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ORIGINAL ARTICLE

Atypical Localization of Eczema Discriminates DOCK8 or STAT3 Deficiencies from Atopic Dermatitis

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Abstract

Purpose Autosomal recessive dedicator of cytokinesis 8 (DOCK8$^{-/-}$) and autosomal dominant signal transducer and activator of transcription 3 (STAT3$^{-/+}$) deficiencies are inborn errors of immunity (IEI) disorders present with the classic features of eczema and create a dilemma during differentiation from atopic dermatitis (AD). Therefore, an appropriate approach is required for eczema to diagnose DOCK8$^{-/-}$ and STAT3$^{-/+}$ early. Here, we described a set of clinical and immunological variables, including atypical AD localizations and lymphocyte subsets, to differentiate DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD.

Methods This multicenter study involved 100 patients with DOCK8$^{-/-}$ and STAT3$^{-/+}$ and moderate/severe AD. We recruited disease manifestations, including detailed localizations of eczema, infections, and allergy. Principle component analysis (PCA) was used to discriminate DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD.

Results There were 43 patients with DOCK8$^{-/-}$, 23 with STAT3$^{-/+}$, and 34 with AD. Pneumonia, severe infections, mucocutaneous candidiasis, and skin abscesses were commonly observed in DOCK8 and STAT3 deficiencies. Atypical skin involvement with neonatal rash, retro auricular, axillary, sacral, and genital eczema discriminate DOCK8$^{-/-}$ and STAT3$^{-/+}$ from AD with high specificity ranges between 73.5 and 94.1% and positive predictive index ranges between 55 and 93.1%. Together with using absolute numbers of CD3^{+}, CD4^{+}, and CD8^{+} T cells, the combined clinical and laboratory features showed perfect differentiation between DOCK8$^{-/-}$ or STAT3$^{-/+}$ and AD via PCA.

Conclusions The described features can be easily implemented by physicians providing early diagnosis of DOCK8 and STAT3 deficiencies.

Keywords DOCK8 deficiency · STAT3 deficiency · Atopic dermatitis · Eczema localizations

Introduction

Hyperimmunoglobulin E syndrome (HIES) consists of a group of inborn errors of immunity (IEI) characterized by a triad of eczema, recurrent cutaneous and sinopulmonary infections, and markedly elevated IgE levels [1]. HIES related to dominant-negative mutations in signal transducer and activator of transcription 3 (*STAT3*) gene are associated with autosomal dominant STAT3 deficiency (STAT3$^{-/+}$), causing recurrent infections and connective tissue abnormalities [2, 3]. While a dedicator of cytokinesis 8 (DOCK8) deficiency (DOCK8$^{-/-}$) was discovered to cause an autosomal recessive (AR) form of HIES, leading to severe infections and allergic manifestations, and recently, according to the International Union of Immunological Societies-IEI classification, it is accepted as combined immunodeficiency [4, 5]. Although these two entities have overlapping features, the history of allergic diseases with severe cutaneous viral infections, autoimmunity, and early development of malignancies have been suggested to favor the clinical diagnosis of DOCK8$^{-/-}$ [6]. Besides that, STAT3$^{-/+}$ is more related to skeletal and connective tissue anomalies with skin and internal abscesses and recurrent pneumonia complicated by pneumatoceles [7, 8]. Other genetic causes of HIES have recently been identified, including mutations in *PGM3*, *ZNF341*, *IL6ST*, *IL6R*, *ERBIN*, *TGFBR1*, *TGFBR2*, and *CARD11* genes [5].

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DOCK8$^{-/-}$ demonstrates severe clinical course and early diagnosis before end-organ toxicity or malignancy is crucial for successful allogeneic hematopoietic stem cell transplantation (HSCT) [9, 10]. While to ensure timely intervention and prevent severe lung disease, early diagnosis in STAT3$^{-/+}$ patients primarily focuses on initiating antimicrobial prophylaxis for all individuals and considering immunoglobulin replacement therapy if necessary [11]. Before the discovery of genetic causes, the National Institutes of Health (NIH) scoring system was developed for the diagnosis of HIES. Accordingly, at least 40 points are suggestive, between 20 and 40 points possible, and below 20 is unlikely for HIES [1, 12]. Besides, the DOCK8 scoring system can help suspect DOCK8$^{-/-}$ [13]. However, according to studies performed on these patients, successful diagnosis with existing clinical scoring systems depends on the emergence of adequate disease features. Therefore, these scores can be insufficient for early diagnosis with few disease manifestations [3, 12, 14].

