The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency

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Background: LPS-responsive beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency caused by biallelic mutations in *LRBA* that abolish LRBA protein expression.
Objective: We sought to report the extended phenotype of LRBA deficiency in a cohort of 22 LRBA-deficient patients.
Methods: Clinical criteria, protein detection, and genetic sequencing were applied to diagnose LRBA deficiency.
Results: Ninety-three patients met the inclusion criteria and were considered to have *possible* LRBA deficiency. Twenty-four patients did not express LRBA protein and were labeled as having *probable* LRBA deficiency, whereas 22 were genetically confirmed as having *definitive* LRBA deficiency, with biallelic mutations in *LRBA*. Seventeen of these were novel and included homozygous or compound heterozygous mutations. Immune dysregulation (95%), organomegaly (86%), recurrent infections (71%), and hypogammaglobulinemia (57%) were the main clinical complications observed in LRBA-deficient patients. Although 81% of LRBA-deficient patients had normal T-cell counts, 73% had reduced regulatory T (Treg) cell numbers. Most LRBA-deficient patients had low B-cell subset counts, mainly in switched memory B cells (80%) and plasmablasts (92%), with a defective specific antibody response in 67%. Of the 22 patients, 3 are deceased, 2 were treated successfully with hematopoietic stem cell transplantation, 7 are receiving immunoglobulin replacement, and 15 are receiving immunosuppressive treatment with systemic corticosteroids alone or in combination with steroid-sparing agents.
Conclusion: This report describes the largest cohort of patients with LRBA deficiency and offers guidelines for physicians to identify LRBA deficiency, supporting appropriate clinical management. (J Allergy Clin Immunol 2016;137:223-30.)

Key words: *LPS-responsive beige-like anchor protein, primary immunodeficiency, common variable Immunodeficiency, autoimmunity, hypogammaglobulinemia, enteropathy, lymphoproliferation*

LPS-responsive beige-like anchor protein (LRBA) is a member of the PH-BEACH-WD40 (pleckstrin homology-beige and Chediak-Higashi-tryptophan aspartic acid dipeptide) protein family, which is highly conserved among species and widely expressed in human tissues.[1] In 2012, we identified 5 patients from 4 different families with homozygous mutations in *LRBA*, describing a novel primary immunodeficiency since known as LRBA deficiency.[2] LRBA deficiency is caused by loss of protein expression of LRBA, which can be caused by either homozygous or compound heterozygous mutations in *LRBA*. LRBA deficiency was first characterized by early-onset hypogammaglobulinemia, autoimmune manifestations, susceptibility to inflammatory bowel disease (IBD), and recurrent infections.[2] However, LRBA case reports have shown patients with IBD accompanied or not by antibody deficiency (common variable immunodeficiency [CVID]),[3,4] a patient with autoimmune manifestations without hypogammaglobulinemia,[5] and, recently, a patient from

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Abbreviations used
ALPS: Autoimmune lymphoproliferative syndrome
ALPS-Ph: Autoimmune lymphoproliferative syndrome of undetermined genetic cause
CVID: Common variable immunodeficiency
HSCT: Hematopoietic stem cell transplantation
IBD: Inflammatory bowel disease
IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
ITP: Idiopathic thrombocytopenic purpura
LRBA: LPS-responsive beige-like anchor protein
Treg: Regulatory T

Saudi Arabia with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)–like disorder.[6] Thus LRBA deficiency has become a clinically variable syndrome with a wide spectrum of clinical manifestations.

In vitro abnormalities in LRBA-deficient patients include decreased IgG antibody production, deficient T-cell activation and proliferation, increased apoptosis, and decreased autophagy in B lymphocytes.[2] Moreover, Charbonnier et al[6] have shown alterations on Treg cells, including impaired cell-mediated suppression, increased apoptosis, and decreased expression of the Treg cell canonical markers, such as CD25, Helios, forkhead box protein 3, and cytotoxic T lymphocyte–associated protein 4.[6] These studies together suggest that LRBA is important in host defense against infections, cell proliferation, cell death, and immune regulation.

A summary of the clinical phenotype and laboratory findings of affected patients is needed to understand the *in vivo* effects of these findings and to facilitate the diagnosis and treatment of LRBA deficiency. This study presents data from the largest LRBA deficiency cohort worldwide, including (1) a description of the clinical and immunologic characteristics of the LRBA-deficient patients with a genetic diagnosis, (2) a list of new mutations in *LRBA*, (3) description of treatment options for LRBA-deficient patients, and (4) a clinical comparison of patients with molecularly diagnosed definitive LRBA deficiency versus patients with an absence of LRBA protein expression but with the wild-type *LRBA* coding sequence.

