

Clinical, Immunologic, and Molecular Spectrum of Patients with LPS-Responsive Beige-Like Anchor Protein Deficiency: A Systematic Review



Sima Habibi, MSc^a, Majid Zaki-Dizaji, PhD^b, Hosein Rafiemanesh, PhD^c, Bernice Lo, PhD^d, Mahnaz Jamee, MD^e, Laura Gámez-Díaz, PhD^f, Fereshte Salami, MSc^a, Ali N. Kamali, PhD^g, Hamed Mohammadi, PhD^h, Hassan Abolhassani, MD, PhDⁱ, Reza Yazdani, PhD^a, Asghar Aghamohammadi, MD, PhD^a, Juan-Manuel Anaya, MD, PhD^j, and Gholamreza Azizi, PhD^k *Tehran, Karaj, and Tabriz, Iran; Doha, Qatar; Freiburg im Breisgau, Germany; Stockholm, Sweden; and Bogotá, Colombia*

What is already known about this topic? LPS-responsive and beige-like anchor protein (LRBA) deficiency leads to a broad spectrum of clinical phenotypes including autoimmunity, chronic diarrhea, hypogammaglobulinemia, and recurrent infections.

What does this article add to our knowledge? LRBA deficiency is an immune dysregulation syndrome without any genotype-phenotype correlation. Autoimmune disorders are the main clinical manifestations in LRBA deficiency.

How does this study impact current management guidelines? LRBA deficiency should be included in the list of monogenic autoimmune diseases and should be routinely screened for in patients with immune dysregulation. Hematopoietic stem cell transplantation is a promising treatment for LRBA-deficient patients with severe and complicated clinical manifestations.

BACKGROUND: LPS-responsive beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency and immune dysregulation syndrome caused by biallelic mutations in the

LRBA gene. These mutations usually abrogate the protein expression of LRBA, leading to a broad spectrum of clinical phenotypes including autoimmunity, chronic diarrhea, hypogammaglobulinemia, and recurrent infections.

OBJECTIVE: Our aim was to systematically collect all studies reporting on the clinical manifestations, molecular and laboratory findings, and management of patients with LRBA deficiency.

METHODS: We searched in PubMed, Web of Science, and Scopus without any restrictions on study design and publication time. A total of 109 LRBA-deficient cases were identified from 45 eligible articles. For all patients, demographic information, clinical records, and immunologic and molecular data were collected.

RESULTS: Of the patients with LRBA deficiency, 93 had homozygous and 16 had compound heterozygous mutations in *LRBA*. The most common clinical manifestations were autoimmunity (82%), enteropathy (63%), splenomegaly (57%), and pneumonia (49%). Reduction in numbers of CD4⁺ T cells and regulatory T cells as well as IgG levels was recorded for 21.6%, 65.6%, and 54.2% of evaluated patients, respectively. B-cell subpopulation analysis revealed low numbers of switched-memory and increased numbers of CD21^{low} B cells in 73.5% and 77.8% of patients, respectively. Eighteen (16%) patients underwent hematopoietic stem cell transplantation due to the severity of complications and the outcomes improved in 13 of them.

CONCLUSIONS: Autoimmune disorders are the main clinical manifestations of LRBA deficiency. Therefore, LRBA deficiency should be included in the list of monogenic autoimmune diseases, and screening for LRBA mutations should be routinely

^aResearch Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

^bLegal Medicine Research Center, Legal Medicine Organization, Tehran, Iran

^cStudent Research Committee, Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^dDivision of Translational Medicine, Research Branch, Sidra Medicine, Doha, Qatar

^eStudent Research Committee, Alborz University of Medical Sciences, Karaj, Iran

^fCenter for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg im Breisgau, Germany

^gCinnaGen Medical Biotechnology Research Center, Alborz University of Medical Sciences, Karaj, Iran

^hStudent Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

ⁱDivision of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

^jCenter for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

^kNon-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

This work was supported by Vice Chancellor for Research, Alborz University of Medical Sciences (grant no. 1396-02-25-1705).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 15, 2019; revised manuscript received and accepted for publication April 9, 2019.

Available online April 14, 2019.

Corresponding author: Gholamreza Azizi, PhD, Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran. E-mail: azizi@abzums.ac.ir.

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.04.011>

Abbreviations used*HSCT*- Hematopoietic stem cell transplantation*ILD*- Interstitial lung disease*IQR*- Interquartile range*LRBA*-LPS-responsive and beige-like anchor protein*Treg*-Regulatory T

performed for patients with these conditions. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2379-86)

Key words: *LRBA* deficiency; Autoimmunity; Polyautoimmunity; Enteropathy; Regulatory T cell; Hematopoietic stem cell transplantation

INTRODUCTION

LPS-responsive and beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency caused by biallelic mutations in *LRBA* that often abrogate expression of LRBA.¹ Initially, LRBA deficiency was characterized as a common variable immune deficiency with autoimmune complications, because LRBA-deficient patients often presented with recurrent infections, hypogammaglobulinemia, and abnormalities in B-cell subsets.²⁻⁴ However, according to the International Union of Immunological Societies, LRBA deficiency is classified as a disease of immune dysregulation with autoimmunity due to regulatory T (Treg)-cell defects.⁵

Several studies reported that the most frequent clinical manifestations in LRBA deficiency are infectious complications (specifically in pulmonary and gastrointestinal tracts), lymphoproliferative disorders, enteropathy (often with villous atrophy), allergic symptoms, and autoimmunity (mostly autoimmune cytopenias and autoimmune endocrinopathies).^{1,2,6} Moreover, hypogammaglobulinemia, CD4⁺ T-cell abnormality (mostly Treg cells, T_H17 cells, and follicular helper T cells), natural killer-cell reduction, and B-cell abnormality (increased numbers of CD21^{low} B cells, decreased class-switched and marginal-zone B cells) are also documented in LRBA deficiency.^{2,7,8} Recently, Lo et al⁹ called this autosomal-recessive disease “LRBA deficiency with autoantibodies, Treg-cell defects, autoimmune infiltration, and enteropathy,” which emphasizes the most prominent features of the disorder.

As expected, since the first published cases in 2012,¹⁰ the numbers of LRBA-deficient patients have increased so that *LRBA* is one of the major genes identified with disease-causing mutations in common variable immunodeficiency cohorts.² Therefore, we aimed to systematically collect the reported LRBA deficiency cases in the literature so far and analyze their clinical records, molecular and immunological findings as well as treatment details to prepare guidelines to assist physicians in diagnosing and managing patients with LRBA deficiency.

METHODS

Search strategy

A comprehensive search, limited to English language, was performed using PubMed, Web of Science, and Scopus databases. The

search terms “Lipopolysaccharide-responsive beige-like anchor protein” or “LPS-responsive beige-like anchor protein” or “LRBA protein” or “LRBA” or “LPS-responsive beige-like anchor deficiency” or “LRBA deficiency” or “LRBA immunodeficiency” or “LRBA mutation” were used in various combinations for calling articles without restrictions on study design and/or publication time. The search was conducted using these terms in the keywords, titles, and abstracts until February 2019. Reference list of all full-text articles were hand-searched and gray literature was reviewed for additional studies as were the reference section of major reviews.

Study selection

The inclusion criteria were (1) cohort and case-series studies reporting on the clinical, immunological, and molecular findings of patients with LRBA deficiency and (2) the case series or case reports in patients with LRBA deficiency and original studies with patients with primary immunodeficiency whose molecular analysis showed a mutation in the *LRBA* gene. Studies were excluded if they did not report a definitive mutation in the *LRBA* gene or were not in English. All study selection processes were performed by 2 reviewers, whereas the third one was consulted in resolving any conflicts that might arise from the overall result of the search. All articles were first classified into 3 categories on the basis of their title and abstract: (1) Eligible, (2) Ineligible, and (3) Unclear (the full-text versions of all the unclear group articles were screened and subsequently reclassified into group 1 or 2). Any disagreement between the 2 investigators about the eligibility of an article was solved by the third reviewer. In some cases, corresponding authors of the articles were contacted.

Data extraction and quality assessment

Data of all included studies were entered in a standardized Microsoft Excel spreadsheet. Data collected included name of the first author, year of publication, number of participants, and demographic information of patients with LRBA deficiency. In addition, clinical, immunologic, and molecular information was collected. Patients appearing in more than 1 article were identified and overlapping data were excluded.

Statistical analysis

Aggregate data analysis was performed with a simple data pooling. By this an overall summary of subgroup data or data from a number of related studies are combined without weighting. Central and descriptive statistics were reported for quantitative data. For variables with abnormal distribution, median and interquartile range (IQR) were calculated. For group comparison, Mann-Whitney, chi-square, or Fisher exact test was used. The differences were considered statistically significant for *P* values that were less than .05. The statistical analyses were performed using SPSS software version 24.0 (IMB Corporation, Armonk, NY).

