

LETTERS TO THE EDITOR

Autosomal recessive hyper-IgE syndrome in two brothers of a Chinese family with a novel mutation in *DOCK8* gene

Editor

The hyper-IgE syndromes (HIESs) are complex primary immunodeficiency disorders, including autosomal dominant form (AD-HIES) and recessive form (AR-HIES). Here, we describe two boys with AR-HIES in a Chinese family and a novel mutation of *DOCK8* gene was identified.

The index patient was an 8-year-old boy. He presented with recurrent flexural skin lesions [similar with atopic dermatitis (AD)] for more than 5 years (Fig. 1a,b) and a 6-month history of severe molluscum contagiosum (Fig. 1c) and verruca plana (Fig. 1d). He had repeated respiratory tract infection, nasosinusitis and otitis media every year, with a history of asthma and peanut allergy. Recently, he developed afebrile seizures twice within 2 months. Pulmonary CT indicated right upper lung pneumonia. Brain MRI revealed a long T1 and long T2 signal in the bilateral frontal parietal lobe and right occipital lobe. He had a 5-year-old brother with similar less severe skin lesions but no seizures (Fig. 1e). Their parents had no history of dermatosis and denied a consanguineous relationship.

Laboratory data revealed increased serum IgG, IgA and IgE, high level of eosinophils and decreased lymphocyte number in both patients. Further analysis showed that naïve CD4 and naïve CD8 cells were significantly decreased while the percentages of T cells that produced IL-4 and IFN- γ were higher in two patients (Table 1).

High-throughput sequencing was carried out, and a 'homozygous' c.646-647delCT was found in the *DOCK8* coding region of the two patients (Fig. 1f), leading to a frame shift and resulting in a premature stop codon at position 226 (p.L216Vfs10), while their father carried a heterozygous mutation and their mother appeared 'normal', which seemed out of line with the Mendelian law. Then, quantitative real-time PCR was performed and revealed a large heterozygous deletion spanning exons 1–48 of the *DOCK8* and exon1 of the downstream gene *KANK* in two patients and their mother. So the patients' diseases were caused by compound heterozygous deletions.

The patients were treated symptomatically to control dermatitis and skin viral infection, skin moisturizer and bleaching bath as prevention. They are free of life-threatening affairs by far, and hematopoietic stem cell transplantation (HSCT) was in preparation.

AR-HIES is a rare form of HIES, characterized by recurrent elevated IgE, severe atopy (AD, allergy and asthma), susceptibility to viral skin infections (molluscum contagiosum, varicella-zoster, herpes simplex, human papilloma), neurological symptoms and early-onset malignancy, with high morbidity and mortality.^{1–3} *DOCK8* deficiency is the most commonly identified genetic cause; in this way, AR-HIES is also called *DOCK8* immunodeficiency syndrome (DIDS).² In our case, the c.646-647delCT is a novel mutation in the Human Gene Mutation Database (HGMD). As most *DOCK8* deficiency is caused by large deletions,⁴ it is noteworthy that multiplex ligation-dependent probe amplification assays (MLPAs) and q-PCR are more reliable in identifying these large deletions rather than Sanger sequencing.² In our patients, the exons 1–48 large deletion will abolish any *DOCK8* protein expression and impairs coordination ability of migration in T cells, causing T-cell death (naïve CD4 cells and naïve CD8 cells in particular),^{2,4} which could explain patients' lymphopenia and selective decreases in naïve CD4 cells and naïve CD8 cells, as well as virus susceptibility. The higher subgroup of IL-4- and IFN- γ -producing T cells indicates a Th1 and Th2 reaction, which could also explain the clinical AD-like skin inflammation.

AR-HIES could be misdiagnosed as AD, as most could fulfil AD diagnostic criteria, including our cases. Besides the extremely high level of IgE, noticing the proneness to the infectious disease, the impairment of the lymphocytes and the selective decreases in naïve CD4 cells and naïve CD8 cells could prompt further diagnostic work-up.⁵ We should raise awareness of this rare disease because early recognition is of clinical importance in prognosis and management.

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S. Wang,^{1,#}  W. Mou,^{2,3,#} Z. Xu,¹ J. Gui,^{2,3} L. Ma^{1,*}

