CASE REPORT
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Confirmation of Hyperimmunoglobulin E Syndrome in Two Patients with an Ocular Problem: Detection of Two New *DOCK8* Mutations

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ABSTRACT

Early diagnosis of primary immunodeficiencies is crucial for timely treatment and preventing unwanted complications. Next-generation sequencing (NGS) and detailed clinical and immunological evaluation can help early detect such disorders. This study aimed to confirm the diagnosis of two cases of autosomal recessive hyper-immunoglobulin E (IgE) syndrome (AR-HIES), presenting with irreversible eye involvement.

Two unrelated patients with suspected AR-HIES were referred to the Immunology, Asthma and Allergy Research Institute (IAARI), Tehran, Iran. Immunological screening tests were performed for AR-HIES, which showed elevated serum IgE levels, eosinophilia, and low T-lymphocyte responses. NGS was performed, and the results were confirmed by Sanger sequencing.

Sequence analysis showed a mutation in intron 17 of the dedicator of cytokinesis 8 (*DOCK8*) gene in the first patient, and a homozygous three base-pair deletion in exon 45 of *DOCK8* in the second

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patient. This is the first time such mutations are reported and these variants are predicted to be damaging. Both patients suffered from persistent viral infections along with cytomegalovirus (CMV) retinitis.

Suspicion of these two novel *DOCK8* mutations can benefit patients presenting with recalcitrant ophthalmic viral involvements and relevant immunological test results. This would lead to earlier referrals for immunologic and genetic confirmation and thus, a more timely intervention with hematopoietic stem cell transplantation (HSCT).

Keywords: Cytomegalovirus; DOCK8 protein, human; Hyperimmunoglobulin E syndrome; Retinitis

INTRODUCTION

Hyperimmunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by a clinical triad of high serum IgE level, recurrent pneumonia, and skin abscesses. Heterozygous mutations of the signal transducer and activator of transcription 3 (*STAT3*) cause the autosomal dominant form of HIES (AD-HIES)[1,2]. In contrast, mutations in the dedicator of cytokinesis 8 (*DOCK8*) are responsible for the autosomal recessive (AR) form of HIES.[3] *DOCK8* transcribes a 7448-base pair mRNA (NM_203447.4) which codes for a 2099-aminoacid protein. Patients who carry mutations in *DOCK8* show a combined immunodeficiency and suffer predominantly from eczema, food allergies, and viral infections. In contrast, patients with mutations in *STAT3*, in addition to the immunologic defects, show non-immunologic manifestations such as dental and skeletal defects.[4] The main clinical findings in HIES patients consist of recurrent viral, bacterial, and fungal infections, respiratory tract infections, and atopy, which are the hallmarks of HIES.[5] Also eyes can be affected by different viral, microbial, or fungal infections. In this process, the infection will gradually lead to vision loss.[6] The immunological findings of AR-HIES patients have been reported in the literature and in our previous reports, consisting of T-cell abnormalities, eosinophilia, IgE elevation, and in some cases decreased IgM.[7,8]

Conventional methods for HIES diagnosis are time-consuming and result in losing the opportunity of hematopoietic stem cell transplantation (HSCT) in these patients.[9,10] An accurate and fast genetic diagnosis is necessary to accelerate the primary treatment to prevent irreversible ocular complications in HIES patients.[11,12] Sometimes, HSCT is postponed or canceled because the infection spreads widely to different organs, including the eyes. Next-generation sequencing (NGS) can act as a fast and accurate identification method to speed up the diagnosis and treatment of patients with underlying immunodeficiency problems.

This study aims to confirm Autosomal Recessive-Hyper IgE Syndrome to achieve a prompt Hematopoietic Stem Cell Transplantation treatment. Using NGS along with clinical and immunological manifestations will help detect this immunological disorder in the cases of patients with irreversible eye problems.

PATIENTS AND METHODS

Patients

The patients described here are a 14-year-old and a 15-year-old boy referred to the immunology, Asthma and Allergy Research Institute (IAARI) due to the clinical manifestation of HIES. The patients suffered from chronic eczema, recurrent infections, and ocular viral infections. Both patients were born to consanguineous parents, and the parents were phenotypically healthy. The ethics committee approved the study (130/2588), and voluntary written consent was obtained from parents to be included.