During daily practice, an important problem facing clinicians during the evaluation of AD is discriminating against HIES and non-HIES diseases. Interestingly, early suspicion for diagnosis can be possible due to some unique AD localizations like retro auricular, axilla, groin, and back areas in DOCK8$^{-/-}$ or STAT3$^{-/+}$ patients [7, 15–17]. Furthermore, DOCK8$^{-/-}$ or STAT3$^{-/+}$ patients usually suffer from distinctive papulopustular, vesicular, and solid infected dermatitis due to *Staphylococcus aureus* or concomitant viral agents (Herpes simplex virus, Human papillomavirus, Molluscum contagiosum, and Varicella-zoster virus), cutaneous abscesses, and mucocutaneous candidiasis. In DOCK8$^{-/-}$ patients, viral infections manifest with higher frequency; conversely, STAT3$^{-/+}$ patients exhibit a heightened vulnerability to mucocutaneous candidiasis [17, 18]. Still, these manifestations are commonly observed with the progression of the disease [19, 20]. To the best of our knowledge, no study aims to differentiate DOCK8$^{-/-}$ or STAT3$^{-/+}$ and AD before developing classical manifestations of diseases.

Herein, we aimed to use some clinical and immunological variables, including atypical AD localizations and lymphocyte subsets, to diagnose DOCK8$^{-/-}$ or STAT3$^{-/+}$ early compared with moderate to severe AD. We believe that these identified features can guide physicians for rapid and early diagnosis.

Material and Methods

Patients

This multicenter study involved 100 patients with DOCK8$^{-/-}$, STAT3$^{-/+}$, and AD from eight immunology centers. The genetic diagnosis of DOCK8$^{-/-}$ and STAT3$^{-/+}$ was made by next-generation, confirmed by Sanger sequencing. In addition, copy number variation analysis or multiplex ligation-dependent probe amplification was performed for deletion in the *DOCK8* gene. Next-generation sequencing was also performed on all AD patients, and there were no pathogenic mutations in HIES-related genes. Clinical and demographic features of the patients were solicited from their medical records. These records included clinical history, laboratory test results, and mutation analysis of each patient. Part of these patients was reported previously [1, 6, 9, 21–23]. All DOCK8$^{-/-}$, STAT3$^{-/+}$, and AD patients had moderate/severe AD, according to SCORAD (moderate 25–50, severe > 50) [24]. The local ethics committee of Marmara University (IRB00009067) approved the study protocol, and written informed consent was obtained from all parents. Due to our patients' young age, a simple oral description of the study was presented to participating children in the presence of their parent(s), and verbal assent was requested.

Clinical and Immunological Evaluations

A questionnaire was filled out for every patient, including demographic and clinical data (age at presentation, onset of symptoms, immunodeficiency, atopy and eczema, past infections, NIH and SCORAD scores). We performed a detailed clinical examination and ordered laboratory tests, including complete blood cell count, serum immunoglobulin levels, and lymphocyte immunophenotyping of whole blood ($CD3^+$ T, $CD3^+$ $CD4^+$ T, $CD3^+$ $CD8^+$ T, $CD19^+$ B, $CD16^+$ $CD56^+$ NK, and $CD4^+$ $CD45RA^+$ $CD31^+$ T cells (RTE—recent thymic emigrants). Peripheral B cells were classified into three distinct populations: naive mature B cells ($CD19^+CD27^-IgD^+$), non-class-switched memory B cells (NCS B—$CD19^+CD27^+IgD^+$), and class-switched memory B cells (CS B—$CD19^+CD27^+IgD^-$) [25–28].

Statistical Analysis

The variables were presented as a median and interquartile range or mean and standard deviation, as indicated. Continuous variables were analyzed using one-way ANOVA or Kruskal–Wallis test with post hoc analysis. The chi-square test was used for categorical variables. Differences in values were considered significant at a p-value < 0.05.

To discover features that can be helpful for diagnosis before the development of known prominent features of DOCK8$^{-/-}$ or STAT3$^{-/+}$ (coarse face, skeletal, and connective tissue anomalies, severe cutaneous infections, severe allergy, autoimmunity, and malignancy), ten basic distinctive clinical and immunological features were selected as potential discriminating features of DOCK8$^{-/-}$ or STAT3$^{-/+}$ than AD. These features included the availability of clinical categorical variables: Recurrent infections-pneumonia (more than two times), localization of dermatitis-Neonatal eczema: NEO_ECZM, Retro auricular

eczema: RA_ECZM, Axillary eczema: AX_ECZM, Sacral eczema: SCR_ECZM, Genital eczema: GNT_ECZM, and NIH-HIES scoring (>40 points). We also evaluated basic continual immunological variables: Absolute counts (C; /mm^3) of CD3$^+$, CD4$^+$, and CD8$^+$ T cells. The mentioned atypical eczema localizations, mainly observed in DOCK8$^{-/-}$ or STAT3$^{-/+}$, were selected according to the previous reports [15, 18]. The efficiency of selected features in differentiation of the DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD patients was examined based on PCA. As the final step of the study, we eliminated the features that do not represent a significant contribution due to the same functions in the group differentiation to gain more useful variables for routine practice.

