J Clin Immunol (2015) 35:189–198
DOI 10.1007/s10875-014-0126-0

ORIGINAL RESEARCH

DOCK8 Deficiency: Clinical and Immunological Phenotype and Treatment Options - a Review of 136 Patients

Susanne E. Aydin · Sara Sebnem Kilic · Caner Aytekin · Ashish Kumar · Oscar Porras · Leena Kainulainen · Larysa Kostyuchenko · Ferah Genel · Necil Kütükcüler · Neslihan Karaca · Luis Gonzalez-Granado · Jordan Abbott · Daifulah Al-Zahrani · Nima Rezaei · Zeina Baz · Jens Thiel · Stephan Ehl · László Marodi · Jordan S. Orange · Julie Sawalle-Belohradsky · Sevgi Keles · Steven M. Holland · Özden Sanal · Deniz C. Ayvaz · Ilhan Tezcan · Hamoud Al-Mousa · Zobaida Alsum · Abbas Hawwari · Ayse Metin · Susanne Matthes-Martin · Manfred Hönig · Ansgar Schulz · Capucine Picard · Vincent Barlogis · Andrew Gennery · Marianne Ifversen · Joris van Montfrans · Taco Kuijpers · Robbert Bredius · Gregor Dückers · Waleed Al-Herz · Sung-Yun Pai · Raif Geha · Gundula Notheis · Carl-Philipp Schwarze · Betül Tavil · Fatih Azik · Kirsten Bienemann · Bodo Grimbacher · Valerie Heinz · H. Bobby Gaspar · Roland Aydin · Beate Hagl · Benjamin Gathmann · Bernd H. Belohradsky · Hans D. Ochs · Talal Chatila · Ellen D. Renner · Helen Su · Alexandra F. Freeman · Karin Engelhardt · Michael H. Albert · On behalf of the inborn errors working party of EBMT

Received: 19 August 2014 / Accepted: 26 December 2014 / Published online: 28 January 2015

Abstract Mutations in *DOCK8* result in autosomal recessive Hyper-IgE syndrome with combined immunodeficiency (CID). However, the natural course of disease, long-term prognosis, and optimal therapeutic management have not yet been clearly defined. In an international retrospective survey of patients with *DOCK8* mutations, focused on clinical presentation and therapeutic measures, a total of 136 patients with a median follow-up of 11.3 years (1.3–47.7) spanning 1693

Electronic supplementary material The online version of this article (doi:10.1007/s10875-014-0126-0) contains supplementary material, which is available to authorized users.

S. E. Aydin · J. Sawalle-Belohradsky · G. Notheis · V. Heinz · R. Aydin · B. Hagl · B. H. Belohradsky · E. D. Renner · M. H. Albert
Dr. von Haunersches Children's Hospital, Ludwig-Maximilians-University, Munich, Germany

S. S. Kilic
Department of Pediatric Immunology, Faculty of Medicine, Uludag University, Bursa, Turkey

C. Aytekin
Department of Pediatric Immunology, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

A. Kumar
BMT/Immune Deficiency, Cincinnati Children's Hospital, Cincinatti, OH, USA

O. Porras
Hospital Nacional De Ninos Dr. Carlos Saenz Herrera Servicio de Immunologia y Reumatologia Pediatrica, San Jose, Costa Rica

L. Kainulainen
Department of Pediatrics, Turku University Hospital, Turku, Finland

L. Kostyuchenko
Pediatric Immunology, Western Ukrainian Specialized Children's Medical Centre, Lviv, Ukraine

F. Genel
Division of Pediatric Immunology, Behcet Uz State Hospital, Izmir, Turkey

N. Kütükcüler · N. Karaca
Department of Pediatrics, Ege University Faculty of Medicine, Izmir, Turkey

L. Gonzalez-Granado
Pedriatrics, Immunodeficiencies Unit, Hospital 12 Octubre, Madrid, Spain

patient years, were enrolled. Eczema, recurrent respiratory tract infections, allergies, abscesses, viral infections and mucocutaneous candidiasis were the most frequent clinical manifestations. Overall survival probability in this cohort [censored for hematopoietic stem cell transplantation (HSCT)] was 87 % at 10, 47 % at 20, and 33 % at 30 years of age, respectively. Event free survival was 44, 18 and 4 % at the same time points if events were defined as death, life-threatening infections, malignancy or cerebral complications such as CNS vasculitis or stroke. Malignancy was diagnosed in 23/136 (17 %) patients (11 hematological and 9 epithelial cancers, 5 other malignancies) at a median age of 12 years. Eight of these patients died from cancer. Severe, life-threatening infections were observed in 79/136 (58 %); severe non-infectious cerebral events occurred in 14/136 (10 %). Therapeutic measures included antiviral and antibacterial prophylaxis, immunoglobulin replacement and HSCT. This study provides a comprehensive evaluation of the clinical phenotype of DOCK8 deficiency in the largest cohort reported so far and demonstrates the severity of the disease with relatively poor prognosis. Early HSCT should be strongly considered as a potential curative measure.

Keywords DOCK8 deficiency · combined immunodeficiency · hyper-IgE syndrome · natural outcome

Abbreviations

DOCK8	Dedicator of cytokinesis 8
CID	Combined immunodeficiency
HIES	Hyper-IgE syndrome
HSCT	Hematopoietic stem cell transplantation
STAT3	Signal transducer and activator of transcription 3
Ig replacement	Immunoglobulin replacement

J. Abbott
Fellow, Allergy and Immunology Department of Pediatrics National Jewish Health, University of Colorado, Denver, CO, USA

D. Al-Zahrani
Pediatric allergy and immunology, King Saud Bin Abdulaziz University for Health Sciences and Department of Pediatrics, National Guard Hospital, King Abdulaziz Medical City–WR, Jeddah, Saudi Arabia

N. Rezaei
Research Center for Immunodeficiencies, Children's Medical Center, Tehran, Iran

N. Rezaei
Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Z. Baz
Department of Pediatrics, St George Hospital University Medical Center, Beirut, Lebanon

