ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
In press.

Measuring Dedicator of Cytokinesis 8 (DOCK8) Expression as a Flow Cytometry Biomarker for DOCK8 Deficiency Detection

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Received: 4 December 2024; Received in revised form: 20 March 2025; Accepted: 23 April 2025

ABSTRACT

The autosomal recessive form of hyperimmunoglobulin E syndrome (AR-HIES), caused by mutations in the *DOCK8* (Dedicator of Cytokinesis 8) gene, presents a wide range of clinical manifestations and phenotypically overlaps with several types of combined immunodeficiency disorders characterized by elevated serum IgE levels. Due to the high rates of morbidity and mortality, as well as the potential curability through hematopoietic stem cell transplantation (HSCT), early and accurate differential diagnosis of this syndrome is crucial for optimal management and improved prognosis. Flow cytometry tests can be beneficial for early diagnosis of many inborn errors of immunity (IEIs), including this syndrome. This study, conducted for the first time on Iranian patients, investigated the expression of the DOCK8 protein.

DOCK8 expression was assessed by flow cytometry in 14 patients (6 males and 8 females) with a clinical diagnosis of DOCK8 deficiency. The diagnosis was ultimately confirmed through genetic testing.

The results showed that DOCK8 expression in patients was significantly lower compared to the healthy control group.

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Flow cytometric evaluation of DOCK8 protein expression offers a rapid and efficient diagnostic method with a sensitive detection range suitable for many cases. This approach can facilitate the diagnosis of DOCK8 deficiency, thereby enabling timely and effective disease management.

Keywords: Flow cytometry; Hyper IgE; Immunodeficiencies; Inborn errors of immunity

INTRODUCTION

Hyper immunoglobulin E (IgE) syndrome (HIES) is a rare combined primary immunodeficiency disorder characterized by elevated IgE levels, recurrent infections, and connective tissue abnormalities, It was first described by Davis et al in 1966.[1] To date, mutations in the *TYK2, STAT3, DOCK8, PGM3*, and *ZNF341* genes have been identified in individuals affected by this syndrome. [2-8] Mutations in the *DOCK8* and *STAT3* genes account for the majority of autosomal recessive and autosomal dominant cases of this syndrome, respectively,[9] While the dominant form is more prevalent globally, regions such as Iran, where consanguineous marriages are common, show a higher frequency of the recessive form, primarily associated with DOCK8 deficiency.[10] Both genetic forms of HIES share clinical features such as recurrent infections and mucocutaneous candidiasis, mainly due to functional defects of Th17 cells. The main reason for this phenotypic convergence is the critical role of DOCK8 in regulating STAT3 activity in immune cells, particularly lymphocytes, leading to impaired differentiation of Th17 cells.[11] DOCK8 is a member of the DOCK protein family known as guanine exchange factors (GEFs), which regulates the activity of GTPases such as Cdc42 and Rac1 involved in various signaling pathways. The expression of DOCK8 is mainly restricted to the hematopoietic cells with the highest levels observed in immune system cells, particularly lymphocytes. DOCK8 functions as an adaptor molecule involved in actin polymerization and cytoskeleton rearrangement, which play a crucial role in various functions of the immune system. Therefore, due to DOCK8 deficiency, all of these functions are impaired. The importance of the DOCK8 protein in regulating and maintaining the proper function of the immune system is reflected in the high mortality and morbidity rates observed in individuals with *DOCK8* gene defects.[12,13] As with other immune disorders, early diagnosis is crucial for this syndrome to ensure timely intervention and the implementation optimal management strategies.[15,16] The diagnosis of HIES relies on a combination of clinical features and laboratory tests, which are classified as the NIH (The National Institutes of Health) Scoring System (scores over 40 points indicate a likely AD-HIES (The Dominant recessive form of hyperimmunoglobulin E syndrome) phenotype, scores of 20-40 points are inconclusive regarding the presence of AD-HIES, and scores below 20 points indicate that the subject is unlikely to have AD-HIES).[17,18] However, initial diagnosis based on clinical manifestations is challenging because of the wide range of clinical manifestations in this syndrome and phenotypic overlap with some forms of combined immunodeficiency with elevated IgE levels. While genetic testing is the definitive method for confirming DOCK8 deficiency in HIES patients, immunological biomarkers can provide a valuable alternative for early diagnosis when genetic testing is not available or feasible. Since DOCK8 mutations typically lead to defective protein expression, this study measured the expression levels of DOCK8 in patients with a clinical diagnosis of DOCK8 deficiency by flow cytometry as a simple and highly sensitive method. The diagnosis was subsequently confirmed through exome sequencing.