Immunological Assessment

Initial tests such as complete blood count and peripheral blood smear were done. Immunological screening studies include immunoglobulin and complement levels, Nitroblue Tetrazolium (NBT) test for neutrophil oxidative burst evaluation, Isohemagglutinin titer for the assessment of ABO-antibodies, enumeration of lymphocyte markers, and lymphocyte proliferative response were performed. All methods of tests performed were previously described by Saghafi et al.[8]

Homozygosity Mapp in Patients

Genomic DNA of patients was isolated either from whole blood or PBMCs by using a Gentra Puregene purification kit (Qiagen, Germany) according to the manufacturer's instructions.

To evaluate homozygosity on chromosome 9, the two microsatellite markers D9S917 and D9S1858 were genotyped on the two samples. Primers and other reagents for homozygosity mapping were purchased from Life Technologies GmbH (Darmstadt, Germany), and Qiagen (Hilden, Germany). The polymerase chain reactions (PCR) for homozygosity mapping were performed according to the protocols accompanying the reagents. The PCR products were separated on an ABI3130xl Genetic Analyzer (Applied Biosystems-Life Technologies, USA), GeneMapper Software v4.1 (Applied Biosystems-Life Technologies, USA) was used for analysis.

Next-generation Sequencing (NGS)

The NGS test was run for these two patients on the HIES chip with several relevant genes (*STAT3*, *DOCK8*, *PGM3*, *TYK2*, *SPINK5*, IL-17, Rac1 & Rac2). Enrichment of genomic DNA and library synthesis was done for each patient by the DNA sample preparation kit (Illumina, San Diego, CA), and the prepared NGS libraries were sequenced based on capillary electrophoresis on a MiSeq instrument (Illumina, San Diego, CA).

DOCK8 PCR

Polymerase Chain Reaction (PCR) and Sanger sequencing were done also to confirm the NGS results. *DOCK8* was amplified from genomic DNA by PCR according to standard protocols using Taq polymerase (PeqLab, Erlangen, Germany) for the desired exons which showed a mutation in NGS results. Primer sequences are available on request.

Mutation Analysis

MiSeq Reporter analysis software (SureCall, Agilent Technologies, CA) was used to analyze and visualize NGS results sequences. The sequencing results of confirmatory done PCRs' chromatograms were obtained by Gene Mapper DNA sequencing software v4.1 (Applied Biosystems, Life Technologies, USA).

RESULTS

Clinical Presentation and Patient Characteristics

Here we present the clinical features of two Iranian male HIES patients born to first relative parents, the patients are aged 14 and 15 and have HIES scores of 35 and 47 respectively, according to the NIH scoring questionnaire.[13] Their main clinical manifestations are reported as follows:

Patient 1

The first patient is a 14-year- old boy referred to IAARI due to hematuria and vasculitis at the age of three years. A skin biopsy showed predominantly mononuclear vasculopathy in the dermis.

He suffered from eczematous dermatitis during infancy and herpetic lesions in the mouth since the age of two years. He had a maculopapular rash infected by *Staphylococcus aureus*. At the age of three years, he was referred to an ophthalmologist because of dry eyes. The ocular exam showed severe meibomian gland dysfunction (MGD) of the eyelid margins and concomitant dry eyes. The cornea of both eyes was normal in appearance and the anterior segments including lenses revealed no abnormality. In posterior segments, the vitreous gel was clear but the macula of the right eye showed prominent atrophy without active disease.

At the same time, hematuria and proteinuria were detected and a complete complement workup was done. The patient presented fever and hepatosplenomegaly and since Coombs' test was positive, hemolytic anemia was suspected, and IVIg therapy was administered to the patient.

Five months later the patient presented tearing and photophobia of the right eye. The cornea showed typical signs of herpetic keratitis which was treated by oral and topical administration of Acyclovir. Unfortunately, the keratitis recurred after of treatment, and maintenance therapy was started. He had a lucid interval of a few months and during this period he also received Doxycycline to control the MGD and dry eye. As the problem was resisted later workup was performed. The results revealed that the patient suffered from a retinal infection of the right eye by cytomegalovirus (CMV) along with retina hemorrhagia and vasculitis. Due to the involvement of the macula and severe retina atrophic in the macular region of the right eye, the patient's central vision was lost forever.