Results

Clinical and Demographic Data

The patient cohort consisted of DOCK8$^{-/-}$ ($n=43$), STAT3$^{-/+}$ ($n=23$), and AD patients ($n=34$). The median age was 12.5 years (range: 8.3–15.1) in DOCK8$^{-/-}$, 14 years (range: 6–19) in STAT3$^{-/+}$, and 6.1 years (range: 3.7–10.8) in AD patients. AD patients were significantly younger than the DOCK8$^{-/-}$ and STAT3$^{-/+}$ patients ($p=0.003$, $p=0.006$, respectively). The NIH-HIES scores were significantly higher in DOCK8$^{-/-}$ and STAT3$^{-/+}$ patients than in AD ($p<0.001$, $p<0.001$, respectively). Pneumonia, severe infections, mucocutaneous candidiasis, and skin abscesses were commonly observed in DOCK8 and STAT3 deficiencies (Table 1). The detailed demographic, clinical, and mutation data of the DOCK8$^{-/-}$, STAT3$^{-/+}$, and AD patients are presented in Table S1.

Immunological Evaluations

The median serum IgE level was significantly higher in STAT3$^{-/+}$ (18,715 IU/ml) than in DOCK8$^{-/-}$ and AD (2,917 IU/ml; $p=0.020$, 2,274 IU/ml; $p=0.032$, respectively). The mean IgM level was lower in DOCK8$^{-/-}$ than in other groups ($p<0.001$). In DOCK8$^{-/-}$, lymphopenia ($p=0.007$ and $p=0.020$, respectively) and eosinophilia ($p=0.009$ and $p=0.011$, respectively) were more prominent than STAT3$^{-/+}$ and AD patients. Furthermore, CD3$^+$ T cells ($p<0.001$ and $p<0.001$, respectively) and CD4$^+$ T cells ($p<0.001$ and $p<0.001$,respectively) counts and percentage of RTE cells ($p=0.004$ and $p=0.003$, respectively) were significantly lower in DOCK8$^{-/-}$ than other groups. Also, those patients exhibited lower numbers of CSB cells compared to AD patients ($p<0.001$). STAT3$^{-/+}$ patients showed lower CD16$^+$56$^+$ NK counts than DOCK8$^{-/-}$ and AD patients ($p=0.002$ and $p=0.008$, respectively; Table 2).

Table 1 The demographic and clinical data of DOCK8- and STAT3-deficient and AD patients

Parameters	DOCK8$^{-/-}$ ($N=43$)	STAT3$^{-/+}$ ($N=23$)	AD ($N=34$)	DOCK8$^{-/-}$ vs AD (p-value)	STAT3$^{-/+}$ vs AD (p-value)	DOCK8$^{-/-}$ vs STAT3$^{-/+}$ (p-value)
Male/female (N, %)*	26 (60.5)/17 (39.5)	11 (48)/12 (52)	22 (65)/12 (35)	0.703	0.205	0.324
Current age (year); median (IQR)**	12.5 (8.3–15.1)	14 (6–19)	6.1 (3.7–10.8)	***0.003***	***0.006***	1.000
Age at AD onset (year); median (IQR)**	0.5 (0.2–1)	0.1 (0.08–1)	0.4 (0.2–1.1)	0.359	0.464	0.088
Age at diagnosis (year); median (IQR)**	4.7 (3.2–8)	5.1 (2.2–9.4)	0.8 (0.33–4)	***0.027***	***0.043***	0.323
Follow-up time (year); median (IQR)**	4.5 (1.5–8.41)	5.2 (0.81–8)	1.1 (0.16–4)	***0.001***	***0.012***	0.984
SCORAD; mean (SD)***	49 (22)	44 (19)	48.4 (12)	0.987	0.590	0.479
NIH-HIES score; median (IQR)**	36 (28–46)	40 (33–52)	17 (12–24)	***<0.001***	***<0.001***	0.152
Pneumonia (N, %)*	36 (83.7)	16 (69.6)	1 (2.9)	***<0.001***	***<0.001***	0.215
Severe infection (N, %)*	24 (55.8)	13 (56.5)	1 (2.9)	***<0.001***	***<0.001***	0.956
Newborn rash (N, %)*	11 (25.6)	18 (78)	9 (26.5)	0.930	***<0.002***	***<0.001***
Mucocutaneous candidiasis (N, %)*	18 (41.9)	14 (60.9)	2 (5.9)	***<0.001***	***<0.001***	0.141
Food allergy (N, %)*	22 (52.4)	8 (34.8)	21 (61.8)	0.412	***0.046***	0.174
Malignancy (N, %)*	4 (9.3)	0 (0)	0 (0)	0.125	-	0.291
Cutaneous infections (N, %)*	30 (73.2)	4 (19)	7 (20.6)	***<0.001***	1.000	***<0.001***
Skin abscesses (N, %)*	16 (37.2)	15 (65.2)	2 (5.9)	***0.001***	***<0.001***	***0.030***

Significant values are presented in bold and italic manner. P-values less than 0.05 are considered significant

Abbreviations: *IQR*, interquartile range (25–75%); *NIH*, National Institute of Health; *SCORAD*, Score of Atopic Dermatitis

*Categorical variables were compared with Chi-square test. Bonferroni correction was made after multiple pairwise comparisons

**Non-normally disturbed continuous variables were compared by Kruskal–Wallis test and Tamhane's test used for post hoc analysis

