in IL-10 and IL-13 regulation in monocytes. Therefore we treated PBMCs from patients with AD who were sensitized to Mala s 13 with lactic acid to remove surface-bound IgE.[E3,E4] By using this treatment, surface levels of IgE on monocytes were reduced (Fig 1, *D*), and IL-10 secretion was significantly increased after Mala s 13 stimulation but not after hTrx stimulation (Fig 1, *E*). In contrast, IL-13 secretion could be reduced after lactic acid treatment followed by hTrx stimulation but not by Mala s 13 stimulation (Fig 1, *E*). An explanation for these discrepancies might be the small fraction of Mala s 13– and hTrx-specific IgE in relation to the patient's total serum IgE levels. In fact, the increase in IL-10 levels after IgE stripping and stimulation with Mala s 13 correlated with the *Malassezia* species–specific IgE/total IgE ratio (Spearman $r = 0.536$, $P = .048$). In turn, this can be explained by the correlation of monocyte surface levels of FcεRI with total serum IgE levels.[6]

Our findings are in contrast to those of previous reports showing an increased IL-10 secretion of FcεRI-activated monocytes.[7,8] This might be due to differences in the experimental setup, such as the use of monoclonal IgE and anti-IgE for receptor cross-linking compared with our assay by using 1 distinct allergen, as well as due to different cell-culture conditions and the time point of analysis. Using anti-IgE stimulation, we could also upregulate IL-10 in PMBCs from patients with AD who were sensitized to *Malassezia* species (see Fig E3 in this article's Online Repository at www.jacionline.org). Therefore this discrepancy between massive IgE receptor cross-linking with anti-IgE and the potentially weaker cross-linking resulting from application of native allergens should be considered in future studies.

The major findings of this study are (1) an IgE-dependent upregulation of the T_H2 cytokine IL-13 by hTrx and (2) an impaired upregulation of IL-10 by hTrx in patients with AD who were sensitized to Mala s 13 and hTrx. IL-10 promotes the development of regulatory dendritic cells and T cells and therefore tolerance, and it is involved in a number of processes involved in the downregulation of a local inflammatory response.[9] The relative lack of antigen-specific IL-10 secretion in PBMCs from patients with AD who were sensitized to *Malassezia* species might contribute to the perpetuation of the local cutaneous inflammation in patients with AD and to further development of T_H2- and IgE-mediated immune responses. Moreover, specific sensitization against hTrx can directly be involved in disease exacerbation in patients with AD because hTrx can be released from dermal or epidermal cells and might then promote inflammatory responses by activating specific T cells and cells expressing receptors for IgE.

We thank Mrs Gabriele Begemann, Petra Kienlin, and Ute Staar for their excellent technical assistance.

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Supported by a grant from the German Research Foundation (DFG) to GRK 1441/1 and DFG-KliFo 250 (WE 1289/8-1). Work at SIAF was supported by the Swiss National Science Foundation (grant nos. 3200_146247 and 32NM30_136032/1 [EuroNanoMed]) and the Karolinska Institutet by the Swedish Research Council.

Disclosure of potential conflict of interest: This study was supported by a grant the German Research Foundation (DFG) to GRK 1441/1 and DFG-KliFo 250 (WE 1289/8-1). Work at SIAF was supported by the Swiss National Science Foundation (grant nos. 3200_146247 and 32NM30_136032/1 [EuroNanoMed]) and the Karolinska Institutet by the Swedish Research Council. S. Hradetzky has received money from the European Academy of Allergy and Clinical Immunology (the Abstract Prize at EAACI Congress 2014). R. Crameri has received funding from the Swiss National Science Foundation. A. Scheynius's institution has received funding from the Swedish Research Council. The rest of the authors declare that they have no relevant conflicts of interest.

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Available online December 6, 2014.
http://dx.doi.org/10.1016/j.jaci.2014.10.038

RAC2 loss-of-function mutation in 2 siblings with characteristics of common variable immunodeficiency

To the Editor:

Common variable immunodeficiency (CVID) represents a heterogeneous group of disorders with variable immunologic and clinical phenotypic features, including hypogammaglobulinemia, recurrent infections, and autoimmunity.[1] Over the past decades, a number of genetic defects have been identified that are associated with CVID. However, these alterations only account for the cause of a minority of CVID cases (<15%).[1] In this article we present a novel genetic defect in the Ras-related C3 botulinum toxin substrate 2 *(RAC2)* gene in 2 siblings previously given a diagnosis of CVID.

