Novel *DOCK8* Mutation

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ABSTRACT

Background: Hyper IgE syndrome (HIES) is a primary immunodeficiency with sporadic, autosomal dominant (*STAT3* mutation) and autosomal recessive (*DOCK8* and *TYK2* mutations) inheritance patterns. HIES secondary to *DOCK8* mutation is characterized by extensive cutaneous viral and staphylococcal infections, recurrent sinopulmonary infections, severe allergic diseases, increased susceptibility to malignancy with lymphopenia, eosinophilia, and elevated immunoglobulin E (IgE). **Methods:** This case report highlights the clinical presentation and immune investigations of a male patient with a novel *DOCK8* mutation. **Results:** Our patient presented with cutaneous viral infections including severe molluscum contagiosum and herpes simplex virus plus skin abscesses and acute otitis media. In addition to infections, he developed intermittent diarrhea, eczematous lesions, abnormal fingernails, oral ulcers, and Bell's palsy. Immune evaluation revealed lymphopenia, in particular low CD8 cells, low mitogen stimulation response, and poor specific antibody production requiring immunoglobulin replacement. Genetic sequencing confirmed a novel mutation in *DOCK8*. **Conclusion:** Patients with significant cutaneous viral and bacterial infections, recurrent sinopulmonary infections, severe allergic diseases, and lymphopenia with associated elevated IgE should be investigated for *DOCK8* mutation. This case report highlights a novel mutation in the *DOCK8* exon 45 aa1970, c.5908 G>C change alanine to proline homozygous change A1970 to P1970

Statement of novelty: This case reports on a novel mutation in *DOCK8*

Introduction

Hyper IgE syndrome (HIES) is classified as a well-defined syndrome with associated primary immunodeficiency (Al-Herz et al. 2011). HIES can be sporadic or familial, with both autosomal dominant and recessive cases described. The autosomal dominant form of HIES is most commonly caused by a mutation in signal transduction and activators of transcription 3 (*STAT3*) (Holland et al. 2007; Minegishi et al. 2007), whereas the less common autosomal recessive forms are linked to mutations in dedicator of cytokinesis 8 (*DOCK8*) (Engelhardt et al. 2009; Zhang et al. 2009) and tyrosine kinase 2 (*TYK2*) (Minegishi et al. 2006).

The human *DOCK8* gene consists of 46–48 exons located on chromosome 9 (Su 2010) and is a member of the DOCK180 superfamily of guanine nucleotide exchange factors, which interacts with Rho GTPase (Ruusala and Aspenstrom 2004). The exact function of *DOCK8* is unknown, but research supports its involvement in regulating cytoskeletal rearrangements that are essential for cellular structure, migration, and adhesion (Meller et al. 2005). Defects in *DOCK8* have been shown to affect the immune system in numerous ways leading to a combined immunodeficiency. *DOCK8* is involved in T-cell survival and the maintenance of CD8 T-cell memory (Lambe et al. 2011). Impaired T-cell activation (Zhang et al. 2009) and reduced numbers of T-cell excision circles (TRECS) suggest impaired

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thymopoiesis with possible restricted diversity of T-cell repertoire in the periphery (Dasouki et al. 2011). Furthermore, patients also have defective Th17 differentiation and long-term persistence (Al Khatib et al. 2009). Murine studies have shown that *DOCK8* mutant B cells were unable to form marginal zone B cells or persist in germinal centers leading to impairment in affinity maturation of T-cell dependent antibody responses (Randall et al. 2009). It has also been described that Toll-like receptor 9 (TLR9) responses were considerably lower in *DOCK8*-deficient B cells and that *DOCK8* functions as an adaptor in the TLR9–MyD88 signaling pathway in B cells (Jabara et al. 2012). Recently, *DOCK8* deficiency has been shown to be associated with an increased production of autoantibodies, defective B cell tolerance, and quantitative and qualitative deficiencies in regulatory T cells (Janssen et al. 2014a). Lastly, the development and survival of mature natural killer T cells are impaired in *DOCK8*-deficient mice (Crawford et al. 2013).

HIES secondary to *DOCK8* mutation has a more severe phenotype compared with the *STAT3* mutations. Patients with *DOCK8* mutations commonly present with significant viral cutaneous infections, sinopulmonary infections, and allergic diseases such as asthma, environmental allergies, and food allergies (Zhang et al. 2009; Alsum et al. 2013). This patient population lacks the extra immune abnormalities observed in *STAT3* mutations, such as musculoskeletal and dental abnormalities and the characteristic coarse facial appearance. Early diagnosis of *DOCK8* mutation patients is critical, as hematopoietic stem cell transplantation (HSCT) is offered to selected patients as a curative therapy.