***Normally disturbed variable was compared with one-way ANOVA test and Tukey test used for post hoc analysis

Differentiation of DOCK8 $^{-/-}$ or STAT3$^{-/+}$ from AD via Eczema Localizations

To provide early diagnosis for patients and predict the possible involved gene (*DOCK8* or *STAT3*), we aimed to understand which clinical and immunological features can be useful in this regard. Following the collection of the clinical features and physical examination of the experts, ten features were chosen to discriminate DOCK8 or STAT3 deficiencies from AD patients (Fig. 1). Apart from face eczema, other features were detected to be important for early diagnosis and DOCK8$^{-/-}$ and STAT3$^{-/+}$ patients showed more atypical localizations than AD (Fig. 2). Although the percentages of neck and trunk eczema were high in the DOCK8$^{-/-}$ and STAT3$^{-/+}$ patients, these skin involvements also observed commonly in AD patients when compared to others features. Therefore, we discharged these two skin localizations for further evaluation. Overall, after omitting these three features and, together with some basic immunological parameters, we selected ten discriminating features to differentiate DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD at the early stage of the disease. These ten unique features were availability

Table 2 The immunological evaluation of DOCK8- and STAT3-deficient patients and AD patients

Parameters; median (IQR)	DOCK8$^{-/-}$ ($N=43$)	STAT3$^{-/+}$ ($N=23$)	AD ($N=34$)	DOCK8$^{-/-}$ vs AD (p-value)	STAT3$^{-/+}$ vs AD (p-value)	DOCK8$^{-/-}$ vs STAT3$^{-/+}$ (p-value)
Evaluation age (years)	4.7 (3.2–8)	5.1 (2.2–9.4)	4.4 (2.2–6.1)	0.240	0.321	0.736
IgG; mg/dl (before IVIG)	1274 (1040–1530)	1420 (1162–1490)	1082 (818–1405)	0.097	0.400	0.968
IgA; mg/dl	118.5 (46.5–211.2)	83 (58–141)	120.5 (74.7–163)	0.777	0.753	0.342
IgM; mg/dl	33.9 (24–55.5)	116.5 (85.2–148.2)	97 (68.7–139.2)	***<0.001***	0.741	***<0.001***
IgE; IU/ml	2,917 (787–6,550)	18,715 (5,571–34,235)	2,274 (569–10,486)	0.797	***0.032***	***0.020***
Lymphocyte (/µl)	2,240 (1,528–2,655)	3,300 (2,295–4,555)	3,255 (2,400–4,325)	***0.007***	0.901	***0.020***
Eosinophil (/µl)	2,020 (915–3,782)	750 (300–1,597)	900 (480–1,400)	***0.009***	0.998	***0.011***
CD3$^+$ T cells count (/µl)	995 (732–1,541)	2,422 (1,825–3,346)	2,197 (1,871–3,154)	***<0.001***	0.892	***<0.001***
CD3$^+$CD4$^+$ T cells count (/µl)	440 (337–730)	1,401 (1,153–2,178)	1296 (962–1,692)	***<0.001***	0.579	***<0.001***
CD3$^+$CD8$^+$ T cells count (/µl)	479 (263–652)	787 (579–1,034)	745 (519–1,086)	0.059	0.996	0.098
CD16$^+$56$^+$ NK cells count (/µl)	283 (126–452)	135 (78–218)	251 (149–433)	0.873	***0.008***	***0.002***
NCS B cells (%)	4.2 (1.8–9.9)	4 (2.3–6.6)	8 (3.7–12)	0.849	***0.005***	0.464
CS B cells (%)	2.4 (0.9–4)	4.1 (2.3–5.8)	11.6 (7.9–17)	***<0.001***	0.130	0.522
RTE (%)	37.2 (26.3–47.8)	57.7 (48.9–64.8)	53.7 (44.2–60.8)	***0.004***	0.931	***0.003***

Abbreviations: *IQR*, interquartile range (25–75%); *IVIG*, intravenous immunoglobulin; *NCSB*, non-class-switched memory B cells; *CSB*, class-switched memory B cells; *RTE*, recent thymic emigrant T cells. Variables were compared by Kruskal–Wallis test due to non-normal distribution, and Tamhane's test was used for post hoc analysis. The significant values are indicated in bold. p-values less than 0.05 are considered significant