RESULTS

Study characteristics

A total of 291 articles were found in the bibliographic databases and were reviewed according to inclusion criteria. One hundred seventy-one articles were duplicated in search databases; 74 articles were excluded according to the defined exclusion criteria. One article was excluded because it did not report any data from LRBA-deficient patients. Finally, 45 articles were considered as eligible for systematic review (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). A total of 205 patients were reported within the eligible articles; however,

TABLE I. Demographic data of patients with LRBA deficiency

Parameters (no. of evaluated patients)	Results
Country of living (%) (n = 97)	Iran (20.6), Israel (12.4), Turkey (11.3), Saudi Arabia (7.2), others (48.5)
Ethnicity (%) (n = 97)	Arab (38.1), Iranian (20.6), Turkish (13.4), Other (27.9)
Sex ratio, M/F, n (%) (n = 99 and NK = 10)	47 (48)/52 (53)
Consanguinity, n (%) (n = 92 and NK = 17)	73 (79)
Familial case, n (%) (n = 95 and NK = 14)	46 (48)
Alive/dead, n (%) (n = 99 and NK = 10)	75 (76)/24 (24)
Age (y) (n = 89 and NK = 20)	Min = 1.0, max = 56.0, median (IQR) = 12.0 (6.5-19.0)
Age at onset (y) (n = 93 and NK = 16)	Min = 0.0, max = 38.0, median (IQR) = 1.8 (0.6-3.5)
Age at diagnosis (y) (n = 48 and NK = 61)	Min = 0.3, max = 46.0, median (IQR) = 7.9 (5.0-14.0)
Delay in diagnosis (y) (n = 44 and NK = 65)	Min = 0.0, max = 32.0, median (IQR) = 5.0 (1.0-9.7)
Age at presentation of infection (y) (n = 33 and NK = 76)	Min = 0.3, max = 38.0, median (IQR) = 2.0 (1.5-4.5)
Age at presentation of autoimmunity (y) (n = 59 and NK = 50)	Min = 0.1, max = 16.0, median (IQR) = 2.0 (1.0-5.0)
Age at presentation of allergy (y) (n = 7 and NK = 102)	Min = 0.5, max = 13.0, median (IQR) = 5.0 (2.0-7.0)
Age at presentation of enteropathy (y) (n = 30 and NK = 79)	Min = 0.1, max = 16.0, median (IQR) = 4.0 (1.0-6.2)
Age at presentation of lymphoproliferation (y) (n = 22 and NK = 87)	Min = 0.6, max = 18.0, median (IQR) = 4.0 (3.0-6.2)

F, Female; M, male; max, maximum; min, minimum; NK, not known.

Note: For age, age at onset, age at diagnosis, and delay in diagnosis, the median is shown (with 25th and 75th percentiles).

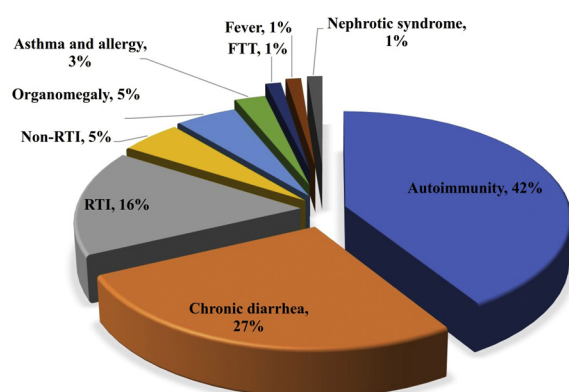


FIGURE 1. Initial clinical presentation of patients with LRBA deficiency. Autoimmunity and chronic diarrhea have been observed as the first disease presentation in most of the LRBA-deficient patients. *FTT*, Failure to thrive; *non-RTI*, non-respiratory tract infection; *RTI*, respiratory tract infection.

96 patients appeared multiple times. Thus, after removing all the repetitive cases, the data of 109 LRBA-deficient patients were used for data analysis. The study selection process is depicted in Figure E1 in this article's Online Repository at www.jaci-inpractice.org.^{1,2,10-52}

Baseline characteristics of patients with LRBA deficiency

In this study, we evaluated 109 patients (52 males, 47 females, and 10 with unknown gender) with the molecular diagnosis of LRBA deficiency. The frequency of mutation in the *LRBA* gene was observed most in Arab (38.1), Iranian (20.6), and Turkish (13.4) patients, respectively. The median (IQR) age of patients at the time of study was 12.0 (6.5-19.0) years. The median (IQR) age of onset was 1.8 (0.6-3.5) years, and the median age at the time of diagnosis was 7.9 (5.0-14.0) years. The median (IQR) diagnostic delay in immunodeficiency was 5.0 (1.0-9.7) years. The longest diagnostic delay was 32.0 years, whereas the

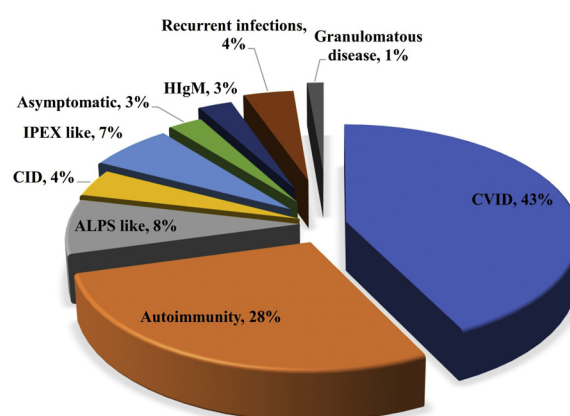


FIGURE 2. Distribution of primary clinical diagnosis of patients with LRBA deficiency. Patients with LRBA deficiency were mostly diagnosed with CVID and autoimmunity. *ALPS*, Autoimmune lymphoproliferative syndrome; *CID*, combined immune deficiency; *CVID*, common variable immunodeficiency; *HIgM*, hyper-IgM; *IPEX*, immunodysregulation polyendocrinopathy enteropathy X-linked.

minimum period of diagnostic delay was immediately following the onset of symptoms (Table I). Forty-six patients were in families with multiple affected. At the time of our analysis, 75 patients (76%) were reported to be alive, whereas 24 (24%) were deceased, mostly due to sepsis and respiratory failure. Septic shock, multiple organ failure, pneumonia, nephroblastoma, severe autoimmune thrombocytopenia, hemorrhage (including intracranial, cerebral, and lung hemorrhage), liver and pulmonary granulomas, disseminated cytomegalovirus, and systemic inflammatory response syndrome were recorded as causes of death in LRBA-deficient patients.

Clinical aspects of patients with LRBA deficiency

A high proportion of patients initially presented with autoimmunity (42%) and chronic diarrhea (27%) (Figure 1). Most patients were diagnosed primarily with common variable

TABLE II. Clinical manifestations of patients with LRBA deficiency

Parameters (no. of evaluated patients)	Results, n (%)
Pneumonia (n = 100 and NK = 9)	49 (49)
Otitis media (n = 100 and NK = 9)	21 (21)
Sinusitis (n = 100 and NK = 9)	24 (24)
Meningitis (n = 100 and NK = 9)	5 (5)
Bronchiectasis (n = 100 and NK = 9)	23 (23)
Abscess (n = 100 and NK = 9)	6 (6)
Osteomyelitis (n = 100 and NK = 9)	1 (1)
Septicemia (n = 100 and NK = 9)	9 (9)
Candidiasis (n = 100 and NK = 9)	10 (10)
Enteropathy (n = 103 and NK = 6)	65 (63)
Arthritis (n = 101 and NK = 8)	18 (18)
Autoimmunity (n = 103 and NK = 6)	84 (82)
Lymphadenopathy (n = 103 and NK = 6)	44 (43)
Splenomegaly (n = 103 and NK = 6)	59 (57)
Hepatomegaly (n = 103 and NK = 6)	41 (40)
Interstitial lung disease (n = 102 and NK = 7)	29 (28)
Granulomatous lesions (n = 102 and NK = 7)	14 (14)
Malignancy (n = 102 and NK = 7)	6 (6)
Allergy and asthma (n = 100 and NK = 9)	14 (14)
Chronic diarrhea (n = 100 and NK = 9)	48 (48)
Clubbing (n = 100 and NK = 9)	19 (19)
Failure to thrive (n = 103 and NK = 6)	38 (37)

NK, Not known.

immunodeficiency (43%) or with autoimmune disorders (28%). **Figure 2** shows the various primary clinical diagnoses of LRBA-deficient patients. The onset of autoimmunity and infection was generally within the first 2 years of life, whereas enteropathy and lymphoproliferative disease occurred later (at age ~4 years). During the course of the disease, autoimmunity, enteropathy, splenomegaly, pneumonia, and chronic diarrhea (82%, 63%, 57%, 49%, and 48%, respectively) were the most common complications in LRBA-deficient patients (**Table II**).

