> , <i>H. influenzae</i> , <i>P. aeruginosa</i>						
P4	4	F384L	2, 2.5	2	NA		+	+	+		
P5	15	T708N	5, 6, 7, 9, 11, 12	6	<i>S. pneumoniae</i>		+	+	+		+
P6	19	R382Q	0.3, 8, 8, 13	4	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>P. aeruginosa</i> , <i>Branhamella catarrhalis</i> , <i>Klebsiella spp.</i>		+	+	+		+
P8	29	T622I	0.25, 1, 2.5, 4, 4.5, 4.75, 5, 10, 13, 14	8	<i>S. aureus</i>	+	+	+	+	Pneumothorax, bronchopleural fistula	
P9	12	R382Q	9	>2	<i>S. pneumoniae</i> , <i>H. influenzae</i>	+	+	+	+		
P10	24	R382W	20, 23	>4	<i>S. pneumoniae</i>		+	+	+		
P11	18	R382W	3, 17	3	<i>P. aeruginosa</i> , <i>S. pneumoniae</i>		+	+	+		
P12	38	K642E	7, 16	>3	<i>S. aureus</i> , <i>H. influenzae</i>						
P13	19	T714I	3, 14	2	<i>S. aureus</i> , <i>S. pneumoniae</i>		+				
P14	36	Vdel463	0		NA		+	+	+	COPD, diffuse interstitial syndrome	
P15	11	Vdel463	0		0						
P16	10	Vdel463	2.5, 3, 3.5, 4, 7	5	<i>S. pneumoniae</i> , <i>H. influenzae</i>	+	+	+	+		
P17	17	T620A	0.7, 8, 11, 12, 14, 15	6	<i>H. influenzae</i>	NA	+	+	+	Pleural fistula, pneumothorax/pneumo-mediastinum	+
P18	25	R382W	Birth to 23	>10	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i>	+	+	+	+		+
P19	15	S611G	4, 5, 14	3	NA	+	+				
P20	23	R382W	3, 9	>2	<i>S. aureus</i>	+					
P21	20	S668Y	0.1, 9	>3	<i>S. pneumoniae</i>		+			Chronic bronchorrhea	
P22	33	R382Q	5, 5.5, 30	3	<i>Prevotella oralis</i>		+	+	+		
P23	10	R382Q	0		0						
P24	16	V343F	4	1	<i>Mycoplasma pneumoniae</i>						
P25	22	R382W	8, 10, 11, 14, 17	>6	<i>S. pneumoniae</i> , <i>H. influenzae</i>	+	+	+	+		

