Journal of Clinical Immunology (2020) 40:851–860
https://doi.org/10.1007/s10875-020-00808-4

ORIGINAL ARTICLE

Prevalence of Immunological Defects in a Cohort of 97 Rubinstein–Taybi Syndrome Patients

Francesco Saettini[1] · Richard Herriot[2] · Elisabetta Prada[3] · Mathilde Nizon[4,5] · Daniele Zama[6] · Antonio Marzollo[7] · Igor Romaniouk[8] · Vassilios Lougaris[9] · Manuela Cortesi[9] · Alessia Morreale[9] · Rika Kosaki[10] · Fabio Cardinale[11] · Silvia Ricci[12] · Elena Domínguez-Garrido[13] · Davide Montin[14] · Marie Vincent[4,5] · Donatella Milani[3] · Andrea Biondi[1] · Cristina Gervasini[15] · Raffaele Badolato[8]

Received: 29 April 2020 / Accepted: 16 June 2020 / Published online: 27 June 2020

Abstract

Although recurrent infections in Rubinstein–Taybi syndrome (RSTS) are common, and probably multifactorial, immunological abnormalities have not been extensively described with only isolated cases or small case series of immune deficiency and dysregulation having been reported. The objective of this study was to investigate primary immunodeficiency (PID) and immune dysregulation in an international cohort of patients with RSTS. All published cases of RSTS were identified. The corresponding authors and researchers involved in the diagnosis of inborn errors of immunity or genetic syndromes were contacted to obtain up-to-date clinical and immunological information. Ninety-seven RSTS patients were identified. For 45 patients, we retrieved data from the published reports while for 52 patients, a clinical update was provided. Recurrent or severe infections, autoimmune/autoinflammatory complications, and lymphoproliferation were observed in 72.1%, 12.3%, and 8.2% of patients. Syndromic immunodeficiency was diagnosed in 46.4% of individuals. Despite the broad heterogeneity of immunodeficiency disorders, antibody defects were observed in 11.3% of subjects. In particular, these patients presented hypogammaglobulinemia associated with low B cell counts and reduction of switched memory B cell numbers. Immunoglobulin replacement therapy, antibiotic prophylaxis, and immunosuppressive treatment were employed in 16.4%, 8.2%, and 9.8% of patients, respectively. Manifestations of immune dysfunctions, affecting mostly B cells, are more common than previously recognized in patients with RSTS. Full immunological assessment is warranted in these patients, who may require detailed investigation and specific supportive treatment.

Keywords Rubinstein–Taybi syndrome · CREBBP · EP300 · hypogammaglobulinemia · antibody deficiency · syndromic immunodeficiency · humoral defects · lymphoproliferation · B cells

Abbreviations

ALPS	Autoimmune lymphoproliferative syndrome
CID	Combined immunodeficiency
CVID	Common variable immunodeficiency
ESID	European Society for Immunodeficiencies
FMF	Familial Mediterranean fever
HSCT	Hematopoietic stem cell transplantation
PID	Primary immunodeficiency
RSTS	Rubinstein–Taybi syndrome
SIgAD	Selective IgA deficiency
USI	Unclassified syndromic immunodeficiency

C Gervasini and R Badolato contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-020-00808-4) contains supplementary material, which is available to authorized users.

✉ Francesco Saettini
francescosaettini@yahoo.it

Extended author information available on the last page of the article

Introduction

Rubinstein–Taybi syndrome (RSTS; OMIM #180849, #613684) is a rare, autosomal dominant developmental disorder characterized by craniofacial dysmorphisms, broad thumbs and toes, intellectual disability, and growth deficiency (Table Table 1). It affects males and females equally, with a recognized prevalence of 1:100,000–1:125,000 in live-born infants. Variants in the genes encoding the cyclic adenosine

Table 1 The incidence of typical features of RSTS (adapted from Milani [1] and Stevens [3])

Feature in patients with RSTS	Incidence (%)	Feature in adults with RSTS	Incidence (%)
Typical facial features	100	Visual difficulties	79
Intellectual disability	~ 100	Keloids	57
Cryptorchidism	78–100	Difficulty eating	53
Broad thumbs/halluces	96	Spinal curvature	49
Microcephaly	35–94	Joint problems	46
Speech delay	90	Hypohidrosis	38
Recurrent respiratory infections	75	Bladder incontinence	35
Delayed bone age	74	Hearing loss	30
Constipation	40–74	Chronic nail fungus	30
Talon cusps	73	Urinary tract infections	25
Gastroesophageal reflux	68	Sleep apnea	25
EEG abnormalities	57–66	Patellar dislocation	22
Renal anomalies	52	Heart problems	17
Refractive defects, glaucoma, retinopathy	> 50	Frequent infections	17
Congenital heart defects	24–38	Anesthesia complications	14
Seizures	25	Neurologic abnormalities due to tethered cord	13
Keloids	24	Hypothyroidism	11
Deafness	24	Malignant tumors	10
Growth retardation	21		
Malignant tumors	3–10		
Spinal cord tethering	< 5		

monophosphate response element–binding protein (CREB)-binding protein (*CREBBP*), causing RSTS type 1, or in the E1A-associated protein p300 (*EP300*), causing RSTS type 2, have been demonstrated in 55% and 8% of patients, respectively [1]. Both genotypes of RSTS have similar clinical phenotypes, although the clinical features are generally milder in RSTS type 2 [2].

Recurrent infections, including otitis media and pneumonia, have been reported in a relevant fraction of RSTS patients. Previous studies suggest that susceptibility to infection is estimated to affect 75% of patients with RSTS [1]. Although the burden of recurrent infections seems to decrease when patients get older, a relevant proportion of adults with RSTS still experience infections [3] (Table Table 1). It is most likely that RSTS patients might be exposed to respiratory tract infections because of microaspiration and gastroesophageal reflux, but dysfunction of immune response might also contribute to increase their risk of infections.