Various autoimmune conditions, including hematological, gastrointestinal, endocrine, neurological, and rheumatologic disorders, were reported in 84 patients (82%). As shown in **Figure 3**, autoimmune hematologic disorders including autoimmune hemolytic anemia and immune thrombocytopenic purpura were the most frequent autoimmune complications (50% and 48%, respectively). Furthermore, about 79% of LRBA-deficient patients presenting with an autoimmune disease developed additional autoimmune disorders. Two, 3, and 4 different types of autoimmune disorders were reported in 27, 25, and 13 LRBA-deficient patients, respectively. Moreover, the coexistence of 5 autoimmune diseases was observed in 1 patient (autoimmune hemolytic anemia, immune thrombocytopenic purpura, vitiligo, celiac disease, and atrophic gastritis). The most concurrent autoimmune disorders were autoimmune hematologic disorders with autoimmune gastrointestinal disorders, reported in 16 patients (17%). Also, gastrointestinal autoimmunity in association with autoimmune endocrine disorders was reported in 8 patients (9%) (see **Figure E2** in this article's Online Repository at www.jaci-inpractice.org). An overlapping phenotype of autoimmunity and enteropathy was observed in 54% of patients. Among patients with lymphoproliferative diseases,

splenomegaly was the most frequent manifestation (57%), followed by lymphadenopathy (43%) and hepatomegaly (40%). Granulomatous lesions (pulmonary, hepatic, splenic, cerebral, and adrenal granulomas) were observed in 14 patients (14%). Furthermore, interstitial lung disease (ILD) was observed in 29 patients (28%), many of which did not have granulomatous changes in their lungs. Malignancies were observed in 6 (6%) patients (lymphoma in 3, nephroblastoma and squamous-cell carcinoma each in 1 patient, and 1 patient with both gastric adenocarcinoma and melanoma).

A delay in diagnosis and treatment was associated with the development of severe complications. Median diagnostic delay among LRBA-deficient patients with malignancy (21.0 years) was higher than in patients without malignancy (5.0 years; $P = .013$). Moreover, diagnostic delay was longer in patients with arthritis (median [IQR], 7.0 [5.3-11.2] vs 3.7 [0.4-8.5]; $P = .028$) and failure to thrive (median [IQR], 8 [4.0-14.0] vs 4 [0.3-8.0]; $P = .047$) than in patients without these complications. In addition, median (IQR) age of onset of immunodeficiency among patients with lymphoproliferative diseases including lymphadenopathy and splenomegaly was higher than among patients without these complications (2.0 [1.0-5.0] vs 1.0 [0.5-2.2], $P = .006$, and 2.0 [0.9-4.0] vs 0.9 [0.4-2.5], $P = .022$, respectively). However, patients with enteropathy (median [IQR], 1.0 [0.5-3.0] vs 2.0 [0.8-7.0]; $P = .052$) and autoimmunity (median [IQR], 1.0 [0.5-3.0] vs 2.0 [1.2-8.5]; $P = .036$) have lower age of onset than do patients without these complications.

Immunological findings of patients with LRBA deficiency

Among 74 LRBA-deficient patients for whom data were available, reduced numbers of CD4⁺ and CD8⁺ T cells were reported in 16 (22%) and 8 (11%) patients, respectively, while 6 patients had abnormalities in both subsets. The number of Treg cells in the peripheral blood was decreased in 21 of 32 patients (66%) (**Table III**). In addition, 29% of patients had reduced frequency of natural killer cells. Analysis of naive/memory (CD45RA/CD45RO) markers showed elevated memory CD4⁺ and CD8⁺ T cells in 52% and 46% of patients, whereas reduced naive CD4⁺ and CD8⁺ T cells were found in 56% and 15% of patients with LRBA deficiency.

Concerning the B-cell compartment, 40 of 75 patients (53%) had low numbers of total B cells. Analysis of different B-cell subsets showed the following: naive B-cell (CD27⁺IgD⁺) counts were increased in 9 (33%) and reduced in 8 (30%) patients, and CD21^{low} B-cell (CD19⁺CD27^{low}CD38^{low}IgM⁺) counts were increased in 7 (78%). Switched memory B-cell (CD19⁺CD27⁺IgM⁺IgD⁻) and plasmablast (CD21^{low}CD38^{low}) counts were reduced in 25 (74%) and 15 (83%) patients, respectively. Finally, 9 of 21 (43%) patients had low transitional B-cell (CD19⁺CD27^{int}CD38⁺⁺IgM⁺⁺) counts and 6 of 21 (29%) patients had increased counts of transitional B cells.

The low levels of serum IgG, IgA, and IgM (according to the age) were observed in 45 (54%), 47 (57%), and 31 (40%) patients with LRBA deficiency, respectively. Reductions in all 3 immunoglobulins (IgG, IgM, and IgA) were reported in 21 (27%) patients. The serum levels of IgG and IgA were significantly lower in patients with pneumonia ($P < .001$ and $P = .001$, respectively) and bronchiectasis ($P < .001$ and $P = .001$,

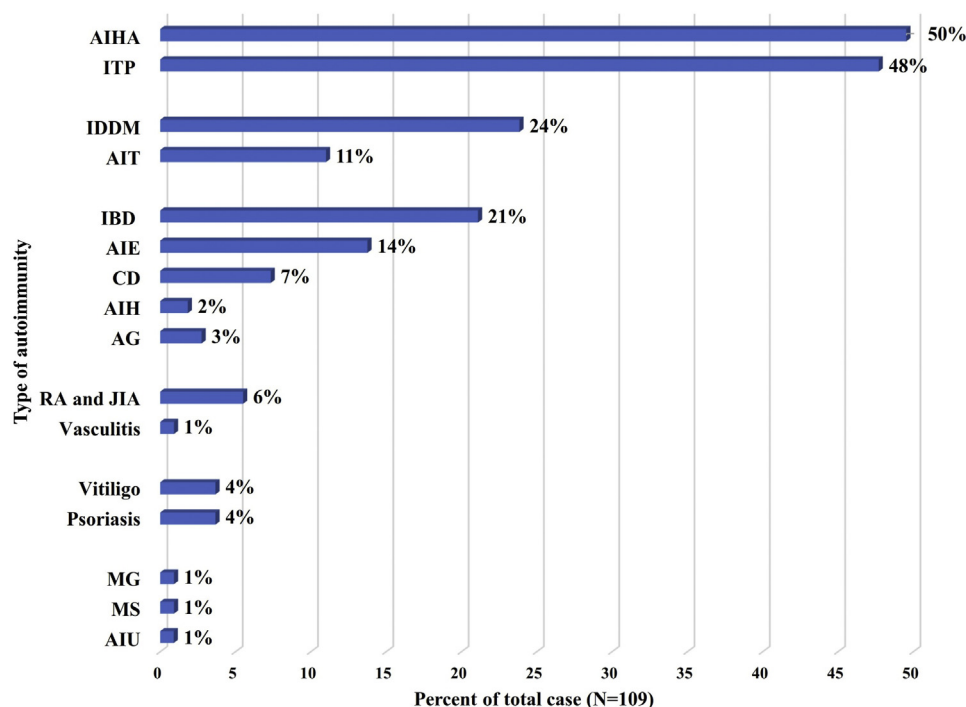


FIGURE 3. The frequency of autoimmune complications in patients with LRBA deficiency. The most frequent autoimmune complications in patients with LRBA deficiency were autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura, insulin-dependent diabetes mellitus, and inflammatory bowel disease. *AG*, Atrophic gastritis; *AIE*, autoimmune enteropathy; *AIH*, autoimmune hepatitis; *AIHA*, autoimmune hemolytic anemia; *AIT*, autoimmune thyroiditis; *AIU*, autoimmune uveitis; *CD*, celiac disease; *IBD*, inflammatory bowel disease; *IDDM*, insulin-dependent diabetes mellitus; *ITP*, idiopathic thrombocytopenic purpura; *JIA*, juvenile idiopathic arthritis; *MG*, myasthenia gravis; *MS*, multiple sclerosis; *RA*, rheumatoid arthritis.

respectively) than in LRBA-deficient patients without these complications.

There was no difference in serum immunoglobulin levels and immune cells when comparing patients with autoimmunity and enteropathy versus patients without these complications. The only statistically significant difference was observed between neutrophil numbers in patients with enteropathy and those without enteropathy (median [IQR], 4000 [2347-6062] vs 2150 [1125-3127], respectively; $P = .020$). Moreover, the serum levels of IgG and IgA was significantly higher in patients with poly-autoimmunity ($P = .023$ and $P = .002$, respectively) than in LRBA-deficient patients without these complications.

Molecular findings of patients with LRBA deficiency

Among the reported patients, 85 different mutations were detected (see [Figure E3](#) in this article's Online Repository at www.jaci-inpractice.org). These variants consisted of 18 missense, 10 splice-site, 36 indel (4 mutations affecting more than 1 exon), and 21 nonsense mutations. Mutations were located throughout the LRBA protein, and there did not appear to be any mutational hotspot.

To investigate the possible effects of different mutations on clinical presentations, we analyzed the relationship of clinical manifestation and laboratory data with type and location of mutations (different domains). Enteropathy was more frequent among patients with nonsense or indel mutations than among patients with missense or splice-site mutations (69% vs 41%, $P = .04$). In other words, 88% of patients with

enteropathy have nonsense or indel mutations. This correlation may suggest that the more “severe” mutations would be more likely to result in enteropathy. In addition, analysis of the location of mutations demonstrated that in patients with enteropathy, 95% of mutations were located in or before the BEACH domain ($P = .04$).