J. Thiel · B. Grimbacher · H. Su · A. F. Freeman · K. Engelhardt
Department of Rheumatology and Clinical Immunology, University Hospital Freiburg, Freiburg, Germany

J. Thiel · S. Ehl · B. Grimbacher · B. Gathmann · K. Engelhardt
Center for Chronic Immunodeficiency (CCI), University Medical Centre Freiburg and University of Freiburg, Freiburg, Germany

L. Marodi
Faculty of Medicine Department of Infectious Diseases and Pediatric Immunology, University of Debrecen, Debrecen, Hungary

J. S. Orange
Texas Children's Hospital Center for Human Immunobiology, Houston, TX, USA

S. Keles
Division of Pediatric Allergy and Immunology, Konya Necmettin Erbakan University, Konya, Turkey

S. M. Holland
Laboratory of Clinical Infectious Diseases, NIAID, National Institutes of Health, Bethesda, MD, USA

Ö. Sanal · D. C. Ayvaz · I. Tezcan
Immunology Division, Children's Hospital, Hacettepe University, Ankara, Turkey

H. Al-Mousa
Pediatric Allergy & Immunology, Department of Pediatrics, King Faisal Specialist Hospital & Research Center Riyadh, Riyadh, Saudi Arabia

Z. Alsum · A. Hawwari
Department of Genetics, Research Center, MBC 03, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

A. Metin
Pediatric Immunology Unit, SB Ankara Diskapi Children's Hospital, Ankara, Turkey

S. Matthes-Martin
St. Anna Children's Hospital, Vienna, Austria

M. Hönig · A. Schulz
Department of Pediatric Hematology/Oncology, University Childrens Hospital, Ulm, Germany

C. Picard
Study Center for Primary Immunodeficiencies, Necker-Enfant Malades Hospital, Assistance Publique - Hôpitaux de Paris (AP-HP), Paris, France

Introduction

In 1966, Davis et al. described two girls suffering from "cold"staphylococcal abscesses, eczema and chronic pulmonary disease, naming this entity "Job's syndrome". Six years later, Buckley, et al., recognized extreme hyperimmunoglobulinemia E in the same underlying syndrome and the term Hyper-IgE syndrome (HIES) was established [1, 2]. Most of these patients represented single cases, but some were found to have pedigrees suggestive of autosomal dominant inheritance [3]. In 2007 signal transducer and activator of transcription 3 (*STAT3*) was identified as the causative gene of autosomal dominant HIES [4–6]. In 2004, Renner et al. had reported an autosomal recessive variant of the HIES characterized by a cellular immunodeficiency predisposing to cutaneous viral infections but lacking the characteristic skeletal abnormalities of autosomal dominant HIES [7]. Bi-allelic mutations or deletions in dedicator of cytokinesis 8 (*DOCK8*) were later reported to be responsible for this combined immunodeficiency (CID) with elevated IgE [8, 9]. The patients in these initial descriptions exhibited a severe disease phenotype including malignancies and early death in 8 of the 38 reported patients [7–9].

No controlled studies exist on the effectiveness of specific treatment approaches for DOCK8 deficiency. The profound CID necessitates immunoglobulin (Ig) replacement and antibiotic prophylaxis. The role of prophylaxis against recurrent viral infections, one of the hallmarks of the disease, is unclear. Systemic treatment with interferon-α 2b has been suggested in three recent reports as treatment for recurring warts or severe herpes simplex virus (HSV) manifestations [10–12]. Several case reports have suggested that successful allogeneic hematopoietic stem cell transplantation (HSCT) can correct the immunodeficiency due to lack of DOCK8 function [13–18].

C. Picard
Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM UMR1163, Imagine Institut, Sorbonne Paris Cité, Paris Descartes University, Paris, France

C. Picard
Pediatric Hematology-Immunology Unit, Necker Enfant Malades Hospital, AP-HP, Paris, France

V. Barlogis
Department of Paediatric Haematology-Oncology, APHM, La Timone Hospital, Aix-Marseille University, Marseille, France

A. Gennery
Institute of Cellular Medicine, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

M. Ifversen
Rigshospitalet, Copenhagen, Denmark

J. van Montfrans
University Medical Center, Utrecht, The Netherlands

T. Kuijpers
Division of Pediatric Hematology, Immunology & Infectious Diseases, Head Emma Children's Hospital Academic Medical Center (AMC), Amsterdam, The Netherlands

R. Bredius
Pediatric SCT Unit and Laboratory for Immunology, Department of Pediatrics, LUMC, Leiden, The Netherlands

G. Dückers
HELIOS Children's Hospital Krefeld, Krefeld, Germany

W. Al-Herz
Department of Pediatrics, Faculty of Medicine, Kuwait University and Allergy and Clinical Immunology Unit, Kuwait City, Kuwait

W. Al-Herz
Department of Pediatrics, Al-Sabah Hospital, Kuwait City, Kuwait

S.-Y. Pai
Division of Hematology-Oncology, Boston Children's Hospital, Boston, MA, USA

S.-Y. Pai
Department of Pediatric Hematology-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

R. Geha · T. Chatila
Division of Immunology, Boston Children's Hospital, Boston, MA, USA

C.-P. Schwarze
Department of Pediatric Hematology/Oncology, University Childrens Hospital, Tuebingen, Germany

B. Tavil · F. Azik
Department of Pediatric Hematology, Ankara Children's Hematology Oncology Hospital, Ankara, Turkey

K. Bienemann
Department of Pediatric Hematology/Oncology, University Childrens Hospital, Duesseldorf, Germany

H. B. Gaspar
Infection, Immunity, Inflammation and Physiological Medicine, Molecular and Cellular Section, Institute of Child Health, University College London, London, UK

H. D. Ochs
Center for Immunity and Immunotherapies Seattle Children's Research Institute, University of Washington, Seattle, WA, USA

M. H. Albert (✉)
Hauner University Childrens Hospital, Lindwurmstr.4, 80337 Munich, Germany
e-mail: michael.albert@med.uni-muenchen.de

Recently, a new variant of autosomal recessive HIES with neurological impairment has been associated with hypomorphic mutations in a critical glycosylation pathway gene, *PGM3* [19].