Despite recurrent and persistent infections being widely appreciated as central phenomena of immune deficiency disorders, immunological abnormalities have not been extensively investigated in RSTS and only isolated cases of immunodeficiency in RSTS, which meet current case definition criteria, have been described [4–10]. In the last decade, there was a growing recognition of the role of immune dysfunctions in the pathogenesis of infections in RSTS patients, but published cases and small case series revealed relatively subtle deficits in immune function [4, 6, 7, 9, 10] and rare, brief descriptors of more significant defects in humoral effector components (Figure S1A). More recently, authors involved in this current study have independently described in detail four RSTS patients with significant immunological abnormalities including primary immunodeficiency (PID), non-malignant lymphoproliferation, and autoimmune cytopenias [11–14].

This study describes the clinical and immunological features of a large cohort of 97 RSTS patients in which we demonstrate a wide spectrum of clinical and laboratory immunological abnormalities. These findings will aid awareness of immune components in the RSTS phenotype, improve diagnosis, clinical decision-making and outcomes in treatment, and facilitate patient and caregivers' counseling.

Methods

One author (F.S.) carried out a systematic review of all studies published as original articles up to October 31, 2019 in PubMed database. The following search string was used: "Rubinstein–Taybi syndrome" or "RSTS." Language included was English. The corresponding authors of all relevant

publications and referring physicians were contacted to obtain updated clinical information on reported cases.

For each identified case, F.S. extracted the following information: sex, age at the time of the last follow-up, type of diagnosis (molecular versus clinical), details of *CREBBP* or *EP300* variant, history of infections/autoimmunity/lymphoproliferation/malignancy, treatment for immunodeficiency, and immunology laboratory results. To be included in this systematic review, studies had to (1) describe patients with a confirmed diagnosis of RSTS and (2) provide data on complete blood count and/or lymphocyte subsets and/or immunoglobulin level and/or specific antibody (against tetanus toxoid and/or pneumococcal polysaccharide) and/or autoantibodies and/or non-malignant lymphoproliferation. All laboratory results were analyzed with reference to age-related normal ranges [15, 16].

Infection was arbitrarily defined as "severe" if required admission and in the presence of a final diagnosis of sepsis, pneumonia, skin/soft tissue abscesses, meningitis/encephalitis, oral abscess, deep abdominal infections, fungemia, or otomastoiditis [17]. In patients with insufficient titer either to tetanus or pneumococcus, a poor vaccine response was defined as a less than 4-fold increase in IgG titer at 4 to 6 weeks after vaccination.

The PubMed search for papers describing the RSTS produced 719 results. Three hundred and eighty-five papers were excluded as irrelevant, and, of the 334 papers remaining after primary screening, 304 did not meet the detailed inclusion criteria (Figure S1B). The 30 included publications described 45 patients [4–14, 18–36] (one patient was reported in two different papers and therefore counted once). We contacted the corresponding authors of all publications included, and referring physicians provided updates on 4 patients who had already detailed immunological phenotypes published.

Multinational colleagues involved in the diagnosis and treatment of patients with PIDs and genetic syndromes were contacted to identify additional patients. Informed consent was obtained from patients, parents, or both. Data of 52 additional unpublished patients were provided by immunologists, hematologists, pediatricians, nephrologists, and geneticists we contacted directly.

The study conformed to the Declaration of Helsinki and was approved by the institutional review boards/ethic committee of Comitato Etico Brianza (Monza, Italy; PID-GENMET). Information on demographics, presentation, complications, laboratory parameters, management, and outcomes were compiled retrospectively by using patient/parent interviews and medical case note reviews. Patients' most recent immunology results are described; laboratory data obtained from patients receiving immune suppressive treatment were excluded.

The diagnosis of unclassified syndromic immunodeficiency (USI) was established according to the European Society for Immunodeficiencies (ESID) working definitions for clinical diagnosis [37].

Patients were classified as having "immunological abnormalities" (IA) in case of alteration of white blood cell and/or lymphocyte counts without other immunological investigations (i.e., lymphocyte subsets and/or immunoglobulin levels) available.

Possible associations between the baseline clinical features and the finding of each one of the abovementioned laboratory or clinical findings were assessed via Pearson' chi-square test or Fisher exact test. Results were deemed significative for p value < 0.05 with a double-tailed test.

JASP (Version 0.12.2) was used to perform statistical analyses.

Results

Patients' Characteristics

Ninety-seven RSTS patients were identified as the final cohort for analysis (Table 2). The median age at last follow-up of the included patients was 12 years (range, < 1–55 years). Fifty-five percent of the patients were male. Forty-nine patients (50.5%) had a molecular diagnosis, while the remaining cases were clinically diagnosed (Table 2).

Severe infections requiring hospitalization occurred in 22.1% of patients. Three patients had sepsis caused by *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella* species. Two patients were hospitalized with meningoencephalitis (varicella zoster virus was isolated in one patient). *Clostridium difficile* and rotavirus enteritis were reported in two patients. Recurrent urinary tract infections requiring admission occurred in 10.5% of patients.

Lower (24.4%) and upper (32.6%) respiratory tract infections were common, often with childhood onset (Table 2). Bronchiectasis was reported in one patient [11]. Only 28% of patients did not report recurrent infections. The most common bacterial pathogens were *Streptococcus pneumoniae* and *Haemophilus influenzae*, with *Staphylococcus aureus*, *Moraxella catarrhalis*, *Enterococcus faecalis*, *Providencia rettgeri*, *Pseudomonas aeruginosa*, and *Klebsiella* species also observed.

Autoimmune and Inflammatory Complications

Autoimmune and inflammatory complications were observed in 12.3% of patients (Table 2). Hematological autoimmunity occurred in 6.2% of patients. Cytopenias included Coombs-positive hemolytic anemia ($n = 1$), immune thrombocytopenia ($n = 3$), and autoimmune neutropenia ($n = 2$). Autoimmune thyroiditis was diagnosed in two patients.