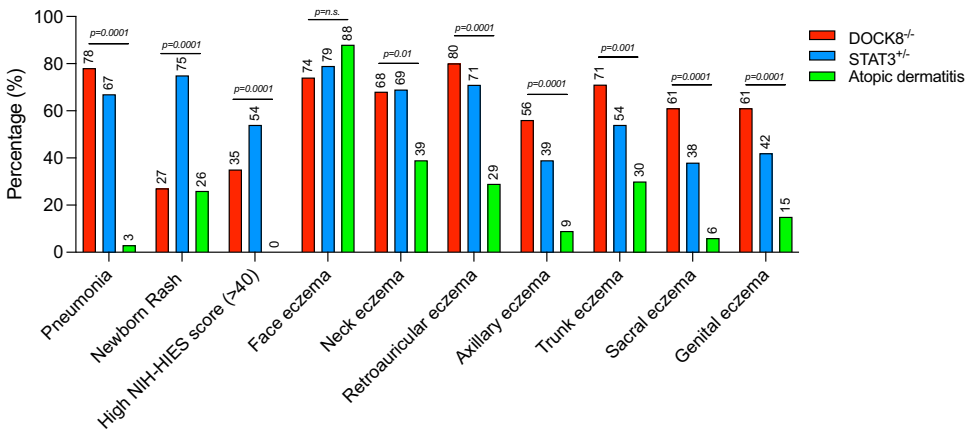

Fig. 1 The selected ten clinical features discriminating DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD patients. The chi-square test was used for categorical variables. Differences in values were considered significant at a p-value < 0.05

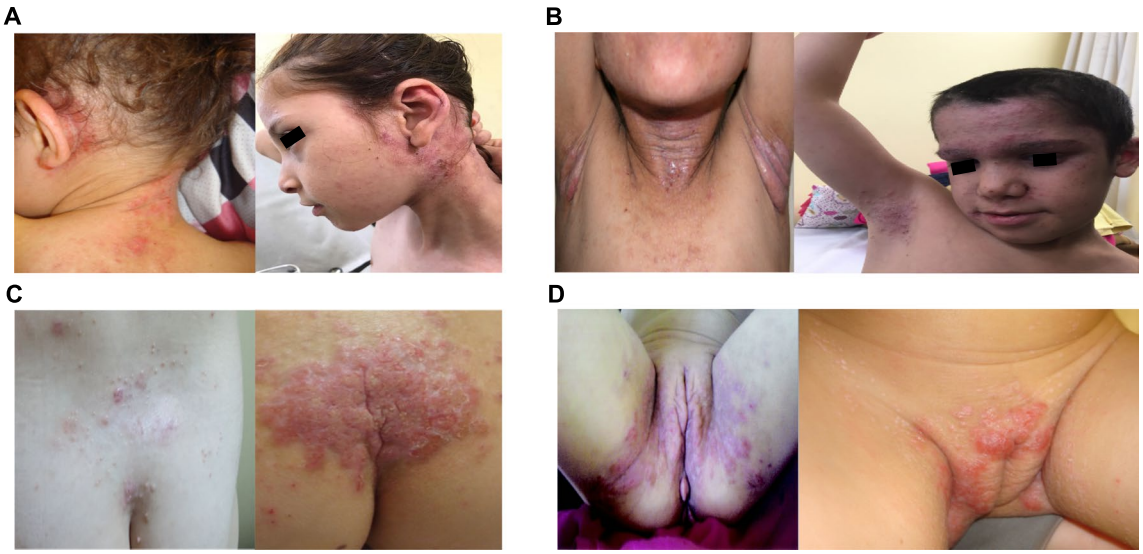

Fig. 2 The atypical skin localizations in DOCK8- and STAT3-deficient patients. **A** Retro auricular eczema (DOCK8_36, STAT3_23), **B** axillary eczema (DOCK8_2, STAT3_16), **C** sacral eczema (DOCK8_31, DOCK8_36), **D** inguinal and genital eczema (DOCK8_10, DOCK8_36)

of recurrent pneumonia, RA_ECZM SCR_ECZM, GNT_ECZM, AX_ECZM, and NEO_ECZM, high NIH-HIES score (> 40 points), low $CD3^+$_C, $CD4^+$_C, and $CD8^+$_C T cells. The score values of these features for each patient are presented in Table S2. We first calculated the sensitivity, specificity, positive predictive index (PPI), and negative predictive index (NPI) of these selected ten parameters (Table 3). We observed that every feature showed high specificity and PPI, delineating the striking roles of these parameters in the selection of $DOCK8^{-/-}$ and $STAT3^{-/+}$ patients. Afterward, the strength of the selected features in the differentiation of the $DOCK8^{-/-}$ or $STAT3^{-/+}$ from AD patients was analyzed by PCA (Fig. 3, A–D). According to PCA results, the 1st and 2nd PCAs explain 63.8% and 59.2% of the variations between the $DOCK8^{-/-}$ and AD, $STAT3^{-/+}$ and AD, respectively. All PCA results are provided in Table S3. These results showed that the selected features are promising in group differentiation. Next, because some features did not contribute significantly, we used the combination of essential properties, revealing a similar effect in discriminating disease groups (Fig. 4, A–D). Therefore, to differentiate $DOCK8^{-/-}$ from AD, PCA showed most better combination with the availability of recurrent pneumonia, RA_ECZM, SCR_ECZM, high NIH-HIES score, and low CD4_C, while for differentiation of $STAT3^{-/+}$ than AD, availability of recurrent pneumonia, NEO_ECZM, RA_ECZM, GNT_ECZM, and high NIH-HIES score (> 40 points) revealed the better combination. The 1st and 2nd PCAs manage to

Table 3 The sensitivity, specificity, positive predictive index, and negative predictive index used ten parameters to differentiate patients with $DOCK8^{-/-}$ or $STAT3^{-/+}$ from AD