Since the first description of DOCK8 deficiency in 2009, laboratory evidence has accumulated allowing a better understanding of the pathophysiology underlying the CID, which affects B-cells, NK-cells, and various T-cell subsets [11, 20–22]. Specifically, CD8 T cells of DOCK8-deficient patients display impaired activation, proliferation and cytokine production, and NKT cells are reduced and their function impaired [8, 9, 20]. DOCK8 is also critical for NK cell function and plasmacytoid dendritic cell development [11, 22].

In order to understand and define the extended clinical and immunological phenotype of DOCK8 deficiency and to establish the natural course of the disease - not taking into account potentially curative early intervention by HSCT - we initiated a retrospective worldwide survey enlisting the Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation (EBMT) and the Registry of the European Society for Immunodeficiencies (ESID). The results of this comprehensive clinical and immunological review of DOCK8 deficiency are presented here.

Methods

Data Accrual

Anonymized case report forms asking for retrospective data retrieved from patients' charts were sent out via the mailing list of the inborn errors working party of the EBMT (http://www.ebmt.org/Contents/Research/TheWorkingParties/IEWP/Pages/Inborn-Errors.aspx) and were posted on the ESID website (www.esid.org). Major centers known to treat patients with DOCK8 deficiency were contacted directly. The cut-off date for data collection was Dec 31st 2012. This study also used the ESID Online Database for data acquisition (www.esid.org). The study was registered and received a waiver of approval by the ethics committee of the Ludwig-Maximilians-University of Munich, Germany.

Patients

All submitted patient data were evaluated and patients were included as study patients by consensus decision of a central review board at the main study center (M.H.A., S.E.A.). Of the 138 case report forms that were submitted, two had to be excluded from the study due to incomplete data. To be enrolled into the final study, patients had to have confirmed bi-allelic mutations or deletions affecting the *DOCK8* gene. If patients had undergone allogeneic HSCT, the date of transplantation was recorded as the last date of follow-up. Analysis of HSCT and resulting outcome as well as detailed analysis of genetic alterations within *DOCK8* were not part of this study. Partial information on 57 patients has been previously published elsewhere [8, 9, 13, 14, 16, 23–27] and 47 patients are also part of a separate study by Engelhardt et al. (accepted for publication in the Journal of Allergy and Clinical Immunology).

Definitions

Life threatening infections were defined as sepsis, meningitis, or pneumonia requiring hospitalization; in the case of pneumonia the need for supplemental oxygen or mechanical ventilation were noted. Other serious events were diagnosis of a cerebral event (stroke, vasculitis, encephalitis), malignancy or death. If a patient experienced more than one serious event, only the first event was registered for the analysis of event free survival.

Ig replacement, antivirals, antifungals and antibiotic prophylaxis were defined as having had these medications more than once for any period of time.

Statistical Analysis

Kaplan Meier survival estimates and cumulative incidence rates were compared using the log rank test (Prism, GraphPad, La Jolla, CA, USA). Cumulative incidence for different events adjusting for competing risks was estimated using the statistics language R 30 with the cmprsk package employing the method by Gray et al. [28]. Other analyses utilized the chi square or Fisher exact test and were accepted as significantly different at a level of $p<0.05$.

Results

Patients

Data from 136 patients (75 female, 61 male) from 94 families with homozygous or compound heterozygous mutations/deletions affecting the *DOCK8* gene were evaluable. Median age at last follow-up was 11.3 years (1.3–47.7) resulting in an observation time of 1693 patient years. A total of 99 patients were from known consanguineous families, and consanguinity was suspected in 15 additional patients who carried homozygous *DOCK8* alterations. A wide variety of ethnicities were represented, with the majority being of Turkish (38 %) and Arabic (27 %) origin.

Clinical Phenotype

In order to define the clinical phenotype of DOCK8 deficiency, we recorded symptoms and serious disease related

Table 1 Clinical symptoms in the patient cohort. Number of patients affected by the respective symptom/complication given in the shaded lines. Some patients had events in multiple sub-categories so that absolute numbers in the non-shaded lines may be higher than in the shaded lines

Symptoms			Number of patients affected	%
Eczema			134/136	99 %
	generalized		128/134	96 %
	difficult to treat		73/134	57 %
Recurrent respiratory infections			124/136	91 %
Allergies			97/136	71 %
	food		82/97	85 %
	asthma		52/97	54 %
	rhinitis		22/97	23 %
	anaphylaxis		16/97	16 %
	drugs		9/97	9 %
	urticaria		3/97	3 %
	Other causes/ manifestations*		17/97	18 %
Abscesses			84/136	62 %
	skin		70/84	84 %
	internal organs		6/84	7 %
	intracranial		4/84	5 %
	not specified		4/84	5 %
Life-threatening infections			79/136	58 %
	bacterial		33	42 %
organism				
	viral		18	23 %
	fungal		13	16 %
	protozoan		1	1 %
	unknown		14	18 %
Organ system	pneumonia		25/79	32 %
	sepsis		23/79	29 %
	cerebral		17/79	22 %
	osteomyelitis		8/79	10 %
	not specified		6/79	8 %
Viral infections			109/135	81 %
	HSV		68/109	62 %
	HPV		43/109	40 %
	molluscum		40/109	37 %
	VZV		25/109	23 %
	EBV		22/109	20 %
	CMV		15/109	14 %
	other		14/109	13 %
Fungal infections			87/136	64 %
	Candida		80/87	92 %
		mucosa	52/87	65 %
		skin	19/87	24 %
		nails	16/87	20 %
		systemic	7/87	9 %
		other	6/87	8 %
	Aspergillus		10/87	11 %
	other		8/87	9 %
Sclerosing cholangitis			7/136	5 %
Failure to thrive	weight or height		67/136	50 %
	weight and height		52/67	78 %
Cerebral event			14/136	14 %
	vascular (including 2 aneurysms)		8/14	57 %
	malignant		3/14	21 %
	encephalopathy		3/14	21 %
	brain and optic nerve atrophy		1/14	7 %
Malignancy			23/136	17 %
	hematological		11/23	48 %
	epithelial		9/23	39 %
	other		5/23	22 %
Autoimmunity			17/136	13 %
	vasculitis		8/17	47 %
	other		6/17	35 %
	AIHA		5/17	29 %
	nephropathy		1/17	6 %
Bronchiectasis			54/124	44 %
Pneumatoceles			4/134	3 %
Deaths			34/136	25 %
Causes of death:	infection		17/34	50 %
	malignancy		9/34	26 %
	vasculitis		2/34	6 %
	progressive multifocal leukencephalopathy		2/34	6 %
	unknown		4/34	12 %

