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Major histocompatibility complex class II deficiency due to a novel mutation in RFXANK in a child of Mexican descent

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Abstract

MHC Class II deficiency (also known as bare lymphocyte syndrome type II) is a rare primary immunodeficiency disorder inherited in an autosomal recessive fashion resulting from the absence of MHC class II molecules on the surface of immune cells. Here, we report a now 18-month-old male born to consanguineous Mexican-American parents who presented at four months with pneumocystis pneumonia, and was subsequently found to have a novel homozygous mutation in *RFXANK* leading to MHC Class II deficiency. He was successfully treated via hematopoietic stem cell transplantation from his matched sibling.

Keywords

MHC class II deficiency; RXFANK; Primary immunodeficiency

To the Editor

Major histocompatibility (MHC) Class II molecules (alternatively known as human leukocyte antigens (HLAs)) allow presentation of exogenous peptides to the T-cell receptor of $CD4^+$ T helper cells, and are essential in the development of a normal adaptive immune response. Mutations in the genes encoding the MHC class II transactivator (CIITA), regulatory factor X-associated protein (RFXAP), regulatory factor X, 5 (RFX5), and ankyrin repeat-containing regulatory factor X (RFXANK)[1, 2] have been associated with the phenotype of bare lymphocyte syndrome. Here, we describe the case of a previously

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healthy, Hispanic male who presented at 4 months of age with a progressive respiratory infection. He was born at full term to a 39 year old gravida 3, para 3 with an uneventful perinatal course. He received all age-appropriate immunizations including hepatitis B, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type B, polio, and pneumococcal conjugate vaccine without issues. He had not received any live vaccines. He was born to parents of Mexican descent who were related (4^{th} generation). Two older siblings were healthy without history of immunodeficiency. At the age of four months he was diagnosed with acute otitis media, which was treated with amoxicillin. Despite antibiotics, he developed progressive respiratory symptoms as well as diffuse rash, leading to hospitalization and treatment of presumed pneumonia with antibiotics. He developed a gradually increasing oxygen requirement in spite of antibiotics, steroids, and diuretic therapy, with acute worsening on day 10 of admission requiring intubation.

Laboratory evaluation showed negative viral testing for influenza and respiratory syncytial virus PCR, and nasopharyngeal PCR that was positive for a picornavirus. Quantitative PCRs for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) were negative from blood. Bacterial and fungal cultures from blood and lower respiratory samples did not reveal a causative organism. Evaluation by otorhinolaryngology did not show anatomic airway abnormalities. Chest X-ray revealed interstitial pneumonia and a pneumomediastinum, which were suggestive of *Pneumocystis jiroveci.* Lactate dehydrogenase and beta-D glucan were elevated at 845 Units/L (normal 135–376 U/L) and 424 pg/mL (normal < 60 pg/ml) respectively, which further supported the diagnosis of Pneumocystis pneumonia. Initial immunologic evaluation showed neutropenia, panhypogammaglobulinemia, and moderate T-cell lymphocytopenia with near absent lymphocyte proliferation in response to mitogen phytohemagluttinin (PHA) as well as to Tetanus and Candida antigens (Supplemental Table 1). He had normal neutrophil oxidative activity by dihydrorhodamine assay.

Flow cytometry for HLA class II showed complete absence of HLA-DR, -DP, -DQ on T-cells, B-cells, and monocytes (Figure 1). Subsequent sequencing showed a homozygous mutation in *RFXANK* (c.C469T, p.R157X) in the patient, confirming the diagnosis of MHC Class II deficiency. These results prompted sequencing of his parents and both siblings, all of whom were heterozygous carriers.

After treatment with Trimethoprim/Sulfamethoxazole for Pneumocystis pneumonia, the patient made a full recovery from an infectious standpoint and was sent home on prophylactic doses of trimethoprim/sulfamethoxazole and fluconazole. Intravenous immunoglobulin replacement was given on a monthly basis. At seven months, he received matched sibling bone marrow transplant after a preparatory regimen consisting of busulfan, fludarabine, and alemtuzumab. His post transplant course was complicated by grade II graft-versus-host-disease (GvHD) treated with steroids well as cytomegalovirus (CMV) reactivation, which resolved following antiviral pharmacotherapy and virus-specific, donor-derived T-cell infusion. Further complications included the development of a sterile pericardial effusion, which resolved after placement of a pericardial window. He is now healthy and off all medications at fourteen months after transplantation, with 100% donor T-cell chimerism.

MHC Class II deficiency is characterized by the absence of the major histocompatibility complex class II gene expression. At least four different trans-acting regulatory genes, prerequisites for the transcription of the MHC class II genes, are responsible for the deficiency. *RFXANK* is the gene encoding the third subunit of RFX, a multiprotein complex that binds the MHC Class II promoter. Maternak *et. al* determined that *RFXANK* is located on 19p12 between MEF2B and CSPG3 and is composed of 10 exons spanning 10 kilobase pairs.[1] Previously, seven different *RFXANK* mutations reported in patients with MHC Class II deficiency [3] Here, we describe a novel nonsense mutation in *RFXANK* leading to MHC Class II deficiency.

Previously, the epidemiology of MHC class II deficiency has been assigned to North African as well as Kuwaiti populations due to the founder mutation c.752delG-25. Additionally, though our patient had $CD4^+$ T-cell lymphocytopenia in his initial evaluation, he lacked the typical CD4:8 inversion that has heretofore been commonly associated with the MHC deficiency phenotype.