TABLE I. Laboratory and immunologic data of 2 patients with RAC2 deficiency

Laboratory test	Proband	Sibling	Reference values*
Complete blood count	Age 1 y	Age 7 y	
WBC/mm^3	9,200	7,800	4,000-11,000
Neutrophils (%)	62	66	20-70 (for age 1 y)
			35-80 (for age 7 y)
Lymphocytes (%)	27↓	25↓	45-75 (for age 1 y)
			30-55 (for age 7 y)
CD3$^+$ (%)	60	62	30-78†
CD4$^+$ (%)	30	25	22-58†
CD8$^+$ (%)	33	35	10-37†
CD4$^+$/CD8$^+$ ratio	0.9↓	0.7↓	1-4†
CD19$^+$ (%)	2.5↓	8.5	3-14†
Serum complement factors	Age 1 y	Age 7 y	
C3 (mg/dL)	79↓	110	83-177
C4 (mg/dL)	27	20	15-45
Neutrophil analyses	Age 7 y	Age 28 y	
CD18$^+$ (%)	70	NA	70-100
CD11a$^+$ (%)	92↑	NA	60-90
CD11b$^+$ (%)	98↑	NA	60-90
CD11c$^+$ (%)	99↑	NA	45-80
NBT test (%)	98	NA	95-100
Chemotaxis without CF (μm)	NA	10↓	22-54
Chemotaxis with CF (μm)	NA	45↓	77-125
Serum immunoglobulins	Age 7 y	Age 10 y	
IgM (mg/dL)	30↓	28↓	40-230
IgG (mg/dL)	430↓	640↓	700-1600
IgA (mg/dL)	5↓	19↓	41-297 (for age 7 y)
			51-297 (for age 10 y)
Vaccine antibodies		Age 27 y	
Antibody level before Pneumovax 23 (U/mL)	NA	1↓	1.2-2
Antibody 3 wk after Pneumovax 23 (U/mL)	NA	8↓	10-14
Antibody 1 y after Pneumovax 23 (U/mL)	NA	8	6-9
Anti-tetanus (IU/mL)	NA	1.56	>0.1
Anti-diphtheria (IU/mL)	NA	0.4	>0.1
Autoantibodies and thyroid markers	Age 7-16 y	Age 10-16 y	
ANA	Negative	Negative	Negative
ANCA	Negative	Negative	Negative
Anti-dsDNA	Negative	Negative	Negative
Anti-TPO (IU/mL)	68↑	81↑	0-35
TSH (mU/L)	11.4↑	11.0↑	0.4-5.5
T3 (μg/dL)	30	33	25-36
T4 (nmol/L)	8	4↓	5-14
PTH (pg/mL)	194↑	NA	15-65
GH (ng/mL)	NA	1.3↓	10-40
Anti-IgA (U/mL)	NA	2.0	1.5-2.9
Other tests	Age 18 y	Age 25 y	
KRECs	2↓	8↓	(85, 22)‡
TRECs	24↓	10↓	(67, 23)‡

ANA, Anti-nuclear antibody; *ANCA*, anti-neutrophil cytoplasmic antibody; *Anti-dsDNA*, anti–double-stranded DNA antibody; *Anti-TPO*, anti-thyroperoxidase antibody; *CF*, chemotactic factor; *GH*, growth hormone; *KRECs*, κ-deleting recombination excision circles; *NA*, not analyzed; *NBT*, nitroblue tetrazolium; *PTH*, parathyroid hormone; *TSH*, thyroid-stimulating hormone.
*Reference: Age-appropriate reference range or value from healthy Iranian subjects.
†The local hospital reference range is not stratified for age between 1 and 7 years.
‡Because of the lack of appropriate reference values for the adult population, results of the TREC and KREC analyses were compared with those of 2 age-matched healthy control subjects.

The proband, a 21-year-old woman of Iranian descent born to first-degree consanguineous parents, presented at 6 months of age with recurrent pneumonia, followed by edema, proteinuria, and membranous glomerulonephritis 6 months later, at which time serum IgA was undetectable and her serum IgG level was increased (see Table E1 in this article's Online Repository at www.jacionline.org). Based on the clinical presentation and an increased anti–streptolysin O titer, a diagnosis of poststreptococcal glomerulonephritis (PSGN) was made along with a tentative diagnosis of selective IgA deficiency. At 1 year of age, the patient had a normal percentage of CD3$^+$ T cells, a slightly reduced ratio of CD4$^+$/CD8$^+$ T cells, and a decreased percentage of CD19$^+$ B cells (Table I). Coagulation factor XI deficiency (activity <1%) was diagnosed at 2 years of age. Dermatologic features developed 3 years later, including urticaria (induced by exposure to sunlight), recurrent erythematous plaques, and food allergy requiring corticosteroid therapy. Her neutrophil markers and nitroblue tetrazolium test results were normal, but the IgG level decreased to 430 mg/dL by 7 years of age. Thus a diagnosis of CVID was made, and intravenous immunoglobulin treatment was initiated (Table I and see Table E1). Other morbidities in the following years included arthralgia, bronchiectasis, hypothyroidism with anti-thyroperoxidase antibodies, and hyperparathyroidism (Table I). Her PSGN progressed to end-stage renal disease requiring renal transplantation. She died as a result of graft rejection and possible cerebral hemorrhage at the age of 21 years.