*other causes: weeds, animals, latex, house-dust, environmental allergies, candida; other manifestations: conjunctivitis, eosinophil esophagitis

complications that were retrieved by retrospective chart review by the submitting physicians (Table 1).

Eczema, recurring respiratory and persistent viral infections - mostly but not exclusively of the skin - were the clinical hallmarks of the disease, occurring in 99, 91 and 80 % of patients. Allergies (71 %) – 85 % of those to food allergens – and abscesses (60 %) were also frequently reported. The CID associated with DOCK8 deficiency led to a high incidence of life-threatening infections, which were reported for 58 % of patients. These were mostly sepsis (29 %), pneumonia (32 %) or cerebral infections (22 %). A wide range of bacterial, viral and fungal organisms were identified as having caused these

Table 2 Microorganisms identified as causative in patients with life-threatening infections. Some patients had none, several had multiple organisms identified even within the same infectious episode, explaining a higher total number for infectious organisms than for life-threatening infections in Table 1

Bacterial	n =	Viral	n =	Fungal/other	n =
Staphylococcus aureus	15	CMV	9	*Aspergillus*	6
Streptococcus pneumoniae	13	EBV	2	*Candida*	6
Haemophilus influenzae	7	VZV	2	*Pneumocystis*	5
Pseudomonas aeruginosa	7	HSV	1	*Cryptosporidium*	1
Proteus mirabilis	4	Rotavirus	1	*Cryptococcus*	1
Enterococcus	2				
Neisseria meningitidis	2				
Salmonella spp	2				
other Staphylococcus	1				
Moraxella	1				
Listeria	1				
Escherichia coli	1				
Leuconostoc	1				
Mycobacterium tuberculosis	1				

infections (Table 2). Bronchiectasis was frequently diagnosed (44 %), while pneumatoceles were rarely reported (3 %).

There was also a striking preponderance of non-infectious cerebral complications with 15 episodes in 14 of 136 patients (15 %). Three of these events were caused by malignancies affecting the CNS, 8 were associated with vascular disease and 4 had other causes (3 undefined encephalopathy, 1 optic nerve and brain atrophy). There was also a strong trend to develop malignancies, which occurred in 23 of 136 patients (17 %) at a median age of 12 years. Failure to thrive was reported in 50 % of patients. The most frequent autoimmune manifestations (13 % of patients) were vasculitis and autoimmune hemolytic anemia. Autoimmune gastrointestinal manifestations were not reported. Table 1 summarizes the clinical symptoms of the study cohort.

The skin is one of the major organs affected by DOCK8 deficiency. Nearly all patients (99 %) exhibited some degree of eczema and 84 % had skin abscesses. Often this was aggravated by mucocutaneous candidiasis, which was reported by 53 % of patients. Recurring HSV and molluscum infections were observed in 62 and 37 % of patients, respectively. Nine (39 %) of the reported malignancies were tumors of the skin.

Immunological Phenotype

Because there is a clinical need to distinguish DOCK8 deficiency from non-mendelian, severe atopic disease by one or more discerning laboratory markers, a number of

