

DOCK8 Deficiency Presenting as an IPEX-Like Disorder

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Abstract

Purpose The dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive-combined immunodeficiency whose clinical spectra include recurrent infections, autoimmunity, malignancies, elevated serum IgE, eczema, and food allergies. Here, we report on patients with loss of function *DOCK8* mutations with profound immune dysregulation suggestive of an immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)-like disorder.

Methods Immunophenotyping of lymphocyte subpopulations and analysis of DOCK8 protein expression were evaluated by flow cytometry. T regulatory (T_{reg}) cells were isolated by cell sorting, and their suppressive activity was analyzed by flow cytometry. Gene mutational analysis was performed by whole-exome and Sanger sequencing.

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Results Patient 1 (P1) presented at 10 months of age with chronic severe diarrhea and active colitis in the absence of an infectious trigger, severe eczema with elevated serum IgE, and autoimmune hemolytic anemia, suggestive of an IPEX-related disorder. Whole-exome sequencing revealed a homozygous nonsense mutation in *DOCK8* at the DOCK-homology region (DHR)-1 (c.1498C>T; p. R500X). Patient P2, a cousin of P1 who carries the same *DOCK8* nonsense mutation, presented with eczema and recurrent ear infections in early infancy, and she developed persistent diarrhea by 3 years of age. Patient P3 presented with lymphoproliferation, severe eczema with allergic dysregulation, and chronic diarrhea with colitis. She harbored a homozygous loss of function *DOCK8* mutation (c.2402 -1G→A). T_{reg} cell function was severely compromised by both *DOCK8* mutations.

Conclusion DOCK8 deficiency may present severe immune dysregulation with features that may overlap with those of IPEX and other IPEX-like disorders.

Keywords Combined Immunodeficiency · DOCK8 · FOXP3 · immune dysregulation · IPEX · IPEX-like · regulatory T cells · T_{reg}

Introduction

The dedicator of cytokinesis 8 (DOCK8) is a 190-kDa protein predominantly expressed in hematopoietic cells which belongs to the DOCK180 family of atypical guanine nucleotide exchange factors (GEF) [1]. DOCK8 has critical roles in both humoral and cellular immune responses. It mediates cell differentiation, survival, adhesion, and migration by coordinating actin cytoskeletal response through cell cycle 42 (Cdc42) activation [2–6]. DOCK8 is critical to the translocation of cutaneous dendritic cells to lymph nodes and the persistence

of memory CD8⁺ T cells in the epidermis [7]. In addition to its regulation of the actin cytoskeleton, DOCK8 regulates the differentiation of T helper (Th) cell subsets [8, 9]. DOCK8 promotes T_H17 cell differentiation by regulating signal transducer and activator of transcription 3 (STAT3) phosphorylation and translocation to the nucleus [8]. In B cells, DOCK8 enables a Toll-like receptor 9 (TLR9)-PYK2-STAT3 cascade that promotes B cell proliferation and memory B cell formation [10]. DOCK8 deficiency gives rise to an autosomal recessive form of the hyper IgE (AR-HIES) syndrome that overlaps in its features with autosomal dominant hyper IgE (AD-HIES) syndrome caused by loss of function mutations in *STAT3* [11–13]. Patients with DOCK8 deficiency suffer from recurrent infections, including candidiasis, cutaneous viral infections (molluscum contagiosum, herpes simplex viruses, human papilloma viruses), and cutaneous and invasive bacterial infections. DOCK8 deficiency results in defective memory T and B cell responses, associated with poor humoral immune responses, and impaired function of CD8 and NK cells, which contributes to the increased risk for cutaneous viral infections and virally driven malignancies [4, 14–16].

DOCK8 deficiency has been associated with a number of immune dysregulatory features, including autoimmune disorders such as vasculitis and autoimmune hepatitis, as well as allergic disorders such as eczema, asthma, and food allergy, with high IgE and hypereosinophilia [17, 18]. The immune dysregulatory features of DOCK8 deficiency overlap with those of primary disorders of immune dysregulation resulting from gene defects affecting regulatory T (T_{reg}) cell differentiation and function. The most famous of these, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), results from loss of function mutations affecting the transcription factor forkhead box P3 (FOXP3). A number of IPEX-like conditions have also been described due to mutations affecting genetic elements critical to T_{reg} cell function [19]. DOCK8 itself has emerged to play an important role in T_{reg} cell homeostasis and function. DOCK8 deficiency is associated with defective T_{reg} cell suppressive function, and patients with DOCK8 deficiency exhibit decreased numbers and depressed function of peripheral blood T_{reg} cells, associated with increased auto-antibody production [20]. In this report, we highlight the capacity of DOCK8 deficiency to present as an immune dysregulatory disorder that overlaps in its phenotype with IPEX-like disorders [21], underscoring the vital function of DOCK8 in immunoregulation.

Methods

Patients The history, clinical and laboratory findings, and genetic analysis of DOCK8-deficient patients P1 and P2 are detailed in the “Results” section and those of patients P3 and

P4 in the [Electronic Supplementary Material](#). All study participants were recruited using written informed consent approved by the respective institutional review boards.