One patient experienced recurrent Churg–Strauss syndrome (CSS) episodes [26]. CSS was diagnosed at the age of 14 years with pulmonary involvement, maxillary sinusitis,

Table 2 Clinical characteristics of the included patients

	Frequency (%), *n*/total studied
Sex	93.8% (91/97)
Male	54.9% (50/91)
Age at the last follow-up	97.9% (95/97)
Median	12
Range	< 1–55
Diagnosis	100% (97/97)
Clinical	49.5% (48/97)
Molecular	50.5% (49/97)
CREBBP	45.4% (44/97)
EP300	5.2% (5/97)
Infections, yes	72.1% (62/86)
Upper respiratory tract infections	32.6% (28/86)
Lower respiratory tract infections	24.4% (21/86)
Sepsis	3.5% (3/86)
Meningitis	2.3% (2/86)
Other severe infections	22.1% (19/86)
Autoimmune/autoinflammatory manifestations	12.3% (8/65)
Autoimmune cytopenia	6.2% (4/65)
Gastrointestinal disease*	8.3% (5/60)
Non-malignant lymphoproliferation	8.2% (5/61)
Malignant tumors	7.8% (5/64)

*Other than constipation or gastroesophageal reflux

pericarditis, eosinophilic peritonitis, high blood eosinophilic count, and positive antineutrophil cytoplasmic antibodies. Recurrent fever, abdominal pain, arthritis, increased erythrocyte sedimentation rate, and C-reactive protein, along with positive family history, lead to the diagnosis of familial Mediterranean fever (FMF) in one 18-year-old male [24]. Heterozygous c.2080A>G variant in the *MEFV* gene was subsequently demonstrated. A diagnosis of Kimura disease was made in a 16-year-old male, based on marked peripheral eosinophilia, markedly elevated serum IgE, and histological findings of hyperplasia of lymphoid follicles, massive eosinophilic infiltration with occasional abscess formation within the germinal center and parafollicular region [25].

Non-malignant Lymphoproliferation

Chronic lymphadenopathy, splenomegaly, and/or hepatomegaly were observed in 8.2% of patients (Table 2). One patient had a clinical picture that resembled autoimmune lymphoproliferative syndrome (ALPS; increased $CD3^+CD4^-CD8^-TCR\alpha\beta$ lymphocytes [4.6%/5.7% total lymphocytes/CD3+], multilineage autoimmune cytopenias, increased B12 vitamin level) with the expansion of $CD21^{low}CD38^{low}CD19^{hi}$ B cells [12]. Whole exome sequencing did not reveal any pathogenetic variant except for a de novo *EP300* variant. When splenomegaly worsened (up to 17 cm diameter), sirolimus was added resulting in the decrease of spleen size and the prevention of cytopenia relapse.

Although data on concomitant viremia in patients with non-malignant lymphoproliferation were not systematically collected, none of five patients with non-malignant lymphoproliferation displayed herpesvirus (i.e., EBV and CMV) infection as detected by PCR. Biopsy materials were not available in any of these patients.

Malignant Disease

Five (7.8%) patients in this cohort had malignancies (Table 2) [18, 19, 30, 36]. These included one case of primary central nervous system diffuse large B cell lymphoma in a 36-year-old. The tumor was surgically removed, and the patient received chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and steroids. One adult had a neuroendocrine tumor that was surgically removed. Acute lymphoblastic leukemia occurred in two patients, but information regarding chemotherapy was not specified in either case. One patient presented with hepatoblastoma at the age of 10 months.

Immunology Laboratory Results

IgG, IgA, or IgM levels were reduced in 12.7%, 19.6%, and 18.2% of patients, respectively (Figs. 1 and 2; Table S1).

Reduced antibody response to challenge with tetanus toxoid or pneumococcal polysaccharide was seen in 28.6% and 71.4% of patients, respectively. High IgM levels were common (30.9%). In the patient described by Saettini [12], hypogammaglobulinemia (with low levels of IgG, IgM, and IgA), was associated with increase of IgM (up to 1400 mg/dl) during the episodes of infection, which persisted for 9 months before reverting to normal, or even low levels. However, in the whole cohort, hypogammaglobulinemia (either low IgG, IgA, or IgM) was not associated with increased number of infections ($p = 1$; $p = 0.1$; $p = 0.15$, respectively; data not shown).

Lymphopenia was observed in 8.3% of patients, while lymphocyte counts were normal in about half of the patients (Fig. 1; Table S2). A consistent proportion of patients showed reduction of $CD3^+$ (22.7%), $CD4^+$ (13.0%), $CD8^+$ (30.4%) T cell, and NK cell (16.7%) counts. Reduced naïve $CD4^+$ T cell counts and inverted CD4+/CD8+ ratio were observed in 40.0% and 8.7% of patients, respectively.

B cell phenotyping showed the decrease of total B cell numbers in 22.7% of patients and the reduction of switch memory B cells in 5 out of 13 patients studied (38.5%). B cell lymphopenia was significantly more common in the patients with decreased levels of IgG or IgM ($p = 0.03$ and $p = 0.001$, respectively; data not shown).

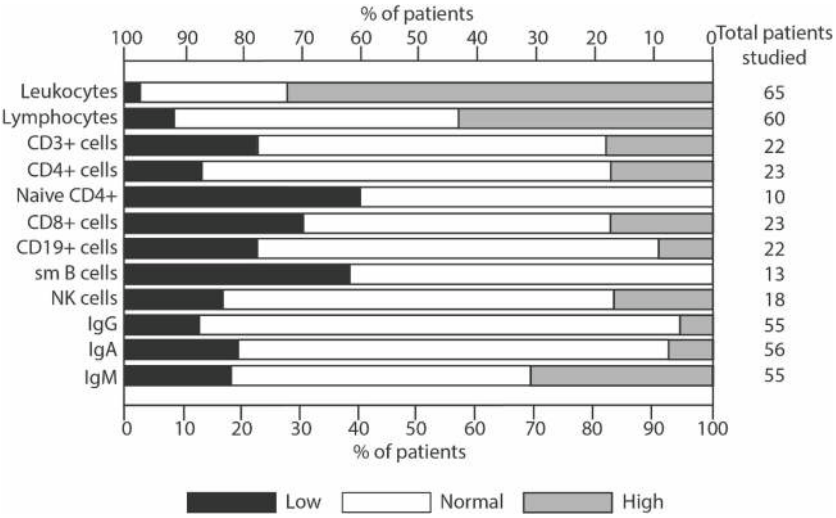
Treatment

Eight percent of the cohort currently received antibiotic prophylaxis (cotrimoxazole, $n = 4$, azithromycin, $n = 1$; Table 3). Five percent of patients were receiving antiviral or antifungal prophylaxis. Ten (16.4%) patients were currently receiving immunoglobulin replacement therapy, with reported benefit (reduction of infections). One patient with normal immunoglobulin levels temporarily received immunoglobulin replacement for recurrent infections despite prompt antibiotic treatment. Ten percent of patients received, or are currently receiving, treatment for lymphoproliferative, autoimmune, or autoinflammatory disease, including steroids, sirolimus, mycophenolate, or colchicine. Specifically, autoimmune cytopenias were variously treated with high doses of intravenous immunoglobulins, steroids, and sirolimus. CSS was treated with corticosteroids, cyclophosphamide, intravenous immunoglobulins, and methotrexate. Colchicine was successfully utilized for treatment of one RSTS patient who also carried an additional *MEFV* variant. Steroids and oral all-transretinoic acid were administered in one patient with Kimura disease.