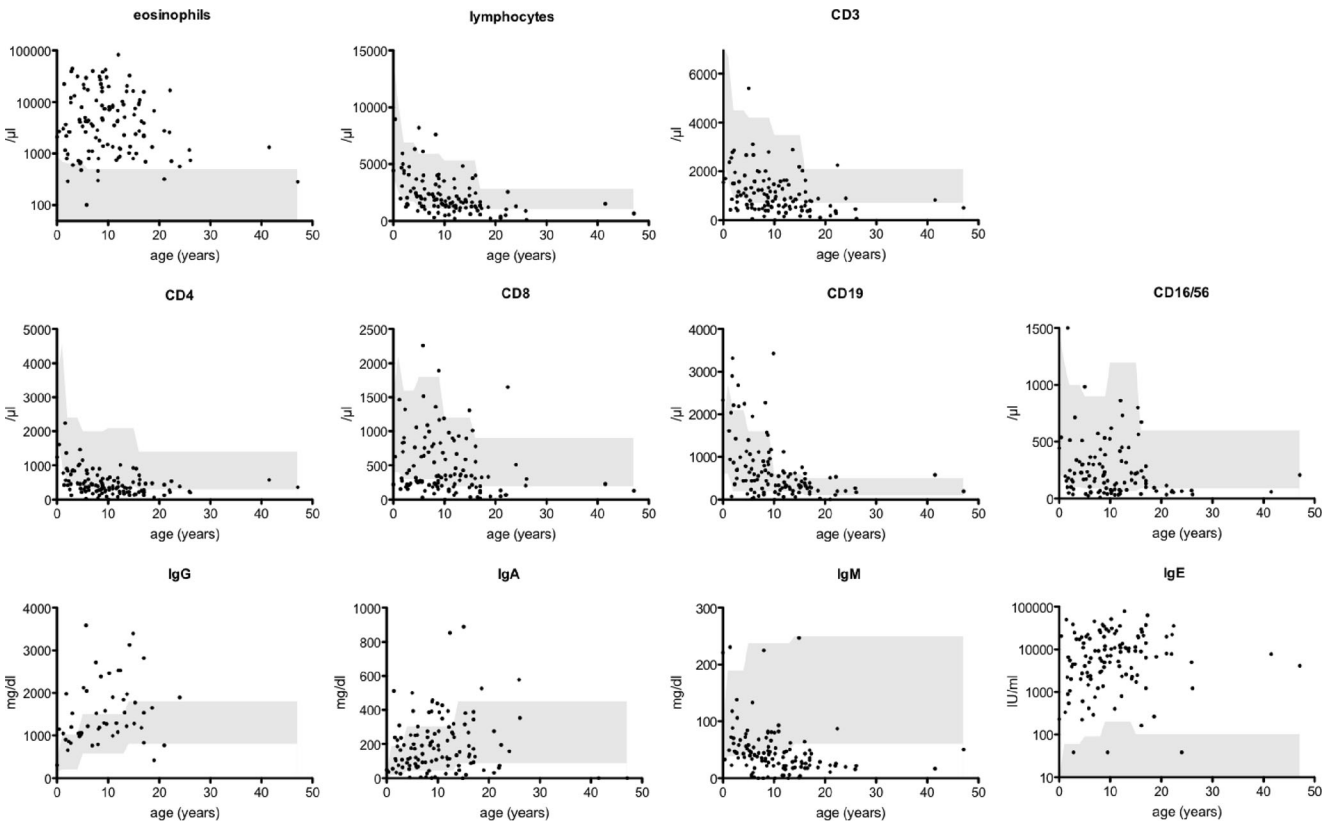

Fig. 1 Age dependent laboratory results as recorded at the last follow-up, except for IgG, which was before initiation of IVIG treatment. *Grey shaded* areas represent age dependent normal levels

immunologic parameters were recorded at the last follow-up visit to define the immunological phenotype of the disease for different age groups.

As expected, almost all patients had a highly elevated IgE level at last follow-up (98 %) with a median level of 2175 IU/ml (range 38–78.100); only three patients (2 %) were reported to have normal IgE levels when evaluated at 5, 11 and 26 years of age. While absolute eosinophil counts were elevated in most patients (96 %), other white blood cells were less strikingly affected. Total lymphocyte counts were below the lower normal margin of their respective age group in 20 % of patients. T-lymphocyte subsets (CD3, CD4, CD8) and NK cells (CD16/56) were decreased in 41, 45, 38 and 28 % of patients, respectively; decreased B-cells (CD19) were seen in 12 % of patients (Fig. 1).

In vitro lymphocyte stimulation was performed in 77 patients; it was reduced by local standards in 82 % of patients while normal in 18 %.

IgG (in the absence of Ig replacement) tended to be either normal or elevated and IgA levels were usually within the normal range. IgM, which was below the normal range in 64 % of patients seems to decline with age in DOCK8-deficient patients as it was decreased in 90 % of patients >12 years of age (Fig. 1).

Eosinophilia, low T-cell counts, elevated IgE and low and declining IgM levels were the most prominent laboratory features of DOCK8 deficiency.

Treatment/Prophylaxis

Because prospective evaluation of the effectiveness of certain therapeutic measures was impossible in this retrospective study, we aimed to identify the therapeutic approaches chosen by the treating physicians by asking for the antiviral, antibacterial, Ig replacement and immunomodulatory treatment regimens.

Of the 87/136 patients (64 %) who received regular Ig prophylaxis, 57 % were considered to be effectively treated by their local physicians. Antibiotic prophylaxis (mostly cotrimoxazole) was instituted in 92/136 patients (68 %). Of 136 patients, 28 (21 %) received antiviral prophylaxis, 26 with (val-) acyclovir, judged by their physicians to be effective in 69 %. Only 14 patients received antifungal prophylaxis, mostly with fluconazole (n=6) or itraconazole (n=5). Immunomodulatory treatment was applied in 32 patients. Interferon-α, which has recently been reported to be effective in the control of severe HSV and recurrent warts was given to 14 patients and considered effective in 43 %. Treatment/prophylaxis data are detailed in Table 3.

As of last follow-up, 36 patients had received an allogeneic HSCT. Detailed analysis of transplant procedures and outcomes is currently underway.

Table 3 Prophylaxis and specific treatment. Prophylaxis and specific treatment as reported for the study cohort, excluding treatment for acute complications such as severe infections. Efficacy was appraised solely by the treating physician without specific efficacy criteria

Prophylaxis/treatment		Number of patients treated (of 136)	Efficacy
Ig replacement	total	87	yes: 50 (57 %) no: 17 no info: 20
Antibiotic prophylaxis	total	92	
	cotrimoxazole	70	yes: 24 (34 %) no: 19 no info: 27
	amoxicillin	5	yes: 4 no: 1
	cephalosporins	4	yes: 3 no info: 1
	other	13	yes: 4 no info: 9
Antiviral prophylaxis	total	28	
	(val-) acyclovir	26	yes: 18 (69 %) no: 4 no info: 4
	cidofovir	2	yes: 1 no: 1
Antifungal prophylaxis	total	14	
	fluconazole	6	yes: 2 no info: 4
	itraconazole	5	yes: 3 no: 2
	other	3	yes: 2 no:1
Immunomodulatory treatment	total	32	
	interferon α	14	yes: 6 (43 %) no: 6 no info: 2
	interferon β	1	no info: 0
	interferon γ	2	no: 1 no info: 1
	cyclosporine	3	yes: 2 no: 1
	imiquimod	9	yes: 5 no: 2 no info: 2
	other	3	yes: 5 no: 2 no info: 2

Natural History

In order to assess the clinical severity and natural history of DOCK8 deficiency, we calculated overall and event-free

