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Cutaneous Manifestations of *DOCK8* Deficiency Syndrome

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Abstract

Background—Mutations in the dedicator of cytokinesis 8 gene (*DOCK8*) cause a combined primary immunodeficiency syndrome that is characterized by elevated serum IgE levels, depressed IgM levels, eosinophilia, sinopulmonary infections, cutaneous viral infections, and lymphopenia. Many patients with *DOCK8* deficiency were previously thought to have a variant of Job's syndrome. Distinguishing between *DOCK8* deficiency and Job's syndrome, also referred to as autosomal dominant hyper-IgE syndrome, on the basis of clinical findings alone is challenging. The discovery of the *DOCK8* mutation has made it possible to differentiate the cutaneous manifestations of these hyper-IgE syndromes.

Observations—Twenty-one patients from 14 families with confirmed homozygous or compound heterozygous mutations in *DOCK8* were evaluated. Clinical findings included dermatitis, asthma, food and environmental allergies, recurrent sinopulmonary infections, staphylococcal skin abscesses, and severe cutaneous viral infections. Malignant neoplasms, including aggressive cutaneous T-cell lymphoma, anal and vulvar squamous cell carcinomas, and diffuse large B-cell lymphoma, developed in 5 patients during adolescence and young adulthood.

Conclusions—*DOCK8* deficiency and Job's syndrome share several clinical features, including elevated serum IgE levels, dermatitis, recurrent sinopulmonary infections, and cutaneous staphylococcal abscesses. However, the presence of recalcitrant, widespread cutaneous viral infections, asthma, and food and environmental allergies, as well as the absence of newborn rash and coarse facies, favors the clinical diagnosis of *DOCK8* deficiency. Rates of malignancy and overall mortality in patients with *DOCK8* deficiency were higher than in those with Job's

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syndrome, highlighting the value of distinguishing between these conditions and the importance of close monitoring for neoplasia.

In 2009, mutations in the dedicator of cytokinesis 8 gene (*DOCK8*) (OMIM 611432) were found to cause a rare, novel autosomal recessive primary immunodeficiency syndrome characterized by decreased numbers of T and B cells, elevated IgE levels, and eosinophilia.[1] Before this, many patients with these mutations had been followed up within a large Job's syndrome/hyper-IgE syndrome (HIES) cohort at the National Institutes of Health (Protocol No. 00-I-0159) because they exhibited clinical features of Job's syndrome. Job's syndrome (OMIM #147060) is characterized by (1) dermatitis, often beginning at or soon after birth[2]; (2) recurrent "cold" bacterial abscesses of the skin, lungs, and joints; (3) pneumatoceles and bronchiectasis as a consequence of recurrent lung infections; (4) markedly elevated serum IgE levels; (5) eosinophilia; (6) coarse facial features; (7) skeletal abnormalities, including osteoporosis, scoliosis, craniosynostosis, and minimal trauma fractures; (8) retention of primary teeth; and (9) joint hyperextensibility.[3]

In 2007, dominant negative mutations in *STAT3* were found to be responsible for most cases of sporadic and autosomal dominant HIES/Job's syndrome (AD-HIES).[4,5] However, an autosomal recessive form of hyper-IgE syndrome (AR-HIES) had also been identified, with an overlapping yet distinct set of clinical features.[6] A single case of tyrosine kinase 2 (*TYK2*) deficiency with elevated IgE levels was described,[7] but it is now clear that mutations in *DOCK8* account for nearly all cases of the autosomal recessive form of hyper-IgE syndrome.[8]

Herein, we report our clinical experience over a 20-year period with a cohort of 21 patients with confirmed *DOCK8* deficiency. We delineate the key cutaneous manifestations and highlight the similarities and differences between *DOCK8* deficiency and Job's syndrome.

REPORT OF REPRESENTATIVE CASES

CASE 1

An 18-year-old man (patient 8.2, Table 1) had a history of dermatitis beginning in early childhood. His condition was associated with elevated IgE levels, eosinophilia, recurrent *Staphylococcus aureus* skin infections, otitis, and sinusitis. His parents were first cousins. His older sister (patient 8.1) and brother (patient 8.3) were evaluated for similar findings; however, his sister died as a result of complications of *Acinetobacter* sepsis. Neither the patient nor his siblings had coarse facies, retention of primary teeth, joint hyperextensibility, or minimal trauma fractures.