Her 28-year-old brother presented at 2 years of age with recurrent sinopulmonary infections and failure to thrive. Urticaria and sinusitis occurred at age 7 years, when selective IgA deficiency was diagnosed with normal T- and B-cell percentages in peripheral blood (Table I and see Table E1). At 8 years of age, he had pneumonia and subsequent PSGN (with an increased anti–streptolysin O titer). Coagulation factor XI deficiency was diagnosed at the age of 10 years. His IgM and IgG serum levels were also reduced at this age (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org), when a diagnosis of CVID was established and intravenous immunoglobulin replacement was commenced. Between 10 and 16 years of age, he had submandibular reactive lymphadenopathy, bronchiectasis, hypothyroidism with anti-thyroperoxidase antibodies, and growth hormone deficiency (Table I). A recent extended lymphocyte immunophenotyping showed severe B-cell lymphopenia and abnormalities in T-cell subpopulations, with reversed ratio of CD4$^+$/CD8$^+$ T cells, decreased percentages of naive CD4$^+$ and CD8$^+$ T cells, and reduced percentages of regulatory T and recent thymic emigrant cells (see Table E3 in this article's Online Repository at www.jacionline.org).

A novel homozygous nonsense mutation in codon 56 (W56X) was identified in the *RAC2* gene in the proband by means of whole-exome sequencing (WES) analysis. Mutations in *F11*, encoding the coagulation factor XI, was excluded by using both Sanger sequencing and WES data, with detailed information on methods provided in the Methods section in this article's Online Repository at www.jacionline.org. All known causative gene defects responsible for CVID were furthermore excluded in this patient based on the WES data. Sanger sequencing confirmed the homozygous *RAC2* mutation in the proband, her brother, and in a heterozygous form in their mother (Fig 1, *A* and *B*). Western blot analysis was subsequently carried out on fibroblast cells transfected with either a wild-type RAC2 plasmid or

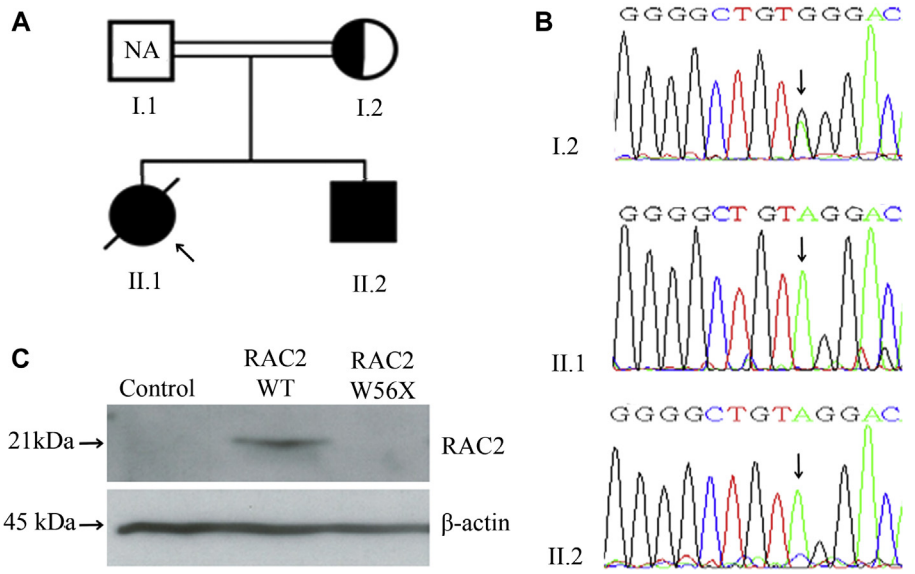

FIG 1. A, Family pedigree (*solid fill*, homozygous; *half fill*, heterozygous carrier). The proband is indicated by an *arrow*. The father's sample was not available *(NA)*. **B,** Sequence analysis of the *RAC2* gene. **C,** Detection of RAC2 expression by using Western blot analysis. *Control*, Fibroblast cells without transfection.

a RAC2 mutant (RAC2W56X)–containing plasmid. The expression of RAC2 was completely absent in cells transfected with the mutant identified in the patients (Fig 1, *C*).