¹Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China,

²Laboratory of Immunology, Beijing Pediatric Research Institute, Beijing

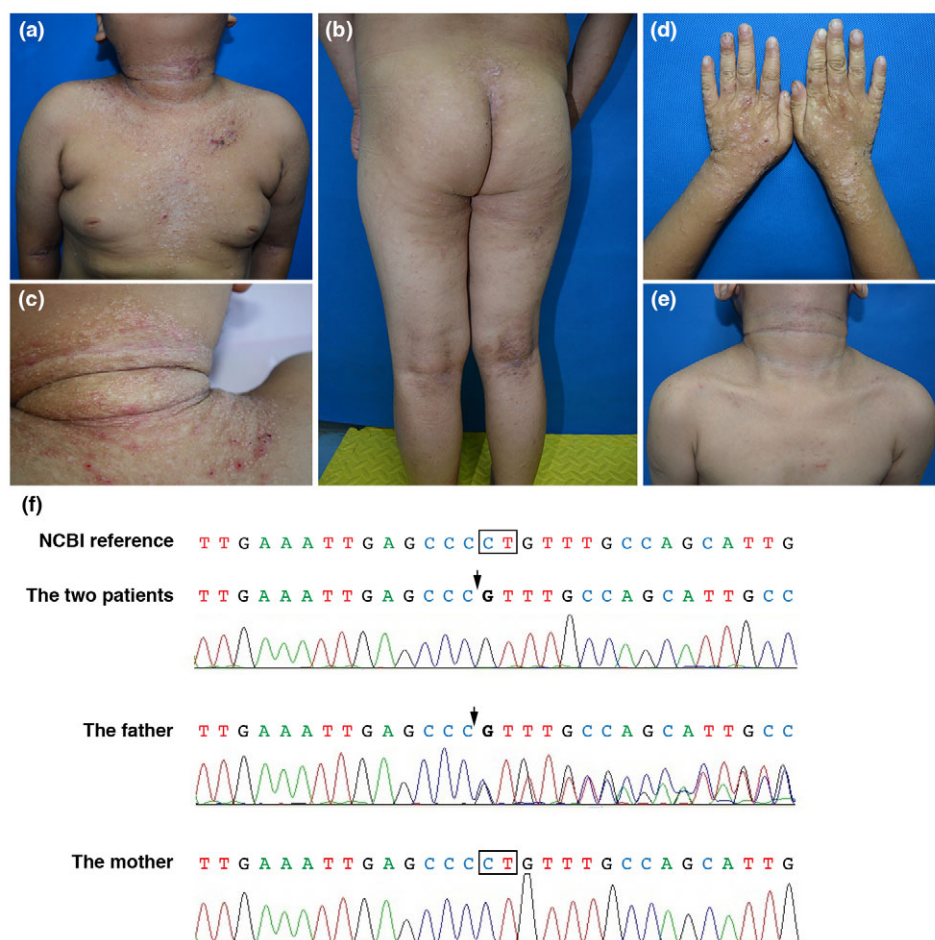


Figure 1 Clinical photographs of our patients showing (a, b) red papules, plaques and multiple skin-coloured papules (molluscum contagiosum) on flexural surface of neck, trunk and legs; (c) large amount of molluscum contagiosum on the neck and chest; (d) multiple flat-topped papules (verruca plana) and red plaques on the dorsum of the hand; (e) similar lesions of the affected brother on the neck and chest. (f) Sequencing results of the family. The two patients were identified a 'homozygous' c.646-647delCT in *DOCK8* gene coding region, while their father carried a heterozygous mutation and their mother appeared 'normal'.

Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China, ³Key Laboratory of Major Diseases in Children, Ministry of Education, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

*Correspondence: L. Ma, M.D. E-mail: bch_maleen@aliyun.com

[#]These authors contributed equally to this work.

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Table 1 Immunologic features of the family