Whilst the skin lesions improved significantly, the patient was back with his left eye complaint. There was an area of necrotizing retinitis in the macula with no overlying vitreal reaction. He was referred for further evaluation and based on the history and ocular findings, presumed CMV retinitis was considered. Despite three intravitreal injections of Ganciclovir, the infection was still active and the visualization of the left eye was 2/10. Therefore, the treatment was continued by oral Valganciclovir. The retinitis was controlled; however, an atrophic scar was left similar to what was detected on the right eye. The image of the retinal lesion is shown in Figure 1.

By obtaining the genetic result and whilst the patient was screened for CT scan before HSCT, an echogenic mass was found in the lower lobe of the left lung. More investigations revealed aspergilloma and the patient had antifungal treatment to be a candidate for HSCT after improvement.

The patient has two phenotypically healthy brothers and a brother who suffered from dermatitis, food allergy, and recurrent infections and died at age 3 due to herpetic meningitis. One stillbirth is also reported from his consanguineous parents.

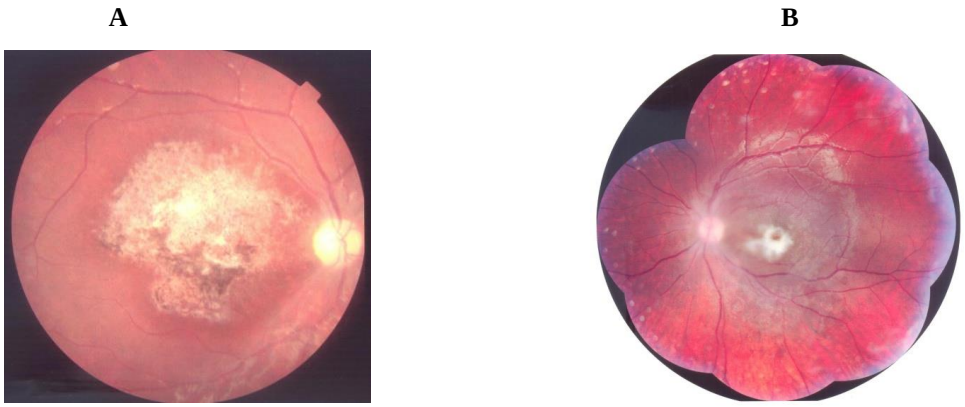

Figure 1. Retinitis in the macula with a (viral) necrotizing area in patient 1; (A) Right, (B) Left eye

Patient 2

The second case is a 15-year- old boy referred to IAARI at age 12 due to his several serious infections. The patient revealed generalized eczema in infancy and suffered from a disseminated cold sore on the face and neck that leads to a 10-day hospitalization.

The patient had a history of several hospitalizations due to recurrent pneumonia and CMV retinitis which resulted in two unsuccessful corneal transplants. At 12 years old, the patient had another hospitalization due to meningitis with a positive CSF result of HSV 1 & 2.

The patient was under interferon therapy along with antibiotic prophylaxis in the last four years which somewhat reduced the infections.

At the age of 15, he showed signs of encephalopathy, and MRI was done and revealed ischemic infarction in the territory of the left internal carotid artery. Fibrinolytic treatment along with rehabilitation is done for the patient.

The patient has a phenotypically healthy brother.

Immunological Assessment

Laboratory screening tests that were done to rule out these patients are all listed in Table 1.

Patients 1 and 2 were homozygous at the *DOCK8* locus for both tested markers; D9S917 and D9S1858 by homozygosity mapping. As the *DOCK8* gene was investigated and the results showed a homozygous mutation in this gene, further investigations by NGS were done. For patient 1, the observed homozygous mutation in intron 17 of *DOCK8*, predicts the loss of the splice donor site, which might lead to one out-of-frame deletion of this intron and potentially lead to the disease phenotype. The reported variations of these two patients are reported in Table 2.

The identified homozygous mutations resulting from NGS were also confirmed by PCR and Sanger sequencing in both cases (Figure 2: patient 1, Figure 3: patient 2).