The patient's dermatitis, while widespread, was severe in anatomical regions that are typical of atopic dermatitis (Figure 1) and fulfilled the UK Working Party's diagnostic criteria for atopic dermatitis.[9] He did not present with a newborn rash (defined as a rash appearing within 35 days of birth), which is commonly observed in patients with Job's syndrome.[2] His dermatitis was partially responsive to combinations of topical steroids, systemic antibiotics, and antihistamines. He did not have asthma, but he did have multiple food allergies.

The patient had molluscum superimposed on areas of eczema for many years. At the age of 4 years, he developed herpetic keratitis in his right eye. Herpes simplex virus (HSV) polymerase chain reaction–positive groin ulcerations developed when he was 17 years old and persisted despite prolonged valacyclovir treatment. A homozygous point mutation in the *DOCK8* gene was identified in the patient, his sister, and his brother, generating a cryptic splice site, leading to abrogation of gene expression. [1,8]

CASE 2

An 18-year-old woman (patient 3.1, Table 1) developed signs and symptoms of an unknown primary immunodeficiency at the age of 2 years (clinical history previously described by Lei et al[10]). She met the criteria for atopic dermatitis and had asthma and multiple food allergies. She had persistent genital HSV infection, herpetic keratitis, eczema herpeticum, molluscum contagiosum, vaginal candidiasis, and recurrent *S aureus* pneumonias and skin infections. At the age of 17years, she developed paranasal and vulvar squamous cell carcinomas (SCCs) as well as a microcystic adenexal carcinoma. [10] She then became erythrodermic and developed diffuse, leonine infiltration of the skin, with overlying crusted erosions (Figure 2). Skin biopsy specimens demonstrated an atypical lymphoid infiltrate with eosinophils and epidermotropism. The diagnosis of cutaneous T-cell lymphoma (CTCL) was supported by positive results on immunophenotyping and T-cell receptor gene rearrangement studies. Also, herpetic acantholysis was observed; HSV-1 was confirmed by the findings of immunohistochemical analysis. Although her CTCL partially responded to chemotherapy, she died of pulmonary aspergillosis 3 months later. Autopsy revealed the presence of a perigastric leiomyoma. Posthumously, the patient was found to have compound heterozygous mutations within *DOCK8*.[1]

CASE 3

A 22-year-old woman (patient 5.1, Table 1) manifested a rash at birth and later developed a dermatitis associated with *S aureus* superinfection. She had asthma and multiple food and environmental allergies. As a teenager, her dermatitis was controlled for several years with topical steroid therapy, use of chlorinated pools, Dakin solution, chlorhexadine washes, and intermittent linezolid therapy for chronic methicillin-resistant *S aureu*s. At the of age 17 years, she developed linezolid-resistant *S aureu*s infection and was placed on a prophylactic regimen of doxycycline and rifampin. Her dermatitis flared after she ingested peanut oil, requiring treatment with prednisone for the next 2 years. She had numerous respiratory tract infections, including miliary *Histoplasma capsulatum* pneumonia.

She had severe primary varicella at the age of 6 years, followed by multiple episodes of herpes zoster. When she was 19 years old, she developed confluent verrucae on the distal aspect of her fingers (Figure 3A). She had molluscum contagiosum, which formed plaques on her face, neck (Figure 3B), chest, abdomen, and periaxillary and pubic areas. The verrucae were refractory to cryotherapy, salicyclic acid, cimetidine, and topical imiquimod under occlusion. Interferon alfa therapy exacerbated her eczema. A trial of oral cidofovir was limited by the elevation of transaminase levels. Intravenous cidofovir was later used, with significant improvement of the verrucae but not of the molluscum.

The patient and her affected sister (patient 5.2) were found to have compound heterozygous deletions within *DOCK8*, resulting in the complete absence of protein.[1] At the age of 21 years, the patient underwent umbilical cord blood hematopoietic stem cell transplantation (HSCT) but developed human herpesvirus 6 encephalitis and died without engraftment 3 months later.