Parameters	Sensitivity (%)		Specificity (%)		PPI (%)		NPI (%)	
	$DOCK8^{-/-}$	$STAT3^{-/+}$	$DOCK8^{-/-}$	$STAT3^{-/+}$	$DOCK8^{-/-}$	$STAT3^{-/+}$	$DOCK8^{-/-}$	$STAT3^{-/+}$
History of newborn Rash	25.5	78.3	73.5	73.5	55.0	66.7	43.9	83.3
History of pneumonia	83.7	69.6	97.1	97.1	97.3	94.1	82.5	82.5
High NIH-HIES score (> 40)	37.2	56.5	100	100	100	100	55.7	77.3
History of retro auricular skin involvement	83.7	73.9	70.6	63.0	78.3	70.6	77.4	80.0
History of axillary skin involvement	57.1	40.9	88.9	91.2	91.2	75.0	63.3	70.5
History of sacral skin involvement	62.8	39.1	94.1	94.1	93.1	81.8	66.7	69.6
History of genital skin involvement	60.5	43.5	85.3	85.3	83.9	66.7	63.0	69.0
Low $CD3^+$ T cells count*	67.4	-	100	-	100	-	70.8	-
Low $CD3^+CD4^+$ T cells count*	81.4	17.4	100	100	100	100	81.0	64.2
Low $CD3^+CD8^+$ T cells count*	39.5	4.3	100	100	100	100	56.7	60.7

Abbreviations: *PPI*, positive predictive index; *NPI*, negative predictive index; *NIH*, National Institute of Health

*Normalization to age-matched healthy controls

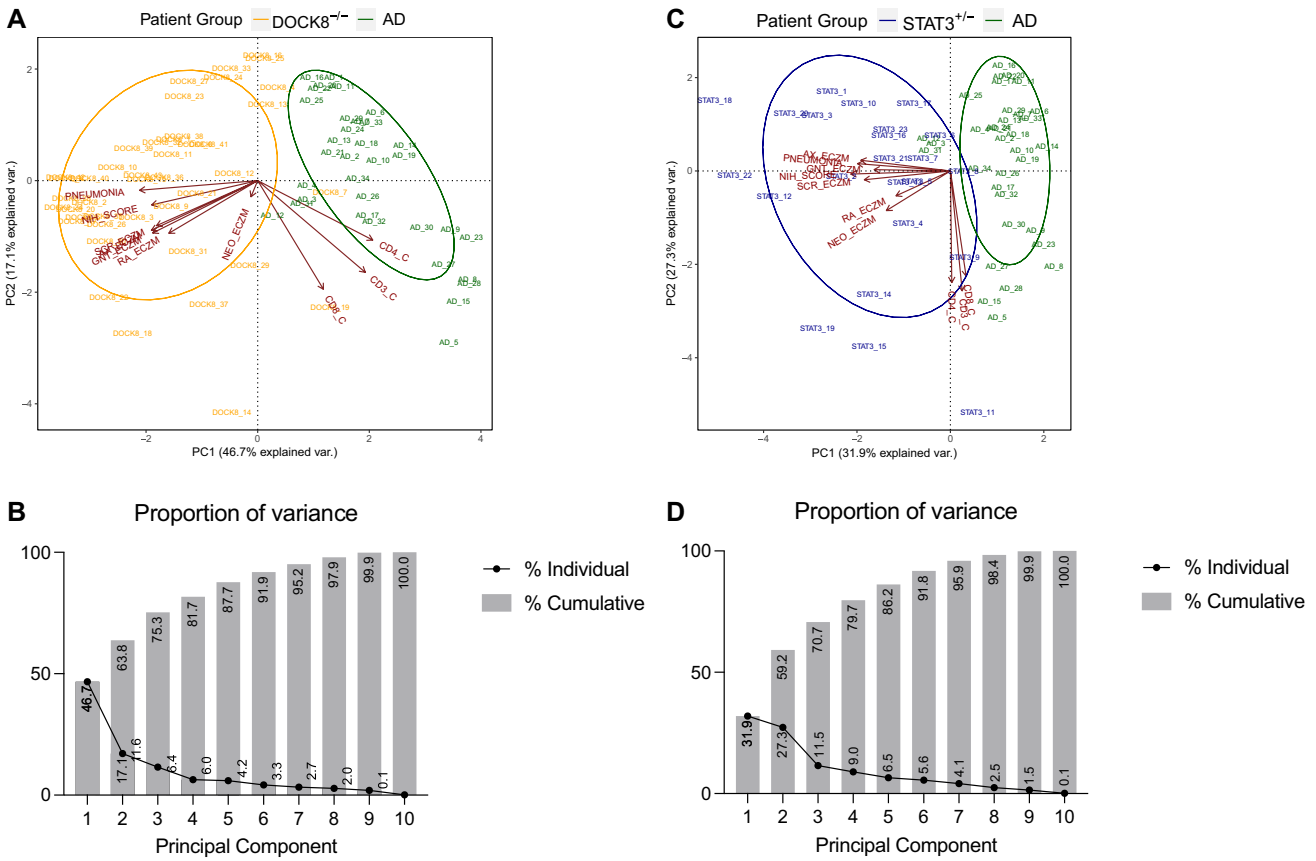

Fig. 3 AD localizations and T cell counts successfully separate DOCK8- or STAT3-deficient patients from AD. **A** Principal component analysis (PCA) with the proportion of variance **B** for DOCK8$^{-/-}$ against moderate to moderate/severe AD, and STAT3$^{-/+}$ against moderate to moderate/severe AD patients (**C** and **D**)