Pt	Age at Time of Study (yr)	STAT3 Mutation	Age at Time of Pneumonia (yr)	No.	Bacteria Detected	Complications			Other Complications	Lobectomy
						Pleural Effusions	Bronchiectasis	Pneumatocyst		
P26	23	V713M	3, 20	>3	<i>S. aureus</i>		+	+		+
P27	10	S614G	5, 6, 7	4	<i>S. pneumoniae</i>					
P28	29	R382Q	1, 4, 6, 16	4	<i>S. aureus</i>	+	+	+		
P29	4	R382Q	2, 3	2	<i>S. aureus, P. aeruginosa</i>					
P30	2	R382Q	0.4	1	NA					
P31	7	K709E	3, 3.5, 6, 7	4	<i>S. pneumoniae, P. aeruginosa, S. aureus</i>	+	+	+	Bronchopleural fistula	+
P32	15	R382W	3.5, 1, 11, 12	5	<i>M. pneumoniae, E. coli, P. aeruginosa, S. aureus</i>				Tracheal stenosis	
P33	26	V637M	2, 11, 15, 19	4	<i>S. aureus, E. coli, P. aeruginosa</i>	+	+	+	Hemoptysis	+
P34	18	V637M	4, 6, 12	>3	<i>P. aeruginosa</i>					
P35	30	Vdel463	3, 5, 5.5, 11	4	<i>S. aureus, S. pneumoniae</i>		+	+		
P37	43	N472D	NA	1	<i>S. aureus</i>				Encysted pleural effusion	
P39	30	R382W	1, 3, 15	>3	NA	+	+	+	Pneumothorax, hemoptysis	+
P40	28	R382W	0.75, 4, 5, 17, 28	>5	<i>S. aureus, H. influenzae</i>	+	+	+		+
P42	11	R382Q	5, 5.5, 7	>3	<i>S. aureus, S. pneumoniae, M. pneumoniae</i>		+	+		
P43	38	Vdel463	* 24, 29, 34, 36, 37	7	<i>S. aureus, Enterobacteria</i>		+	+		
P44	11	Vdel463	3	2	<i>S. pneumoniae</i>	+	+	+		
P45	1	Vdel463	1	1	<i>S. pneumoniae</i>	+	+			
P46	19	N472D	9, 13	2	NA		+			
P47	37	V637M	3	>3	<i>S. aureus</i>	NA	+	+	Hemoptysis	
P48	45	I665N	16, 28	>3	NA		+	+		
P49	17	I665N	7	1	NA					
P50	19	K709E	13	>4	NA					
P51	19	R382W	2, 14, 16	>3	NA	+	NA	NA		
P52	8	P639S	1, 2	2	<i>S. aureus, S. pneumoniae</i>		+	+		
P54	25	G617V	1, 2, 4	4	<i>S. aureus, S. pneumoniae</i>	+	+	+	Pyopneumothorax	+
P56	38	Y657C	NA	3	<i>S. aureus, S. pneumoniae, H. influenzae</i>		+			
P57	27	V637M	0.6, *	3	<i>S. aureus</i>		+	+		+

Pt	Age at Time of Study (yr)	STAT3 Mutation	Age at Time of Pneumonia (yr)	No.	Bacteria Detected	Complications			Other Complications	Lobectomy
						Pleural Effusions	Bronchiectasis	Pneumatocyst		
P58	46	Q649H	NA	NA	<i>S. pneumoniae</i>					
P59	0.1	Vdel463	0		0			+		
P60	7	F384L	0		0					

Abbreviations: COPD = chronic obstructive pulmonary disease, NA = not available.

* Several bouts of pneumonia during childhood at undetermined ages.

Table 5
Aspergillus Species-Related Manifestations in the French Cohort of STAT3-Deficient Patients

Pt	STAT3 Mutation	Age* (yr)	>3 Previous Pneumonia Episodes	Bronchiectasis	Pneumatocele	Bronchial Colonization	Aspergilloma	Invasive Pulmonary Aspergillosis	Culture	<i>Aspergillus</i> Species	Surgery
P1	V637M	10	+	+	Bilateral	+		Possible	-	<i>A. fumigatus</i>	
P3	F384L	30	+	+	Unilateral	+			+	<i>Aspergillus</i> spp.	
P6	R382Q	13, 16	+	+	Bilateral	+	+	Proven	+	<i>A. fumigatus</i>	+
P11	R382W	16	+		+			Possible	-	NA	
P18	R382W	10	+	+	Unilateral		+	Proven	+	<i>A. fumigatus</i>	+
P20	R382W	9	+			+			-**	<i>Aspergillus</i> spp.	
P32	R382W	3	+	+	+	+		Possible	+	<i>A. fumigatus</i>	
P33	V637M	15, 19	+	+	Bilateral		+	Proven	+	<i>A. fumigatus</i>	+
P39	R382W	14	+	+	Bilateral	+	Suspected		+	<i>A. fumigatus</i>	
P40	R382W	10, 11	+	+	Bilateral	+	+	Proven	+	<i>A. fumigatus</i>	+
P52	P639S	1.5	+	+		+			+	<i>A. fumigatus, A. versicolor</i>	
P54	G617V	NA	+	+	+	+			-	<i>Aspergillus</i> spp.	+
P56	Y657C	NA	+	+				Possible	-	NA	

Abbreviations: See previous tables.