COMMENT

Careful characterization of the clinical aspects of 21 patients with *DOCK8* deficiency (Table 1) has led to the identification of features that can be helpful to distinguish them from those with Job's syndrome:

1. The skeletal and dental abnormalities commonly found in Job's syndrome, including coarse facial features, retention of primary teeth, joint hyperextensibility, and pathologic fractures, were rarely seen in patients with *DOCK8* deficiency (Table 2).
2. Dermatitis in patients with *DOCK8* deficiency was typically observed in the classic distribution for atopic dermatitis and was more severe than in Job's syndrome. Approximately 90% of the *DOCK8* cohort studied met the UK Working Party criteria for atopic dermatitis, compared with 65%[2] of the patients with Job's syndrome who were evaluated at the National Institutes of Health, Bethesda, Maryland.
3. Fifteen of 21 *DOCK8*-deficient patients (71%) had substantial food and environmental allergies, and nearly 50% had asthma. In contrast, asthma and allergies, particularly anaphylaxis to foods, are uncommon in Job's syndrome. [11]
4. The incidence of newborn rash was 24% in our *DOCK8*-deficient cohort, in contrast to 81% in patients with Job's syndrome.[2]
5. Extensive, recurrent, and treatment-resistant cutaneous viral infections (HSV, varicella zoster virus, human papillomavirus [HPV], and molluscum contagiosum) occurred in 95% of patients with *DOCK8* deficiency, a finding not commonly observed in Job's syndrome.
6. Four *DOCK8*-deficient patients (19%) developed 1 or more aggressive cutaneous malignant neoplasms, including SCC and CTCL, in each case before the age of 30 years. To our knowledge, skin cancer has not been observed in patients with Job's syndrome.

The DOCK8 protein is an atypical guanine exchange factor that is expressed in mature peripheral T cells, hematopoietic stem cells, and thymocytes.[12] Through its role as a guanine exchange factor, DOCK8 is thought to interact with Rho GTPases such as CDC42 and RAC, which mediate the actin cytoskeleton reorganization that is necessary for such processes as hematopoietic stem cell homing and mobilization as well as T-cell polarization and activation.[13] Intriguingly, the Wiskott-Aldrich syndrome (WAS) protein (WASP), reduced or absent in WAS, functions downstream of DOCK8 as an effector of CDC42 signaling.[13] Similar to *DOCK8*-deficient patients, patients with WAS present with eczema, elevated IgE

levels, frequent infections, lymphopenia, and predisposition to hematopoietic malignant neoplasms. It has been suggested that T-cell dysfunction, specifically a skewed T_H2 phenotype, leads to dermatitis in patients with WAS.[14]

The susceptibility of *DOCK8*-deficient patients to cutaneous viral infection may be multifactorial. Proper functioning of $CD8^+$ T cells is important for host antiviral defense. In vitro, CD8 cells exhibit reduced proliferation in response to T-cell receptor anti-CD3 and anti-CD28 antibody stimulation.[1] Moreover, Zhang et al[1] found that the production of interferon gamma and tumor necrosis factor a. by $CD8^+$T cells from 2 *DOCK8*-deficient patients was impaired. It has been suggested that *DOCK8* may play a role in leukocyte migration to infected skin.[12] Finally, epidermal barrier defects resulting from dermatitis may increase the frequency of viral infection.

In contrast, mucocutaneous candidiasis is less common in *DOCK8* deficiency than in Job's syndrome. In the latter, there is a profound deficiency of $CD4^+$ T_H17 cells, which are involved in the secretion of interleukin 17 and interleukin 22, key mediators of anti-*Candida* host defense. *DOCK8*-deficient patients have been found to have decreased numbers of T_H17 cells but not to the degree seen in Job's syndrome.[15–17]

The young age at onset (range, 16–25 years) and the high rate of mucocutaneous SCCs (4 of 21, or 19%) in patients with *DOCK8* deficiency is striking. Three patients had a history of chronic verrucae corresponding to the location of tumor formation, indicating a possible link between HPV infection and SCC. One patient with anal SCC (patient 2.1, Table 1) died of metastatic disease.