One patient underwent hematopoietic stem cell transplantation (HSCT) at the age of 6 months because of clinical and laboratory features resembling Omenn's syndrome (erythroderma, lymphoproliferation, hypereosinophilia, hyper-IgE, reduced T cell proliferation). Maternal engraftment was excluded by molecular studies. Genetic analyses for RSTS and for other disorders associated with lymphopenia (gene list in the Online Repository) were negative. The patient is currently in good clinical condition 15 years after the transplantation procedure.

Genotype–Phenotype Correlation

In the group of patients with molecular diagnosis, we identified 44 patients with heterozygous point variants of *CREBBP* spanning the whole gene (Fig. 3A), including 12 non-sense and 11 frameshift variants, 12 in-frame del or indels, 7 missense variants, and one intronic variant predicted to exert a splicing effect. One patient presented with reciprocal translocation. We also identified 5 patients with *EP300* variants (Fig. 3B): three missense, one indel, and one frameshift variant.



Sm = switched memory

Fig. 1 Summary of immunological characteristics of the RSTS cohort

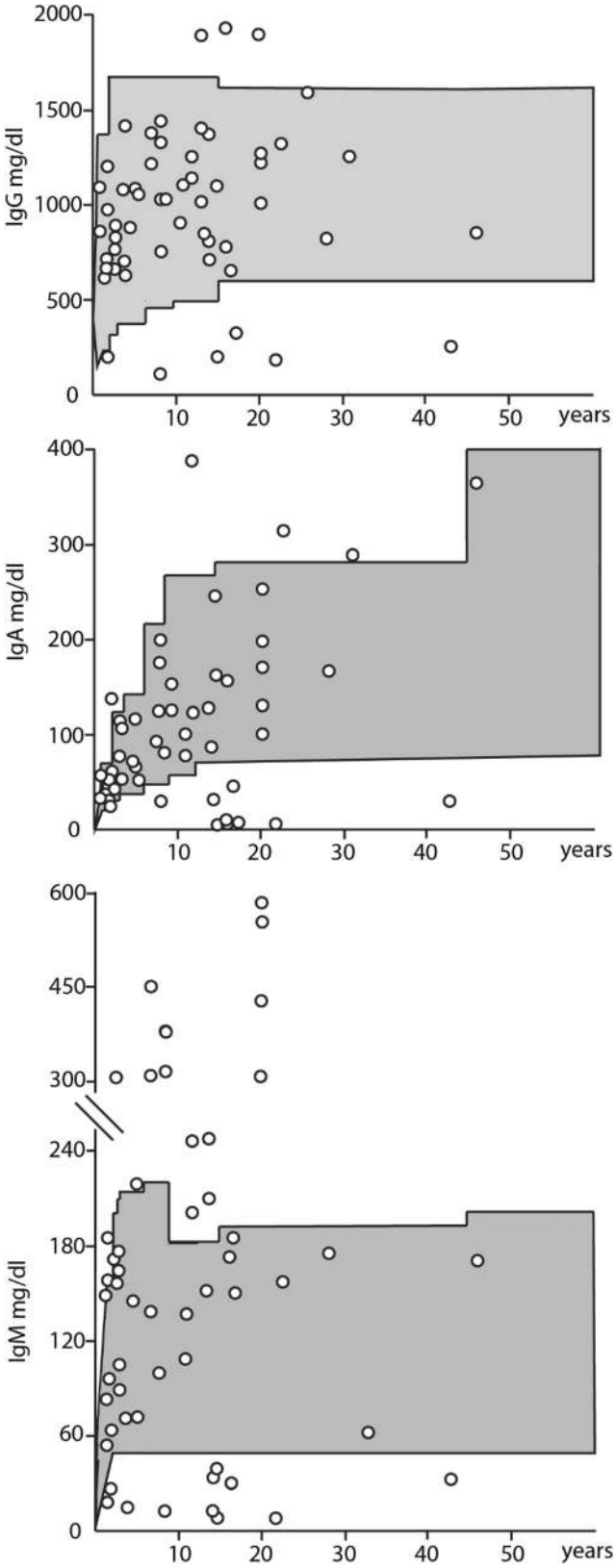


Fig. 2 Age-related changes in immunoglobulin counts in patients with RSTS. Ig count 5th to 95th percentile normal ranges are comprised in the checked area. One patient described with low immunoglobulin levels [8] was not included in this figure

Table 3 Summary of treatment characteristics of the RSTS cohort

	Frequency, *n*/total studied (%)
Ig replacement therapy	10/61 (16.4%)
Antibiotic prophylaxis	5/61 (8.2%)
Antiviral prophylaxis	1/61 (1.6%)
Antifungal prophylaxis	2/61 (3.3%)
Immunosuppressive treatment	6/61 (9.8%)
Hematopoietic stem cell transplantation	1/61 (1.6%)

Clinical diagnosis of USI was reached in 17 patients (34.7%) (Figure S2B). IA was detected in 22 patients (44.9%). Ten patients showed no immune alterations. However, we were unable to draw a correlation between the genotype (i.e., type of protein changes or affected domain) and the immunological features of the patients.

Of note, three patients with defined RSTS (either by clinical or molecular diagnosis) carried additional variants in known genes related to inborn error of immunity. Two patients carried the common *BAFF-R* monoallelic polymorphism (c.62C>G; p.Pro21Arg) [11, 13] that has been previously associated to CVID [38]. One clinically diagnosed RSTS patient received a diagnosis of FMF after a monoallelic variant (c.2080A>G; p.Met694Val) in the *MEFV* gene was detected [24].