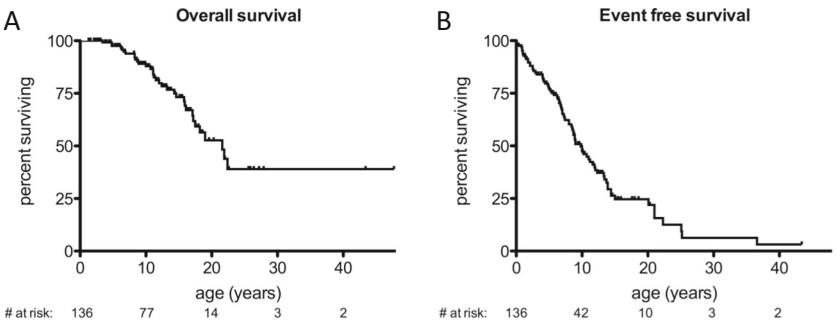

Fig. 2 Overall (**A**) and event free (**B**) survival of the entire study cohort. DOCK8-deficient patients who had a HSCT were censored at the date of transplant. Events were defined as: life-threatening infection, cerebral event (stroke, vasculitis, encephalitis), malignancy or death. | : censored event

survival of the entire study cohort independent of potentially curative therapy by allogeneic HSCT. Transplanted patients were not excluded from the survival analysis, but their follow-up was censored on the date of HSCT.

Overall probability of survival at 10, 20 and 30 years was 87 % (95 % confidence interval 79–93 %), 50 % (35–64 %) and 37 % (20–53 %), respectively (Fig. 2A). Defining serious disease-related events as outlined above resulted in event free survival probabilities at 10, 20 and 30 years of 46 % (95 % confidence interval 36–56 %), 21 % (8–28 %) and 4 % (0–11 %), respectively (Fig. 2B). Cumulative incidences for life-threatening infections, cerebral events and malignancies over time were calculated as 52 % (95 % confidence interval 42–67 %), 10 % (4–16 %) and 6 % (1–11 %) at 10 years; 73 % (61–85 %), 18 % (9–27 %) and 31 % (18–44 %) at 20 years; and 88 % (75–100 %), 32 % (7–57 %) and 48 % (7–79 %) at 30 years, respectively (Fig. 3). Thirty-four patients (25 %) had died, mostly from infections and malignancy. The causes of death are detailed in Table 1 and supplemental Table 1.

In summary, DOCK8 deficiency is a profound CID with severe skin and lung features and a high risk of malignancy, which results in serious complications and premature death in the majority of patients.

Discussion

This international multicenter study offers a comprehensive clinical and immunological description of the largest cohort of DOCK8-deficient patients to date. It confirms previous reports of DOCK8 deficiency, which results in a mostly severe CID with a striking resemblance of severe atopic disease. It was originally classified as an autosomal recessive variant of HIES, sharing clinical features with other CIDs such as Wiskott-Aldrich syndrome and STK4/MST1 deficiency [27, 29–31]. This study also provides robust data supporting the clinical significance of the CID caused by DOCK8 deficiency. Most importantly, DOCK8 deficiency causes markedly excess premature mortality, with a median survival of only 20 years even with extensive supportive therapies such as prophylactic antimicrobial chemotherapy or Ig replacement. As a result of the high morbidity and the resulting reduced quality of life, the current consensus within the immunological community is to offer allogeneic HSCT to all patients, preferably early in their disease course. This review confirms the wisdom of that consensus. A number of reports indicate that the outcome of HSCT using related, unrelated or mismatched related donors is favorable [13–17, 25, 32]. A separate study on behalf of the Inborn Errors Working Party of the EBMT is currently evaluating the outcome of HSCT in DOCK8-deficient patients.

Given the distinct clinical phenotype of DOCK8 deficiency, which is characterized by eczema, recurrent bacterial skin and lung infections, chronic viral skin infections, and severe allergies in combination with a cellular immunodeficiency and increased risk for malignancy, it would seem straightforward to diagnose affected patients early. There is, however, considerable overlap with other PIDs and DOCK8 deficient patients with rather mild and atypical phenotypes have been described. Since genetic testing is rather arduous given the

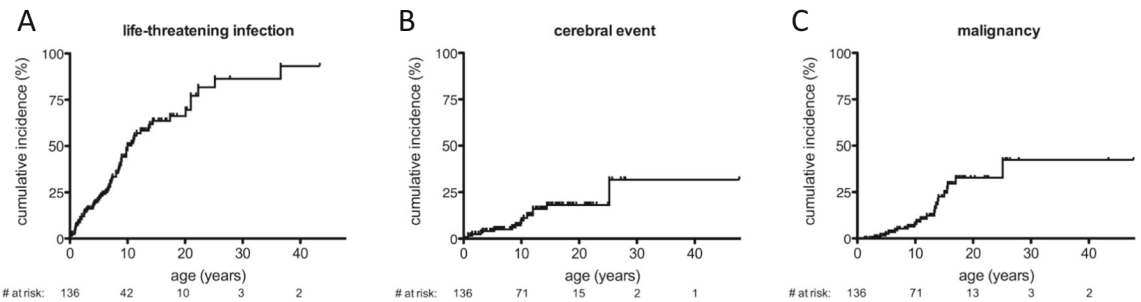

Fig. 3 Cumulative incidences of life-threatening infections (**A**), cerebral events (stroke, vasculitis, encephalitis) (**B**) or diagnosis of malignancy (**C**). | : censored event

size of the *DOCK8* gene, recent descriptions of flow cytometry-based assays to detect the DOCK8 protein may be helpful in screening patients [32, 33]. Of course, mutations that allow for expression of a non-functional DOCK8 protein may be missed. Targeted next generation sequencing based genetic evaluation has also been described in the diagnosis of DOCK8 deficiency [34].