Antibodies and Flow Cytometry Anti-human monoclonal antibodies (mAbs) to the following antigens were used for staining: CD3 (UCHT1), CD4 (RPA-T4), CD8 (RPA-T8), CD127 (A019D5), CD25 (BC96), CD19 (HIB19), CD27 (IV T-128), IgD (IA6-2), IFN- γ (4S.B3), IL-4 (8D4-8), IL-17 (BL168) (Biolegend), CTLA4 (14D3), FOXP3 (PCH101), and Helios (22F6) (eBioscience) and the appropriate isotype controls. Whole blood was incubated with mAbs against surface markers for 30 min on ice. Intracellular staining with FOXP3, Helios, and CTLA4 was performed using eBioscience fixation/permeabilization buffer according to the manufacturer’s instructions. Indirect intracellular staining for DOCK8 was performed for both patients on freshly isolated peripheral blood mononuclear cells (PBMCs) using BD Biosciences fixation/permeabilization buffer with polyclonal mouse anti-DOCK8 antibodies (Santa Cruz) or mouse IgG1 isotype control (Biolegend), followed by secondary detection with FITC antimouse IgG1 (Biolegend) in P1. For P2, DOCK8 intracellular staining was performed on PBMC using polyclonal rabbit anti-DOCK8 antibody (Sigma-Aldrich, St. Louis, MO) or Rabbit IgG XP (R) isotype control (cell signaling), followed by secondary detection Brilliant Violet 421TM donkey antirabbit IgG (Biolegend). For intracellular cytokine staining, cell suspensions were incubated with phorbol myristate acetate (PMA) (Sigma-Aldrich; 50 ng/mL), ionomycin (Sigma-Aldrich; 500 ng/mL), and GolgiPlugTM (BD Biosciences; according to the manufacturer’s instructions) for 4 h in complete medium. Permeabilization and intracellular IFN- γ , IL-4, and IL-17 staining was carried out using an eBioscience fixation/permeabilization kit as described above. Data were collected with a Fortessa cytometer (BD Biosciences) and analyzed with FlowJo software (TreeStar).

DOCK8 Mutation Identification and Sequencing Whole-exome sequencing was performed as described [22]. For Sanger sequencing analysis, *DOCK8* sequences were derived from genomic DNA by polymerase chain reaction (PCR) amplification and sequenced bidirectionally using dye-terminator chemistry, as described [11].

T_{reg} Cell Suppression Assay This assay was performed on isolated PBMCs. T cells were purified by cell sorting for CD4⁺ CD25⁺ CD127^{low} T_{reg} and CD4⁺ CD25⁻ T effector cells (T_{eff}). The suppression assay was done as outlined in our previous reports [20, 22].

Results

The index case (patient P1) was a 3-year-old boy born to consanguineous parents (Fig. 1a) who presented at 10 months of age with persistent diarrhea and poor weight gain starting at 1 year of age that did not respond to multiple dietary modifications. His physical examination was notable for weight below the fifth percentile for age and an eczematous rash involving his face (Fig. 1b), trunk, and extremities. His eczema started at the age of 3 months, and while it was complicated by intermittent secondary bacterial infections, it responded well to therapy with topical steroids and emollients. His upper gastroenterology endoscopy was normal while his initial colonoscopy showed nonspecific colitis for which he was treated with parenteral nutrition and oral steroid. Despite the initial favorable clinical response, his diarrhea relapsed in the setting of negative infectious studies which included routine stool cultures for enteric bacterial pathogens and frequent stool exams for ova and parasites. Testing for other infectious agents, including rotavirus, adenovirus, *Clostridium difficile*, giardia, and cryptosporidium, was negative on multiple

occasions. Subsequently, multiple immunosuppressive medications were tried, including pulse steroid, azathioprine, and cyclosporine, without sustained clinical improvement. Repeated colonoscopy demonstrated chronic active colitis with diffuse superficial ulceration (Fig. 1c, d). Colonic tissue histopathology showed a diffuse mixed inflammatory cell infiltrate, including polymorphonuclear leukocytes, lymphocytes, and plasma cells associated with bifid crypts and crypt abscesses (Fig. 1d). These findings were concerning for the possibility of evolving ulcerative colitis for which he was managed with azathioprine and mesalamine. His blood counts revealed a mild anemia with peripheral eosinophilia (Table E1). Evaluation of serum immunoglobulins (IgA, IgM, IgG), specific antibody titers, and lymphocyte subsets was normal. His IgE levels were elevated (> 5000 kU/L), and his specific IgE was highly positive for multiple foods including milk, soy, wheat, egg, peanut, and tree nuts. Autoimmune workup showed a positive direct Coombs test, consistent with an autoimmune hemolytic anemia, but was negative for anti-nuclear antibodies, antineutrophil cytoplasmic antibodies, antithyroid antibodies and celiac disease screening tests. On