METHODS

For more information, see the Methods section in this article's Online Repository at www.jacionline.org.

RESULTS

LRBA classification

Between January 2012 and May 2015, a total of 93 patients referred to us met the inclusion criteria for LRBA deficiency (see Figs E1 and E2 in this article's Online Repository at www.jacionline.org). Eighty-four patients were included for LRBA protein testing, fulfilling the clinical suspicion of possible LRBA deficiency. Of these, 43 (52%) patients had normal test results for LRBA expression by means of either Western blotting or flow cytometry. Two patients had an overexpression of LRBA protein, 17 (20%) had a reduction of LRBA protein expression, and 24 (28%) did not express LRBA protein in PBMCs after either PHA, anti-CD3/anti-CD28 plus IL-2, or phorbol 12-myristate 13-acetate plus ionomycin stimulation (see Fig E3 in this article's Online Repository at www.jacionline.org). These 24 patients were considered to have probable LRBA deficiency. Fourteen of the 24 patients had either homozygous or compound heterozygous mutations in *LRBA*. In addition, we identified biallelic mutations in *LRBA* in 1 of 17 patients with reduced LRBA protein levels and in 7 additional patients who were not tested for LRBA protein expression but were directly sequenced by using whole-exome sequencing or targeted sequencing (see Fig E4 in this article's Online Repository at www.jacionline.org). In total, 22 patients were classified as having definitive LRBA deficiency based on the mutation identified.

Demographic features of LRBA-deficient patients

Our LRBA deficiency cohort comprises all patients who had a lack of LRBA protein expression with either homozygous or compound heterozygous deleterious mutations in *LRBA*. Patients were similarly distributed by sex: 12 (55%) were male, and 10 (45%) were female. Most patients were children and adolescents: 72% were less than 18 years old at inclusion, with a mean age of 13 years; the average age of onset was 4 years. The latest diagnosis of immune deficiency was at age 17 years in patient 656 (Table I).

At the time of analysis, 19 patients were reported to be alive, whereas 3 had died. Ten (45%) patients from 6 different families had consanguineous parents (patients 109, 134,[7] 236, 237, 657, and 773), all of them carrying homozygous mutations. Six families were multiplex families, with 2 (patients 105, 134, 553, 604, and 657) or 3 (patient 236[8]) siblings affected (Table I).

LRBA-deficient patients had variable diagnoses of their condition at the time of evaluation because they presented with different clinical complications. Nine (41%) patients received a previous diagnosis of CVID, and 4 (18%) presented with variable autoimmune manifestations. Four (18%) additional patients had been classified as having autoimmune lymphoproliferative syndrome (ALPS) of undetermined genetic cause (ALPS-Ph), and 2 (9%) had been classified as having IPEX-like syndrome. In addition, 1 patient was given a diagnosis of granulomatous disease, and 1 had spina bifida with a myelomeningocele in addition to recurrent pulmonary infections (see Fig E2 in this article's Online Repository at www.jacionline.org). Finally, patient 236-3, the brother of 2 affected siblings (236-1 and 236-2), is currently healthy, although all 3 siblings carry the same homozygous mutations in *LRBA*.

Clinical manifestations

The main clinical complication of LRBA deficiency was immune dysregulation (n = 20 [95%]), followed by the presence of organomegaly (n = 18 [86%]) and recurrent infections (n = 15 [71%]). Hypogammaglobulinemia and lung abnormalities were found in 12 (57%) and 11 (52%) patients, respectively (Figs 1 and 2). In addition, 1 patient had a neurologic/psychiatric condition, and 1 is deaf.

Twenty patients of the 21 symptomatic subjects had immune dysregulation: enteropathy was seen in 13 patients (see Fig 2, *A* and Fig E5 in this article's Online Repository at www.jacionline.org), autoimmune hemolytic anemia in 12 patients, and idiopathic thrombocytopenic purpura (ITP) in 11 patients. Eight patients had granulomatous-lymphocytic interstitial lung disease, and 5 presented with type I diabetes or neutropenia. Chronic autoimmune hepatitis was observed in 3 patients. Eczema and uveitis were present in 2 patients each. Finally, 1 patient had alopecia at age 12 years.