MATERIALS AND METHODS

Patients and Controls

Fourteen Iranian patients with a clinical diagnosis of AR-HIES were invited to cooperate with the Immunodeficiency Research Center of Tehran University of Medical Sciences between 2022 and 2024. The patients were selected based on the immunology and allergy specialist's assessment, by examining the patient's family and medical records, as well as based on the classification of the International Union of Immunological Societies (IUIS) and the criteria for probable diagnosis criteria of HIES by the European Society of Immunodeficiency Disorders (ESID) including elevated serum IgE>10 times the normal for age, pathologic susceptibility to infectious diseases, no evidence of T-cell deficiency (low T cell numbers, low

naive T cells, reduced proliferation) and no evidence of B cell deficiency. This study revealed that 10 patients (4 males, 6 females) with an average age of 9.7 years, from 10 different consanguineous families had DOCK8 deficiency, and 4 other patients exhibited normal expression of DOCK8 and had mutations in other genes. The following investigations were conducted on these 10 patients. Additionally, 10 age and sex-matched healthy donors were included as a control group. In accordance with the Helsinki Declaration, informed consent was obtained from patients before enrolment. Moreover, the NIH Score was calculated for the patients.

DOCK8 Expression by Flow Cytometry

The blood sample was fixed, permeabilized, and stained with primary and secondary antibodies Anti-DOCK8 (Abcam, UK) and anti-IgG (Abcam, UK), respectively, and then analyzed by flow cytometry using a BD FACS Calibur (BD Biosciences, San Jose, CA, USA).

Mutational Analysis

Genomic DNA was isolated from peripheral blood using the DNA Blood Mini Kit (Favorgen, Taiwan). Whole-exome sequencing was performed, and then the detected Mutations were confirmed by Sanger sequencing.

Statistical Analysis

The flow cytometry test results were evaluated with FlowJo 7.6.1 software, the data were then transferred to GraphPad PRISM 8 (GraphPad Software, San Diego, CA) software. Mann-Whitney tests were used to compare the two groups. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut-off value for the studied diagnostic marker. *p* values less than 0.05 were considered statistically significant.

RESULTS

Clinical Information and Laboratory Findings of Patients with DOCK8 Deficiency

All patients were born to first-degree consanguineous parents. The age of onset of clinical manifestations ranged from 2.5 months to 1.5 years, with an average of 0.8 years. The average age at diagnosis was 9.7 years, reflecting a diagnostic delay of 8.8 years. Clinical manifestations included eczema, skin abscess, pneumonia, pulmonary manifestations, sinusitis/otitis, candidiasis, and viral infections. The NIH score was also calculated for the patients, with an average of 37.2. According to the NIH scoring system, cases with a score below 40 make the presence AD-HIES form (associated with STAT3 mutations) unlikely. Therefore, the results of the NIH score were consistent with our study (Table 1). IgE levels were markedly elevated in all patients, ranging from 700 to over 10,000 IU/ml. Immunoglobulin levels were generally normal, although a decreasing trend in IgM levels was observed in half of the patients. CD4 Lymphopenia was observed in most patients compared to the healthy control group (Table 2).

DOCK8 expression by Flow cytometry

Despite the varying levels of DOCK8 expression, the test successfully detected most patients. DOCK8 expression was assessed in lymphocytes, and the mean fluorescence intensity (MFI) of DOCK8 was significantly lower in patients compared to the control group (p=0.0001).

