41 of 60 patients with autosomal-recessive hyper-IgE syndrome carry deletions and point mutations in DOCK8


*Depart of Immunology and Molecular Pathology, UCL Medical School, London, UK; †Centrum voor IMMUNologie, Aligery & Rheumatoologie, Department of Pediatrics, The Daniel Greenfeld School of Medicine at the University of California at Los Angeles, Los Angeles, CA 90095.

INTRODUCTION

Background: The Hyper-IgE Syndromes (HIES) are rare primary immunodeficiencies with both autosomal dominant (AD) and autosomal recessive (AR) forms. However, most patients are sporadic cases. Approximately 60-70% of patients with hyper-IgE syndrome have dominant mutations in STA35, and a single patient was described to have a ZFY2K mutation, so the remaining hyper-IgE syndrome patients, the genetic etiology has not yet been identified.

Objectives: We aimed to identify a gene that is mutated or deleted in AR-HIES.

Methods: We performed genome-wide single nucleotide polymorphism analysis for nine subjects with AR-HIES to locate copy number variations from DOCK8 mutation analysis, because homozygosity mapping with microsatellite markers revealed homozygosity at the DOCK8 locus, making DOCK8 mutations unlikely.

RESULTS

Substitution homologous (ARH001-ARH004) or compound heterozygous ARH005) microdeletions were identified in five patients at the exons of chromosome 9p. In all patients the deleted interval involved DOCK8.

DOCK8 deficiencies was associated with impaired proliferation of CD4+ and CD8+ T cells.

THE CLINICAL PHENOTYPE OF DOCK8 DEFICIENCY

Skin disease

- Skin abrasions: 82.7% (72%)
- Candidiasis: 21/7% (84%)

- Severe acne, often colonized with Staphylococcus aureus: 36/9% (95%)

Respiratory - Upper or lower RTI: 100%

Upper respiratory tract infections: 89/5% (92%)

Recurrent pneumonitis: 89/5% (90%)

Bronchiolitis: 11/3% (33%)

Atopy

- Multiple allergies (food, environmental, drug): 42/6% (67%)
- Asthma: 1/3% (52%)

Viral infections - Severe, recurrent and partially mutisminating viral infections: 34/5% (67%)

- CMV: 9/3% (25%)
- JC virus: 9/3% (25%)
- Fatal PML

HYPOTHETICAL FUNCTION OF DOCK8

DOCK8 is likely to function as a guanine-nucleotide exchange factor (GEF) for the Rho-GTPases Cdc42 and Rac1, turning them into the active, GTP-bound form upon receptor engagement (e.g. receptor tyrosine kinases, antigen receptors and adhesion receptors). An unknown protein possibly stabilizes the interaction of DOCK8 with Cdc42 and Rac1. GTPase activation induces dynamic filamentosus cell reagarrangements at lamellipodia formation, possibly via WAP, leading to cell growth, migration and adhesion. Given the clinical phenotype of the AR-HIES patients with DOCK8 deficiency, we propose an important role of DOCK8 in T-cell activation dynamics, which might be important for the formation of the immunological synapse, leading to T-cell activation, proliferation, and differentiation.

SUMMARY

We found homozygous or compound heterozygous deletions and point mutations in DOCK8 in 41 of 60 patients with AR-HIES, originating mostly from Turkey and the Middle East. This is the largest cohort of its kind to date of genetically defined AR-HIES. Our finding is complemented by the work of Zhang and colleagues, who published mutations in DOCK8 in a cohort of twelve patients with a similar phenotype.