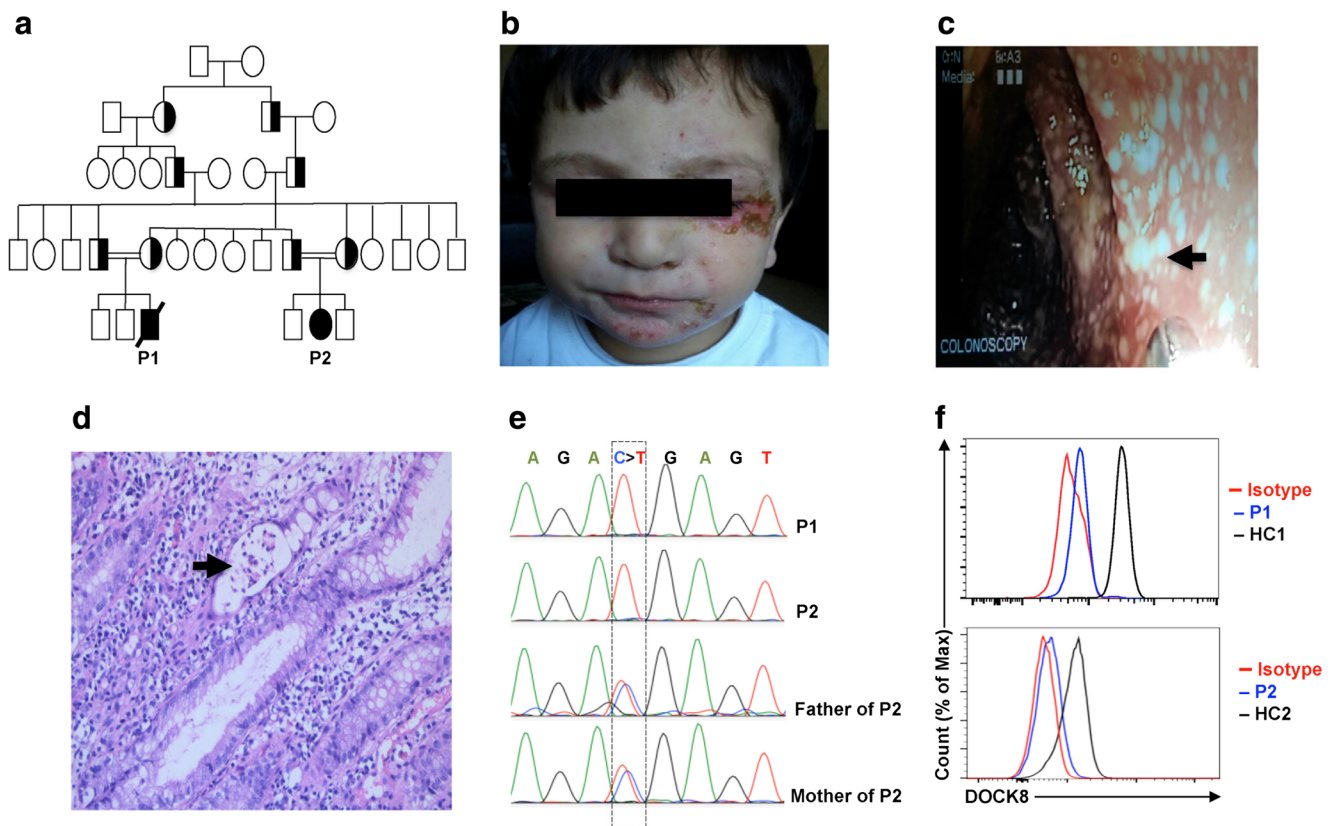


Fig. 1 Identification of an autosomal recessive homozygous *DOCK8* nonsense mutation in two related patients with an IPEX-like phenotype. **a** Pedigree of the extended family of patients P1 and P2. Squares represent males while circles are for females. Filled symbol denote patients, and half-filled symbols denote carriers. The double lines between the parents indicate consanguinity. **b** Representative picture showing facial eczematous lesions in P1 with secondary bacterial

infection. **c** Large intestinal mucosal lesions in P1 identified by colonoscopy. **d** Tissue pathology of active colonic lesions in P1. Arrow indicates a crypt abscess. **e** Sanger sequencing fluorograms showing germline homozygous *DOCK8* mutation in patients P1 and P2 and its heterozygous carriage in the parents of P2. **f** Flow cytometric analysis of *DOCK8* expression in CD3⁺ T cells of P1 and P2 as compared to that of healthy controls

follow-up, he developed a pneumonia complicated by severe acute respiratory distress syndrome leading to his death at the age of 3 years.

The presence of persistent diarrhea with active colitis, eczema, and allergic dysregulation and Coombs-positive autoimmune hemolytic anemia led us to investigate genetic lesions associated with IPEX and IPEX-like-related disorders [21]. Flow cytometry revealed normal expression of FOXP3, CD25, and CTLA4 on T_{reg} cells. Sanger sequencing analysis of the *FOXP3* gene was normal. Whole-exome sequencing analysis identified 96 homozygous gene variants (Table E2). While many variants associated with missense or in-frame deletions/insertions scored benign by PolyPhen and/or SIFT protein function prediction algorithms, the one deleterious gene variant identified that could explain his presentation was in *DOCK8*. He was found to have a homozygous c.1498 C>T mutation in *DOCK8*, resulting in a premature stop codon (p. R500X), which was confirmed by Sanger sequencing (Fig. 1e). No other deleterious variants were found in genes associated with early-onset inflammatory bowel disease or IPEX-like phenotype, including *IL10*, *IL10RA/B* and *LRBA*. The *DOCK8* mutation, which mapped to the DOCK homology domain 1 of the DOCK8 protein, was not found in dbSNP 38 or the 1000 Genomes database. Flow cytometric analysis of his peripheral blood T cells showed the complete absence of DOCK8 expression, indicative of a DOCK8-null phenotype (Fig. 1f).