ROC analysis of DOCK8 expression revealed an area under the curve of 0.97, which distinguished DOCK8-deficient patients from normal controls (p=0.0004). At a cut-off of 151.1%, the sensitivity was 100%, while the specificity was 80% (Figure 1).

Mutational Analysis

Whole-exome sequencing was performed on 14 patients clinically diagnosed with DOCK8 deficiency. In four patients with normal DOCK8 expression, no mutations were detected in the *DOCK8* gene. However, in patients with DOCK8 expression deficiency, various mutations were detected in the DOCK8 coding gene, including large deletions and point mutations. Despite the confirmed mutations in the DOCK8 gene in three patients (P2, P5 and P6), their DOCK8 expression levels remained within the range observed in healthy control samples. (Table 3). Mutations detected through exome sequencing were confirmed by Sanger sequencing.

Table 1. Demographic and clinical findings of patients with DOCK8 deficiency

NO.	1	2	3	4	5	6	7	8	9	10
Gender	F	M	F	F	F	M	F	F	M	M
Age of onset (years)	0.2	1	1.5	1	1	0.5	0.5	0.5	1	1.5
Age of Diagnosis (years)	4	13	16	12	5	12	11	5	9	10
Eczema	+	+	+	+	+	+	+	+	+	+
Skin abscesses	-	-	-	-	+	-	+	-	-	-
Pneumonia	+	+	+	+	+	-	+	+	-	-
Lung complications	+	+	+	+	+	+	+	+	+	+
Sinusitis/Otitis	+	+	+	+	+	+	+	+	+	+
Candidiasis	+	+	+	+	+	-	+	+	+	+
Viral infection	+	+	+	+	+	+	+	+	+	+
Retained teeth	-	-	-	-	-	-	-	-	-	-
Scoliosis	-	-	-	-	-	-	-	-	-	-
Characteristic face	-	-	-	-	-	-	-	-	-	-
Pathogenic bone fracture	-	-	-	-	-	-	+	+	-	-
Hyperextensibility	-	-	-	-	-	-	-	-	-	-
Vascular abnormalities	-	-	-	-	-	-	-	-	-	-
Lymphoma	-	-	-	-	-	-	-	-	-	-
NIH score	37	34	40	41	37	35	39	40	34	38