The affected gene encodes RAC2, a hematopoietic-specific member of the Rho family of guanosine triphosphatases (Rho GTPase), which are crucial regulators of cell signaling and the actin cytoskeleton. Because RAC2 deficiency has mainly been associated with neutrophil dysfunction,[2] neutrophils from the proband were analyzed by using transmission electron microscopy. The number of primary (azurophilic) and secondary (specific) granules per square micrometer of cytoplasm was significantly reduced in the proband ($3.8 \pm 0.7/\mu m^2$ vs $5.9 \pm 1.3/\mu m^2$ in the control subject; $P = 2.3 \times 10^{-5}$, Student *t* test). Furthermore, the shape of the secondary granules in the proband was often more elongated or collapsed (Fig 2, *C*) compared with that in the control subject (Fig 2, *D*). Cytoplasmic inclusions were also more frequent in the proband (Fig 2, *A*). The majority of inclusions were very dense and composed of a multimembrane layer surrounded by a double membrane (Fig 2, *E*) and were interpreted as autophagosomes. Morphologic differences between the primary granules of the proband and the control subject were not observed. Finally, a chemotactic defect was observed in the neutrophils derived from the affected brother (Table I).

To date, only *de novo* dominant negative mutations affecting *RAC2* (D57N) have been reported in 2 male infants.[3-5] The first case presented with a complex neutrophil dysfunction disease, which was characterized by multiple and progressive soft-tissue infections during the first few weeks of life, neutrophilia, and a neutrophil chemotaxis defect.[3,4] The second case was an apparently healthy 2-week-old infant, who exhibited reduced numbers of T-cell receptor excision circles (TRECs) in the Wisconsin statewide newborn screening for T-cell lymphopenia.[5] Further testing revealed leukocytosis, neutrophilia, $CD4^+$ T-cell lymphopenia, and reduced serum IgA and IgM levels.[5] He later had fever, omphalitis, and a paratracheal abscess, and neutrophil chemotaxis was severely reduced.[5] Both infants underwent successful hematopoietic cell transplantations.[4,5]

For the first time, we describe a homozygous loss-of-function *RAC2* mutation in 2 patients with early-onset and progressive hypogammaglobulinemia. As shown in Table E4 in this article's Online Repository at www.jacionline.org, the clinical and laboratory findings of our patients differ from those of the previously reported cases in many respects. Notably, our patients did not present with severe clinical abnormalities in the neonatal period associated with neutrophil dysfunction. This might be explained by the fact that the previously reported cases involved expression of a dominant negative protein, which affected the GTPase activity not only of RAC2 but also of RAC1, the other major RAC GTPase expressed in human neutrophils.[6,7] Nevertheless, neutrophils from our patients showed reduced chemotaxis activity and, as revealed by using transmission electron microscopic analysis, reduced numbers of neutrophil granules, as well as morphologic changes of the secondary granules, suggesting that neutrophil functions were still affected by the *RAC2* loss-of-function mutation. The antibody deficiency observed in our patients supports an important role of RAC2 in T- and B-cell development, as also suggested by murine studies,[8] as well as some of the immunologic features observed in the second infant carrying the D57N mutation.[5] No Guthrie cards were available from our patients that would allow a retrospective analysis of TRECs. However, we did observe a reduced number of TRECs and κ-deleting recombination excision circles in the patients' peripheral blood compared with age-matched control values, which, in line with the immunophenotyping data, might suggest a decreased number of recent thymic emigrants and a relative B-cell lymphopenia in both patients (Table I and see Table E2). It is also of note that the antibody deficiency in our patients and the B-cell lymphopenia in the brother was progressive, a feature that was not possible to evaluate in the previous cases