Among the 109 patients with LRBA deficiency, 93 were homozygous and 16 were compound heterozygous. Although protein expression data were not available for all patients, 3 patients (with compound heterozygosity) have been reported with residual LRBA protein expression, including p.L1834P/p.A2535V/p.V2249F, p.S1233F/p.Q2506*, and p.I2824P mutations.^{1,23,52} The median (IQR) for age (11.0 [6.0-19.0] vs 17.5 [12.0-30.7]; $P = .01$), age of onset of immunodeficiency (1.4 [0.6-3.0] vs 7.0 [0.5-11.0]; $P = .05$), and age of onset of autoimmunity (2.0 [0.9-5.0] vs 6.0 [3.0-7.0]; $P = .05$) was lower in homozygous patients than in patients with compound heterozygosity. The frequency of consanguinity, chronic diarrhea, bronchiectasis, and hepatomegaly was higher in homozygous patients than in patients with compound heterozygosity ($P < .001$, $P = .002$, $P = .02$, and $P = .015$, respectively).

The therapeutic approach in patients with LRBA deficiency

High-dose intravenous immunoglobulin therapy was used in 6 patients (6%), whereas low-dose immunoglobulin replacement therapy was commenced in 54 patients (50%). For management

TABLE III. Immunologic profile of patients with LRBA deficiency

Parameters	Results
WBC ($\times 10^3$ cell/ μ L) (n = 46 and NK = 63)	Min = 1,100, max = 21,000, median (IQR) = 6,115 (4,650-8,772)
Absolute lymphocyte counts (cells/ μ L) (n = 55 and NK = 54)	Min = 160, max = 11,750, median (IQR) = 2,494 (1,682-3,700)
Absolute neutrophil counts (cells/ μ L) (n = 41 and NK = 68)	Min = 288, max = 10,080, median (IQR) = 3,652 (1,912-5,967)
CD3 ⁺ T cells (cell/ μ L) (n = 58 and NK = 51)	Min = 103, max = 7760, median (IQR) = 1,706 (1,027-2,312)
CD8 ⁺ T cells (cell/ μ L) (n = 58 and NK = 51)	Min = 40, max = 3590, median (IQR) = 667 (363-1,074)
CD4 ⁺ T cells (cell/ μ L) (n = 58 and NK = 51)	Min = 60, max = 5090, median (IQR) = 676 (368-1,187)
CD4CD45RO, n (%) (n = 23 and NK = 86)	Low = 2 (9%), normal = 9 (39%), high = 12 (52%)
CD4CD45RA, n (%) (n = 25 and NK = 84)	Low = 14 (56%), normal = 10 (40%), high = 1 (4%)
Regulatory T cells, n (%) (n = 32 and NK = 77)	Low = 21 (66%), normal = 11 (34%)
CD19 ⁺ B cells (cell/ μ L) (n = 61 and NK = 48)	Min = 0, max = 2,480, median (IQR) = 164 (60-468)
Transitional B cell*, n (%) (CD19 ⁺ CD27 ^{int} CD38 ⁺⁺ IgM ⁺⁺) (n = 21 and NK = 88)	Low = 9 (43), normal = 6 (29), high = 6 (29)
Naive B cell*, n (%) (CD19 ⁺ CD27 ⁻ IgM ⁺ IgD ⁺) (n = 27 and NK = 82)	Low = 8 (30), normal = 10 (37), high = 9 (33)
Marginal zone B cell*, n (%) (CD19 ⁺ CD27 ⁺ IgM ⁺⁺ IgD ⁺) (n = 6 and NK = 103)	Low = 4 (67), normal = 2 (33)
Switched-memory B cell*, n (%) (CD19 ⁺ CD27 ⁺ IgM ⁻ IgD ⁻) (n = 34 and NK = 75)	Low = 25 (74), normal = 9 (27)
Plasmablast*, n (%) (n = 18 and NK = 91) (CD21 ^{low} CD38 ^{low})	Low = 15 (83), normal = 2 (11), high = 1 (6)
CD21 ^{low} B cell*, n (%) (CD19 ⁺ CD27 ^{low} CD38 ^{low} IgM ⁺) (n = 9 and NK = 100)	Normal = 2 (22), high = 7 (78)
NK cell, n (%) (n = 59 and NK = 50)	Low = 17 (29), normal = 41 (70), high = 1 (2)
IgG (mg/dL) (n = 71 and NK = 38)	Min = 0, max = 2200, median (IQR) = 500 (310-896)
IgA (mg/dL) (n = 65 and NK = 44)	Min = 0, max = 440, median (IQR) = 40 (6-69)
IgM (mg/dL) (n = 66 and NK = 43)	Min = 0, max = 2000, median (IQR) = 50 (24-136)
IgE (IU/mL) (n = 27 and NK = 82)	Min = 0, max = 80, median (IQR) = 1 (0-4)
Specific antibody response (%) (n = 31 and NK = 78)	17 (55)

NK, Not known; NK cell, natural killer cell; WBC, white blood cell.

The median is shown (with 25th and 75th percentiles).

*% of B cells.

of autoimmune and inflammatory diseases, 59 (54%) patients received systemic corticosteroids and 44 (40%) received steroids in combination with immunosuppressive drugs including cyclosporine, mycophenolate mofetil, sirolimus, tacrolimus, sulfasalazine, or azathioprine. Thirty-two patients (29%) were treated with infliximab, basiliximab, rituximab, or abatacept. Surgical procedures were performed on 13 patients (splenectomy in 10 patients, and thymectomy, mastoidectomy, and tonsillectomy in 1 patient each). Furthermore, subtotal gastrectomy was performed in 1 patient with gastric adenocarcinoma. Two patients were administered growth hormone replacement, and 1 was treated with G-CSF therapy. Finally, because of the severity of complications, hematopoietic stem cell transplantation (HSCT) was performed in 18 patients (17%). Five patients died within 1 to 3 months post-HSCT. The mean follow-up for the remaining survived cases (72%) was 26 months.

DISCUSSION

LRBA deficiency is characterized by a broad spectrum of clinical manifestations including immune dysregulation, autoimmune disorders, organomegaly, chronic diarrhea, and recurrent infections alone or in combination. In the present study, we systematically reviewed the clinical, immunological, and molecular features of LRBA-deficient patients. Our results showed that the median age at onset of symptoms was 1.8 years, indicating

that LRBA-deficient patients tend to develop their symptoms within the first years of their life.^{1,2,10}

Our review clearly shows that patients experienced autoimmune manifestations in the first 2 years of life, before presenting with other clinical conditions including allergy, enteropathy, and lymphoproliferative diseases. Approximately 42% of the patients initially presented with autoimmunity, and in 28% of the cases, the clinical diagnosis was solely autoimmunity without immunodeficiency. In line with our observations, Burns et al¹⁵ showed that mutations in *LRBA* may initially present as an autoimmune disorder without impaired antibody production. Moreover, a tendency toward polyautoimmunity was observed, because nearly 77% of all LRBA-deficient patients present with more than 1 autoimmune manifestation. Altogether, these data indicate that LRBA-deficient patients are more likely to present with an autoimmune disorder as the initial clinical manifestation; therefore, LRBA deficiency should be included in the monogenic list of autoimmune diseases and should be routinely screened for in patients with these conditions.

Eighty percent of the patients had normal T-cell counts. However, 66% had diminished numbers of Treg cells. Most of the patients had reduced numbers of switched-memory B cells and plasmablasts, whereas CD21^{low} B-cell counts were increased in 78% of patients. Therefore, this review confirms that LRBA-deficient patients present with B-cell count abnormalities, mainly of switched-memory B cells and plasmablasts.¹² Moreover, the

increased numbers of CD21^{low} B cells and the reduced numbers of Treg cells observed in these patients correlate with the high frequency of inflammatory and autoimmune disease manifesting in these patients.³⁷

Clinical features and complications were heterogeneous, even within families in which more than 1 family member harbored the same mutation. We did not observe genotype-phenotype correlation in LRBA deficiency (except for severe mutations and enteropathy), suggesting the likely existence of unidentified modifier genes or environmental factors that influence or determine the phenotypic outcomes observed in these patients. Previously, Gamez-Diaz et al¹ and Alkhairy et al¹² along with our previous study⁴² highlighted that no obvious genotype-phenotype correlation has been identified in LRBA-deficient patients. Among reported cases, 93 were homozygous, and 16 were compound heterozygous, with mutations distributed throughout the LRBA protein. The ability to predict complications (what about enteropathy?) would aid clinical management, but the identification of genetic defects in these immune disorders did not provide a more precise categorization of LRBA deficiency. Most of the mutations in LRBA abolished protein expression.^{11,12} The transcribed mRNA or translated protein resulting from the mutations might be unstable and, as a result, may be degraded rapidly or lead to truncated, nonfunctioning protein. Our study did not find any relationship between clinical and laboratory findings with mutation type and location, except for enteropathy. Usually, nonsense and indel mutations have greater deleterious effects on the protein than do missense and splicing mutations. In addition, the closer the pathogenic mutation is to the 5' end of the gene, the greater the probability that the protein expression is abolished. Three patients have been reported with residual LRBA protein expression. Although residual LRBA protein expression may reduce disease severity, there is insufficient data at this time to support this claim.