Discussion

We present the first comprehensive overview of immunological defects in a large cohort of patients with RSTS. Immunological features of RSTS patients are broadly heterogeneous, ranging from asymptomatic patients to subjects with antibody deficiency resembling CVID to profound combined immunodeficiencies necessitating HSCT in childhood.

Syndromic immunodeficiencies are genetic syndromes with abnormalities in other organ systems in addition to the immune defects, which may not be the primary clinical problem. In these conditions, the immunological abnormalities may be found in only a fraction of patients. While some syndromic immunodeficiency are already classified as inborn error of immunity (e.g., ataxia–telangiectasia syndrome, ADA1 deficiency), a growing number of immune defects have been described in genetic syndromes with growth deficiency, gastrointestinal dysfunction, cutaneous abnormalities, neurologic dysfunction, inborn errors of metabolism, chromosome instability and/or defective DNA repair, and chromosomal abnormalities [39].

Increased susceptibility to respiratory tract infections has been described as a common feature of RSTS. The incidence of infections in our cohort is similar to that reported elsewhere in the literature [1, 3]. Our study demonstrates that clinically

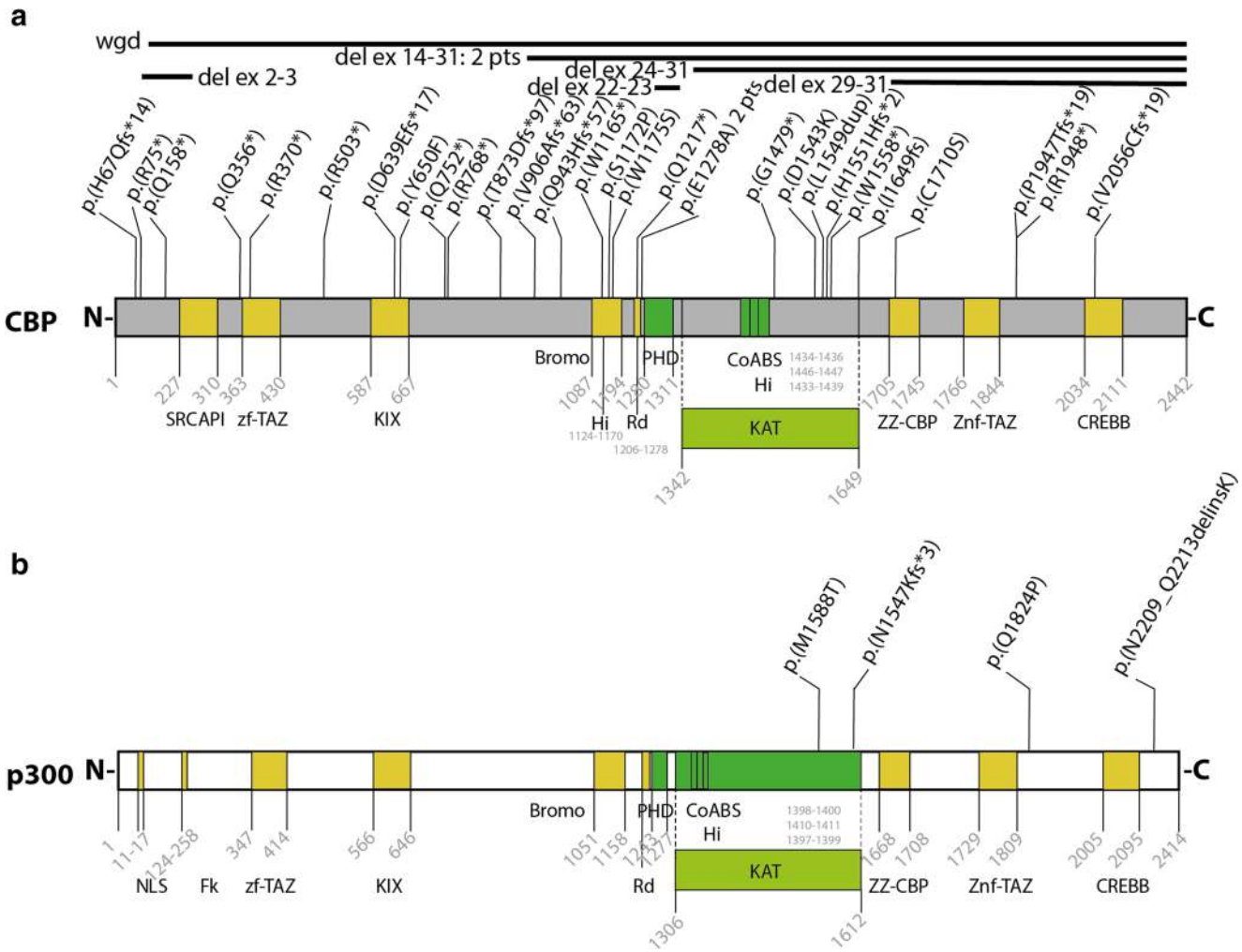


Fig. 3 Schematic representation (not in scale) of the CBP (**A**) and p300 (**B**) proteins with the mutation at protein level and the protein domains indicated above and below the figures, respectively. In order (from N-terminus to C-terminus), the depicted domains are as follows: SRCAPi = interaction with SRCAP, zf-TAZ = TAZ zinc finger, KIX = CREB interaction, Bromo = bromodomain, Hi = interaction with histones, Ring = ring domain, PHD = plant homeodomain, KAT = lysine acetyltransferase, COaBS = CoA-binding site, ZZ_CBP = zinc finger, ZnF_TAZ = TAZ zinc finger, CREBB = Creb_binding. The protein domains are indicated accordingly to NCBI reference sequence: NP_004371.2 (CBP) and NP_001420.2 (p300). In the bottom, whole gene deletion (wgd) and partial gene deletions are represented with bars. Recurrent mutations are reported for whole *CREBBP* gene deletions (four cases), partial *CREBBP* gene deletion involving exons 14–31 (two patients), the *CREBBP* point mutation leading to p.(E1551Hfs*51) (two patients), and the *EP300* gene mutation corresponding to p.(M1558T) (two patients). Reciprocal translocation t(2;16)(q36.3;p13.3) and splicing mutation c.4395-5C>G are not depicted