explain 73.8% and 58.5% of the variations between the DOCK8$^{-/-}$-AD and STAT3$^{-/+}$-AD, respectively. The score values of these particular features for each patient are presented in Table S2. Overall, these features represent a simple and practical approach to differentiate DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD at an early stage of the disease.

Discussion

In this study, we described clinical and immunological features useful in differentiating DOCK8$^{-/-}$ and STAT3$^{-/+}$ from AD patients. Common and similar symptoms between DOCK8$^{-/-}$, STAT3$^{-/+}$ and AD patients create a diagnostic dilemma and often lead to delays in correct diagnosis. Furthermore, in most cases, definitive molecular diagnosis is possible with gene sequencing and assessment of large deletions for DOCK8 deficiency; however, this approach usually takes longer. Therefore, predicting the underlying genetic defect and making an early diagnosis is vital in these diseases. For this purpose, we determined atypical skin localizations of eczema and combined them with basic T cell counts that help discriminate DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD at an early stage of the disease. Physicians can easily implement these features, thus providing wide usage during daily practices.

AD is typically seen in the extensor regions of extremities in childhood and is usually less observed in axillary, groins, sacral, and genital areas [29]. In this large and multicenter cohort, we observed that these atypical regions are commonly involved in DOCK8$^{-/-}$ and STAT3$^{-/+}$, which can be essential for early diagnosis. Previously, Eberting et al. reported 43 patients with a clinical diagnosis of HIES and observed common newborn rash in this population. Additionally, this study showed some atypical localizations complicated with superficial infections, especially in retro auricular fissures, axillae, and groin regions. However, the frequency and comparative evaluation between AD and HIES was not performed in that study for these unusual localizations; also, the lack of genetic confirmation of HIES restricted our knowledge of which subtype of HIES these lesions can be more common [15]. In our study, we compared DOCK8$^{-/-}$ and STAT3$^{-/+}$ with AD and found that these atypical localizations trended to be observed more in DOCK8-deficient patients. Furthermore, in DOCK8$^{-/-}$, these atypical eczema localizations were most