Recently, abatacept (CTLA4-Ig) has been introduced as a promising therapy for improving the clinical symptoms in patients with LRBA deficiency.⁵² Abatacept is designed to modulate the T-cell costimulatory signal mediated through the CD28-CD80/86 pathway. Blockade of this costimulatory axis with abatacept appears to help restore Treg-cell functions⁵³ and can be used to treat certain autoimmune and inflammatory diseases.⁵⁴ The report by Lo et al⁵² showed for the first time that the use of abatacept in patients with LRBA deficiency resulted in the improvement of ILD, autoimmune complications, and functional antibody responses. After the success of that study, abatacept was used in 3 LRBA-deficient patients with enteropathy, 2 of them showing amelioration and 1 with additional amelioration to his arthritis and uveitis.⁵² Al Sukaiti et al²² reported the efficacy of abatacept in an LRBA-deficient patient with a defect in class switching, who presented with polyautoimmunity and ILD. As mentioned, in addition to autoimmunity, abatacept was found to be effective in ameliorating pulmonary symptoms. Several studies showed that initiation of abatacept therapy alleviated the lymphocytic ILD and led to good respiratory improvement.^{16,22,39,47,52} However, in a cohort of patients with LRBA deficiency, fungal infections possibly related to immunosuppressive therapy were reported.^{1,16} Moreover, in a case report by Eren Akarcan et al,⁴⁷ 1 patient developed fungal esophagitis and pneumonia a few days after the initiation of abatacept therapy, leading to interruption of treatment. However, so far, analysis of long-term effects, safety, and cost-effectiveness of abatacept therapy has not been reported; thus,

further studies are needed to clarify the benefits and side effects of this therapy.

Eighteen LRBA-deficient patients underwent HSCT due to the severity of clinical manifestations including lymphoproliferation, autoimmunity, enteropathy, pancytopenia, and/or infections unresponsive to treatment. The outcome of HSCT in patients indicates that the average of follow-up in the survived patients was 26 months. Therefore, it seems that HSCT is a promising treatment for LRBA-deficient patients with severe and complicated clinical manifestations who do not respond to conventional therapies.

Acknowledgment

We thank the Clinical Research Development Center of Imam Ali-Karaj Hospital.

REFERENCES

- Gamez-Diaz L, August D, Stepensky P, Revel-Vilk S, Seidel MG, Noriko M, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. *J Allergy Clin Immunol* 2016;137:223-30.
- Azizi G, Abolhassani H, Mahdavi SA, Chavoshzadeh Z, Eshghi P, Yazdani R, et al. Clinical, immunologic, molecular analyses and outcomes of Iranian patients with LRBA deficiency: a longitudinal study. *Pediatr Allergy Immunol* 2017;28:478-84.
- Abolhassani H, Aghamohammadi A, Fang M, Rezaei N, Jiang C, Liu X, et al. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. *Genet Med* 2019;21:243-51.
- Abolhassani H, Chou J, Bainter W, Platt C, Tavassoli M, Momen T, et al. Clinical, immunological and genetic spectrum of 696 patients with combined immunodeficiency. *J Allergy Clin Immunol* 2017;141:1450-8.
- Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J Clin Immunol* 2018;38:96-128.
- Wang J. Lipopolysaccharide-responsive beige-like anchor (LRBA), a novel regulator of human immune disorders. *Austin J Clin Immunol* 2014;1:1004.
- Alroqi FJ, Charbonnier LM, Baris S, Kiykim A, Chou J, Platt CD, et al. Exaggerated follicular helper T-cell responses in patients with LRBA deficiency caused by failure of CTLA4-mediated regulation. *J Allergy Clin Immunol* 2018;141:1050-9.
- Azizi G, Mirshafiey A, Abolhassani H, Yazdani R, Ghanavatinejad A, Noorbakhsh F, et al. The imbalance of circulating T helper subsets and regulatory T cells in patients with LRBA deficiency: correlation with disease severity. *J Cell Physiol* 2018;233:8767-77.
- Lo B, Fritz JM, Su HC, Uzel G, Jordan MB, Lenardo MJ. CHAI and LATAIE: new genetic diseases of CTLA-4 checkpoint insufficiency. *Blood* 2016;128:1037-42.
- Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am J Hum Genet* 2012;90:986-1001.
- Alangari A, Alsultan A, Adly N, Massaad MJ, Kiani IS, Aljebreen A, et al. LPS-responsive beige-like anchor (LRBA) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency. *J Allergy Clin Immunol* 2012;130:481-8.
- Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, Chavoshzadeh Z, et al. Spectrum of phenotypes associated with mutations in LRBA. *J Clin Immunol* 2016;36:33-45.
- Bakhtiar S, Gamez-Diaz L, Jarisch A, Soerensen J, Grimbacher B, Belohradsky B, et al. Treatment of infantile inflammatory bowel disease and autoimmunity by allogeneic stem cell transplantation in LPS-responsive beige-like anchor deficiency. *Front Immunol* 2017;8:e52.
- Bakhtiar S, Ruemmele F, Charbit-Henrion F, Levy E, Rieux-Laucat F, Cerf-Bensussan N, et al. Atypical manifestation of LPS-responsive beige-like anchor deficiency syndrome as an autoimmune endocrine disorder without enteropathy and immunodeficiency. *Front Pediatr* 2016;4:e98.
- Burns SO, Zenner HL, Plagnol V, Curtis J, Mok K, Eisenhut M, et al. LRBA gene deletion in a patient presenting with autoimmunity without hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;130:1428-32.