Patient 2 (P2) is a 4-year-old girl, cousin of patient P1, who presented for evaluation following her cousin's death. She had a generalized eczematous rash since early infancy. Her eczema was managed successfully with topical steroids and emollients with no history of skin superinfections. At 12 months of age, she started to have recurrent ear infections that were treated with antibiotics and which were eventually controlled by the placement of bilateral tympanostomy tubes. At the age of 3 years, she started to have chronic diarrhea, similar to her cousin's history. On physical exam, the patient had a generalized eczema and bilateral perforated eardrums. Her complete blood counts, immunoglobulins, and tetanus IgG antibody titer were normal (Table E1). Her total IgE was 408 IU/mL, and she had positive specific IgE antibodies to milk, soy, peanut, sesame, and tree nuts. Sanger sequencing analysis of *DOCK8* identified the same homozygous mutation that was described in P1 (c.1498 C>T; p. R500X), also leading to the complete absence of DOCK8 expression (Fig. 1e, f). She was started on antimicrobial prophylaxis and monthly IVIG infusion with good clinical improvement. Currently, the patient is being evaluated for hematopoietic stem cell transplantation (HSCT) from her full-matched healthy sibling [23].

We examined the impact of DOCK8 deficiency on T_{reg} cell phenotype and function in our patients. The frequencies of T_{reg} cells in the peripheral blood of patients P1 and P2 were comparable to those of healthy controls (Fig. 2a, b). Analysis

of T_{reg} cell markers revealed normal expression of FOXP3, CTLA4, and CD127 in both patients, but decreased expression of CD25 in patient P2 and decreased Helios expression in both patients (Fig. 2c, d). Strikingly, the capacity of patient T_{reg} cells to suppress the in vitro proliferation of the patient T cells in response to anti-CD3 mAb stimulation was absent, thus establishing the presence of a profound functional defect in the patient T_{reg} cells (Fig. 2e, f).

Further analysis of peripheral blood lymphocyte populations in patient P2 revealed findings characteristic of DOCK8-deficient subjects, including an inverted CD4⁺ to CD8⁺ T cell ratio, and profound deficiency of CD27⁺ IgD⁻ memory B cells (Fig. E1) [18].

We further analyzed the immunological features of another DOCK8-deficient patient with severe immune dysregulation. Patient 3 (P3) is a 6-year-old girl who has had severe atopic dermatitis since early infancy. She later evolved generalized lymphadenopathy and hepatosplenomegaly, with a lymph node biopsy showing cortical lymphoid hyperplasia with no dysplastic changes or granulomas. At 5 years of age, she developed chronic diarrhea in the setting of negative infectious studies. Multiple antimicrobial medications were tried without sustained clinical improvement. Her upper and lower gastrointestinal endoscopies showed eosinophilic esophagitis, chronic inactive gastritis, and chronic colitis with an eosinophilic infiltrate (Fig. 3a, b). Subsequently, she was started on oral steroids and a mast cell stabilizer with resolution of her diarrhea and significant weight gain. Evaluation of serum immunoglobulins, specific antibody titers, and lymphocyte subsets was normal apart from the high IgE (> 5000 kU/L) (Table E1). Her specific IgE was highly positive for multiple foods including egg, peanut, and tree nuts. Mutational analysis revealed a homozygous splice junction mutation in *DOCK8* (c.2402 -1G→A). Her brother, patient P4, is a 4-year-old boy who presented with atopic dermatitis. He had no history of recurrent infections, diarrhea, or hospitalization. Immunological evaluation showed high IgE with no other abnormalities (Table E1). He was found to have the same mutation as his sister. Both patients had markedly decreased staining of DOCK8 protein in their CD4⁺ T cells, consistent with reduced expression of mutant DOCK8 protein (Fig. 3c).

Analysis of the T_{reg} cell phenotype of patients P3 and P4 revealed normal expression of FOXP3 (Fig. 3d, e). Expression of the T_{reg} cell marker Helios was decreased, similar to the findings in patients P1 and P2 (Fig. 3e). Patient P3 also exhibited decreased CD25 and CTLA4 expressions, while CD127 expression was unaffected. Also, similar to patients P1 and P2, the T_{reg} cell suppression function of patients P3 and P4 was severely compromised (Fig. 2f). Overall, these results confirmed the functional incapacitation of T_{reg} cell function by DOCK8 deficiency.