Germline loss of function *DOCK8* mutations found in patients with combined immunodeficiency were first described in 11 patients by Zhang et al. in 2009. Since this time other groups have been characterizing this primary immunodeficiency (Engelhardt et al. 2009; Al-Herz et al. 2012; Sanal et al. 2012; Alsum et al. 2013; Xue et al. 2014). We present here a novel case of *DOCK8* mutation, including clinical presentation and immune investigation findings.

Results

A 13-year-old male patient from a nonconsanguineous Caucasian family was initially referred for intermittent diarrhea, recurrent molluscum contagiosum, skin abscesses, eczematous skin lesions, and lymphopenia. At 9 years of age, this patient developed diarrhea

occurring every 3–4 months, lasting for 1 week, with as many as 10 episodes per day. The diarrhea episodes were associated with severe abdominal cramping and mucus with absence of blood in stools or associated fever. Infectious history was significant for severe molluscum contagiosum to the trunk and extremities beginning at childhood. Additional viral infections included extensive herpes simplex virus infection limited to the skin at 23 years of age. A history of bacterial infections was significant for 2 skin abscesses located on the left arm managed with incision and drainage at 13 years of age, and acute otitis media managed with oral antibiotics at 15 years of age. In addition to cutaneous infections, he had widespread nummular eczematous lesions over his extremities, trunk, and scalp beginning at 7 years of age. These lesions were initially diagnosed as psoriasis and managed with topical corticosteroids with minimal benefit. He had abnormal fingernails described as pitted and hypertrophied with associated peeling and crusting around the nailbed. Additional significant findings included intermittent oral ulcers and left-sided Bell's palsy. There was no history of allergic diseases.

Family history included a healthy nonconsanguineous mother and father, both from the Netherlands. He has an older sister who is healthy. The paternal grandmother had extensive atopic dermatitis. On the maternal side there was a female first cousin with vitiligo and another first female cousin with leukemia diagnosed at 12 years of age.

Initial immune investigations were completed at 13 years of age (Tables 1 and 2). There was evidence of poor specific antibody response to tetanus (pre-vaccine titer 0.55 IU/mL, post-vaccine titer 0.85 IU/mL) and pneumococcus (post-vaccine titer 31.2 mg/L). Based on the poor specific antibody response, monthly intravenous immunoglobulin was started at 14 years of age. Genetics confirmed novel *DOCK8* mutation exon 45 aa1970, c.5908 G > C change alanine to proline homozygous change A1970 to P1970 (Figures 1 and 2).

Discussion

The characteristic infectious and noninfectious features of *DOCK8* mutation associated HIES are described in our patient with a novel mutation. As demonstrated in our patient, *DOCK8* mutations lead to a number of cutaneous findings such as viral cutaneous infections secondary to molluscum contagiosum,

Table 1: Immune evaluation of the patient.

	13 years old	18 years old	23 years old
Complete blood count			
White blood cell count	4.3 (4.0–10.0 × 10 ⁹ /L)	3.6 L (4.0–10.0 × 10 ⁹ /L)	4.1 (4.0–10.0 × 10 ⁹ /L)
Hemoglobin	135 (120–160 g/L)	139 L (140–175 g/L)	146 (140–175 g/L)
Platelets	226 (150–400 × 10 ⁹ /L)	208 (150–400 × 10 ⁹ /L)	172 (150–400 × 10 ⁹ /L)
Neutrophils	2.40 (2.00–7.50 × 10 ⁹ /L)	2.25 (2.00–7.50 × 10 ⁹ /L)	2.55 (2.00–7.50 × 10 ⁹ /L)
Lymphocytes	1.20 (1.50–7.00 × 10 ⁹ /L)	0.76 (1.50–4.00 × 10 ⁹ /L)	0.88 (1.50–4.00 × 10 ⁹ /L)
Eosinophils	0.20 (0.02–0.50 × 10 ⁹ /L)	0.24 (0.02–0.50 × 10 ⁹ /L)	0.23 (0.02–0.50 × 10 ⁹ /L)
Monocytes	0.40 (0.05–0.80 × 10 ⁹ /L)	0.34 (0.05–0.80 × 10 ⁹ /L)	0.42 (0.05–0.80 × 10 ⁹ /L)
Markers (cells/uL)			
CD3	629 (800–3500)	426 (700–2100)	520 (700–2100)
CD4	449 (400–2100)	314 (300–1400)	358 (300–1400)
CD8	130 (200–1200)	88 (200–900)	136 (200–900)
CD19	438 (200–600)	239 (100–500)	127 (100–500)
CD3–(CD16+56)	155 (70–1200)	65 L (90–600)	250 (90–600)
Immunoglobulins			
IgG	5.5 (6.6–15.3 g/L)	9.1 (6.6–15.3 g/L) on IVIG	ND
IgA	0.4 (0.5–2.2 g/L)	0.3 L (0.5–2.9 g/L)	ND
IgM	0.2 (0.4–1.5 g/L)	< 0.2 (0.4–1.5 g/L)	ND
IgE	4.2 IU/mL (< 200 IU/mL)	ND	ND
Albumin	42 (33–58 g/L)	ND	52 (33–58 g/L)
Total protein	67 (53–85g/L)	ND	82 (53–85g/L)