16. Kostel Bal S, Haskoğlu S, Serwas NK, Islamoglu C, Aytekin C, Kendirli T, et al. Multiple presentations of LRBA deficiency: a single-center experience. *J Clin Immunol* 2017;37:790-800.
17. Seidel MG, Hirschmugl T, Gamez-Diaz L, Schwinger W, Serwas N, Deutschmann A, et al. Long-term remission after allogeneic hematopoietic stem cell transplantation in LPS-responsive beige-like anchor (LRBA) deficiency. *J Allergy Clin Immunol* 2015;135:1384-90.
18. Tesi B, Priftakis P, Lindgren F, Chiang SC, Kartalis N, Lofstedt A, et al. Successful hematopoietic stem cell transplantation in a patient with LPS-responsive beige-like anchor (LRBA) gene mutation. *J Clin Immunol* 2016;36:480-9.
19. Massaad MJ, Zhou J, Tsuchimoto D, Chou J, Jabara H, Janssen E, et al. Deficiency of base excision repair enzyme NEIL3 drives increased predisposition to autoimmunity. *J Clin Invest* 2016;126:4219-36.
20. Revel-Vilk S, Fischer U, Keller B, Nabhani S, Gamez-Diaz L, Rensing-Ehl A, et al. Autoimmune lymphoproliferative syndrome-like disease in patients with LRBA mutation. *Clin Immunol* 2015;159:84-92.
21. Johnson MB, De Franco E. Recursively inherited LRBA mutations cause autoimmunity presenting as neonatal diabetes. *Diabetes* 2017;66:2316-22.
22. Al Sukaiti N, AbdelRahman K, AlShekaili J, Al Orami S, Al Sinani A, Al Rahbi N, et al. Agammaglobulinemia despite terminal B-cell differentiation in a patient with a novel LRBA mutation. *Clin Transl Immunol* 2017;6:e144.
23. Serwas NK, Kansu A, Santos-Valente E, Kuloglu Z, Demir A, Yaman A, et al. Atypical manifestation of LRBA deficiency with predominant IBD-like phenotype. *Inflamm Bowel Dis* 2015;21:40-7.
24. Ye Z, Zhou Y, Huang Y, Wang Y, Lu J, Tang Z, et al. Phenotype and management of infantile-onset inflammatory bowel disease: experience from a tertiary care center in China. *Inflamm Bowel Dis* 2017;23:2154-64.
25. Besnard C, Levy E, Aladjidi N, Stolzenberg MC, Magerus-Chatinet A, Alibeu O, et al. Pediatric-onset Evans syndrome: heterogeneous presentation and high frequency of monogenic disorders including LRBA and CTLA4 mutations. *Clin Immunol* 2018;188:52-7.
26. Levy E, Stolzenberg MC, Bruneau J, Breton S, Neven B, Sauvion S, et al. LRBA deficiency with autoimmunity and early onset chronic erosive polyarthritis. *Clin Immunol* 2016;168:88-93.
27. Schreiner F, Plamper M, Dueker G, Schoenberger S, Gamez-Diaz L, Grimbacher B, et al. Infancy-onset T1DM, short stature, and severe immunodysregulation in two siblings with a homozygous LRBA mutation. *J Clin Endocrinol Metab* 2016;101:898-904.
28. Maffucci P, Filion CA, Boisson B, Itan Y, Shang L, Casanova JL, et al. Genetic diagnosis using whole exome sequencing in common variable immunodeficiency. *Front Immunol* 2016;7:e220.
29. Charbonnier LM, Janssen E, Chou J, Ohsumi TK, Keles S, Hsu JT, et al. Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. *J Allergy Clin Immunol* 2015;135:217-27.
30. Sari S, Dogu F, Hwa V, Haskoğlu S, Dauber A, Rosenfeld R, et al. A successful HSCT in a girl with novel LRBA mutation with refractory celiac disease. *J Clin Immunol* 2016;36:8-11.
31. Bratanic N, Kovac J, Pohar K, Trebusak Podkrajsek K, Ihan A, Battelino T, et al. Multifocal gastric adenocarcinoma in a patient with LRBA deficiency. *Orphanet J Rare Dis* 2017;12:1-8.
32. Shokri S, Nabavi M, Hirschmugl T, Aghamohammadi A, Arshi S, Bermanian MH, et al. LPS-responsive beige-like anchor gene mutation associated with possible bronchiolitis obliterans organizing pneumonia associated with hypogammaglobulinemia and normal IgM phenotype and low number of B cells. *Acta Med Iran* 2016;54:620-3.
33. Seidel MG, Bohm K, Dogu F, Worth A, Thrasher A, Florkin B, et al. Treatment of severe forms of LPS-responsive beige-like anchor protein deficiency with allogeneic hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2018;141:770-5.
34. Siklar Z, de Franco E, Johnson MB, Flanagan SE, Ellard S, Ceylaner S, et al. Monogenic diabetes not caused by mutations in Mody genes: a very heterogeneous group of diabetes. *Exp Clin Endocrinol Diabetes* 2018;126:612-8.
35. Vairo FP, Boczek NJ, Cousin MA, Kaiwar C, Blackburn PR, Conboy E, et al. The prevalence of diseases caused by lysosome-related genes in a cohort of undiagnosed patients. *Mol Genet Metab Rep* 2017;13:46-51.
36. Fang M, Abolhassani H, Lim CK, Zhang J, Hammarstrom L. Next generation sequencing data analysis in primary immunodeficiency disorders—future directions. *J Clin Immunol* 2016;36:68-75.
37. Azizi G, Abolhassani H, Yazdani R, Mohammadikhajehdehi S, Parvaneh N, Negahdari B, et al. New therapeutic approach by sirolimus for enteropathy treatment in patients with LRBA deficiency. *Eur Ann Allergy Clin Immunol* 2017;49:235-9.
38. Al-Mayouf SM, Naji H, Alismail K, Alazami AM, Sheikh F, Conca W, et al. Evolving spectrum of LRBA deficiency-associated chronic arthritis: is there a causative role in juvenile idiopathic arthritis? *Clin Exp Rheumatol* 2017;35:327-9.
39. Shamriz O, Shadur B, NaserEddin A, Zaidman I, Simanovsky N, Elpeleg O, et al. Respiratory manifestations in LPS-responsive beige-like anchor (LRBA) protein-deficient patients. *Eur J Pediatr* 2018;177:1163-72.
40. Güven A, Johnson M, De Franco E. A diabetic infant with homozygous LRBA mutation: the youngest patient reported. *J Clin Res Pediatr Endocrinol* 2016;8:16-7.
41. Azizi G, Abolhassani H, Zaki-Dizaji M, Habibi S, Mohammadi H, Shaghagh M, et al. Polyautoimmunity in patients with LPS-responsive beige-like anchor (LRBA) deficiency. *Immunol Invest* 2018;47:457-67.
42. Azizi G, Abolhassani H, Habibi S, Rahamooz T, Mohammadi H, Jafarnejad-Ansariha F, et al. Two faces of LRBA deficiency in siblings: hypogammaglobulinemia and normal immunoglobulin levels. *J Investig Allergol Clin Immunol* 2018;28:48-50.
43. Sharapova SO, Haapaniemi E, Sakovich IS, Rojas J, Gamez-Diaz L, Mareika YE, et al. Novel LRBA mutation and possible germinal mosaicism in a Slavic family. *J Clin Immunol* 2018;38:471-4.
44. De Bruyne M, Bogaert DJ, Venken K, Van den Bossche L, Bonroy C, Roels L, et al. A novel LPS-responsive beige-like anchor protein (LRBA) mutation presents with normal cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and overactive TH17 immunity. *J Allergy Clin Immunol* 2018;142:1968-71.
45. Rajpurkar M, Buck S, Lafferty J, Wakeling E, Ravindranath Y, Savasan S. Acquired pure red cell aplasia and acquired amegakaryocytic thrombocytopenia associated with clonal expansion of T-cell large granular lymphocytes in a patient with lipopolysaccharide-responsive beige-like anchor (LRBA) protein deficiency [published online ahead of print September 4, 2018]. *J Pediatr Hematol Oncol*. <https://doi.org/10.1097/MPH.0000000000001292>.
46. Soler-Palacin P, Garcia-Prat M, Martin-Nalda A, Franco-Jarava C, Riviere JG, Plaja A, et al. LRBA deficiency in a patient with a novel homozygous mutation due to chromosome 4 segmental uniparental isodisomy. *Front Immunol* 2018;9:e2397.
47. Eren Akarcan S, Eder Karaca N, Aksu G, Aykut A, Yilmaz Karapinar D, Cetin F, et al. Two male siblings with a novel LRBA mutation presenting with different findings of IPEX syndrome. *JMM Case Rep* 2018;5:e005167.
48. Li R, Zheng Y, Li Y, Zhang R, Wang F, Yang D, et al. Common variable immunodeficiency with genetic defects identified by whole exome sequencing. *Biomed Res Int* 2018;2018:3724630.
49. Fernandez KS, Antony R, Kumar A. Patients with “ALPS-like phenotype” diagnosed with immune dysregulation due to LRBA deficiency. *Pediatr Blood Cancer* 2019;66:e27558.
50. Tafaroji J, Salami F, Mahdaviyani S, Shirvani A, Chavoshzadeh Z. Gastrointestinal manifestations of Iranian patients with LRBA deficiency. *Immunol Genet J* 2018;1:93-102.
51. Mozdarani H, Kiaee F, Fekrvand S, Azizi G, Yazdani R, Zaki-Dizaji M, et al. G2-lymphocyte chromosomal radiosensitivity in patients with LPS responsive beige-like anchor protein (LRBA) deficiency. *Int J Radiat Biol* 2019;95:680-90.
52. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. AUTO-IMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science* 2015;349:436-40.
53. Lee S, Moon JS, Lee CR, Kim HE, Baek SM, Hwang S, et al. Abatacept alleviates severe autoimmune symptoms in a patient carrying a de novo variant in CTLA-4. *J Allergy Clin Immunol* 2016;137:327-30.
54. Linsley PS, Greenbaum CJ, Speake C, Long SA, Dufort MJ. B lymphocyte alterations accompany abatacept resistance in new-onset type 1 diabetes. *JCI Insight* 2019;4:126136.

ONLINE REPOSITORY

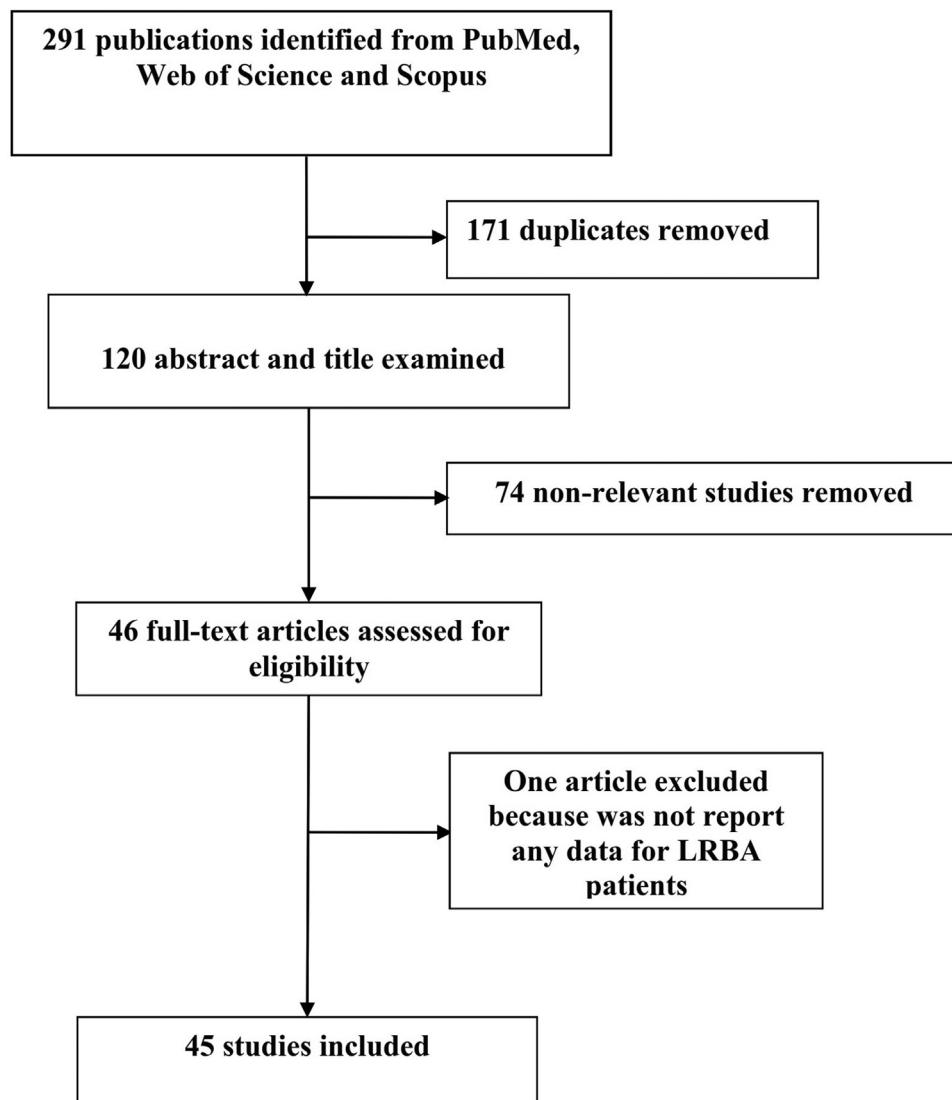


FIGURE E1. Flowchart of the systematic search and study selection process.