DOCK8: Dedicator of Cytokinesis 8; NIH: The National Institutes of Health score

Table 2. Immunological parameters in DOCK8 patients

NO.	1	2	3	4	5	6	7	8	9	10
Eosinophil (Count/μL)	4300↑ (<700)	1700↑ (<700)	630 (<700)	550 (<700)	3800↑ (<700)	255 (<700)	965↑ (<700)	2200↑ (<700)	830↑ (<700)	1455↑ (<700)
IgG (mg/dL)	1501↑ (500-1300)	1310 (630-1340)	820 (630-1340)	600↑ (630-1340)	1650↑ (500-1300)	670 (630-1340)	712 (760-2300)	1220 (500-1300)	1061 (760-2300)	927 (760-2300)
IgM (mg/dL)	58 (40-180)	41↓ (55-350)	82 (55-350)	107 (55-350)	33↓ (40-180)	45↓ (55-350)	51↓ (70-380)	49 (40-180)	119 (70-380)	55↓ (70-380)
IgA (mg/dL)	121 (40-180)	88 (70-300)	220 (70-300)	151 (70-300)	155 (40-180)	117 (70-300)	246 (70-300)	67 (40-180)	434↑ (70-310)	129 (70-310)
IgE (IU/mL)	>5000↑ (<60)	2500↑ (<100)	1020↑ (<100)	755↑ (<100)	2110↑ (<60)	1130↑ (<100)	>10000↑ (<90)	>5000↑ (<60)	744↑ (<90)	2200↑ (<90)
CD3 (%)	23.5↓ (30-78)	28.5↓ (35-78)	43.5 (35-78)	22.9↓ (35-78)	28.5 (30-78)	29.2↓ (35-78)	51.4 (35-78)	23.2↓ (30-78)	27.4↓ (30-78)	31.2 (30-78)
CD4 (%)	17.8↓ (22-62)	21.1↓ (22-65)	13.7↓ (22-65)	42.1 (22-65)	19.6↓ (22-62)	21.7↓ (22-65)	41.1 (22-62)	20.9↓ (22-65)	14.7↓ (22-65)	29.3 (22-65)
CD8 (%)	11.1↓ (12-36)	28.2 (10-37)	43.1 (10-37)	27.3 (10-37)	16.3 (12-36)	8.5↓ (10-37)	20.1 (10-37)	10.8↓ (12-36)	20.5 (10-37)	31.7 (10-37)
CD19 (%)	16.1 (9-38)	17.1↑ (3-14)	13.3 (3-14)	11.6 (3-14)	15.1 (9-38)	19.2↑ (3-14)	20.4 (9-38)	7.2 (3-14)	13.5 (3-14)	28.7↑ (3-14)
CD56 (%)	10.1 (3-15)	7.3 (3-15)	4.1 (3-15)	16.2↑ (3-15)	5.6 (3-15)	8.7 (3-15)	12.5 (3-15)	6.3 (3-15)	8.7 (3-15)	9.1 (3-15)

Note: Normal range of values for age in parentheses. IgG: Immunoglobulin G; IgM: Immunoglobulin M; IgA: Immunoglobulin A; IgE: Immunoglobulin E

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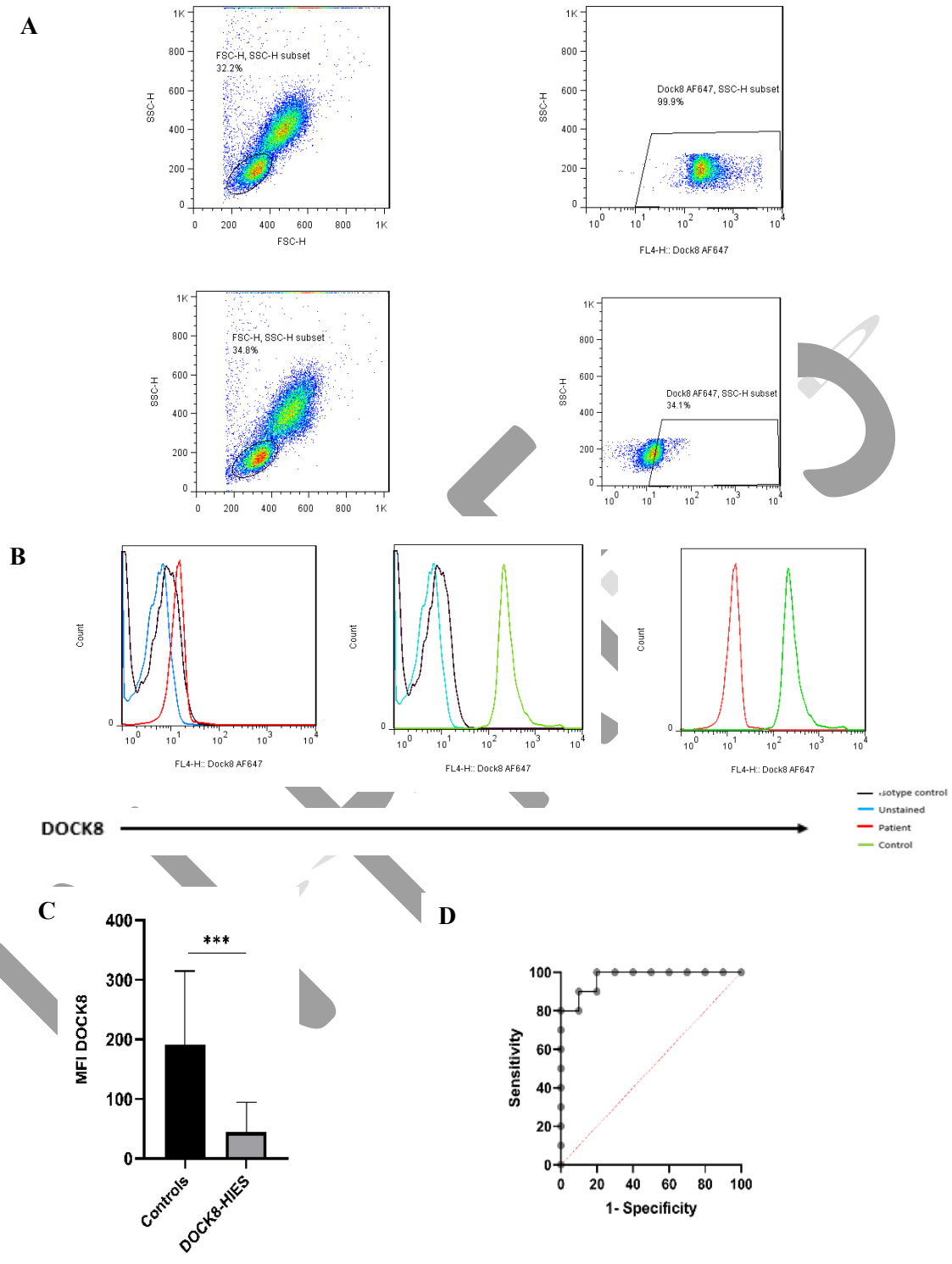