The patient described in case 2 developed a micro-cystic adenexal carcinoma as well as rapidly progressive CTCL; viral origins are not known to be associated with either of those cancers. Another patient (No. 5.2) was diagnosed as having diffuse large B-cell lymphoma at the age of 15 years. Patients with primary immunodeficiencies often have an increased risk of lymphoproliferative malignant neoplasms; impaired immune surveillance may play a role. Also, *DOCK8* may function as a tumor suppressor, because loss of protein expression has been observed in certain lung, liver, and brain tumors.[18–21]

When the cardinal features of Job's syndrome or *DOCK8* deficiency are present, it may be possible to make a diagnosis based on clinical findings alone (Table 3). However, early diagnosis may be challenging, particularly in the absence of affected siblings. Genetic testing may be essential in these instances, and results likely have prognostic significance. In our experience, mortality in *DOCK8*-deficient patients occurs in the second and third decades of life, whereas patients with Job's syndrome often live into their fifth and sixth decades.

Treatment of *DOCK8*-related cutaneous manifestations is difficult. Medications aimed at improving dermatitis, such as topical steroids and calcineurin inhibitors, may exacerbate cutaneous viral infections. Because patients have a high risk of cutaneous *S aureus* infections, systemic antistaphylococcal antibiotic therapy is helpful to treat and prevent atopic dermatitis flares. Strategies to decrease *S aureus* colonization, including the use of topical antiseptics and dilute bleach baths, are important adjunctive measures. Narrow-band

UV-B therapy was attempted in 1 patient (case 3) but was discontinued after it exacerbated her preexisting molluscum and verrucae. Phototherapy may also further increase the known risk of SCC in this population.

Patients with cutaneous HSV and varicella zoster virus infections were treated with systemic acyclovir or valacyclovir, although resistance was encountered in case 2. In our experience, treatment of HPV and molluscum is a significant challenge: destructive methods are typically unsuccessful, and topical preparations, including compounded cidofovir and imiquimod, are of limited value given the extent of disease, the patients' impaired immune response, and exacerbation of skin discomfort. Systemic cidofovir was used successfully for the treatment of verrucae in case 3. Interferon alfa has been used, with limited benefit, but may exacerbate dermatitis.

Given the predisposition of *DOCK8*-deficient patients to develop skin cancers at an early age, sunprotective measures should be emphasized. Regular total-body skin examinations are recommended, especially to monitor for anogenital SCC in patients with a known history of HPV infection. A low threshold for biopsy of clinically atypical skin lesions is suggested.

Allogeneic HSCT, which was performed in case 3, has been successfully used for other primary immunodeficiencies, including WAS and chronic granulomatous disease. [22–25] To date, reports of 6 patients with *DOCK8* deficiency who have undergone HSCT describe mixed outcomes.[26–29] Gatz et al[28] described 2 patients, aged 10 and 17 years, whose cutaneous disease completed cleared by 14 and 10 months, respectively, after matched unrelated HSCT. A third patient achieved full donor chimerism after a matched-related HSCT at the age of 8 years but died of bacteremia 2 months later.[29] A fourth patient, a 7-year-old girl, underwent matched-related HSCT, with normalization of her immune profile and absence of severe infections 6 years later.[27] Most recently, it was reported that 2 sisters underwent HSCT, both at the age of 9 years; the elder died of transplant-related complications, but the younger was doing well 2 years after transplantation.[26]

Hematopoietic stem cell transplantation represents a promising therapeutic option for *DOCK8*-deficient patients, but the potential benefits of improving the severe skin symptoms and correction of the immunodeficiency must be balanced by the risks imparted by additional immunosuppression associated with myeloablation and prophylaxis for graft-vs-host disease. Whether transplantation will prevent development of malignant neoplasms is unknown. Finally, it is unclear whether transplantation should be considered early in an attempt to prevent later complications or used after other treatment strategies have failed.

The clinical and laboratory aspects of *DOCK8* deficiency and Job's syndrome are overlapping but distinct. Management of these patients is made more difficult because their disease is genetic and unremitting. The importance of stable long-term relationships with a dermatologist and a primary care provider who work closely together cannot be overemphasized. Assiduous attention to skin infections and careful scrutiny for signs of malignancy may improve quality and quantity of life for patients with this complex disease.