We further analyzed the frequencies of different Th cells in circulation in the surviving patient P2 and in patients P3 and P4

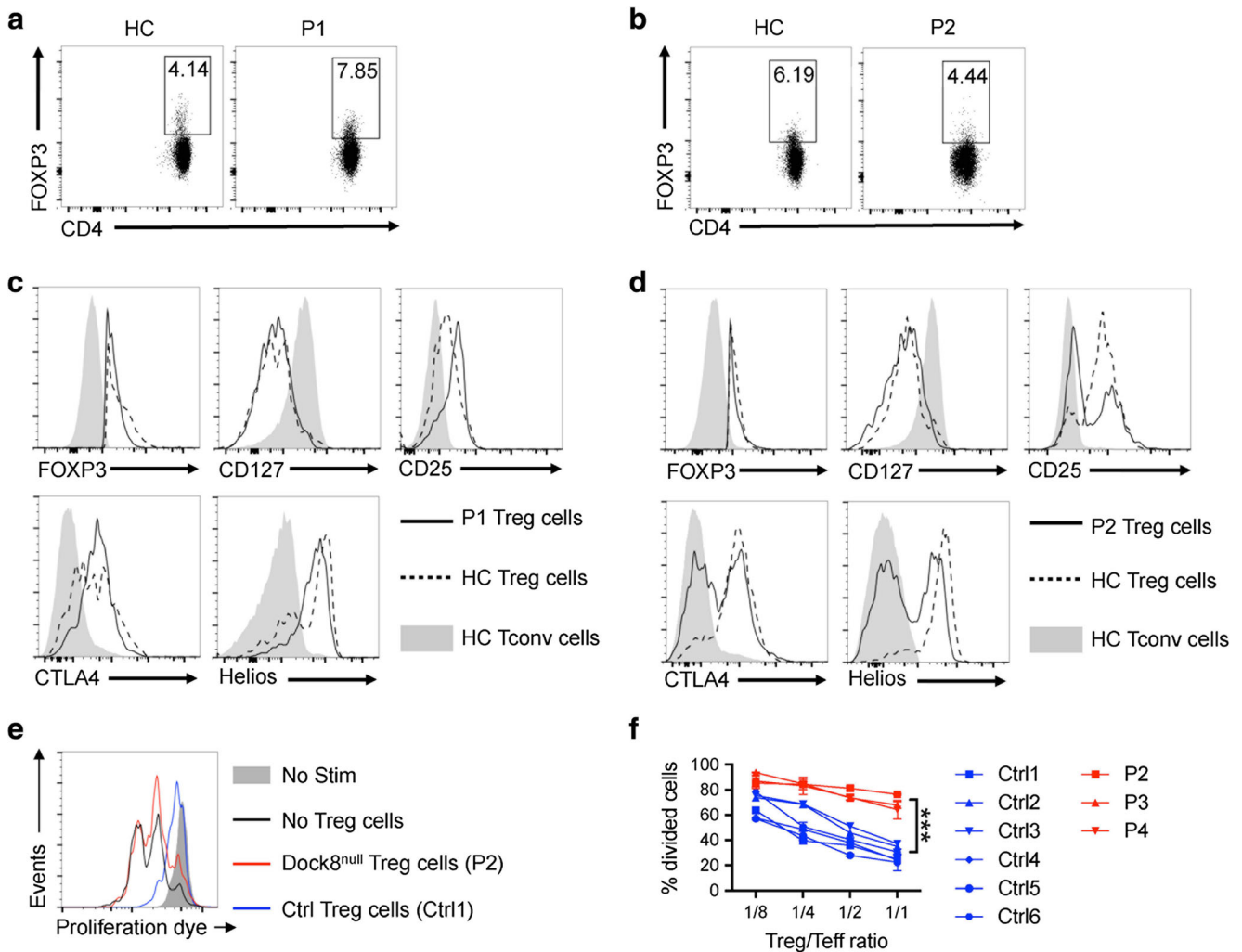


Fig. 2 DOCK8 deficiency leads to profound T_{reg} cell dysfunction. **a, b** Representative dot plot analysis of FOXP3 expression in CD4⁺ T cells of P1 (**a**) and P2 (**b**) as compared to that of a control subject. **c, d** Representative flow cytometric histogram plots of FOXP3, CD127, CD25, CTLA4, and Helios expressions in FOXP3⁺ CD4⁺ T cells of P1 (**c**) and P2 (**d**) (solid lines) versus those of healthy control (HC) subjects (dotted lines). Gray area represents expression in conventional T cells

(T_{conv}) of a HC subject. **e** Flow cytometric analysis of CellTrace Violet proliferation dye dilution in cell-sorted control T_{eff} (CD4⁺ CD25⁻) cells stimulated with anti-CD2/CD3/CD28 mAb-coated bead in the absence or presence of T_{reg} cells (CD4⁺ CD25⁺ CD127^{low}) from HC subjects or from P2 only. **f** Representative curves of in vitro suppression assays in response to different T_{reg}/T_{eff} ratio in DOCK8-deficient patients P2, P3, and P4 and in control subject. ****p* < 0.001 by two-way ANOVA

as compared to control subjects. In all three patients, the frequency of circulating IL-4⁺ CD4⁺ T cells was markedly increased, indicative of Th2 cell skewing (Fig. 4a, b) [8]. Circulating IL-17⁺ CD4⁺ T cells were profoundly deficient, while IFN-γ⁺ CD4⁺ T cells were normal, consistent with our previous studies on DOCK8-deficient subjects (Fig. 4a, b) [8]. Overall, these findings were consistent with the patients suffering immunopathological alterations related to DOCK8 deficiency.