Figure 1. DOCK8 (Dedicator of Cytokinesis 8) expression assay by flow cytometry. Gating strategy for DOCK8 positive population cells in healthy control (up) and patient (down) (a). An overlay histogram of DOCK8 expression in patient P4 compared to a healthy control subject (b). Statistical comparison of DOCK8 expression between the patient groups and healthy controls, *** p<0.0001 (c). ROC curves (Receiver operator characteristic curves) to determine the optimal cut-off values of DOCK8 expression in distinguishing patients from healthy controls (d).

Table 3. Mutations detected in DOCK8 patients

Patient	Mutation detected	Variant classification (ACMG Score)
P1	Homozygous deletion of exons 18 to 24	Pathogenic
P2	c. 3577C>G (Not registered in the public databases, but reported before)	VUS
P3	Homozygous deletion of exons 14 to 26	Pathogenic
P4	Homozygous deletion of exons 5 to 48	Pathogenic
P5	NM_203447.4:c.5132C>A	Pathogenic
P6	c. 3577C>G Not registered in the public databases, but reported before)	VUS
P7	Homozygous deletion of exons 24 to 30	Pathogenic
P8	Homozygous deletion of exons 1 to 10	Pathogenic
P9	NM_001190458: exon24: c.2933_2934del	Likely pathogenic
P10	Homozygous deletion of exons 20 to 38	Pathogenic

DOCK8: Dedicator of Cytokinesis 8; VUS: Variant of Uncertain Significance

DISCUSSION

The first description of DOCK8 deficiency was provided by Zhang et al .in 2009. It is an autosomal recessive combined immunodeficiency syndrome, characterized by severe viral cutaneous infections and elevated serum IgE levels.

DOCK8 deficiency is more prevalent in populations with a high incidence of consanguineous marriages, such as in Iran. Effective management of HIES is crucial, particularly for individuals with DOCK8 deficiency, who may experience more aggressive symptoms compared to those with AD-HIES. Hematopoietic stem cell transplantation (HSCT) has shown promising results, highlighting the importance of early and accurate diagnosis for achieving optimal treatment outcomes. Due to the variety of mutations in the DOCK8 gene, the diverse functions of the mutant gene, and the shared functional pathways with other genes, a broad range of clinical manifestations can occur in this disease. These manifestations may sometimes overlap with those of AD-HIES, which is caused by loss-of-function mutations in the STAT3 gene, as well as with other forms of CID characterized by elevated IgE levels. Given the challenges of early diagnosis based on clinical manifestations, there is a growing emphasis on evaluating immunological diagnostic markers using rapid and accessible methods, such as flow cytometry, particularly in situations where genetic testing is not readily available.