Patients with the autosomal dominant variant of HIES caused by *STAT3* mutations frequently exhibit signs of connective tissue disease such as skeletal abnormalities or pneumatoceles [4], features virtually absent in this DOCK8 cohort. Also, STAT3 deficient patients lack the profound immunodeficiency found in DOCK8 deficiency [35]. Although the Wiskott-Aldrich syndrome shares remarkably many clinical features with DOCK8 deficiency such as eczema, allergies, severe infections, autoimmunity and increased risk for malignancy, it can easily be differentiated by the accompanying thrombocytopenia [36]. Consistent with this phenotypic similarity, a recent study highlighted that DOCK8 interacts with the Wiskott-Aldrich syndrome protein (WASP) forming a macromolecular complex that is important for NK cell effector function [21]. Even though one report has shown that DOCK8 deficient patients can exhibit reduced T-cell receptor excision circle (TREC) numbers later in life [24], DOCK8 deficiency cannot be reliably diagnosed by TREC-based newborn screening; it still requires clinical vigilance and appropriate laboratory investigation. Increased awareness of the extended clinical and immunological phenotypes of DOCK8 deficiency may help in diagnosing patients with unusually mild phenotypes [37].

Immunological data collected in this study define DOCK8 deficiency as a disease associated with CID, eosinophilia, very high levels of IgE and varying degrees of T-cell lymphopenia and IgM serum levels that decrease with age. The strong predisposition towards viral infections may be explained in part by the role DOCK8 plays in peripheral CD8 T, NKT and NK cell survival and function, as well as dendritic cell migration and formation of the lytic immunological synapse [20, 22, 26, 38]. The failure of DOCK8 deficient patients to mount effective and long-lasting antibody responses can be explained by the fact that the DOCK8 protein acts as an adaptor molecule in B-cell signaling leading to the generation of memory B-cells [39].

Of note, three patients never had elevated IgE levels, but their phenotype did not differ from the rest of the cohort; all suffered from severe infections. One of the three died at 5 years from malignancy; the others were alive at 11 and 26 years, respectively. All had large deletions in the DOCK8 gene.

As a retrospective study, this report has its limits. However in the absence of a prospective registry for DOCK8-deficient patients, the formal assessment of the clinical and immunological phenotype reported here will not only facilitate establishing the diagnosis of DOCK8-deficiency, but will also be useful for the design of prospective studies with the aim to establish optimal treatment protocols. Some reporting bias cannot be excluded since presumably they were mainly patients with a phenotype consistent with HIES who were tested for DOCK8 deficiency, thus possibly missing atypical or very mild phenotypes. On the other hand, severely affected family members who had died before a molecular diagnosis was possible were not included, which might underestimate the severity of the clinical phenotype. It is likely that poor outcomes in the past could be improved upon with earlier initiation of better medical care available today. However, with more patients being transplanted at earlier ages, it will become increasingly difficult to assess the natural history of DOCK8 deficiency in such a large cohort.

In summary, by comprehensively evaluating the clinical phenotype of DOCK8 deficiency in a large international cohort, this study demonstrates the severe morbidity and mortality of this disease. These data will help in making early diagnoses of DOCK8 deficiency, enabling timely HSCT or - possibly in the future - stem cell gene therapy.

Acknowledgments This work was supported in part by the Division of Intramural Research, NIAID, NIH (SH, HS, AF).

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

References

1. Davis S, Schaller J, Wedgwood R, Harvard MD. Job's syndrome. Lancet. 1966;287(7445):1013–5.
2. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Pediatrics. 1972;49(1):59–70.
3. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections–an autosomal dominant multisystem disorder. N Engl J Med. 1999;340(9):692–702.
4. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007;357(16):1608–19.
5. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007;448(7157):1058–62.
6. Renner ED, Torgerson TR, Rylaarsdam S, Anover-Sombke S, Golob K, LaFlam T, et al. STAT3 mutation in the original patient with job's syndrome. N Engl J Med. 2007;357(16):1667–8.
7. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr. 2004;144(1):93–9.
8. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol. 2009;124(6):1289–1302.
9. Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, et al. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med. 2009;361(21):2046–55.