While prophylactic antibiotics and immunoglobulin replacement are important in the symptomatic treatment of MHC class II deficiency, hematopoietic stem cell transplant (HSCT) is the only available cure. Unfortunately, MHC class II deficiency patients seem to be at increased risk for the development of GvHD post-transplant, with a higher risk associated with pre-existing viral infections [4]. While this patient did indeed develop Grade II GvHD, it is possible that early recognition and successful treatment of his CMV reactivation led to an overall successful outcome. The case presented illuminates a novel mutation in *RFXANK* clinically manifested in a patient of Mexican descent. As patients with MHC II deficiency are not identified by the TREC assay, once diagnosis is suspected, HLA-DR expression should be included in the subsequent work-up. Additionally, Pneumocystis pneumonia should be kept in the differential when evaluating any child with lymphopenia and/or severe respiratory illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Masternak K, Barras El, Zufferey M, Conrad B, Corthals G, Aebersold R, et al. A gene encoding a novel RFX-associated transactivator is mutated in the majority of MHC class II deficiency patients. Nature Genetics. 1998; 20
2. Krawczyk M, Masternak K, Zufferey M, Barras E, Reith W. New functions of the major histocompatibility complex class II-specific transcription factor RFXANK revealed by a high-resolution mutagenesis study. Mol Cell Biol. 2005; 25:8607–8618. [PubMed: 16166641]
3. Wiszniewski W, Fondaneche MC, Louise-Plence P, Prochnicka-Chalufour A, Selz F, Picard C, et al. Novel mutations in the RFXANK gene: RFX complex containing in-vitro-generated RFXANK mutant binds the promoter without transactivating MHC II. Immunogenetics. 2003; 54:747–755. [PubMed: 12618906]

4. Renella R, Picard C, Neven B, Ouachee-Chardin M, Casanova JL, Le Deist F, et al. Human leucocyte antigen-identical haematopoietic stem cell transplantation in major histocompatiblity complex class II immunodeficiency: reduced survival correlates with an increased incidence of acute graft-versus-host disease and pre-existing viral infections. Br J Haematol. 2006; 134:510–516. [PubMed: 16848795]

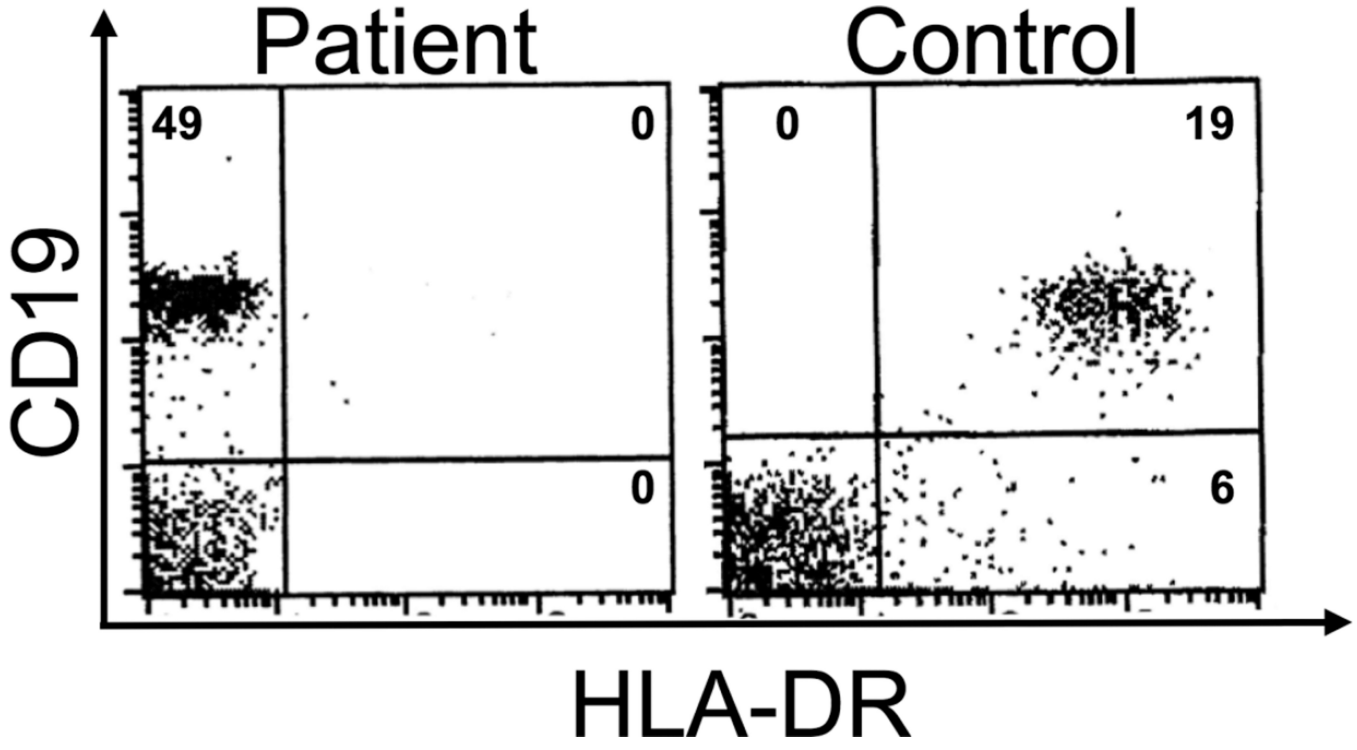

Figure 1.
Flow cytometry showed complete absence of HLA-DR expression on patient B-lymphocytes versus a time-matched control.