

SHORT REPORT

A novel large deletion of the DOCK8 gene in a Chinese family with autosomal-recessive hyper-IgE syndrome

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Abstract

Background Autosomal-recessive hyper-IgE syndrome (AR-HIES; OMIM 243700) is a rare primary immunodeficiency disorder mainly caused by mutations in the dedicator of cytokinesis-8 (DOCK8) gene. DOCK8 is highly expressed in the immune system and plays important roles in regulation of lymphocyte functions.

Objective We analysed the molecular basis of AR-HIES in a Chinese family.

Methods A Chinese pedigree of typical AR-HIES was subjected to mutation detection in the DOCK8 gene. All exons of the DOCK8 gene and adjacent exon–intron border sequences were amplified using polymerase chain reaction and directly sequenced.

Results We identified a novel large deletion of 1481 bp in the DOCK8 gene, encompassing the totality of exon 11 (c.1126_1285del).

Conclusion Our data expand the spectrum of mutations in the DOCK8 gene underlying AR-HIES.

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Conflicts of interest

None declared.

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Autosomal-recessive hyper-IgE syndrome (AR-HIES) (OMIM 243 700) is a rare primary immunodeficiency disorder characterized by recalcitrant cutaneous viral infections, recurrent sinopulmonary infections, severe atopic dermatitis, food and environmental allergies, early-onset malignancy, elevated serum immunoglobulin E (IgE) levels and eosinophilia. In 2009, loss-of-function mutations in the dedicator of cytokinesis-8 (DOCK8) gene (OMIM 611 432) were found to account for the majority of patients with AR-HIES. DOCK8 belongs to the DOCK180-related family of guanine nucleotide exchange factors and is highly expressed in the immune system, especially in lymphocytes.¹ Through interaction with Rho GTPases including RAC and CDC42, DOCK8 plays important roles in regulation of lymphocyte migration, activation, proliferation and survival.^{1,2} The patients with DOCK8 deficiency present multiple abnormalities of the immune system, including lymphopenia with impaired proliferative responses and activation defects of both CD4+ and CD8+ T cells as well as impaired differentiation of Th17 T cells.^{3–6} In the present work, we report a novel large deletion of the DOCK8 gene responsible for AR-HIES in a Chinese family.

This pedigree clearly shows an autosomal-recessive inheritance (Fig. 1a). The proband was a 14-year-old girl born

to consanguineous parents. She presented with recurrent upper respiratory infections, atopic dermatitis and multiple allergies to milk, eggs and fish since infancy. From the age of 1 year, she began to exhibit persistent, widespread papules. The patient was admitted to our hospital in August 2010 because of these refractory skin lesions. Her parents and the other two sisters were healthy. Physical examination showed generalized flesh-coloured, dome-shaped and pearly papules mainly on the face and folds (Fig. 1b–d). Laboratory tests revealed total white blood cell count of $5.45 \times 10^9/L$ with eosinophilia (20%, normal 0.5–5.0%) and lymphopenia (13.2%, normal 20–40%). Serum IgE was $>3000 \text{ kU/L}$ (normal <150). Lymphocyte phenotyping revealed decreased CD4+ T cell (14.20%, normal 27–53%) with an abnormal CD4+/CD8+ ratio (0.54, normal 0.97–2.31). Pathological findings of the skin lesions were consistent with molluscum contagiosum. Antiviral therapy was administered, but without significant improvement. Two years later, the patient died from severe pulmonary infection despite treatment with potent antibiotics in the local hospital. Her clinical presentation and laboratory findings prompted an evaluation for AR-HIES.

After informed consent and obtaining approval of the ethics committee of the institute, peripheral blood samples were

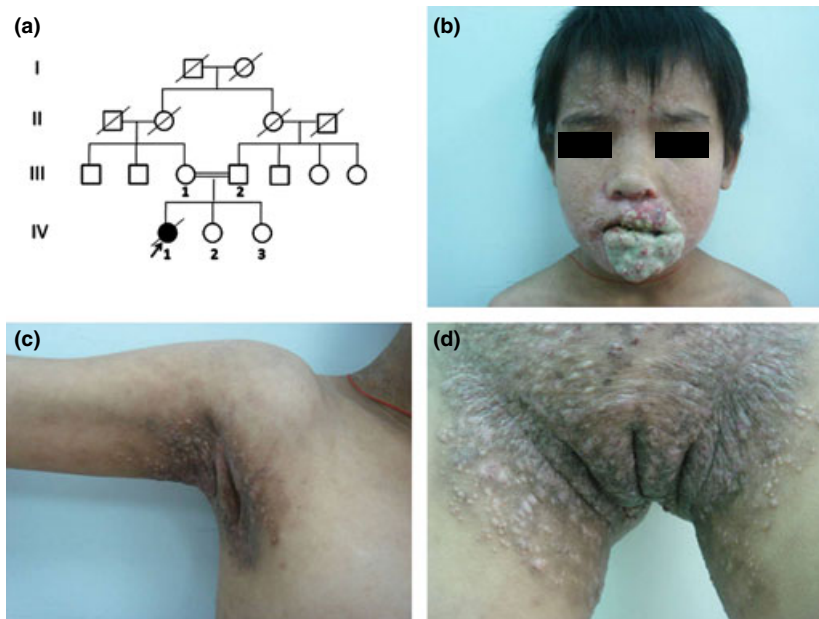


Figure 1 (a) Pedigree of a Chinese family with autosomal recessive hyper-IgE syndrome (AR-HIES). Filled symbol represents the patient. Open symbols represent unaffected individuals. The double lines represent a consanguineous union. (b-d) Clinical features of the patient with AR-HIES. Generalized flesh-colored, domeshaped papules mainly on the face and folds.

obtained from five members of the family and 120 unrelated controls. Genomic DNA was isolated from these samples according to standard techniques. All 46 exons and flanking intronic regions of the *DOCK8* gene were polymerase chain reaction amplified and subsequently sequenced.