10. Al-Zahrani D, Raddadi A, Massaad M, Keles S, Jabara HH, Chatila TA, et al. Successful interferon-alpha 2b therapy for unremitting warts in a patient with DOCK8 deficiency. Clin Immunol. 2014;153(1):104–8.
11. Keles S, Jabara HH, Reisli I, McDonald DR, Barlan I, Hanna-Wakim R, et al. Plasmacytoid dendritic cell depletion in DOCK8 deficiency: rescue of severe herpetic infections with IFN-alpha 2b therapy. J Allergy Clin Immunol. 2014;133(6):1753–1755.
12. Papan C, Hagl B, Heinz V, Albert MH, Ehrt O, Sawalle-Belohradsky J, et al. Beneficial IFN-alpha treatment of tumorous herpes simplex blepharoconjunctivitis in dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol. 2014;133(5):1456–8.
13. Bittner TC, Pannicke U, Renner ED, Notheis G, Hoffmann F, Belohradsky BH, et al. Successful long-term correction of autosomal recessive hyper-IgE syndrome due to DOCK8 deficiency by hematopoietic stem cell transplantation. Klin Pädiatr. 2010;222(6):351–5.
14. Gatz SA, Benninghoff U, Schutz C, Schulz A, Honig M, Pannicke U, et al. Curative treatment of autosomal-recessive hyper-IgE syndrome by hematopoietic cell transplantation. Bone Marrow Transplant. 2011;46(4):552–6.
15. Boztug H, Karitnig-Weiss C, Ausserer B, Renner ED, Albert MH, Sawalle-Belohradsky J, et al. Clinical and immunological correction of DOCK8 deficiency by allogeneic hematopoietic stem cell transplantation following a reduced toxicity conditioning regimen. Pediatr Hematol Oncol. 2012;29(7):585–94.
16. Barlogis V, Galambrun C, Chambost H, Lamoureux-Toth S, Petit P, Stephan JL, et al. Successful allogeneic hematopoietic stem cell transplantation for DOCK8 deficiency. J Allergy Clin Immunol. 2011;128(2):420–422.
17. Ghosh S, Schuster FR, Adams O, Babor F, Borkhardt A, Comoli P, et al. Haploidentical stem cell transplantation in DOCK8 deficiency - successful control of pre-existing severe viremia with a TCRass/CD19-depleted graft and antiviral treatment. Clin Immunol. 2014;152(1–2):111–4.
18. Metin A, Tavil B, Azik F, Azkur D, Ok-Bozkaya I, Kocabas C, et al. Successful bone marrow transplantation for DOCK8 deficient hyper IgE syndrome. Pediatr Transplant. 2012;16(4):398–9.
19. Sassi A, Lazaroski S, Wu G, Haslam SM, Fliegauf M, Mellouli F, et al. Hypomorphic homozygous mutations in phosphoglucomutase 3 (PGM3) impair immunity and increase serum IgE levels. J Allergy Clin Immunol. 2014;133(5):1410–1419.
20. Crawford G, Enders A, Gileadi U, Stankovic S, Zhang Q, Lambe T, et al. DOCK8 is critical for the survival and function of NKT cells. Blood. 2013;122(12):2052–61.
21. Ham H, Guerrier S, Kim J, Schoon RA, Anderson EL, Hamann MJ, et al. Dedicator of cytokinesis 8 interacts with talin and Wiskott-Aldrich syndrome protein to regulate NK cell cytotoxicity. J Immunol. 2013;190(7):3661–9.
22. Mizesko MC, Banerjee PP, Monaco-Shawver L, Mace EM, Bernal WE, Sawalle-Belohradsky J, et al. Defective actin accumulation impairs human natural killer cell function in patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol. 2013;131(3):840–8.
23. Chu EY, Freeman AF, Jing H, Cowen EW, Davis J, Su HC, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. Arch Dermatol. 2012;148(1):79–84.
24. Dasouki M, Okonkwo KC, Ray A, Folmsbeel CK, Gozales D, Keles S, et al. Deficient T cell receptor excision circles (TRECs) in autosomal recessive hyper IgE syndrome caused by DOCK8 mutation: implications for pathogenesis and potential detection by newborn screening. Clin Immunol. 2011;141(2):128–32.
25. McDonald DR, Massaad MJ, Johnston A, Keles S, Chatila T, Geha RS, et al. Successful engraftment of donor marrow after allogeneic hematopoietic cell transplantation in autosomal-recessive hyper-IgE syndrome caused by dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol. 2010;126(6):1304–1305.
26. Randall KL, Chan SS, Ma CS, Fung I, Mei Y, Yabas M, et al. DOCK8 deficiency impairs CD8 T cell survival and function in humans and mice. J Exp Med. 2011;208(11):2305–20.
27. Sanal O, Jing H, Ozgur T, Ayvaz D, Strauss-Albee DM, Ersoy-Evans S, et al. Additional diverse findings expand the clinical presentation of DOCK8 deficiency. J Clin Immunol. 2012;32(4):698–708.
28. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16(3):1141–54.
29. Alsum Z, Hawwari A, Alsmadi O, Al-Hissi S, Borrero E, Abu-Staiteh A, et al. Clinical, immunological and molecular characterization of DOCK8 and DOCK8-like deficient patients: single center experience of twenty-five patients. J Clin Immunol. 2013;33(1):55–67.
30. Al-Herz W, Ragupathy R, Massaad MJ, Al-Attiyah R, Nanda A, Engelhardt KR, et al. Clinical, immunologic and genetic profiles of DOCK8-deficient patients in Kuwait. Clin Immunol. 2012;143(3):266–72.
31. Nehme NT, Pachlopnik Schmid J, Debeurme F, Andre-Schmutz I, Lim A, Nitschke P, et al. MST1 mutations in autosomal recessive primary immunodeficiency characterized by defective naive T-cell survival. Blood. 2012;119(15):3458–68.
32. Jing H, Zhang Q, Zhang Y, Hill BJ, Dove CG, Gelfand EW, et al. Somatic reversion in dedicator of cytokinesis 8 immunodeficiency modulates disease phenotype. J Allergy Clin Immunol. 2014;133(6):1667–75.
33. Pai SY, de Boer H, Massaad MJ, Chatila TA, Keles S, Jabara HH, et al. Flow cytometry diagnosis of dedicator of cytokinesis 8 (DOCK8) deficiency. J Allergy Clin Immunol. 2014;134(1):221.–223.
34. Nijman IJ, van Montfrans JM, Hoogstraat M, Boes ML, van de Corput L, Renner ED, et al. Targeted next-generation sequencing: a novel diagnostic tool for primary immunodeficiencies. J Allergy Clin Immunol. 2014;133(2):529–34.
35. Kane A, Deenick EK, Ma CS, Cook MC, Uzel G, Tangye SG. STAT3 is a central regulator of lymphocyte differentiation and function. Curr Opin Immunol. 2014;28C:49–57.
36. Albert MH, Notarangelo LD, Ochs HD. Clinical spectrum, pathophysiology and treatment of the Wiskott-Aldrich syndrome. Curr Opin Hematol. 2011;18(1):42–8.
37. Aan de Kerk DJ, van Leeuwen EM, Jansen MH, van den Berg JM, Alders M, Vermont CL, et al. Aberrant humoral immune reactivity in DOCK8 deficiency with follicular hyperplasia and nodal plasmacytosis. Clin Immunol. 2013;149(1):25–31.
38. Harada Y, Tanaka Y, Terasawa M, Pieczyk M, Habiro K, Katakai T, et al. DOCK8 is a Cdc42 activator critical for interstitial dendritic cell migration during immune responses. Blood. 2012;119(19):4451–61.
39. Jabara HH, McDonald DR, Janssen E, Massaad MJ, Ramesh N, Borzutzky A, et al. DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. Nat Immunol. 2012;13(6):612–20.