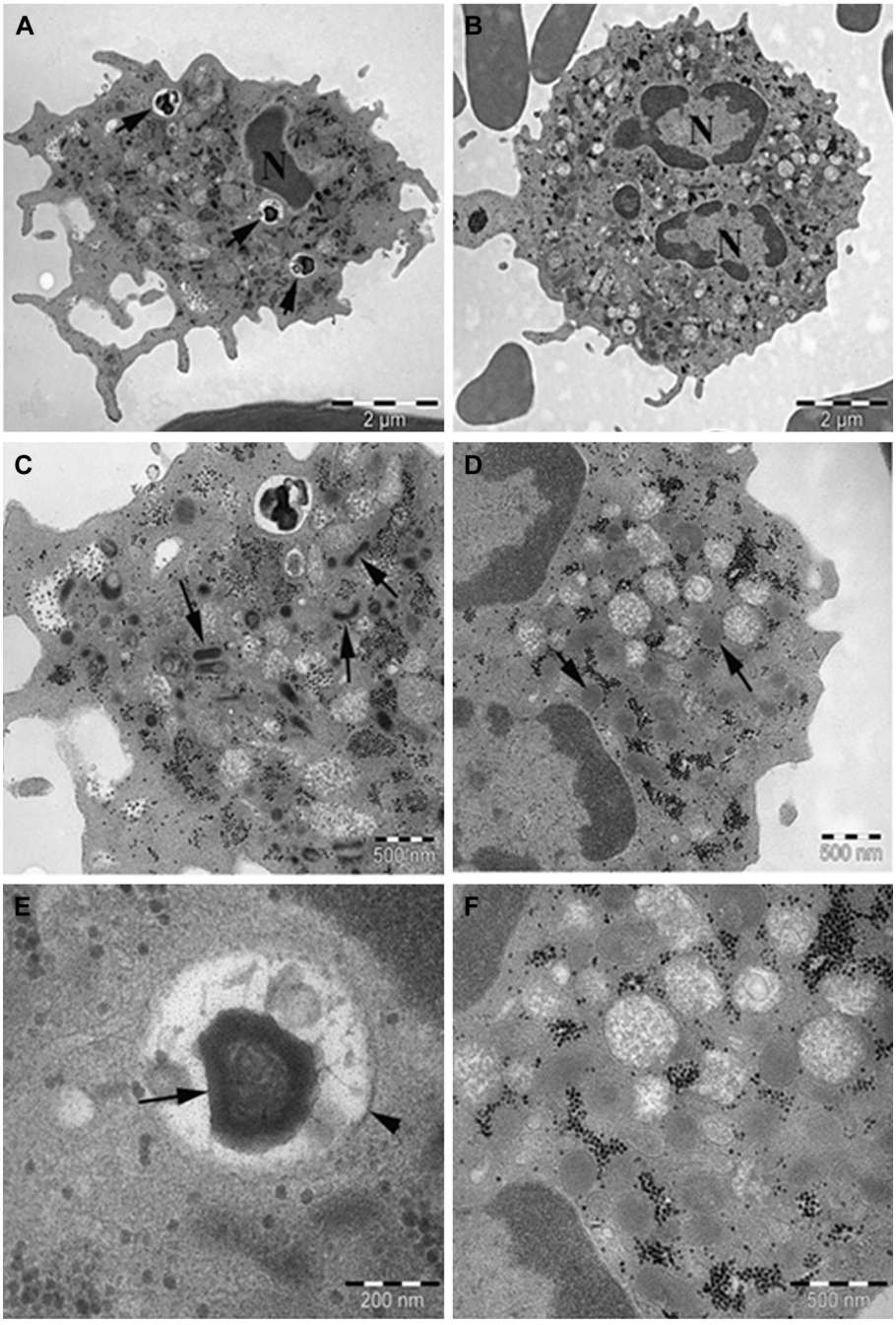

FIG 2. Transmission electron microscopic images of neutrophils. **A,** Proband: cytoplasmic inclusions *(arrow)*. **B,** Control subject: normal ultrastructure. **C,** Proband: fewer cytoplasmic granules, with most secondary granules displaying an elongated or collapsed shape *(arrow)*. **D,** Control subject: normal rounded secondary granules *(arrow)*. **E,** Proband: cytoplasmic inclusion, showing a dense multimembrane layered structure *(arrow)* surrounded by a double membrane *(arrowhead)*. **F,** Control subject: normal ultrastructure.

because they received hematopoietic cell transplantation already at the age of 10 and 3 months, respectively. The urticaria in our patients might be further related to the mast cell defects, as observed in *Rac2*$^{-/-}$ bone marrow–derived mast cells.[9] However, pinpointing a specific mechanism will require additional investigations. Other phenotypes in our patients, such as multiple hormone deficiencies, coagulation factor XI deficiency, and PSGN, might not be attributable directly to the *RAC2* mutation because expression of *RAC2* is highly regulated and considered hematopoietic specific. However, these phenotypes might be secondary to the overall increased susceptibility to infections (especially for PSGN) and/or autoimmunity in our patients (evident by an increased serum level of B cell–activating factor [BAFF] in the brother, data not shown). Thus the polyendocrinopathies, coagulopathy, and kidney disease observed might be part of a syndromic entity related to RAC2 deficiency, as is the case in

selected forms of primary immunodeficiency with autoimmune features.

Our patients illustrate that different types of mutations in a given gene might be associated with vastly different clinical phenotypes.[10] Further investigation of the mutation identified in this report might help to elucidate the function of this gene in relation to this CVID-like but more complex immunodeficiency.

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Supported by the Swedish Research Council, the Swedish Cancer Society, the Jeffrey Modell Foundation, the European Research Council (242551-ImmunoSwitch), the German Federal Ministry of Education and Research (BMBF 1315883), and a National Institutes of Health grant (5R01DK062757-12).