significant hypogammaglobulinemia is the most frequent immune manifestation of RSTS. Decreased immunoglobulin levels were found in one-fifth of the cohort and are commonly associated with decreased total B cells, reduction in class-switched memory B cells, and impaired serological response to tetanus or pneumococcus. Indeed, bacterial isolates identified in RSTS patients were those typical of subjects with antibody deficiency. These results suggest that some of the patients with RSTS might present with manifestations and immunological abnormalities which are reminiscent of CVID and ALPS [40, 41]. We suggest that future research studies should prospectively collect data on the lymphocyte immunophenotype in RSTS patients to determine whether specific T (double negative) or B cell ($CD21^{low}CD38^{low}CD19^{hi}$) population may have a role in the pathogenesis of complications such as non-malignant lymphoproliferation. Moreover, in three subjects with RSTS, hypogammaglobulinemia was observed at adult age, possibly reflecting a progressive humoral deficit, which was very mild or undetectable during their infancy. Because many studies are focused on infancy, they might miss the appearance of immunological defects in older subjects and underestimate the risk of serious infections in these patients.

Despite these similarities with PID characterized by hypogammaglobulinemia, we noted bronchiectasis only in one RSTS patient. But, pulmonary functions and chest imaging were not routinely performed in these patients, suggesting

that prospective studies will be needed to define the evolution and lung sequelae of recurrent infections in RSTS patients. In addition, other inherited defects of immune system could be suspected in RSTS patients. In about one-third of patients, IgM were above normal levels, similarly to what observed in class-switch recombination defects such as Hyper IgM syndrome. Although reduction of total T cells, of T cell subpopulations, or of NK cells was frequent among RSTS, we did not observe signs of combined immune defects such as viral or other opportunistic infections. On the contrary, a large fraction of RSTS patients presented an increased fraction of lymphocytes, which would be suggestive of polyclonal lymphoproliferation secondary to infections or to cellular dysregulation.

Overall, this study suggests that about half of the patients with RSTS presented clinical manifestations which are compatible with a diagnosis of USI. Similarities with CVID, SIgAD, and CID were found in 7%, 4%, and 2% of patients, respectively (Electronic Supplementary Material; Figure S2). Moreover, one-third of the cohort showed immunological abnormalities which could not be further defined on the basis of available data. We also report that patients with RSTS have a high incidence (12.3%) of autoimmune/autoinflammatory manifestations. Of note, these conditions have not previously been associated with RSTS as common complications. Dual molecular diagnoses or multilocus genomic variations have recently been described in up to 5% of patients undergoing whole exome sequencing [42]. This figure rises to 10% in patients screened for PIDs [43]. Three patients (3.1%) presenting RSTS together with autoimmune diseases carried genetic variants affecting other genes that contributed to complex phenotypes. These patients, diagnosed with FMF or carrying a *BAFF-R* variant, showed clinical benefit from immunosuppression or high dose immunoglobulin. In this context, we believe that the increasingly accessible and affordable use of whole exome sequencing will improve the potential for disease-aware physicians to make dual molecular diagnoses and to design more patient-specific, personalized treatment regimens [42, 43].

CREBBP gene and *EP300* are involved in a number of basic cellular activities, such as DNA repair, growth, differentiation, apoptosis of cells, and tumor suppression by serving as transcriptional co-activators in different signaling pathways. The incidence of malignancies in our cohort is similar to that reported in the literature [1]. Cancer types in our cohort included hepatoblastoma, acute lymphoblastic leukemia, and neuroendocrine tumor which are not typically associated with PID [44]. We have been unable to detect a correlation between the immunological features and the genetic variants or specific changes of protein structure, probably because of the small size of the sub-cohort of patients with molecular RSTS diagnosis. Hence, it is not possible to predict whether specific variants are directly or mechanistically associated with development of immune defects.

On the basis of this study, physicians who evaluate patients with RSTS should be aware that immunodeficiency and autoimmune/autoinflammatory symptoms can be frequently observed in these patients. Evaluation of serum immunoglobulin levels might be a simple and inexpensive marker to screen for immunological defects. Recurrent infections are common in RSTS [1] and probably recognize a multifactorial substrate. In this context, the number of infections might not be sufficient (e.g., does not correlate) per se to determine the risk of hypogammaglobulinemia. We recommend the determination of serum immunoglobulins and lymphocyte subpopulations in every patient with RSTS. This approach would be important for the recognition of patients at risk before the appearance of life-threatening infections. We also recommend to test antibody titers to vaccine for the identification of patients with poor response to immunization who might benefit of further investigation.

This study has provided information on the frequency of immunological defects and their management in a large cohort of patients with RSTS. In these subjects, immunoglobulin replacement therapy is employed when antibody deficiency is detected in order to obtain a reduction in the number, frequency, and severity of bacterial infections. We have also reported that, despite opportunistic or persistent viral infections were not detected in RSTS patients, 4.9% of them are continuously treated with antiviral and/or antifungal drugs for infection prophylaxis. Although these patients may present a quantitative defect of T or NK subsets, the results of our study do no support this recommendation until further and broader investigations (e.g., viral PCR in patients with non-malignant lymphoproliferation, lymphocyte subsets, and lymphocyte proliferative response to specific antigens and mitogens) will be collected. Prospective studies are needed to clarify whether prophylaxis regimens are necessary and clinically justifiable in this setting.

This study has a number of limitations. Almost half of the patients were retrieved through the literature and some relevant data are missing. We were not able to systematically determine the age when the infections have been recognized. Even though most of the included publications involve young patients, it is possible that recurrent or severe infections, immune dysregulation, and autoimmune complications may become more evident in older subjects. Considering that the immunological phenotype may become manifest in adulthood, some of the patients reported in the literature could have developed immunological abnormalities later in life. Therefore, the exact prevalence of immunodeficiency in RSTS might be underestimated. Conversely, most of the data of patients for whom we have updates were collected through immunologists and thus we may overestimate the prevalence of such manifestations due to the selection bias.

Conclusions

RSTS can commonly associate with a clinical and immunological phenotype of PID and/or immune dysregulation, with a high burden of infectious and autoimmune complications. Full immunological workup is warranted in these patients, who may require detailed investigation and specific supportive treatment.