The patient was found to carry a homozygous large deletion of 1481 bp in the *DOCK8* gene, removing the totality of exon 11

(c.1126_1285del). The deletion results in the premature stop codon TGA at amino acid position 412 and cause a truncated form of the *DOCK8* protein lacking 1687 amino acid (p.Ser376GlyfsX38). Non-allelic homologous recombination (NAHR) between two 15 bp-length repeated sequences located at intron10 and 11, respectively, contributes to the deletion. Her parents and two other sisters were found to be heterozygous for

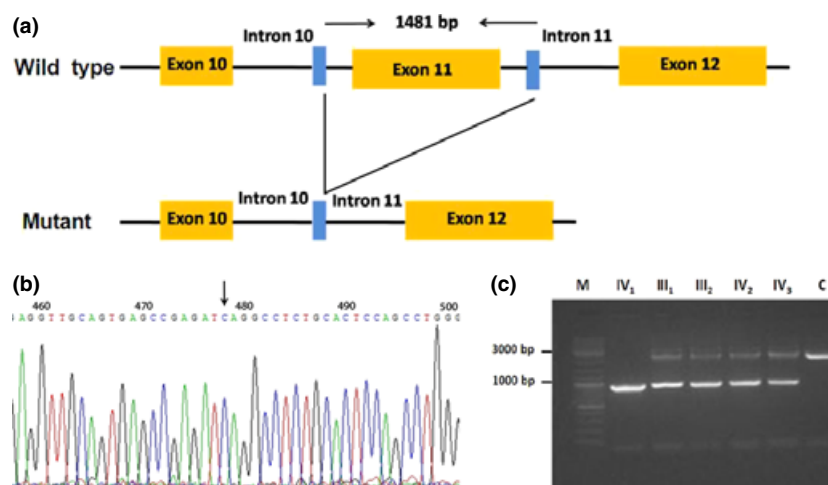


Figure 2 Mutation analysis. (a) Schematic representation of the large deletion of the *DOCK8* gene. A 1481-bp deletion removing the entire exon 11 (c.1126_1285del) is caused by non-allelic homologous recombination between two repeated sequences of cagtgcgacgagtc in intron 10 and 11, respectively. Blue block represents the repeated sequence. (b) Arrow represents the breakage-reunion point. (c) Agarose gel electrophoresis results of PCR products containing the deletion region of the *DOCK8* gene in the family members. M, molecular weight marker; IV₁, a single 866-bp fragment showing the homozygous deletion of the patient; III₁, III₂, IV₂ and IV₃: two fragments as 2347-bp and 866-bp fragments showing the heterozygous deletion of the *DOCK8* gene in the patient's parents and two sisters; C, a 2347-bp band representing the nondeletion control.

the mutation. The novel mutation was not observed in 120 unrelated, healthy Chinese control individuals (Fig. 2a–c).

The hyper-IgE syndromes (HIES) are complex primary immunodeficiency disorders that are inherited in an autosomal-dominant or autosomal-recessive manner or, in some cases, occur sporadically. Autosomal-dominant HIES results from mutations in STAT3. Affected individuals are mainly prone to staphylococcal skin and pulmonary infections and present a variety of extraimmune manifestations, including distinct dental, skeletal and connective tissue abnormalities.⁷ In contrast, patients with AR-HIES are characterized by a broader infectious susceptibility profile, including virus infections of the skin, as well as severe allergies and various malignancies. As the DOCK8 gene was found to be associated with AR-HIES in 2009, more than 30 DOCK8 gene mutations have been identified in different populations.^{1,2,8} Among them, large deletions are the most common, although point mutations, splice site mutations, small insertions and deletions also can be identified in some cases.³ The molecular mechanisms underlying large deletions, however, remain to be elucidated.

In this study, we identified an unreported large deletion in the DOCK8 gene. It is noteworthy that the deletion results from NAHR. In addition to our study, NAHR has been revealed to contribute to large deletions in two previously reported cases with DOCK8 deficiency.⁴ Hence, we assume that the frequent occurrence of NAHR may be an important cause for high proportion of large deletions in the DOCK8 gene mutations.

The disease-causing mutations of the DOCK8 gene, regardless of types, typically exhibit nonsense-mediated decay and lead to absent or trace amounts of expressed DOCK8 protein. From the reported cases with AR-HIES, there is no significant difference in phenotypic features among the various mutation genotypes in patients with DOCK8 deficiency. Most of affected individuals follow a progressive course and probably die from fatal

infections or cancers in the second and third decades of life.⁸ The girl reported here had suffered from a variety of infectious diseases since birth and, unfortunately, died from severe pulmonary infection at the age of 16.

In conclusion, we identified a novel large deletion of the DOCK8 gene in the Chinese family of a patient with AR-HIES. This study expands the database on the DOCK8 gene mutations in AR-HIES.

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