Disclosure of potential conflict of interest: This work was supported by the Swedish Research Council, the Swedish Cancer Society, the Jeffrey Modell Foundation, the European Research Council (242551-ImmunoSwitch), the German Federal Ministry of Education and Research (BMBF 1315883), and a National Institutes of Health (NIH) grant (5R01DK062757-12). R. R. Graham is employed by Genentech. T. W. Behrens is employed by Genentech, from which he has received stock/stock options. The rest of the authors declare that they have no relevant conflicts of interest.

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Available online December 12, 2014.
http://dx.doi.org/10.1016/j.jaci.2014.10.039

Long-term remission after allogeneic hematopoietic stem cell transplantation in LPS-responsive beige-like anchor (LRBA) deficiency

To the Editor:

LPS-responsive vesicle trafficking, beach and anchor containing protein (LRBA) deficiency has been identified as a primary immunodeficiency (PID) characterized by recurrent infections associated with autoimmunity, such as inflammatory bowel disease and autoimmune cytopenias (see Fig E1 in this article's Online Repository at www.jacionline.org).[1-3] A wide range of immunosuppressive treatment measures have only induced temporary relief in affected subjects. Although allogeneic hematopoietic stem cell transplantation (HSCT) is the current treatment for many forms of PIDs, HSCT is less established in patients with autoimmune disease[4,5] and has not yet been reported in LRBA-deficient patients.

We studied a consanguineous family of Kurdish origin with a systemic autoimmune disorder. Patient 1's symptoms started at 2 years of age with immune thrombocytopenia (ITP; Fig 1, *A*). Serum immunoglobulin concentrations were slightly increased, and the cellular immunophenotype was normal (Table I and see Table E1 in this article's Online Repository at www.jacionline.org). A lymph node biopsy performed because of generalized lymphoproliferative disease (LPD) revealed a follicular lymphatic hyperplasia with abundant (about 20% to 30%) $CD3^+$ and $CD4^-$ and $CD8^-$ double-negative T lymphocytes (DNT cells; Fig 1, *C*), suggesting an immune dysregulation, lymphocyte maturation, or apoptosis defect compatible with autoimmune lymphoproliferative syndrome (ALPS).[6,7] HSCT was performed with the clinically healthy HLA-identical mother as the donor (see the additional text in this article's Online Repository at www.jacionline.org), leading to complete remission with persisting full donor chimerism and without signs of acute or chronic graft-versus-host disease (GvHD). Four years after HSCT, ITP relapsed but responded well to high-dose intravenous immunoglobulin (IVIG) treatment. When romiplostim was started, platelet counts normalized, and administration of romiplostim (5 μg/kg, every 4 to 6 weeks) without further need for immunosuppression or IVIG has led to sustained but treatment-dependent remission.[8]

Patient 2, the now 11-year-old younger sister of patient 1, became symptomatic at 5 years of age (fulminant autoimmune hemolytic anemia; Fig 1, *B*). Immunosuppression was started immediately (corticosteroids, mycophenolate mofetil, and vincristine), leading to a sustained remission (Fig 1, *B*). Rituximab was administered

METHODS

Clinical investigations

Informed consent for this study was obtained from the proband and her relatives in accordance with the principles of the ethics committee of the Tehran University of Medical Sciences.

Immunologic analyses

During follow-up, we performed different investigations according to previously published methods, including measurement of complete blood counts, serum immunoglobulin levels,[E1] vaccine responses,[E2] frequency and/or function of regulatory T cells,[E3] naive T cells,[E4] and recent thymic emigrant T cells.[E4] A neutrophil chemotaxis assay was performed with zymosan-activated serum, as previously described.[E5]

Serum BAFF measurement

The concentration of BAFF was assessed in stored serum samples by using the Human BAFF (TNFSF13B) SimpleStep ELISA Kit (Abcam, Cambridge, United Kingdom), according to the manufacturer's instructions. Two healthy control subjects were included. Statistical analysis (nonparametric analysis [Kruskal-Wallis test]) was performed with Excel software.

Flow cytometric immunophenotyping

Venous blood was collected in EDTA tubes, and the samples were processed within 36 hours. Antibody combinations were used for polychromatic 8-color surface staining panels and optimized, as previously published.[E6]

WES and validation by means of Sanger sequencing

The methods for DNA library preparation, read mapping, and variant analysis and the analysis protocol for WES were performed, as described previously.[E1] Sanger sequencing with specific primers (forward, GGAATGA CATGGAGCTGGAC; reverse, AAGATGGGCACATTGAGGAC) was performed to validate the potential disease-causing variant. PCR reactions were performed, as described previously.[E1] The purified PCR products were sequenced by Macrogen Incorporated (Seoul, South Korea).