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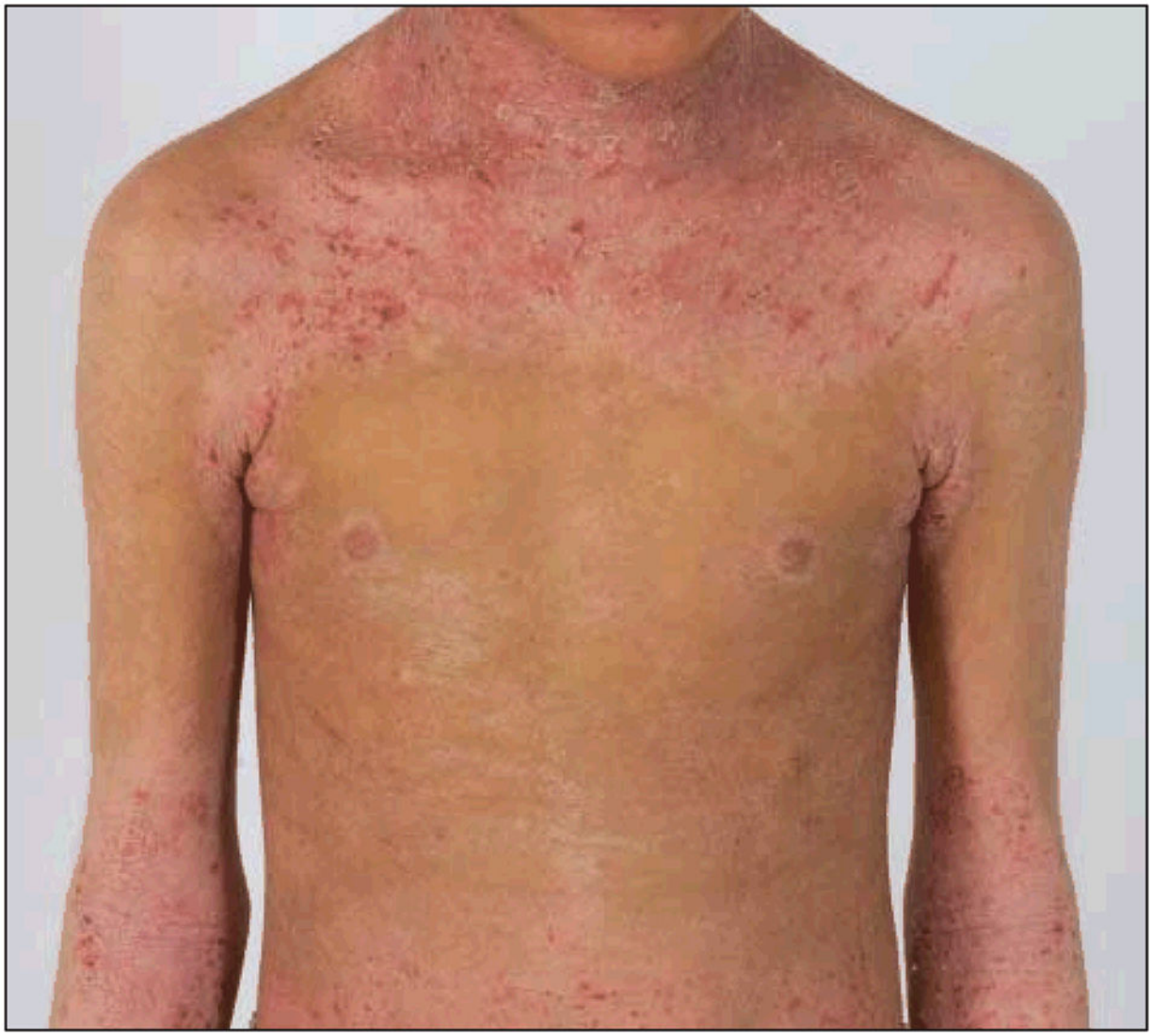

Figure 1.
Case 1. A 12-year-old boy with severe dermatitis highlighting the neck, upper chest area, axillae, antecubital fossae, and waistline. Numerous excoriations are present within the eczematous plaques.