	Index patient	Affected brother	Father	Mother	Healthy control
Immunoglobulins[†]					
IgG (g/L)	21.80 [†] (6.46–14.51)	13.20 [†] (4.82–12)	n.d.	n.d.	–
IgA (g/L)	3.35 [†] (0.28–2.22)	2.94 [†] (0.22–1.18)	n.d.	n.d.	–
IgM (g/L)	0.63 (0.55–2.32)	0.52 [‡] (0.54–2.09)	n.d.	n.d.	–
IgE (IU/ml)	8788.8 [†] (≤155)	8878.4 [†] (≤60)	n.d.	n.d.	–
Blood count[†]					
Leucocyte count (×10 ⁹ /L)	13.67 [†] (4.00–10.00)	19.86 [†] (4.00–10.00)	n.d.	n.d.	–
Eosinophil count (×10 ⁹ /L)	2.99 [†] (0.05–0.50)	9.06 [†] (0.05–0.50)	n.d.	n.d.	–
Lymphocyte subpopulations[‡]					
Lymphocyte count (/mL)	2.2 × 10 ⁶	2.9 × 10 ⁶	1.3 × 10 ⁶	3.6 × 10 ⁶	2.2 × 10 ⁶
T cells (/mL(%))					
CD3+	1.2 × 10 ⁶ (55.4)	2.3 × 10 ⁶ (80.8)	1.1 × 10 ⁵ (84.0)	2.8 × 10 ⁵ (78.3)	1.4 × 10 ⁶ (65.4)
CD3 + CD4+	4.0 × 10 ⁵ (18.2)	4.6 × 10 ⁵ (15.7)	4.6 × 10 ⁵ (35.6)	1.4 × 10 ⁶ (38.5)	6.9 × 10 ⁵ (31.4)
CD3 + CD4 + CD27 + CD45RA– (central memory)	1.7 × 10 ⁵ (7.5)	1.4 × 10 ⁵ (4.8)	2.1 × 10 ⁵ (16.1)	8.2 × 10 ⁵ (22.5)	1.9 × 10 ⁵ (8.4)
CD3 + CD4 + CD27 + CD45RA+ (naïve)	1.0 × 10 ⁵ (4.7)	1.9 × 10 ⁵ (6.4)	1.4 × 10 ⁵ (10.6)	4.8 × 10 ⁵ (13.2)	5.0 × 10 ⁵ (22.7)
CD3 + CD4 + CD27–CD45RA– (effector memory)	1.1 × 10 ⁵ (4.8)	1.1 × 10 ⁵ (3.7)	1.1 × 10 ⁵ (8.7)	1.0 × 10 ⁵ (2.7)	4.4 × 10 ³ (0.2)
CD3 + CD4 + CD27–CD45RA+ (TEMRA)	2.6 × 10 ⁴ (1.2)	2.4 × 10 ⁴ (0.8)	2070 (0.2)	3920 (0.1)	55 (0.003)
CD3 + CD8+	4.6 × 10 ⁵ (20.7)	1.2 × 10 ⁶ (40.4)	5.1 × 10 ⁵ (39.3)	1.2 × 10 ⁶ (34.6)	4.6 × 10 ⁵ (20.9)
CD3 + CD8 + CD27 + CD45RA– (central memory)	2.3 × 10 ⁵ (10.2)	2.2 × 10 ⁵ (7.6)	1.0 × 10 ⁵ (8.0)	3.1 × 10 ⁵ (9.1)	1.3 × 10 ⁵ (6.0)
CD3 + CD8 + CD27 + CD45RA+ (naïve)	8.9 × 10 ⁴ (4.0)	1.2 × 10 ⁵ (4.0)	1.8 × 10 ⁵ (14.2)	5.8 × 10 ⁵ (16.6)	3.3 × 10 ⁵ (14.8)
CD3 + CD8 + CD27–CD45RA– (effector memory)	7.5 × 10 ⁴ (3.4)	4.2 × 10 ⁵ (14.2)	8.3 × 10 ⁴ (6.4)	6.8 × 10 ⁴ (2.0)	1.6 × 10 ³ (0.07)
CD3 + CD8 + CD27–CD45RA+ (TEMRA)	7.1 × 10 ⁴ (3.2)	4.3 × 10 ⁵ (14.7)	1.4 × 10 ⁵ (10.8)	2.4 × 10 ⁵ (6.9)	55 (0.003)
CD4 + CD127–CD25 + FOXP3 + (Treg)	3977 (0.2)	5047 (0.2)	5397 (0.4)	8116 (0.2)	332 (0.2)
B cells (/mL(%))					
CD19+	2.3 × 10 ⁵ (10.6)	3.3 × 10 ⁵ (11.3)	8.4 × 10 ⁴ (6.43)	3.5 × 10 ⁵ (9.85)	4.3 × 10 ⁵ (19.4)
CD19 + CD24 + CD38 + (transitional)	6.0 × 10 ⁴ (2.7)	1.0 × 10 ⁵ (3.6)	3.0 × 10 ³ (0.2)	2.2 × 10 ⁴ (0.6)	2.2 × 10 ⁵ (5.0)
CD19 + CD24–CD38 + (Plasma blasts)	4.4 × 10 ⁴ (2.0)	3.9 × 10 ⁴ (1.3)	2.8 × 10 ⁴ (2.2)	4.9 × 10 ⁴ (1.4)	5.5 × 10 ⁴ (2.5)
CD19 + CD27 + IgD– (memory)	1.3 × 10 ⁴ (0.6)	1.8 × 10 ⁴ (0.6)	2.1 × 10 ⁴ (1.6)	8.0 × 10 ⁴ (2.2)	3.9 × 10 ⁴ (1.7)
CD19 + CD27–IgD+ (naïve)	1.1 × 10 ⁴ (0.5)	2.4 × 10 ⁴ (0.8)	5.0 × 10 ⁴ (3.9)	2.1 × 10 ⁵ (6.0)	3.3 × 10 ⁵ (14.8)
NK cells (/mL(%))					
CD3–CD56 + CD16+	4.0 × 10 ⁵ (17.97)	6.2 × 10 ⁴ (2.15)	5.4 × 10 ⁴ (4.15)	2.0 × 10 ⁵ (5.68)	1.0 × 10 ⁵ (4.71)
Cytokine-producing CD3 + T cells(%)					
IL-4	3.97	5.36	2.58	1.68	0.636
IL-10	9.03	6.97	4.78	8.40	9.16
IFN- γ	0.581	1.39	0.188	0.335	0.102
Proliferation					
α CD3/ α CD28	Normal	Normal	Normal	Normal	Normal
NK cell cytotoxic activity					
K562	Normal	Normal	Normal	Normal	Normal

[†]The data in brackets are normal ranges. n.d., not determined.

[‡]Lymphocyte subpopulations were stained using antibodies from BD Biosciences (San Jose, California) and analysed with FlowJo software (Tree Star, Ashland, OR, USA) using a FACS Calibur flow cytometer (BD Biosciences, San Jose, CA, USA).
CD, cluster of differentiation; TEMRA, terminally differentiated effector memory; NK, natural killer.