As seen in Figure 2, Sanger sequencing of patient 1 confirmed a homozygous Single Nucleotide Variation

as G>C mutation on position +1 in the 5' splice donor site of intron17 (c.2007+1G>C). So, the *DOCK8* splice site mutation is the cause of HIES in this patient.

Also, in patient 2, Sanger sequencing (Figure 3) confirmed the variation reported by NGS and showed a deletion of three nucleotides in exon 45.

Table 1. Laboratory findings of autosomal recessive hyper immunoglobulin E syndrome (AR-HIES) patient with detected DOCK8 deletion

Laboratory Tests		Case 1 Results	Case 2 Results	Normal Values
White Blood Cells WBC (cells/µL)		4700	7410	4000-10'000
Eosinophil count (cells/µL)		**3149↑**	**2193↑**	Up to 600
Lymphocyte count (cells/µL)		**658↓**	**852↓**	(1000-3500)
IgE (IU/mL)		**3951↑**	**2579↑**	1.53-114
IgG (mg/dL)		661	700	608-1572
IgA (mg/dL)		121	**600↑**	45-236
IgM (mg/dL)		76	80	52-242
C3 (mg/dL)		**42↓**	120	88-177
C4 (mg/dL)		17	40	15-45
CH50 (U)		**60↓**	128	70-160
NBT (%)		100		90-100
Isohemaglutinin Titer	Anti-A	neg		More than 1:8
	Anti-B	neg		More than 1:8
	Blood Group	AB		
CD3 (%)		55.26	**53.06↓**	55-83
CD4 (%)		**23.59↓**	29.28	28-57
CD8 (%)		20.75	23.57	10-39
CD19 (%)		**33.14↑**	15.19	6-19
CD16/CD56 (%)			8.99	5-15
Lymphocyte Transformation Test (LTT Ratio) Results of age-matched healthy controls are in parenthesis	PHA	**2.3↓** (4)	**2.3↓** (4)	More than 3
	BCG	**1.9↓** (4.1)	**1.94↓** (4)	More than 2.5
	Candida	2 (3.9)	2 (3.82)	More than 2.5
HIES Score*		35	47	

*HIES scoring system developed with the use of both clinical and laboratory test criteria (*Grimbacher* et al, *1999*)[13].

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Table 2. Genetic reported findings of autosomal recessive hyper immunoglobulin E syndrome (AR-HIES) patients with the relevant detected DOCK8 deletion

Case No.	Gene	Reported Variations				
		Site of mutation	Nucleotide Exchange	Mutation	Type of variation	Amino Acid Change
1	*Dock8*	Intron 17	G>C	c.2007+1G>C	Homozygous SNV	mRNA splicing defect
2	*Dock8*	Exon 45	GAA deletion	c.5864_5866 delAGA	Homozygous Deletion	Frame-shift