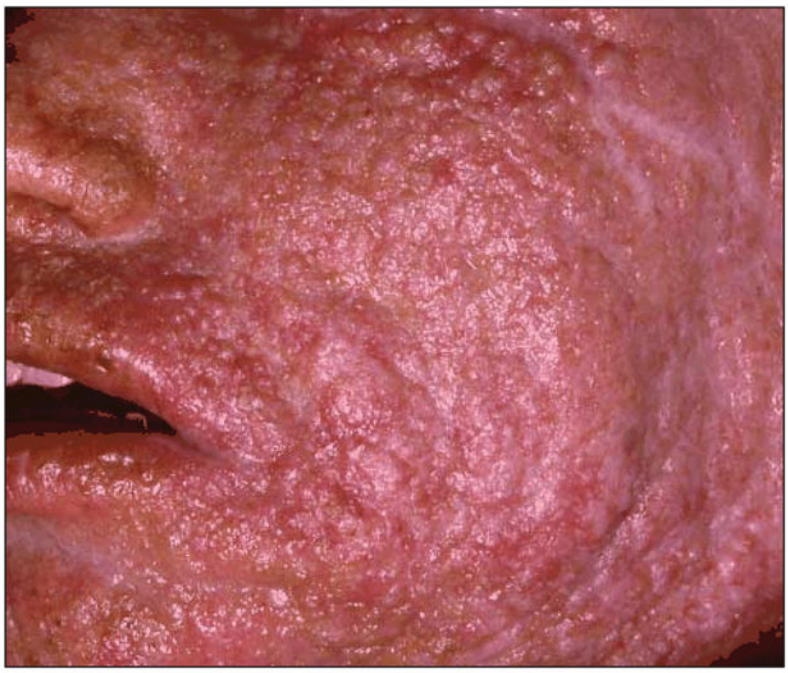

Figure 2.

Case 2. An 18-year-old woman with leonine infiltration of the skin associated with cutaneous T-cell lymphoma and overlying eczema herpeticum.

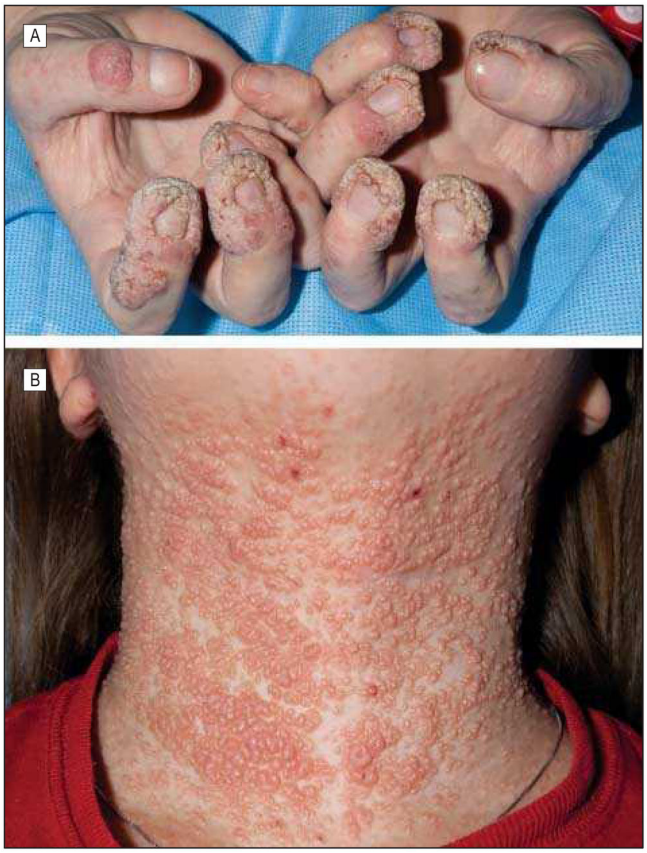

Figure 3.
Case 3. A 22-year-old woman with multiple concurrent severe cutaneous viral infections. A, Periungal verruca vulgaris. B, Confluent molluscum contagiosum lesions on the neck.