Note: ND, no data.

Table 2: Initial immune evaluation of the patient.

	13 years old	18 years old	23 years old	Normal ranges
Specific antibodies				
Tetanus	0.55 IU/mL	ND	ND	> 0.1 IU/mL
Measles	Negative	ND	ND	> 1:16
Mumps	Positive	ND	ND	> 1:16
Rubella	Negative	ND	ND	> 1:16
Varicella	ND	ND	ND	> 1:16
Polio 1,2,3	1 < 1:8; 2 1:32; 3 < 1:8	ND	ND	> 1:16
Isohemagglutinin	Anti-B 1:32	ND	ND	> 1:8
Mitogen response (patient–control)				
PHA	ND	171–451	ND	50% control

Note: ND, no data.

herpes simplex virus (HSV), varicella-zoster virus, and human papillomavirus plus recurrent *Staphylococcus aureus* skin infections (Zhang et al. 2009). These infections can result in eczema herpeticum, chronic ulcerating orolabial or angogenital HSV infections, or HSV keratitis. The susceptibility to viral cutaneous infections is likely secondary to multiple factors including impaired CD8 T-cell memory response and reduced production of interferon gamma and tumor necrosis factor α by CD8+ T cells in *DOCK8*-deficient patients (Zhang et al. 2009; Chu et al. 2012). In addition, *DOCK8* may play a role in leukocyte migration to

infected skin, and the breakdown of the epidermal barrier from dermatitis can predispose patients to viral infections (Zhang et al. 2010; Chu et al. 2012). Mucocutaneous candidiasis is less common in *DOCK8* patients compared with those with *STAT3* mutations (Chu et al. 2012).

Similar to *STAT3* mutations, *DOCK8* deficiency can be difficult to differentiate from severe atopic dermatitis and other dermatitis, especially with higher rates of other allergic diseases such as food allergy also occurring with *DOCK8* mutations. A recent study concluded

Electropherogram of wild type vs. patient sequence with homozygous mutation c. [5908G>C];[5908G>C] in *DOCK8* (NM_203447.3) resulting in amino acid substitution p. [Ala1907Pro];[Ala1907Pro].

Figure 1: Novel *DOCK8* mutation exon 45 aa1970, c.5908 G > C change alanine to proline homozygous change A1970 to P1970.

Human *DOCK8* showing the N Terminal domain, DOCK homology region (DHR)-1 domain, Armadillo (ARM)-type fold domain, DOCK homology region (DHR)-2 domain, C Terminal domain, their boundaries and the location of the A1907P mutation.

Figure 2: *DOCK8* with major domains labelled with boundary amino acids identified. The disease-associated mutation lies within the DOCK homology region (DHR)-2 domain.

that CD3 and CD4 T-cell lymphopenia with decreased naïve CD8 T cells and decreased memory B cells is strongly suggestive of *DOCK8* deficiency rather than severe atopic dermatitis (Janssen et al. 2014b).