Discussion

Whereas DOCK8 deficiency typically manifests as a combined immunodeficiency, with recurrent viral, bacterial, and fungal infections, it also presents with several features of

immune dysregulation, including allergic dysregulation, lymphoproliferation, and autoimmunity, which may dominate the clinical picture [13, 17, 18]. The clinical findings in our index case, patient P1, were skewed towards immune dysregulation, with prominence of enteropathy and colitis as clinical features in the absence of an obvious infectious agent, in addition to the other features such as allergic dysregulation and autoimmunity [21, 24]. The triad of an enteropathy not attributable to an infectious agent, eczema with allergic dysregulation, and autoimmunity in a male child raised suspicion of IPEX or an IPEX-like disorder, leading to the identification of DOCK8 deficiency as the underlying disorder. Two other patients, P2 and P3, also suffered from enteropathy and allergic dysregulation in the absence of an overt autoimmunity. The intense immune dysregulation suffered by the DOCK8-deficient

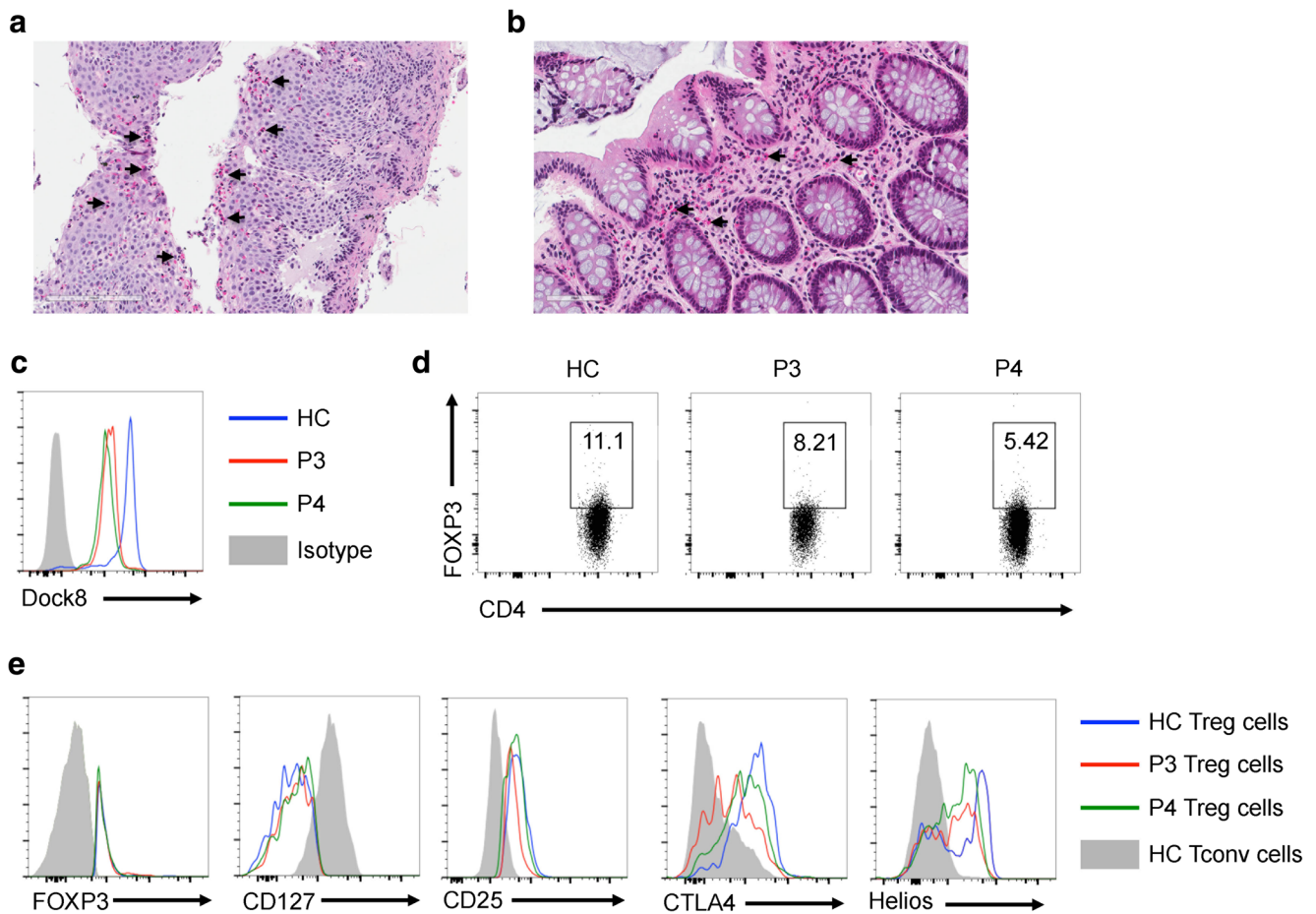


Fig. 3 Pathological and immunological features of patient P3. **a, b** Representative pictures of esophageal and colonic tissue pathologies in patient P3. Representative arrows illustrate eosinophil cell infiltration. **c** Flow cytometric analysis of DOCK8 expression in $CD3^+$ T cells of P3 and P4 as compared to that of a HC subject. **d** Representative dot plot analysis of FOXP3 expression in $CD4^+$ T cells of P3 and P4 as compared