Table 1

Characteristics of Patients With *DOCK8* Deficiency

	Patient No.																				
Characteristic	**1.1**	**2.1**	**3.1**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**7.1**	**8.1**	**8.2**	**8.3**	**9.1**	**9.2**	**10**	**11.1**	**11.2**	**11.3**	**12.1**	**13.1**	**14.1**
Age, y	7	21[a]	18[a]	20	16	22	16	16	13[a]	18[a]	18	26	26	23	12	6	4	1	26[a]	8	16
Sex	F	M	F	M	F	F	F	M	F	F	M	M	M	F	F	M	F	M	M	M	F
Newborn rash	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	+	−	+	+	−	−
Coarse facies	−	−	NR	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Retention of primary teeth	−	NR	NR	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−
Joint hyperextensibility	−	NR	NR	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Minimal trauma fractures	−	−	NR	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Atopy																					
Eczema	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+
Allergies	F, E	F, E	F	−	−	F, E	F, E	F, E	F	F, E	F, E	F	F	−	F	F	F	−	E	−	−
Asthma	−	+	+	+	+	+	+	−	−	−	−	−	−	−	+	+	+	−	+	−	−
Infections																					
Respiratory	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
Skin and mucous membrane																					
Bacterial	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+
Viral																					
Viral warts	−	+	−	+	+	+	+	+	+	−	−	+	+	+	−	+	−	−	+	+	−
HSV	+	−	+	−	+	−	+	−	+	+	+	−	+	−	+	+	+	−	−	−	+
Molluscum contagiosum	−	−	+	+	+	+	−	−	+	−	+	+	−	−	+	+	−	−	−	+	−
Severe primary varicella	−	−	−	+	+	+	−	−	−	−	−	−	−	−	−	−	+	−	+	+	+
Herpes zoster	−	+	−	−	−	+	−	−	−	+	−	−	−	−	+	−	−	−	−	−	+
Mucocutaneous candidiasis	+	−	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	+	−	−	+
Malignantneoplasms																					
Squamous cell carcinoma	−	A	V, P	−	−	−	−	−	V	−	−	−	C	−	−	−	−	−	−	−	−
Lymphoma	−	−	CTCL	−	−	−	DLBCL	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Other	−	−	MAC	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

Abbreviations: A, anal; C, cheek; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; *DOCK8*, dedicator of cytokinesis 8 gene; E, environmental; F, food; MAC, microcystic adnexal carcinoma; NR, no record; P, paranasal; V, vulvar; −, negative; +, positive.

[a]Deceased.

Table 2

Frequency of Features in Patients With *DOCK8* Deficiency

Feature	Patients Affected, %
Newborn rash	24
Coarse facies	0
Retention of primary teeth	5
Joint hyperextensibility	11
Minimal trauma fractures	5
Atopy	
Eczema	91
Allergies (food and environmental)	71
Asthma	48
Infections	
Respiratory	91
Skin and mucous membrane	
Bacterial	81
Viral (total)	95
Viral warts	62
HSV	57
Molluscum contagiosum	48
Severe primary varicella	33
Herpes zoster	24
Mucocutaneous candidiasis	43
Malignant neoplasms	
Squamous cell carcinoma	19
Lymphoma	10

Abbreviations: *DOCK8*, dedicator of cytokinesis 8 gene; HSV, herpes simplex virus.

Table 3

Relative Frequency of Features of *DOCK8* Deficiency vs Job's Syndrome

Feature	*DOCK8* Deficiency	Job's Syndrome
Eczematous dermatitis	++++	++++
Newborn rash	+	+++
Coarse facies	−	+++
Retention of primary teeth	+	++++
Joint hyperextensibility	+	+++
Minimal trauma fractures	+	+++
Elevated serum IgE levels	++++	++++
Eosinophilia	++++	++++
Asthma	+++	+
Allergies	+++	++
Skin abscesses	++	+++
Mucocutaneous viral infections	++++	+
Mucocutaneous candidiasis	++	+++
Sinopulmonary infections	++++	++++
Squamous cell carcinoma	++	−
Lymphoma	+	+

Abbreviation: *DOCK8*, dedicator of cytokinesis 8 gene.