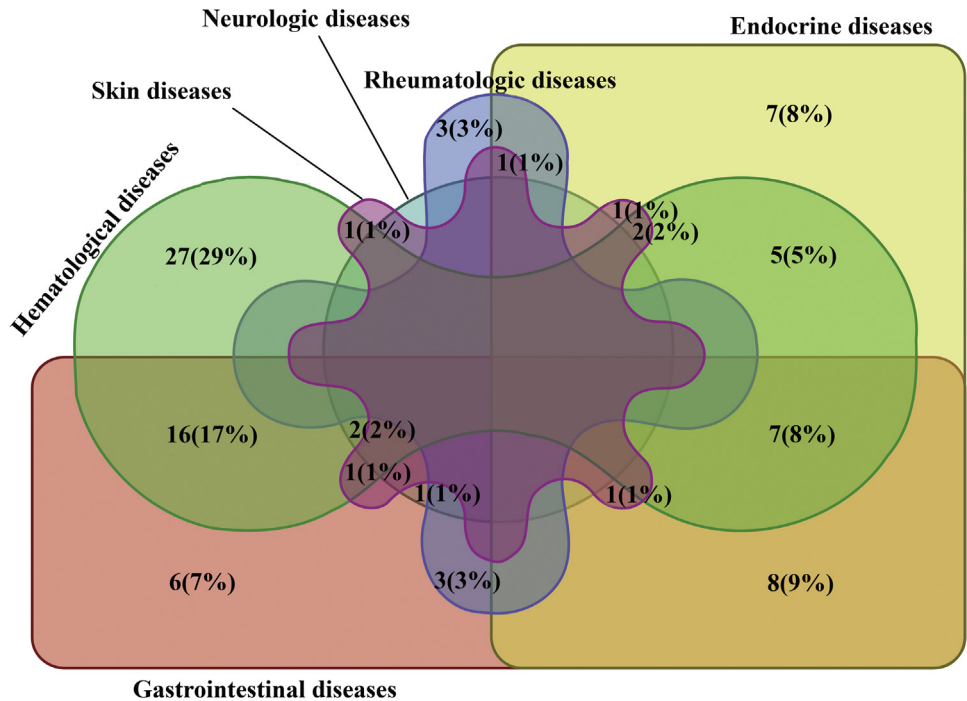


FIGURE E2. Venn diagram showing polyautoimmunity in LRBA-deficient patients. LRBA-deficient patients have a tendency to develop different autoimmune disorders. Autoimmune hematologic disorders were the most common concurrent autoimmune diseases with autoimmune gastrointestinal disorders in these patients.

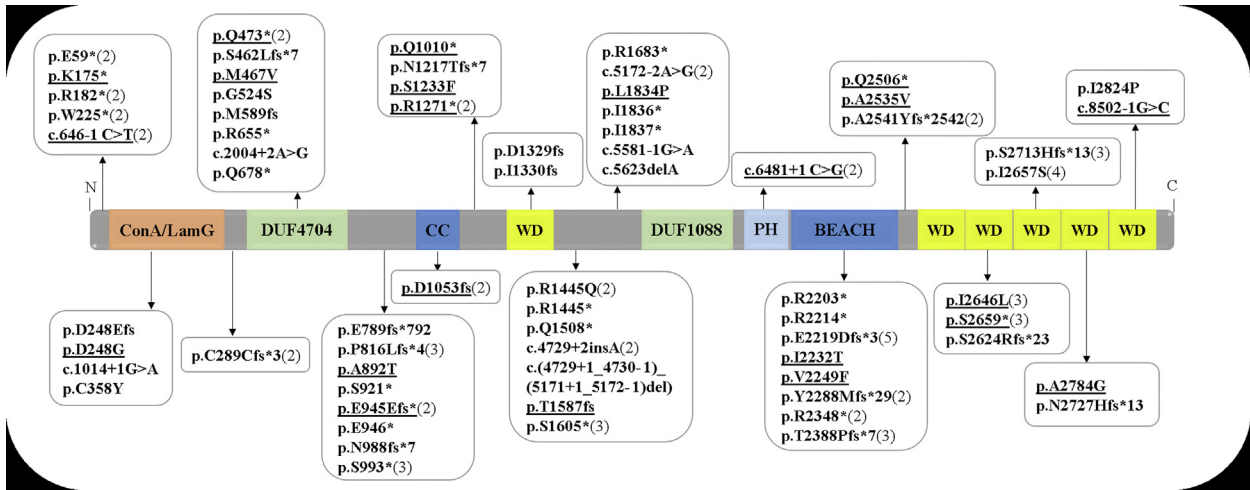


FIGURE E3. Graphic illustration of LRBA protein domains, indicating locations of published genetic mutations in LRBA deficiency patients. Mutations in LRBA occurred throughout the length of the gene, without hotspots. Amino acids are designated by their single letter code. An asterisk (*) indicates a premature stop codon. The 4 reported large deletions/duplications (exons 1-2 and exons 1-30 deletion, exon 41 deletions, and exons 49-53 duplication) are not displayed in the figure. The compound heterozygous mutations have been indicated with underlining. The number in the parentheses in the figure and caption shows the number of reported cases with that mutation. *BEACH*, Beige/BEACH domain; *CC*, coiled coil; *Con A*, concanavalin A-like lectin/glucanase domain; *DUF*, the domain of unknown function; *Lam G*, laminin G domain; *PH*, PH domain associated with beige/BEACH; *WD*, WD-40 repeat.

TABLE E1. Summary of characteristics of the studies included in this systematic review

Reference	Author, Year	No. of patients	Sex (F/M)	Clinical diagnosis	Type of article
E1	Gamez-Diaz et al, 2016	22	10/12	CVID = 10, autoimmunity = 3, ALPS = 4, asymptomatic = 1, recurrent infections = 1, IPEX like = 2, granulomatous disease = 1	Original
E2	Azizi et al, 2017	17	9/8	CVID = 12, CSD = 2, autoimmunity = 1, recurrent infections = 1, asymptomatic = 1	Case series
E3	Lopez-Herrera et al, 2012	5	2/3	CVID = 3, ND = 2	Original
E4	Alangari et al, 2012	5	4/1	CVID = 2, CID = 3	Original
E5	Alkhairy et al, 2016	31	17/14	CVID = 12, CID = 3, IPEX like = 1, ALPS = 4, asymptomatic = 1, ND = 10	Review
E6	Bakhtiar et al, 2017	1	0/1	Autoimmunity	Case report
E7	Bakhtiar et al, 2016	3	2/1	CVID = 1, ND = 2	Original
E8	Burns et al, 2012	1	1/0	Autoimmunity	Letter to Editor
E9	Kostel Bal et al, 2017	7	4/3	Autoimmunity = 4, ALPS = 2, asymptomatic = 1	Original
E10	Tesi et al, 2016	1	0/1	CVID	Case report
E11	Massaad et al, 2016	3	1/2	Asymptomatic	Original
E12	Revel-Vilk et al, 2015	4	0/4	ALPS = 3, asymptomatic = 1	Original
E13	Johnson and De Franco, 2017	10	7/3	Autoimmunity	Case series
E14	Al Sukaiti et al, 2017	1	0/1	Autoimmunity	Case report
E15	Serwas et al, 2015	1	1/0	ND	Case report
E16	Lo et al, 2015	9	2/7	CVID = 5, autoimmunity = 4	Original
E17	Ye et al, 2017	1	1/0	Autoimmunity	Original
E18	Besnard et al, 2018	1	ND	Autoimmunity	Original
E19	Levy et al, 2016	2	0/2	Autoimmunity	Case report
E20	Schreiner et al, 2016	2	1/1	CVID = 1, autoimmunity = 1	Case series
E21	Maffucci et al, 2016	2	1/1	CVID = 2	Original
E22	Charbonnier et al, 2015	6	4/2	IPEX like = 1, CVID = 3, CID = 1, autoimmunity = 1	Original
E23	Sari et al, 2016	1	1/0	CVID	Case report
E24	Bratanic et al, 2017	1	0/1	CVID	Case report
E25	Shokri et al, 2016	1	0/1	CVID	Case report
E26	Seidel et al, 2018	12	5/4/ND = 3	CVID = 4, autoimmunity = 1, IPEX like = 1, ALPS = 1, ND = 5	Letter to Editor
E27	Siklar et al, 2018	2	1/1	Autoimmunity = 2	Original
E28	Vairo et al, 2017	1	0/1	CVID	Case series
E29	Fang et al, 2016	8	3/5	CVID = 7, CSD = 1	Original
E30	Azizi et al, 2017	4	3/1	CVID = 4	Case series
E31	Al-Mayouf et al, 2017	1	0/1	CVID	Case report
E32	Seidel et al, 2015	2	2/0	CVID = 1, ALPS = 1	Letter to Editor
E33	Shamriz et al, 2018	10	2/8	Asymptomatic = 2, ALPS = 2, autoimmunity = 4, ND = 2	Original
E34	Güven et al, 2016	1	1/0	Autoimmunity	Case report
E35	Sharapova et al, 2018	2	1/1	Autoimmunity = 1, ND = 1	Letter to Editor
E36	Azizi et al, 2018	4	2/2	CVID = 2, autoimmunity = 1, asymptomatic = 1	Practitioner's Corner
E37	Azizi et al, 2018	9	4/5	CVID = 7, CSD = 1, autoimmunity = 1	Original
E38	De Bruyne et al, 2018	1	1/0	Autoimmunity	Letter to Editor