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TABLE E1. Immunoglobulin levels at different ages for patients with RAC2 deficiency

Age (y):	1	4	5	6	7	8	9	10	11	12	14	15	16	19	20
Proband															
IgM (mg/dL)	180	40	95	110	30↓	42	182	NA	NA	NA	73	40	NA	50	NA
IgG (mg/dL)	1800↑	800	650↓	940	430↓*	380↓	600↓	NA	NA	NA	780	790	NA	700	NA
IgA (mg/dL)	0↓	20	0↓	0↓	5↓	5↓	0↓	NA	NA	NA	30↓	40↓	NA	0↓	NA
IgE (IU/mL)	9	NA	NA	NA	<5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sibling															
IgM (mg/dL)	NA	NA	NA	NA	105	190	17↓	28↓	36↓	19↓	0↓	NA	21↓	NA	58
IgG (mg/dL)	NA	NA	NA	NA	900	750	754	640↓*	520↓	600↓	99↓	NA	542↓	NA	130↓
IgA (mg/dL)	NA	NA	NA	NA	0↓	0↓	0↓	19↓	19↓	9↓	0↓	NA	0↓	NA	10↓
IgE (IU/mL)	NA	NA	NA	NA	5.3	NA	NA	NA	NA	NA	<5	NA	NA	NA	NA

Age-matched reference levels: *1-3 years*—IgM, 55-210 mg/dL; IgG, 700-1600 mg/dL; IgA, 19-220 IU/mL; IgE, <100 IU/mL; *4-5 years*—IgM, 40-230 mg/dL; IgG, 700-1600 mg/dL; IgA, 48-345 mg/dL; *6-7 years*—IgM, 40-230 mg/dL; IgG, 700-1600 mg/dL; IgA, 41-297 mg/dL; IgE, <100 IU/mL; *8-10 years*—IgM, 40-230 mg/dL; IgG, 700-1600 mg/dL; IgA, 51-297 mg/dL; *11-13 years*—IgM, 40-230 mg/dL; IgG, 700-1600 mg/dL; IgA, 44-395 mg/dL; and ≥*14 years*—IgM, 40-230 mg/dL; IgG, 700-1600 mg/dL; IgA, 70-400 mg/dL; IgE, <100 IU/mL.

NA, Not analyzed.

*Treatment with intravenous immunoglobulin was started, with controlled kidney disorder and normal total protein and albumin levels.

TABLE E2. IgG subclass levels in the 2 siblings with RAC2 deficiency

	Proband	Sibling
IgG subclass level (mg/dL)	**Age 4 y**	**Age 10 y**
IgG_1 (reference values)	405 (253-1019)	50↓ (289-934)
IgG_2 (reference values)	73 (54-435)	<15↓ (82-516)
IgG_3 (reference values)	172↑ (9-102)	12↓ (20-103)
IgG_4 (reference values)	15 (1-108)	<5 (0.3-111)

Reference: Age-appropriate reference range from healthy Iranian subjects.

TABLE E3. Lymphocyte subpopulations in the sibling with RAC2 deficiency

Laboratory test	Sibling	Reference range
Age at testing 26 y		
$CD4^+CD25^+FOXP3^+$ regulatory T cells (%)	1.4↓	3.4-5.66
FOXP3 expression in PBMCs (%)	1.5↓	2.7-4.8
Regulatory T-cell suppressor capacity (%)	18↓	30-80
$CD45RA^+CD62L^+CD4^+$ naive T cells (%)	17.4↓	35-54
$CD31^+CD45RA^+CD62L^+CD4^+$ recent thymic emigrant T cells (%)	26.4↓	32-50
Age at testing 28 y		
NK cells (%)	11.7	3-22
$CD19^+$ cells (%)	0↓	6-23
$CD3^+$ cells (%)	87↑	56-84
$CD4^+$ cells (%)	26↓	31-52
$CD8^+$ cells (%)	57↑	18-35
CD4/CD8 cell ratio	0.5↓	1.0-3.6
NK T cells (%)	7.7	2.1-13.7
$CD4^-CD8^-$ T cells (%)	3.8	3-10.2
$CD4^+CD8^-$ T cells (%)	0.6	0.2-1.4
$CD4^+CD38^+$ T cells (%)	51	50-79
$CD4^+$HLA-DR^+ T cells (%)	30↑	5-25
$CD4^+CD38^+$HLA-DR^+ T cells (%)	10↑	2-6
$CD8^+CD38^+$ T cells (%)	55	33-80
$CD8^+$HLA-DR^+ T cells (%)	66↑	5-25
$CD8^+CD38^+$HLA-DR^+ T cells (%)	42↑	3-18
$CCR7^+CD45RA^+CD45RO^-CD4^+$ naive T cells (%)	9.8↓	20.2-51.1
Effector memory $CD4^+$ T cells (%)	55.2	27.5-56.8
T_H1 cells (%)	21.0	4.5-25.5
T_H2 cells (%)	3.1	1.5-11.3
Central memory $CD4^+$ T cells (%)	10.2	7.7-17.5
T cells (naive/effector memory)	0.2↓	0.3-3.2
T_H17 cells	39.4↑	15.1-37.0
Naive $CD8^+$ T cells (%)	1.8↓	28.4-66.7
Effector memory $CD8^+$ T cells (%)	67.0↑	11.5-42.6
Activated effector memory $CD8^+$ T cells (%)	1.9	0-22.4
Activated cytolytic effector $CD8^+$ T cells (%)	0.2	<5.9
Effector $CD8^+$ T cells (%)	15.9	7.4-24.6
Central memory $CD8^+$ T cells (%)	1.0	0.5-5.6