To date, DOCK8 expression has not been investigated in Iranian patients. Evaluating this diagnostic marker can be valuable in accelerating the diagnostic process and ultimately improving disease management.

The NIH score was calculated for DOCK8 patients to assess its potential utility in differentiating them from those with LOF STAT3 mutations. The average NIH score for the patients was 37.2, indicating that LOF-STAT3 is an unlikely diagnosis. This finding aligns with our results, suggesting that the NIH score can be useful in distinguishing DOCK8 patients from those with LOF-STAT.[17,18]

A decrease in IgM level was observed in half of the patients, which has also been reported in other studies. The levels of IgA and IgG were within the normal range for most patients, with two and three patients, respectively, exhibiting elevated levels.[19-21]

As previously documented in the literature, seven patients exhibited TCD4 cell lymphopenia, which is associated with impaired T cell activation,

proliferation and survival in DOCK8-deficient patients.[20]

We evaluated the usefulness of flow cytometry for assessing DOCK8 expression as a diagnostic test; a statistically significant difference was observed between the patient and control groups.

Despite the confirmation of genetic mutations, DOCK8 protein expression in three patients (P2, P5, and P6) was not significantly different from the healthy controls. The c. 3577C>G and c. 5132C>A mutations respectively are the missense and nonsense point mutations in the coding regions of the *DOCK8* gene . Although these point mutations do not significantly affect DOCK8 protein expression, based on the patients' clinical phenotypes, these variants are likely nonfunctional; however, definitive confirmation requires further studies. In other cases, deletion mutations in the exonic regions of the *DOCK8* gene have caused a significant deletion of this gene and consequently impaired DOCK8 protein expression, this has been reported frequently in DOCK8 deficiency.

Various factors contribute to the complexity of interpreting the DOCK8 protein expression, including the different DOCK8 gene mutations and their effects on DOCK8 protein expression, the presence of residual protein expression and somatic reversion, which has been reported in some DOCK8 mutations and may lead to partial expression of DOCK8 protein in certain cell lineages.[14] The association between genotype and phenotype in DOCK8 deficiency is complex due to the wide range of clinical manifestations. One contributing factor is revertant mosaicism, a repair process primarily observed in older patients. These patients typically have a lower atopy score and total clinical score compared to those without revertant mosaicism, which may reduce and moderate the intensity of symptoms over time. This phenomenon enhances patient survival, although they remain susceptible to infections and their potentially lethal complications.[22]

Furthermore, in some cases, the presence of hypomorphic DOCK8 function may explain the relatively mild and unconventional phenotype observed in certain patients, thereby broadening the spectrum of DOCK8-associated disease.[23] In combination with the repair mechanisms observed in lymphocytes, this can also help explain the clinical manifestations of DOCK8 deficiency, even in patients with normal IgE levels.

Based on DOCK8 protein expression in 10 patients, the diagnostic efficiency of this test was evaluated using ROC analysis. The area under the curve (AUC) demonstrated the test's ability to distinguish DOCK8 deficiency from healthy controls.

Considering the heterogeneous nature of primary immunodeficiency disorders, immunophenotypic analysis using flow cytometry as a quantitative and reliable method can facilitate and expedite the differential diagnosis of these deficiencies, serving as the first step in the initial screening of suspected IEI cases. In this study, detecting defective DOCK8 expression through flow cytometry proved to be a valuable approach for confirming the diagnosis of DOCK8 deficiency, especially in cases where genetic analysis is unavailable.

STATEMENT OF ETHICS

The Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC. 1400.585) approved this study.