* Age at time of *Aspergillus* spp.-related disease.

** Direct examination of bronchoalveolar lavage revealed *Aspergillus* filaments, whereas culture remained negative.

Table 6
Prophylaxis Against Infections in the French Cohort of STAT3-Deficient Patients

	No. of Patients	
	Before 2007*	After 2007*
No prophylaxis	3	8
Antibacterial prophylaxis	43/46	50/60
Corrimoxazole alone	22	29
Penicillins (Cloxacillin)	3 (1)	8 (7)
Alternating antibiotic prophylaxis	18	12
+/- Corrimoxazole	NA	7
+/- Pristinamycin	NA	6
+/- Macrolide	NA	3
+/- Cephalosporin or penicillin	NA	8
+/- Other (quinolone, rifampicin, fucidic acid)	NA	4
Azithromycin [†]	1	3
IgG treatment (IV or SC)	12/46	32/60
IgG treatment alone	2	2 _{ss}
Antibiotic prophylaxis and IgG treatment	10	30
Antifungal prophylaxis	16/42	30/60
Primary	11	20
Itraconazole	10	18
Voriconazole	1	2
Secondary	5	10
Itraconazole	4	5
Voriconazole	1	5
Voriconazole + caspofungin	0	1

Abbreviations: IgG = immunoglobulins, IV = intravenous, SC = subcutaneous.

* 2007 is considered the date of reference for the STAT3 mutation identification period.

[†] Azithromycin was always added to a preexisting prophylactic regimen and was included for immune modulation rather than antibacterial prophylaxis.

Table 7
IgG Treatment in the French Cohort of STAT3-Deficient Patients

Pt	Age at Initiation (yr)	NIH Score	Year at Initiation	Route of Injection	Frequency of Ig Treatment	Birth to IgG	No. of Pneumonia Episodes Age 5 yr to IgG	After IgG Therapy
P1	9	57	2004	IV then SC	Continuous	5	3	1
P2	9	50	2009	SC	Continuous	>3	1	0
P3	39	72	2010	IV then SC	Continuous	>4	2	0
P5	11	62	2006	IV	Continuous	5	4	1
P6	9	73	2000	IV then SC	Continuous	3	2	1
P9	11	51	2009	IV	Continuous	>2	2	0
P10	20	73	2006	IV	Continuous	>3	2	1
P11	13	74	2005	IV	Continuous	>3	1	1
P16	7	59	2007	IV	Continuous	5	5	0
P17	9	52	2002	IV	Continuous	2	2	4
P18	25	84	2010	IV	Continuous	>10	2	0
P19	13	70	2009	IV	Continuous	3	1	0
P21	18	74	2008	IV then SC	Discontinuous	>3	2	0
P25	11-16	86	1999-2003	IV	Discontinuous	3	3	2
P26	20	69	2007	IV	Continuous	3	1	0
P27	8	53	2008	IV	Continuous	4	3	0
P28	29	67	2009	IV	Continuous	4	0	0
P29	3	33	2009	IV	Continuous	2	2	0
P30	1	25	2009	IV	Continuous	1	1	0
P31	6	64	2009	IV then SC	Continuous	3	3	1
P32	14	54	2009	NA	Continuous	5	3	0
P33	24	73	2007	IV	Continuous	>3	1	0
P34	14	64	2007	IV	Stopped in 2008	>3	2	0
P36	20	44	2009		Continuous	0	0	0
P39	22	74	2002	IV	Continuous	>3	0	0
P40	28	73	2010	IV	Continuous	>5	2	0
P42	7	59	2005	IV	Continuous	>3	3	0
P43	37	79	2008	IV	Continuous	7	3	0

Pt	Age at Initiation (yr)	NIH Score	Year at Initiation	Route of Injection	Frequency of Ig Treatment	No. of Pneumonia Episodes		
						Birth to IgG	Age 5 yr to IgG	After IgG Therapy
P44	4	55	2003	NA	Continuous	2	2	0
P50	4	77	1995	IV	Continuous	>4	3	1
P52	<1	51	2002	IV	Continuous	1	1	0
P57	12	79	1995	IV	Continuous	1	1	0

Abbreviations: See previous tables. Ig = immunoglobulins, IV = intravenous route of injection with a monthly frequency, SC = subcutaneous route of injection with a weekly frequency.