Sinopulmonary infections such as recurrent otitis media, sinusitis, and pneumonias are frequently observed

and can be associated with complications such as bronchiectasis (Zhang et al. 2009; Alsum et al. 2013). Our patient had a past history of acute otitis media. Various pathogens have been associated with pneumonia including *Streptococcus pneumonia*, *Haemophilus influenza*, adenovirus, and respiratory syncytial virus as well as eosinophilic lung disease (Zhang et al. 2009;

Tsuge et al. 2014). Recurrent sinopulmonary infections experienced in our patient and others with *DOCK8* mutation are consistent with the humoral immune abnormalities identified. Opportunistic infections including *Pneumocystis jiroveci* and vaccine strain varicella-zoster virus induced central nervous system vasculopathy can occur, although they are less frequent (Zhang et al. 2009; Sabry et al. 2014). Diarrhea, which has been described in other patients with *DOCK8* (Dinwiddie et al. 2013), was a significant complaint for our patient. Diarrhea can be secondary to infections such as salmonella, giardiasis, and norovirus (Sanal et al. 2012). Other gastrointestinal involvement includes cryptosporidium-associated liver disease (Al-Herz et al. 2012; Shah et al. 2014). Additional features described in *DOCK8* patients include neurologic complications such as vasculitis, aneurysms, and central nervous system lymphoma, sclerosing cholangitis, and granulomatous soft tissue lesions (Engelhardt et al. 2009; Al-Herz et al. 2012; Sanal et al. 2012).

Unlike patients with *STAT3* mutations, many patients with *DOCK8* mutations also have significant allergic diseases such as food allergy causing anaphylaxis, environmental allergies, and asthma (Zhang et al. 2009). Eosinophilic esophagitis has also been reported (Zhang et al. 2009). Increased rates of allergic diseases are likely secondary to increased Th2 CD4 T cells (Lambe et al. 2011). Patients are often found to have high serum IgE and eosinophilia as the result. Although a common finding, our patient did not show any signs of allergic diseases.

Similar to many other primary immunodeficiencies, *DOCK8* is associated with higher rates of autoimmunity and malignancy. In patients with long-standing cutaneous viral infections, vulvar, facial, and anal squamous cell carcinomas can occur (Zhang et al. 2009). Lymphoid malignancies such as Epstein-Barr virus (EBV) negative diffuse B-cell lymphoma, EBV-positive Burkitt lymphoma, and cutaneous T-cell lymphoma are also noted (Zhang et al. 2009). It has been suggested that impaired CD8 T cells in *DOCK8* deficiency may lead to impaired tumor surveillance resulting in an increased susceptibility to malignancies (Zhang et al. 2009). Specific autoimmune conditions reported include autoimmune hemolytic anemia, colitis, vasculitis, uveitis, and systemic lupus erythematosus (Al-Herz et al. 2012; Alsum et al. 2013; Jouhadi et al. 2014). It is possible that the oral ulcers and Bell's palsy experienced by our patient was an autoimmune manifestation.

Common laboratory findings include lymphopenia, eosinophilia, elevated IgE and low IgM, decreased T- and B-cell numbers, variable impaired responses to mitogen stimulation, and poor antibody response. Our patient had lymphopenia affecting mostly CD8 T cells and low immunoglobulin levels. He also had evidence of poor function low mitogen stimulation response and poor specific antibody production. He did not have eosinophilia or elevated IgE.

There is growing consensus that HSCT should be offered to patients before significant infections with associated complications and development of malignancy occur (Bittner et al. 2010; Barlogis et al. 2011; Gatz et al. 2011; McDonald et al. 2012; Metin et al. 2012). Patients with impaired antibody production may benefit from immunoglobulin replacement to reduce the frequency of sinopulmonary infections. Management of cutaneous manifestations in this patient population is difficult. Medications used to improve dermatitis such as topical corticosteroids can make cutaneous viral infections worse (Chu et al. 2012). Systemic antiviral medications are used for cutaneous viral infections although resistance has occurred, whereas topical treatments are generally not effective given the extent of the disease (Chu et al. 2012). Interferon alpha has been used with variable success for cutaneous viral infections and tumorous herpes simplex blepharoconjunctivitis (Keles et al. 2014; Papan et al. 2014). Bleach baths and topical antibacterial medications are helpful to control *Staphylococcal aureus* colonization. All patients require sun protection given the predisposition for skin malignancy and careful monitoring for the development of malignancy.

Overall, *DOCK8* deficiency is a rare combined primary immunodeficiency characterized by recalcitrant cutaneous viral infections, recurrent sinopulmonary infections, allergic diseases, autoimmunity and malignancy with associated eosinophilia, elevated IgE, and poor number and functioning of both T and B cells. Patients with these features should be investigated for possible *DOCK8* mutations. Our data presented expands the spectrum of *DOCK8* mutations.

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