FUNDING

This study was financially supported by the Tehran University of Medical Sciences (Grant Number: 1400-2-101-54424).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

We sincerely thank the patients and their families for participating in this study.

We also appreciate the cooperation of the Research Center for Immunodeficiencies (RCID) and the Tehran University of Medical Sciences (TUMS).

DATA AVAILABILITY

Upon reasonable request (By contacting the corresponding author).

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Davis S, Schaller J, Wedgwood R, Harvard M. Job's syndrome: recurrent," cold", staphylococcal abscesses. Lancet. 1966;287(7445):1013–5.
2. Minegishi Y, Karasuyama H. Hyperimmunoglobulin E syndrome and tyrosine kinase 2 deficiency. Curr Opin Allergy Clin Immunol. 2007;7(6):506–9.
3. 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.
4. 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.
5. 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):1410–9.e13.
6. Zhang Y, Yu X, Ichikawa M, Lyons JJ, Datta S, Lamborn IT, et al. Autosomal recessive phosphoglucomutase 3 (PGM3) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity, and neurocognitive impairment. J Allergy Clin Immunol. 2014;133(5):1400–9.e5.
7. Béziat V, Li J, Lin J-X, Ma CS, Li P, Bousfiha A, et al. A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. Sci Immunol. 2018;3(24)\:eaat4956.
8. Frey-Jakobs S, Hartberger JM, Fliegauf M, Bossen C, Wehmeyer ML, Neubauer JC, et al. ZNF341 controls STAT3 expression and thereby immunocompetence. Sci Immunol. 2018;3(24)\:eaat4941.
9. 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):1289–302.e4.
10. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, et al. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol. 2006;56(2):145–51.
11. Al Khatib S, Keles S, Garcia-Lloret M, Karakoc-Aydiner E, Reisli I, Artac H, et al. Defects along the TH17 differentiation pathway underlie genetically distinct forms of the hyper IgE syndrome. J Allergy Clin Immunol. 2009;124(2):342–8.e5.
12. Côté JF, Vuori K. Identification of an evolutionarily conserved superfamily of DOCK180-related proteins with guanine nucleotide exchange activity. J Cell Sci. 2002;115(Pt 24):4901–13.
13. Meller N, Merlot S, Guda C. CZH proteins: a new family of Rho-GEFs. J Cell Sci. 2005;118(Pt 21):4937–46.
14. Keles S, Charbonnier LM, Kabaleeswaran V, Reisli I, Genel F, Gulez N, et al. DOCK8 regulates STAT3 activation and promotes Th17 cell differentiation. J Allergy Clin Immunol. 2016;138(5):1384.
15. Goussetis E, Peristeri I, Kitra V, Traeger-Synodinos J, Theodosaki M, Psarra K, et al. Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome. J Allergy Clin Immunol. 2010;126(2):392–4.
16. Wakim M, Alazard M, Yajima A, Speights D, Saxon A, Stiehm ER. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann Allergy Asthma Immunol. 1998;81(2):153–8.
17. 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.
18. Woellner C, Gertz EM, Schäffer AA, Lagos M, Perro M, Glocker EO, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125(2):424–32.e8.
19. Aydin SE, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, et al. DOCK8 deficiency: clinical and immunological phenotype and treatment options—a review of 136 patients. J Clin Immunol. 2015;35(2):189–98.
20. Zhang Q, Davis JC, Dove CG, Su HC. Genetic, clinical, and laboratory markers for DOCK8 immunodeficiency syndrome. Dis Markers. 2010;29(3–4):131–9.
21. Engelhardt KR, Gertz ME, Keles S, Schäffer AA, Sigmund EC, Glocker C, et al. The extended clinical phenotype of 64 patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol. 2015;136(2):402–12.
22. 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.
23. Kienzler AK, van Schouwenburg PA, Taylor J, Marwah I, Sharma RU, Noakes C, et al. Hypomorphic function and somatic reversion of DOCK8 cause combined immunodeficiency without hyper-IgE. Clin Immunol. 2016;163:17–21.