Compliance with Ethical Standards

The study conformed to the Declaration of Helsinki and was approved by the institutional review boards/ethic committee of Comitato Etico Brianza (Monza, Italy; PID-GENMET).

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Negri G, Milani D, Colapietro P, Forzano F, Della Monica M, Rusconi D, et al. Clinical and molecular characterization of Rubinstein-Taybi syndrome patients carrying distinct novel mutations of the EP300 gene. Clin Genet. 2015;87:148–54.
2. Fergelot P, Van Belzen M, Van Gils J, Afenjar A, Armour CM, Arveiler B, et al. Phenotype and genotype in 52 patients with Rubinstein–Taybi syndrome caused by EP300 mutations. Am J Med Genet Part A. 2016;170A:3069–82.
3. Stevens CA, Pouncey J, Knowles D. Adults with Rubinstein-Taybi syndrome. Am J Med Genet Part A. 2011;155:1680–4.
4. Naimi DR, Munoz J, Rubinstein J, Hostoffer RW. Rubinstein-Taybi syndrome: an immune deficiency as a cause for recurrent infections. Allergy Asthma Proc. 2006;27(3):281–4.
5. Kimura H, Ito Y, Koda Y, Hase Y. Rubinstein-Taybi syndrome with thymic hypoplasia. Am J Med Genet. 1993;46(3):293–6.
6. Villella A, Bialostocky D, Lori E, Meyerson H, Hostoffer RW. Rubinstein-Taybi syndrome with humoral and cellular defects: a case report. Arch Dis Child. 2000;83(4):360–1.
7. Freitas NM, Imbronito AV, La Scala CSK, Lotufo RFM, Pustiglioni FE. Periodontal disease in a Rubinstein-Taybi syndrome patient: case report. Int J Paediatr Dent. 2006;16(4):292–6.
8. Rivas F, Fragoso R, Ramos-Zepeda R, Vaca G, Hernandez A, Gonzalez-Quiroga G, et al. Deficient cell immunity and mild intermittent hyperaminoacidemia in a patient with the Rubinstein-Taybi syndrome. Acta Paediatr. 1980;69(1):123–5.
9. Hamilton MJ, Newbury-Ecob R, Holder-Espinasse M, Yau S, Lillis S, Hurst JA, et al. Rubinstein-Taybi syndrome type 2: report of nine new cases that extend the phenotypic and genotypic spectrum. Clin Dysmorphol. 2016;25:135–45.
10. Pasic S. Rubinstein-Taybi syndrome associated with humoral immunodeficiency. J Investig Allergol Clin Immunol. 2015;25(2):137–8.
11. Rivalta B, Zama D, Pancaldi G, Facchini E, Cantarini ME, Miniaci A, et al. Evans syndrome in childhood: long term follow-up and the evolution in primary immunodeficiency or rheumatological disease. Front Pediatr. 2019;23;7:304.
12. Saettini F, Moratto D, Grioni A, Maitz S, Iascone M, Rizzari C, et al. A novel EP300 mutation associated with Rubinstein-Taybi syndrome type 2 presenting as combined immunodeficiency. Pediatr Allergy Immunol. 2018;29(7):776–81.
13. Lougaris V, Facchini E, Baronio M, Lorenzini T, Moratto D, Specchia F, et al. Progressive severe B cell deficiency in pediatric Rubinstein-Taybi syndrome. Clin Immunol. 2016;173:181–3.
14. Herriot R, Miedzybrodzka Z. Antibody deficiency in Rubinstein-Taybi syndrome. Clin Genet. 2016;89(3):355–8.
15. Shearer WT, Rosenblatt HM, Gelman RS, Oyomopito R, Plaeger S, Stiehm ER, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 Study. J Allergy Clin Immunol. 2003 Nov;112(5):973–80.
16. Sheffield protein reference unit. Available at: www.immqas.org.uk/pru.asp?ID5316. Accessed October 31, 2019. doi: https://doi.org/10.1002/ajh.24187. Epub 2015 Oct 6.
17. Farruggia P, Fioredda F, Puccio G, Porretti L, Lanza T, Ramenghi U, et al. Autoimmune neutropenia of infancy: data from the Italian Neutropenia Registry. Am J Hematol. 2015 Dec;90(12):E221–2.
18. Romaniouk I, Romero A, Runza P, Nieto C, Mouzo R, Simal F. Management of neuroendocrine tumor in a patient with Rubinstein-Taybi syndrome in chronic hemodialysis. Nefrologia. 2018;38(4):446–8.
19. Mar N, Digiuseppe JA, Dailey ME. Rubinstein–Taybi syndrome – a window into follicular lymphoma biology. Leuk Lymphoma. 2016;57(12):2908–10.
20. Kamenarova K, Simeonov E, Tzveova R, Dacheva D, Penkov M, Kremensky I, et al. Identification of a novel de novo mutation of CREBBP in a patient with Rubinstein-Taybi syndrome by targeted next-generation sequencing: a case report. Hum Pathol. 2016;47(1):144–9.
21. Torres LC, De LL CM, Delboni TP, Okay TS, Carneiro-Sampaio M, Sugayama S. Rubinstein-Taybi syndrome: a female patient with a de novo reciprocal translocation T(2; 16)(Q36.3; P13.3) and dysgranulopoiesis. Clinics. 2010;65(1):107–9.
22. Torres LC, Sugayama SMM, Arslanian C, Sales MM, Carneiro-Sampaio M. Evaluation of the immune humoral response of Brazilian patients with Rubinstein-Taybi syndrome. Brazilian J Med Biol Res. 2010;43(12):1215–24.
23. Kosaki R, Kikuchi S, Koinuma G, Higuchi M, Torii C, Kawasaki K, et al. Two patients with Rubinstein-Taybi syndrome and severe pulmonary interstitial involvement. Am J Med Genet A. 2010;152A(7):1844–6.
24. Kalyoncu U, Tufan A, Karadag O, Kisacik B, Akdogan A, Calguneri M. Rubinstein-Taybi syndrome and familial Mediterranean fever in a single patient: two distinct genetic diseases located on chromosome 16p13.3. J Natl Med Assoc. 2006;98(10):1692–3.
25. Kim CJ, Nam JH, Chung HY, Kook JH, Kim SY, Woo YJ. Kimura disease in a patient with Rubinstein-Taybi syndrome. Pediatr Int. 2004;46(5):609–11.
26. Bayle P, Bazex J, Lamant L, Lauque D, Durieu C, Albes B. Multiple perforating and non perforating pilomatricomas in a patient with Churg-Strauss syndrome and Rubinstein-Taybi syndrome. J Eur Acad Dermatology Venereol. 2004;18(5):607–10.
27. Altintas F, Cakmakkaya S. Anesthetic management of a child with Rubinstein-Taybi syndrome. Paediatr Anaesth. 2004;14(7):610–1.
28. Çaksen H, Bartsch O, Okur M, Temel H, Açikgöz M, Yilmaz C. Rubinstein-Taybi syndrome and CREBBP c.201-202delTA mutation: a case presenting with varicella meningoencephalitis. Genet Couns. 2009;20(3):255–60.
29. Shashi V, Fryburg JS. Vascular ring leading to tracheoesophageal compression in a patient with Rubinstein-Taybi syndrome. Clin Genet. 1995;48:324–7.
30. Jonas DM, Heilbron DC, Ablin AR. Rubinstein-Taybi syndrome and acute leukemia. J Pediatr. 1978;92(5):851–2.
31. Levinson ED, Spencer RP. Bone scan-demonstrated urinary tract abnormalities in a patient with Rubinstein-Taybi syndrome. Clin Nucl Med. 1980;5(10):454–6.