SNV= Single Nucleotide Variation, IVS= Intervening Sequence

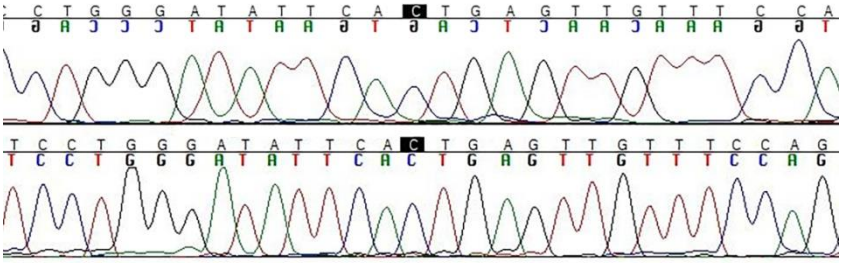

Figure 2. Chromatogram of intron 17 in patient 1 by Sanger sequencing

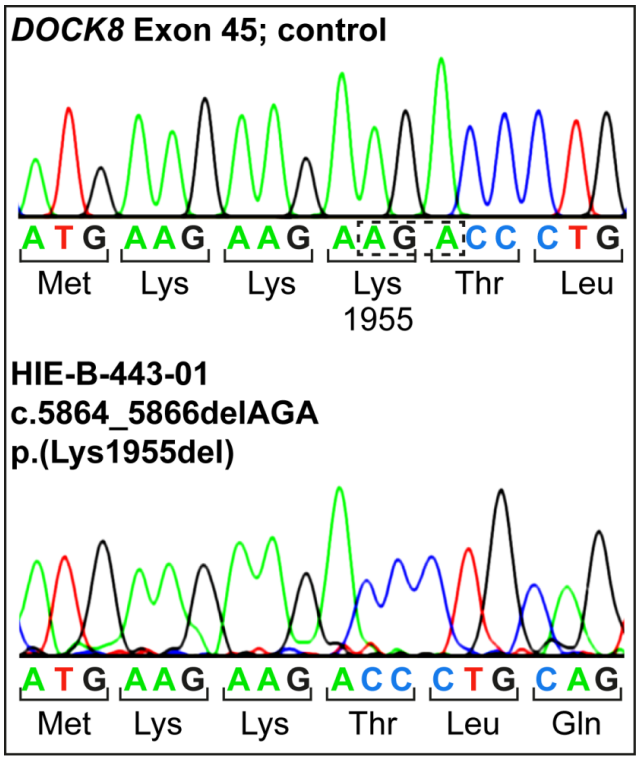

Figure 3. Chromatogram of exon 45 in patient 2 by Sanger sequencing.

DISCUSSION

The laboratory findings of two AR-HIES cases along with their clinical complaint with a focus on their ophthalmic presentations have been reported. The evidence for HSCT candidacy of these patients according to NGS reports and other laboratory findings was confirmed.

Both cases were born from first cousins' consanguineous marriages and as we know, the rate of autosomal recessive diseases such as DOCK8 deficiency is more frequent in populations with high consanguinity as reported previously.[14] We attempted to demonstrate the most complicated conditions in these patients to prevent any delay in similar patients' diagnoses. As seen in these patients' clinical presentation, most of their clinical phenotypes are consistent with the previous reports related to DOCK8 deficiency studies.[15] However, various and unusual manifestations have been also reported in rare diseases; such as vocal cords involvement in HIES.[16]

As it is obvious in Table 1, both patients had eosinophilia and elevated IgE levels that are consistent with findings of Su, in 2010. In that study, the elevated serum IgE and eosinophilia of 32 studied cases were reported 100% and 90%, respectively.[7] Also in 2015 Engelhardt et al, showed 98% elevated serum IgE and 92% eosinophilia in 64 patients.[17]

The other immunoglobulin classes in these two patients were in normal levels except IgA level in patient 2 which was very high. That is consistent with the report of Su, and Engelhardt et al, which showed elevated IgA levels in 19% and 34% of *DOCK8* deficient patients, respectively.[7,17]

Complement levels showed a low level of C3 and CH50 in patient 1 which may be due to his vasculitis beginning in early life. Vasculitis was reported in previous reports of *DOCK8* patients' studies.[15,18]

As seen in Table 1, both patients showed low absolute lymphocyte count. Our results confirmed by the previous reports showed 44%[7] and 19%[17] lymphopenia in these patients. Whilst lymphopenia is seen in both cases, lymphocyte phenotyping revealed a decrease in CD3+ cells in patient 2. In similar studies, a reduction in the percentage of patients' T Lymphocytes (CD3+ population) was reported 72%[7] and 27%.[17] As reported in Zhang et al, study, the most significant laboratory finding in DOCK8 deficiency as a combined primary immunodeficiency, is lymphopenia[19] in which both subpopulations of T-cells (CD4+ and CD8+) are affected. We found a decreased CD4+ in patient 1 consonant to previous reports showed 75% [7] and 29%[17] decreased percentages of CD4+ in the patients. *DOCK8* which is expressed in immune system cells plays important roles in lymphocytes' expansion, function, and regulation which is relevant to the etiology of viral recurrent infections in *DOCK8* deficient patients.[3,20,21] Therefore, *DOCK8* deficient patients especially have compromised lymphocytes' function and show impairment in CD4+ and CD8+ proliferative responses.[22,23] Decreased CD8+ cells in *DOCK8* deficient patients were reported as 52%[7] and 29%.[17]

These varying findings can be confirmed by different percentages reported by other studies and are consistent with multiple abnormalities of the immune system.