to that of a control subject. **e** Representative flow cytometric histogram plots of FOXP3, CD127, CD25, CTLA4, and Helios expressions in $FOXP3^+ CD4^+$ T_{reg} cells of P3 (red tracing) and P4 (green tracing) versus those of a HC subject (blue tracing). Gray area represents expression in T_{conv} cells of a HC subject (Color figure online)

subjects was reflected by the lack of suppressor function by the T_{reg} cell of patients available for testing, namely, P2, P3, and P4, a finding in agreement with the profound deficiency in T_{reg} cell suppression previously documented in DOCK8-deficient subjects [20]. Overall, the triad of enteropathy/colitis, eczema with allergic dysregulation, and autoimmunity manifested by patient P1 and the partial phenotypes of enteropathy and allergic dysregulation manifested by patients P2 and P3 overlap with the phenotypes of IPEX and IPEX-like disorders. Thus, DOCK8 deficiency should be considered in the differential diagnosis of these disorders.

A number of primary genetic defects impacting T_{reg} cell differentiation and function have been described. The most famous of these, IPEX, is a disorder originally associated with loss of function mutations in *FOXP3*. While the classical IPEX presentation is a triad of enteropathy, eczema with allergic dysregulation, and autoimmunity, including autoimmune endocrinopathies, cytopenias, and organ-specific autoimmunity (lung, liver, kidney, etc.) [25–27]. It is now recognized

that the clinical phenotypes of IPEX may evolve over time and may also present with partial phenotypes, associated with both classical, fully penetrant *FOXP3* mutations as well as hypomorphic ones [24, 28]. Furthermore, a number of IPEX-like conditions have been described due to mutations affecting genetic elements critical to T_{reg} cell function [19, 21]. These include loss of function mutations in *IL2RA* [29] *CTLA4* [30, 31], *LRBA* [22, 32], *STAT5b* [33], and *ITCH* [34], as well as in some cases of gain of function (GOF) mutations in *STAT1* [35] and *STAT3* [36, 37]. These conditions also present with various combinations of IPEX-related phenotypes as well as distinguishing features of their own. In particular, the intersection between immunodeficiency and immune dysregulation observed in some patients with DOCK8 deficiency is shared by some other IPEX-like disorders, including *CTLA4* and *LRBA* deficiencies as well as in some cases of *STAT1* and *STAT3* GOF mutations. The myriad of clinical phenotypes of these disorders is not surprising, given the broad impact of their underlying gene defects on different