CD62L, CD62 ligand; *FOXP3*, Forkhead box protein 3; *NK*, natural killer.

TABLE E4. Comparison of cases with RAC2 deficiency

Parameters	Proband	Sibling	Colorado case[E7,E8]	Wisconsin case[E9]
Sex	Female	Male	Male	Male
Mutation	W56X Hom	W56X Hom	D57N Het	D57N Het
Effect of mutation	Absent expression	Absent expression	Dominant negative	Dominant negative
Age at onset of clinical symptoms	6 mo	2 y	5 wk	26 d
Age at genetic diagnosis	19 y	23 y	Within 10 mo of life	Within 5 wk of life
Clinical features	Recurrent pneumonia, hypogammaglobulinemia, PSGN, factor XI deficiency, urticaria, allergy, bronchiectasis, hypothyroidism, hyperparathyroidism, ESRD	Recurrent sinopulmonary infections, hypogammaglobulinemia, urticaria, PSGN, factor XI deficiency, lymphadenopathy, bronchiectasis, hypothyroidism, GH deficiency	Recurrent perirectal abscess, umbilical stump involution failure, infected urachal cyst, failure of surgical wound healing	Periumbilical erythema, macrocytic anemia, paratracheal abscess
WBC/mm^3	Normal	Normal	High	High
Neutrophils (%)	Normal	Normal	High	High
Lymphocytes (%)	Reduced	Reduced	Low-normal	Reduced/normal
T cells (%)	Normal	Normal	Low-normal	Reduced/normal
B cells (%)	Reduced	Normal at age 7 y, reduced at age 28 y	Low-normal	Reduced/normal
IgM (mg/dL)	Normal, then reduced	Normal, then reduced	Normal	Reduced
IgG (mg/dL)	Normal, then reduced	Normal, then reduced	Normal	Normal
IgA (mg/dL)	Reduced	Reduced	Normal	Reduced
Neutrophil chemotaxis	NA	Moderately reduced	Markedly reduced	Markedly reduced
Oxidative burst*	Normal	NA	Normal	Normal
CD18$^+$ (%)	Normal	NA	NA	Normal
CD11a$^+$ (%)	Slightly increased	NA	NA	NA
CD11b$^+$ (%)	Slightly increased	NA	Normal	Normal
CD11c$^+$ (%)	Increased	NA	Normal	NA
C3 (mg/dL)	Slightly reduced	Normal	Reduced/normal†	NA
C4 (mg/dL)	Normal	Normal	NA	NA
KRECs	Reduced	Reduced	NA	NA
TRECs	Reduced	Reduced	NA	Reduced
Organisms isolated	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	*Escherichia coli*, *Enterococcus* species and *Pseudomonas aeruginosa*	*Stenotrophamonas* and *Prevotella* species
Treatment	Antibiotics, IVIG, immunosuppressive therapy, levothyroxine, renal transplant	Antibiotics, IVIG, immunosuppressive therapy, levothyroxine	Antibiotics, prednisolone, granulocyte transfusion, BMT	Surgical debridement, abscess drainage, granulocyte transfusion, HSCT
Outcome	Dead at 21 y from transplant rejection and suspected cerebral hemorrhage	Alive	Cured after BMT	Cured after HSCT

All clinical immunologic details of the previously reported cases can be found in Ambruso et al[E7] and Kurkchubasche et al[E8] (the Colorado case) and Accetta et al[E9] (Wisconsin case).

BMT, Allogeneic bone marrow transplantation; *ESRD*, end-stage renal disease; *GH*, growth hormone; *Het*, heterozygous; *Hom*, homozygous; *HSCT*, allogeneic cord blood hematopoietic stem cell transplantation; *IVIG*, intravenous immunoglobulin; *KRECs*, κ-deleting recombination excision circles; *NA*, not analyzed.

*Oxidative burst tested with phorbol myristate acetate.

†Serum complement is mentioned to be reduced and normal in Kurkchubasche et al[E8] and Accetta et al,[E9] respectively.