The lymphocyte transformation test in both patients was less than normal. The decreased T-cell proliferation response is because of the defective lymphocyte survival in these patients as seen in previous reports.[23]

As a consequence, of lymphocyte dysfunction, viral infections are seen in *DOCK8* deficient patients and due to reports of different groups, CMV and HSV are the most popular infections in these patients. Consonant to our reported patients, up to 88% of AR-HIES patients in Su study showed the same viral infection[7] and up to 78% of patients reported by Engelhardt had viral infections.[17]

Lee et al, had reported a novel *DOCK8* deletion with a notable cytomegalovirus retinitis.[24] The reported patient showed a large deletion encompassing exons 1 to 9.

CMV is a common infection present in the eye, but in immunodeficient patients with reduced cellular responses, it may act as a harmful virus, causing necrotizing retinitis.[25] Due to the underlying immunodeficiency diseases, the infectious agents become opportunistic infections, and despite conventional therapy, we do not have any appropriate response to usual treatments. Untreated CMV retinitis inexorably progresses to decreased visual acuity and finally, blindness. Thus a quick way to diagnose the main disease to prevent irreversible eye damage in these patients is quite necessary.

Based on the diagnosis management proposed in Saghafi et al, study for the patients with the clinical diagnosis of HIES, the patients were evaluated.[26] Also our patients were diagnosed to have NIH scores 35 and

47 based on the HIES questionnaire. According to the HIES scoring system, a score of more than 40, shows HIES diagnosis is probable (>40 points: HIES probable). A score less than 40 and more than 20, indicates possible diagnosis (20< possible >40), and a score less than 20 has an unlikely implication of disease.[13,17] Considering the relevant scores, patient 1 was diagnosed as possible HIES and patient 2 was diagnosed as a probable one. The patient suffering from notable CMV retinitis in Lee et al, study had a HIES score of 48.

Finally, both of them were found to carry a newly found *DOCK8* mutation in different locations which can rationalize the scoring difference. It is noticeable that both of these mutations were out of Dock Homology Regions; DHR-1 and DHR-2. These two diagnosed homozygous mutations are a splice-site mutation in patient 1 and a frame-shift mutation in patient 2 which were disease-causing new mutations. Up to our knowledge, there is not any relationship between *DOCK8* mutations' site and clinical findings.

A mutation in Intron 17 of *DOCK8* in patient 1 and exon 45 of *DOCK8* in patient 2 was detected. The comparison of the family history of patient 1 and patient 2, also deleterious condition prediction by SureCall software in two patients, it is debatable that the site of mutation may be important. The prediction made by SureCall software also suggested a disease-causing mutation for each of the new mutations and according to the complicated clinical presentations, severe problems are seen in both cases.

The advantages of NGS technology and target enrichment are a useful method for genetic diagnosis and can improve simultaneous analyses due to its increased resolution and cost-effectiveness. We suggest performing prenatal diagnosis using the candidate genes, including the present point mutations for *DOCK8* in the families who are suspected of HIES. Moreover, registration of more HIES cases can help to make a correlation between the type and site of mutations and clinical presentations.

This report whilst seeking to introduce two AR-HIES patients can also increase the body of knowledge in the category of autosomal recessive HIES patients and emphasis a rapid genetic diagnostic manner as NGS. AR-HIES patients as followed in this study which has more severe outcomes than the AD-HIES patients need more caution and necessity for a rapid and timely justified genetic diagnosis and subsequently, HSCT.

The limitation of this study is stopping medications that interfere with the results of tests such as LTT. This can result in the severity of infection in the patients. Therefore, a rapid test like the genetic tests can be helpful in the diagnosis of AR-HIES.

We have found the genetic cause of two AR-HIES patients followed in this study and reviewed their clinical and laboratory findings. The finding of two new mutations in *DOCK8* can pave the way for the detection and confirmation of AR-HIES. Early genetic diagnosis by NGS could be very helpful to manage these patients for HSCT. According to the possible ocular symptoms in patients which may be due to a suspected underlying immunodeficiency disorder, here we can suggest to immunologists be aware of the immunological and genetic testing for the identification of AR-HIES.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest and are responsible for the content of the paper.

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