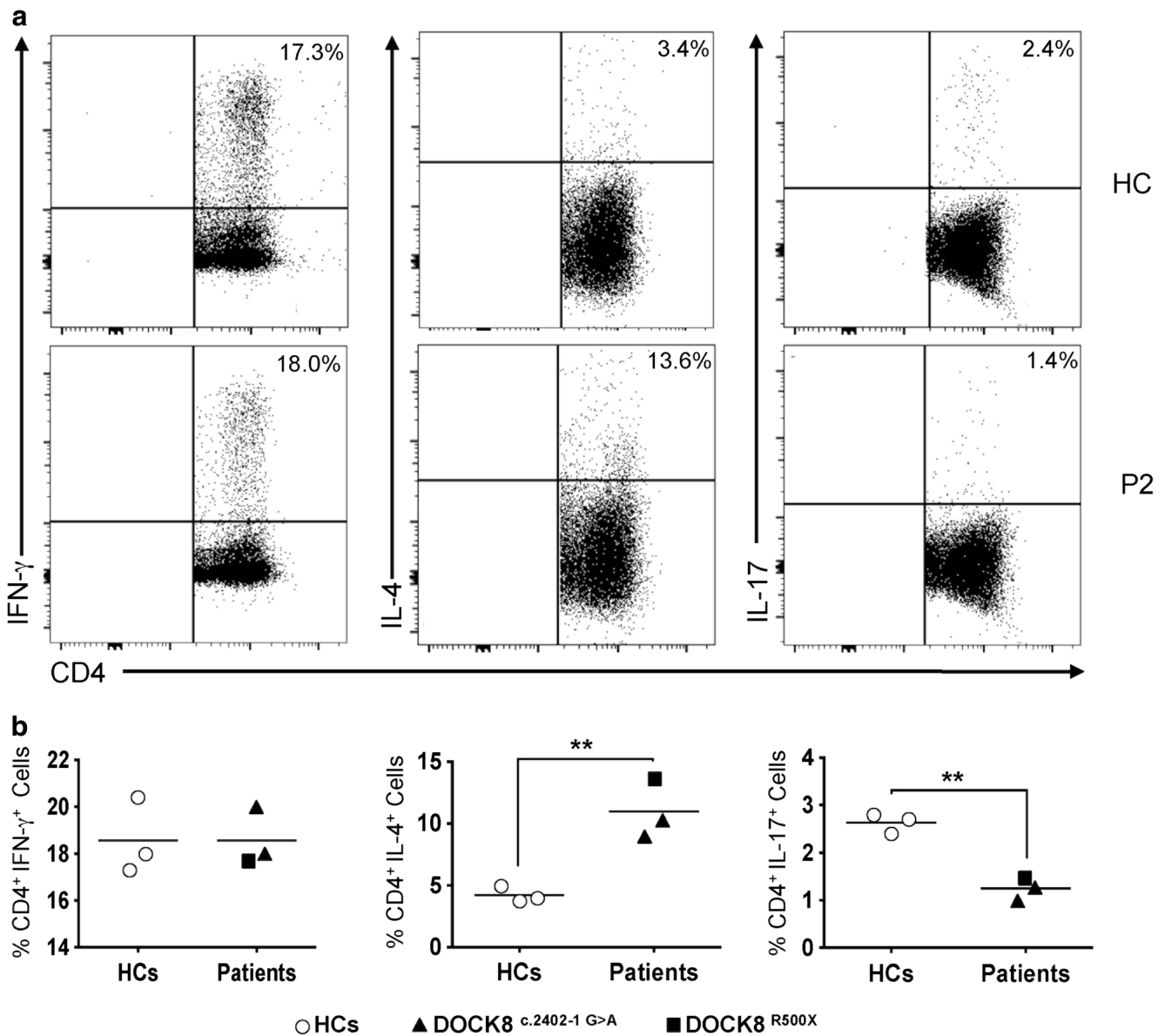


Fig. 4 Exacerbated T_H2 and impaired T_H17 cell responses in patient P2. **a** Flow cytometric analyses of IFN- γ , IL-4, and IL-17 expressions by peripheral CD4⁺ T cells from controls and patient P2. **b** The frequencies

of IFN- γ -, IL-4-, and IL-17-producing CD4⁺ cells in three healthy controls and three DOCK8-deficient patients. ***p* < 0.01 by unpaired two-tailed Student's *t* test

arms of the immune system as well as the interaction of these defects with host genetic and exposure factors.

There are several mechanisms by which DOCK8 deficiency may impact T_{reg} cell function [13]. DOCK8 regulates the actin cytoskeleton by virtue of its activation of CDC42, which in turn activates the Wiskott-Aldrich protein (WASP) [6]. WASP, together with the WASP-interacting protein (WIP) promotes actin polymerization upon T cell activation. DOCK8 physically interacts with the WASP/WIP complex, thus enabling tight spatial regulation of the actin cytoskeleton by the complexed proteins [6]. WASP deficiency in T_{reg} cells incapacitates their function, suggesting that DOCK8 deficiency may impair T_{reg} cell function in part by preventing the

activation of WASP/WIP [38, 39]. Another mechanism by which DOCK8 deficiency may act to impair T_{reg} cell function involves STAT3, a transcription factor that plays an essential role in T_{reg} cell function [8]. DOCK8 amplifies STAT3 activation by a variety of cytokines, and its deficiency would likely impair STAT3 activation in T_{reg} cells [8]. Further studies would be required to dissect the contribution of the respective mechanism to T_{reg} cell dysfunction in DOCK8 deficiency.

Several mechanisms could contribute to the enteropathy in our DOCK8-deficient subjects. While an infectious etiology is always suspect and should be sought out, evidence of a frank infection was lacking. In mice with Foxp3 deficiency, the absence of T_{reg} cell function leads to a breakdown in mucosal

tolerance to the gut commensal microbiota [40]. This loss of immune regulation gives rise to a gut mucosal inflammatory response driven by the commensal bacteria that is TLR-dependent and which could be abrogated by concurrent deficiency of the TLR adaptor protein MyD88 [40]. Both IPEX- and DOCK8-deficient patients also suffer from food allergies, which may contribute to the Th2 inflammatory response in the gut [17, 18, 41, 42]. Avoidance of the suspected food allergens may contribute to the management of enteropathy in these subjects.

It is well appreciated that the clinical manifestations of patients with the same genetic mutations may vary depending on interactions with other genetic elements and with environmental exposures. In this report, the divergence in the phenotypic presentation of the same *DOCK8* gene defect was especially pronounced for the siblings P3 and P4, the former suffering severe disease manifestations while the latter was very mildly affected. In that regard, the recent identification of Nei endonuclease VIII-like 3 (*NEIL3*), encoding the base excision repair enzyme NEIL3, as a modulator of autoimmunity in LPS-responsive beige-like anchor (LRBA) deficiency, a heritable disorder of dysregulation and autoimmunity, provides one such example of gene-gene interactions influencing disease phenotype [43]. We postulate that similar interaction(s) in our patients may have influenced their disease phenotype in favor of intense immune dysregulation and IPEX-like manifestations.

Finally and in terms of therapy, the definitive treatment of DOCK8 deficiency is bone marrow transplantation [23]. The emergence of immune dysregulation in the context of an immunodeficiency disorder presents challenges in terms of therapy. The benefits of interim-focused interventions aimed at restraining potentially life-threatening immune dysregulation, including IPEX-like manifestations, should be carefully weighed against the risk of compounding the immune deficiency by such interventions.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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