Table 8
Non-Hodgkin Lymphoma in the French Cohort of STAT3-Deficient Patients

Pt	Age at NHL Diagnosis (yr)	STAT3 Mutation	NHL Type	Immunohistochemistry	Disease Stage	Site Involved	Treatment	Response/Follow-Up
P12	34	K642E	DLBCL *	CD20+, CD10+, CD5-, Bcl2+, Bcl6+, LMP-	I	Single right inguinal lymph node (8×4×3cm)	R-CHOP 14 × 6	CR/3 yr
P20	17	R382W	Burkitt-like NHL	CD20+, CD10+, Bcl2-, Bcl6+, Ki67 100%, LMP-	I	Single right inguinal lymph node	R-CHOP × 6 (intrathecal CT × 4)	CR/6 yr
P25	8	R382W	Burkitt NHL	CD20+, CD30-, Ki67 100%, LMP-, c-myc rearranged	IV	Intraabdominal tumor, mesenteric lymph nodes, bone marrow	French LMB protocol (COP, COPADM, CYM)	CR/14 yr
P26	21	V713M	Anaplastic NHL	CD30+, CD15-, ALK-, EMA-, TIA1+, LMP-	IV	Lymph nodes above and below diaphragm, liver, bone marrow	CEEP × 2, MTX + Aracytine × 1, intensification by BEAM with ASCT	CR/2 yr

Abbreviations: See previous tables. ALK = anaplastic lymphoma kinase, ASCT = autologous stem cell transplantation, BEAM = carmustine + etoposide + cytarabine + melphalan, CEEP = prednisone + Eldisine + cyclophosphamide + epirubicin, CHOP = prednisone + vincristine + cyclophosphamide + Adriamycin, CR = complete remission, CT = chemotherapy, DLBCL = diffuse large B-cell lymphoma, LMB protocol = *Lymphome Malin B* (French protocol), LMP = latent membrane protein, MTX = methotrexate.

* —.[AQ][AQ: Pt 12: DLBCL has an asterisk--add footnote or delete asterisk.]

Table 9
Frequency of Laboratory and Clinical Signs in Large Series of STAT3-Deficient Patients, Present and Previous Reports

	Source (First Author, ref.) (%)			
	Schimke ⁶² (n=48)	Woellner ⁷⁰ (n=64)	Jiao ²⁹ (n=12)	French Cohort (PR) (n=60)
NIH score >40	96	76.7	NA	82
Hypereosinophilia	93	70.7	NA	80
IgE	96	NA	100	96
B memory lymphopenia	NA	NA	NA	94.5
Th17 lymphopenia	100	53	NA	93
Neonatal rash	74	64.9	45	48
Dermatitis	98	90.6	100	92
Skin abscesses	85	90.6	100	100
Pneumonia	94	95.3	100	90
Pneumatocoe	48	74.6	45	52
Candidiasis	56	43.1	64	85
Other severe infections	89	56.7	nd	43
Retention of deciduous teeth	79	80	27	65
Bone fractures	60	45.8	18	42
Dysmorphism	90	90.6	100	95
Large interalar distance	22	51.9	NA	85
Cathedral palate	22	54.7	NA	53
Hyperextensibility	60	52.7	55	50
Scoliosis	42	26	27	38
Lymphoma	NA	NA	9	7

Abbreviations: See previous tables. PR = present report.