32. Rohlfing B, Lewis K, Singleton EB. Rubinstein-Taybi syndrome: report of an unusual case. Am J Dis Child. 1971;121(1):71–4.
33. Sinnette C, Odeku EL. Rubinstein-Taybi syndrome: the first case in an African child and the first case recognized at birth. Clin Pediatr (Phila). 1968;7:488–92.
34. Berkhout A, Prociv P, Anthony H, Anthony LT, Clare N. Two cases of neuroangiostrongyliasis: a rare disease because rarely considered or rarely diagnosed? J Paediatr Child Health. 2019;55(12):1463–9.
35. Noble A, Drouin E, Faure C. Eosinophilic esophagitis and gastritis in Rubinstein-Taybi syndrome. J Pediatr Gastroenterol Nutr. 2007;44(4):498–500.
36. Shaheed MM, Khamaheh R, Rifai SZ, Abomelha AM. Rubinstein Taybi syndrome and lymphoblastic leukemia. Saudi Med J. 1999;20(10):800–2.
37. ESID Registry Working Party. ESID Registry - Working definitions for clinical diagnosis of IEI 2019;1–33. **Available from:** https://esid.org/content/download/16792/456144/file/ESIDRegistry_ClinicalCriteria.pdf
38. Pieper K, Rizzi M, Speletas M, Smulski CR, Sic H, Kraus H, et al. A common single nucleotide polymorphism impairs B-cell activating factor receptor's multimerization, contributing to common variable immunodeficiency. J Allergy Clin Immunol. 2014;133:1222–1225.e10.
39. Ming J.E., Stiehm E.R. Syndromic immunodeficiencies. In: Rezaei N., Aghamohammadi A., Notarangelo L. (eds) Primary immunodeficiency diseases. 2017; Springer, Berlin, Heidelberg.
40. Oliveira JB, Bleesing JJ, Dianzani U, Fleisher TA, Jaffe ES, Lenardo MJ, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood. 2010;116(14):e35–40.
41. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, et al. The EUROclass Trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111(1):77–85.
42. Posey JE, Harel T, Liu P, Rosenfeld JA, James RA, Coban Akdemir ZH, et al. Resolution of disease phenotypes resulting from multilocus genomic variation. N Engl J Med. 2017;376(1):21–31.
43. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, et al. Primary immunodeficiency diseases: genomic approaches delineate heterogeneous Mendelian disorders. J Allergy Clin Immunol. 2017 Jan;139(1):232–45.
44. Notarangelo LD. PIDs and cancer: an evolving story. Blood. 2010;116(8):1189–90.

Affiliations

Francesco Saettini[1] · Richard Herriot[2] · Elisabetta Prada[3] · Mathilde Nizon[4,5] · Daniele Zama[6] · Antonio Marzollo[7] · Igor Romaniouk[8] · Vassilios Lougaris[9] · Manuela Cortesi[9] · Alessia Morreale[9] · Rika Kosaki[10] · Fabio Cardinale[11] · Silvia Ricci[12] · Elena Domínguez-Garrido[13] · Davide Montin[14] · Marie Vincent[4,5] · Donatella Milani[3] · Andrea Biondi[1] · Cristina Gervasini[15] · Raffaele Badolato[8]

1 Pediatric Hematology Department, Fondazione MBBM, University of Milano Bicocca, via Pergolesi 33, 20900 Monza, Italy

2 Immunology Department, Aberdeen Royal Infirmary, Aberdeen, UK

3 Department of Pathophysiology and Transplantation, Pediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

4 Service de Génétique Médicale, CHU de Nantes, 44000 Nantes, France

5 Inserm, CNRS, l'institut du thorax, Universite de Nantes, 44000 Nantes, France

6 Pediatric Oncology and Hematology Unit "Lalla Seràgnoli", Department of Pediatrics, Sant'Orsola Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

7 Department of Women's and Children's Health, Pediatric Hemato-Oncology, University Hospital of Padova, Padova, Italy

8 Departamento de Nefrología, Hospital Universitario de Santiago, Santiago de Compostela, Spain

9 Department of Clinical and Experimental Sciences, Pediatrics Clinic and Institute for Molecular Medicine A. Nocivelli, ASST-Spedali Civili of Brescia, University of Brescia, Brescia, Italy

10 Division of Medical Genetics, National Center for Child Health and Development, 2-10-1 Okura Setagaya-ku, Tokyo 157-8535, Japan

11 Policlinic Giovanni XXIII, Bari, Italy

12 Pediatric Immunology, Meyer Children's University Hospital, Florence, Italy

13 Molecular Diagnostic Unit, Fundación Rioja Salud, Logrono, La Rioja, Spain

14 Division of Immunology and Rheumatology, Department of Paediatric Infectious Diseases, Regina Margherita Children's Hospital, University of Turin, Turin, Italy

15 Department of Medical Genetics, University of Milan, Milan, Italy