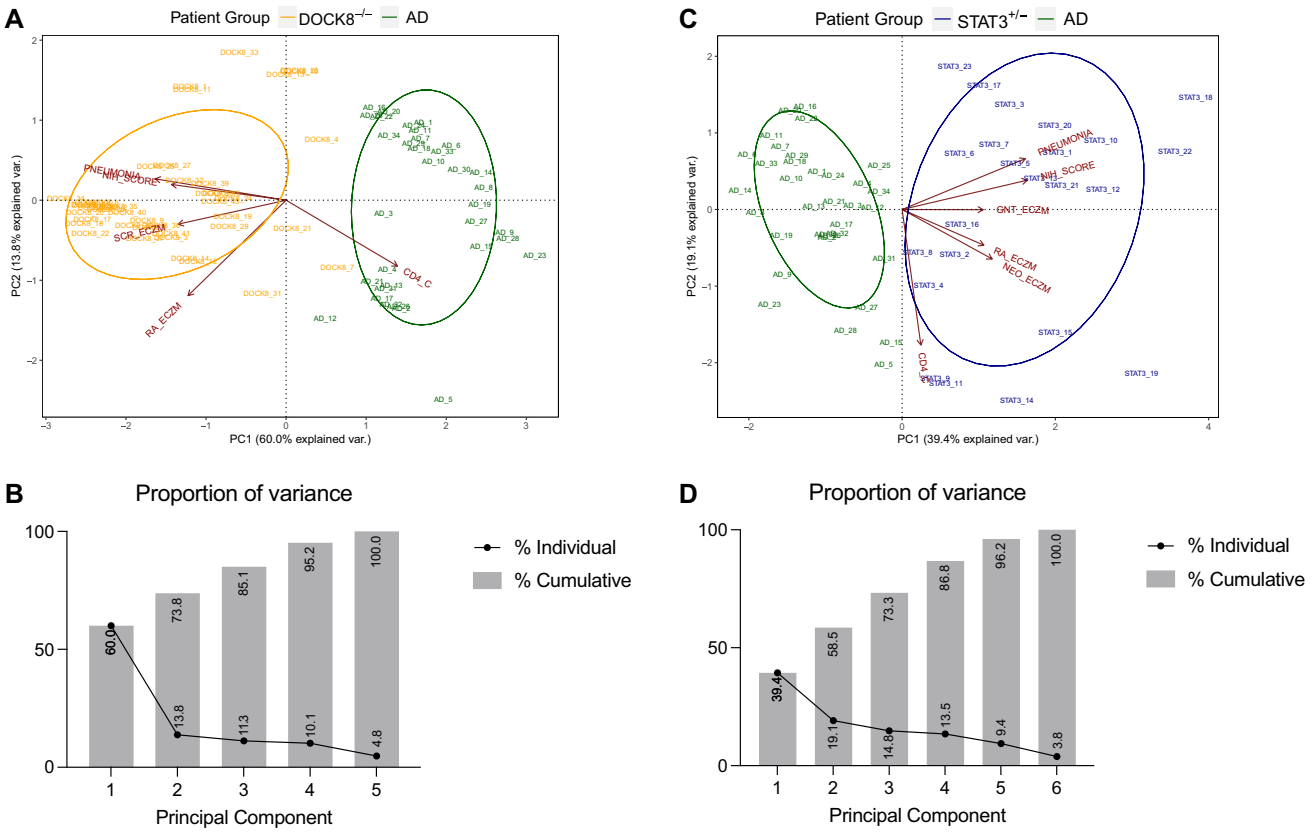

Fig. 4 Selected features differentiate DOCK8- or STAT3-deficient patients from AD. PCA with the proportion of variance for selected features to differentiate DOCK8$^{-/-}$ (**A** and **B**) or STAT3$^{-/+}$ from moderate/severe AD (**C** and **D**)

frequent in the retro auricular and sacral areas compared to AD. While for STAT3$^{-/+}$, these were more common as neonatal, retro auricular, and genital eczema compared to AD.

STAT3$^{-/+}$ is characterized by the frequent observation of newborn rash, pneumonia, and high NIH-HIES scores [1, 2, 30, 31], while low CD3^{+}, CD3^{+}CD4^{+}, and CD3^{+}CD8^{+} T cells are mostly associated with DOCK8$^{-/-}$ [6, 9, 30, 32, 33]. Together with atypical eczema localizations, we selected these most useful discriminating features for early diagnosis. The success rate of the combined features showed that simple, unique manifestations could be essential to suspect DOCK8$^{-/-}$ or STAT3$^{-/+}$ since the treatment of both diseases is different from AD, and the prior one needs HSCT while the latter requires antimicrobial prophylaxis and, in certain cases, immunoglobulin replacement therapy to manage disease manifestations effectively. According to our knowledge, this is the first study in the literature evaluating combined skin features with lymphocyte subpopulation abnormalities to distinguish DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD.

In our cohort, the NIH-HIES scores were significantly higher in the DOCK8$^{-/-}$ and STAT3$^{-/+}$ than in the AD, and no one had a score above 40 in the AD patients. The NIH-HIES scoring system does not allow diagnostic accuracy in all DOCK8$^{-/-}$; it can be distinctive, especially in STAT3$^{-/+}$. Therefore, in 2015, Engelhardt et al. developed the DOCK8 score system, which was useful in distinguishing patients with *DOCK8* mutations from patients with *STAT3* mutations. However, the utility of this scoring system has yet to be confirmed in large cohorts of AD patients with high serum IgE levels [13]. Our established features can be applied to create a new scoring system. Although we detected that the set of these variables revealed a reliable formula, the low number of patients did not allow us to generate a significant relationship in multiple logistic regression analysis. Therefore, more patients will help create a scoring system using our variables.

The primary limitation of our study was the age disparity between the patient and control groups. As our AD patients were younger than DOCK8$^{-/-}$ or STAT3$^{-/+}$ patients, the influence of age on the results remains uncertain. It is important to acknowledge that AD patients may present new findings over time, necessitating further investigation. Hence, our study should be regarded as a foundational step, highlighting the need for better-controlled studies to elucidate the potential impact of age on explored features.

In conclusion, the provided straightforward clinical and immunological features can be useful to discriminate

DOCK8$^{-/-}$ or STAT3$^{-/+}$ from AD at an early stage of the disease. These distinctive features hold the potential for timely diagnosis and treatment. Importantly, our study provides a basis for better studies with stringent controls, further enhancing the understanding and application of these discriminative markers.

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Author Contribution N.K. and S.B. conceptualized the study. N.K., A.K., and S.B. wrote the manuscript. A.K., V.C., K.S.A., and S.B. performed the statistical analysis. N.K., V.C., S.B.E., I.A.H., H.K., A.A., E.A., N.Y., S.N.G., I.R., S.K., S.C., S.S.K., N.E.K., N.G., F.G., A.O., A.D.Y., E.K.A., and S.B. cared for patients and provided samples intellectually contributed to the manuscript and discussions. All authors read the manuscript and contributed to the revision and discussions.

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Data Availability The data generated during the study are included in this published article and its supplementary file.

Declarations

Ethical Approval The Ethics Committee of Marmara University School of Medicine approved the study.

Consent to Participate Informed consent for participation was obtained from the family.

Consent for Publication Informed publication consent was obtained from the family.

Conflict of Interest The authors declare no competing interests.

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