(continued)

TABLE E1. (Continued)

Reference	Author, Year	No. of patients	Sex (F/M)	Clinical diagnosis	Type of article
E39	Rajpurkar et al, 2018	1	0/1	CVID	Case report
E40	Soler-Palacin et al, 2018	1	1/0	Autoimmunity	Case report
E41	Eren Akarcan et al, 2018	2	0/2	IPEX like = 2	Case series
E42	Li et al, 2018	3	3/0	CVID = 3	Case series
E43	Fernandez et al, 2019	1	0/1	ALPS = 1	Letter to Editor
E44	Tafaroji et al, 2018	1	1/0	Recurrent infections = 1	Case report
E45	Mozdarani et al, 2019	11	6/5	CVID = 7, HlgM = 1, recurrent infections = 2	Original

ALPS, Autoimmune lymphoproliferative syndrome; CVID, combined immunodeficiency; CVID, common variable immunodeficiency; F, female; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked; M, male; ND, not defined; PAD, primary antibody deficiency.

REFERENCES

- E1. Gamez-Diaz L, August D, Stepensky P, Revel-Vilk S, Seidel MG, Noriko M, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. *J Allergy Clin Immunol* 2016;137:223-30.
- E2. Azizi G, Abolhassani H, Mahdavian SA, Chavoshzadeh Z, Eshghi P, Yazdani R, et al. Clinical, immunologic, molecular analyses and outcomes of Iranian patients with LRBA deficiency: a longitudinal study. *Pediatr Allergy Immunol* 2017;28:478-84.
- E3. Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am J Hum Genet* 2012;90:986-1001.
- E4. Alangari A, Alsultan A, Adly N, Massaad MJ, Kiani IS, Aljebreen A, et al. LPS-responsive beige-like anchor (LRBA) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency. *J Allergy Clin Immunol* 2012;130:481-8.
- E5. Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, Chavoshzadeh Z, et al. Spectrum of phenotypes associated with mutations in LRBA. *J Clin Immunol* 2016;36:33-45.
- E6. Bakhtiar S, Gamez-Diaz L, Jarisch A, Soerensen J, Grimbacher B, Belohradsky B, et al. Treatment of infantile inflammatory bowel disease and autoimmunity by allogeneic stem cell transplantation in LPS-responsive beige-like anchor deficiency. *Front Immunol* 2017;8:e52.
- E7. Bakhtiar S, Ruemmele F, Charbit-Henrion F, Levy E, Rieux-Laucat F, Cerf-Bensussan N, et al. Atypical manifestation of LPS-responsive beige-like anchor deficiency syndrome as an autoimmune endocrine disorder without enteropathy and immunodeficiency. *Front Pediatr* 2016;4:e98.
- E8. Burns SO, Zenner HL, Plagnol V, Curtis J, Mok K, Eisenhut M, et al. LRBA gene deletion in a patient presenting with autoimmunity without hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;130:1428-32.
- E9. Kostel Bal S, Haskologlu S, Serwas NK, Islamoglu C, Aytekin C, Kendirli T, et al. Multiple presentations of LRBA deficiency: a single-center experience. *J Clin Immunol* 2017;37:790-800.
- E10. Tesi B, Priftakis P, Lindgren F, Chiang SC, Kartalis N, Lofstedt A, et al. Successful hematopoietic stem cell transplantation in a patient with LPS-responsive beige-like anchor (LRBA) gene mutation. *J Clin Immunol* 2016;36:480-9.
- E11. Massaad MJ, Zhou J, Tsuchimoto D, Chou J, Jabara H, Janssen E, et al. Deficiency of base excision repair enzyme NEIL3 drives increased predisposition to autoimmunity. *J Clin Invest* 2016;126:4219-36.
- E12. Revel-Vilk S, Fischer U, Keller B, Nabhani S, Gamez-Diaz L, Rensing-Ehl A, et al. Autoimmune lymphoproliferative syndrome-like disease in patients with LRBA mutation. *Clin Immunol* 2015;159:84-92.
- E13. Johnson MB, De Franco E. Recessively inherited LRBA mutations cause autoimmunity presenting as neonatal diabetes. *Diabetes* 2017;66:2316-22.
- E14. Al Sukaiti N, Abdelrahman K, AlShekaili J, Al Oraihi S, Al Sinani A, Al Rahbi N, et al. Agammaglobulinemia despite terminal B-cell differentiation in a patient with a novel LRBA mutation. *Clin Transl Immunol* 2017;6:e144.
- E15. Serwas NK, Kansu A, Santos-Valente E, Kuloglu Z, Demir A, Yaman A, et al. Atypical manifestation of LRBA deficiency with predominant IBD-like phenotype. *Inflamm Bowel Dis* 2015;21:40-7.
- E16. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. AUTO-IMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science* 2015;349:436-40.
- E17. Ye Z, Zhou Y, Huang Y, Wang Y, Lu J, Tang Z, et al. Phenotype and management of infantile-onset inflammatory bowel disease: experience from a tertiary care center in China. *Inflamm Bowel Dis* 2017;23:2154-64.
- E18. Besnard C, Levy E, Aladjidi N, Stolzenberg MC, Magerus-Chatinet A, Alibeu O, et al. Pediatric-onset Evans syndrome: heterogeneous presentation and high frequency of monogenic disorders including LRBA and CTLA4 mutations. *Clin Immunol* 2018;188:52-7.
- E19. Levy E, Stolzenberg MC, Bruneau J, Breton S, Neven B, Sauvion S, et al. LRBA deficiency with autoimmunity and early onset chronic erosive polyarthritis. *Clin Immunol* 2016;168:88-93.
- E20. Schreiner F, Plamper M, Dueker G, Schoenberger S, Gamez-Diaz L, Grimbacher B, et al. Infancy-onset T1DM, short stature, and severe immunodysregulation in two siblings with a homozygous LRBA mutation. *J Clin Endocrinol Metab* 2016;101:898-904.
- E21. Maffucci P, Filion CA, Boisson B, Itan Y, Shang L, Casanova JL, et al. Genetic diagnosis using whole exome sequencing in common variable immunodeficiency. *Front Immunol* 2016;7:e220.
- E22. Charbonnier LM, Janssen E, Chou J, Ohsumi TK, Keles S, Hsu JT, et al. Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy,

- enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. *J Allergy Clin Immunol* 2015;135:217-27.
- E23. Sari S, Dogu F, Hwa V, Haskologlu S, Dauber A, Rosenfeld R, et al. A successful HSCT in a girl with novel LRBA mutation with refractory celiac disease. *J Clin Immunol* 2016;36:8-11.
- E24. Bratanic N, Kovac J, Pohar K, Trebusak Podkrajsek K, Ihan A, Battelino T, et al. Multifocal gastric adenocarcinoma in a patient with LRBA deficiency. *Orphanet J Rare Dis* 2017;12:1-8.
- E25. Shokri S, Nabavi M, Hirschmugl T, Aghamohammadi A, Arshi S, Bemanian MH, et al. LPS-responsive beige-like anchor gene mutation associated with possible bronchiolitis obliterans organizing pneumonia associated with hypogammaglobulinemia and normal IgM phenotype and low number of B cells. *Acta Med Iran* 2016;54:620-3.
- E26. Seidel MG, Bohm K, Dogu F, Worth A, Thrasher A, Florin B, et al. Treatment of severe forms of LPS-responsive beige-like anchor protein deficiency with allogeneic hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2018;141:770-5.
- E27. Siklar Z, de Franco E, Johnson MB, Flanagan SE, Ellard S, Ceylaner S, et al. Monogenic diabetes not caused by mutations in Mody genes: a very heterogeneous group of diabetes. *Exp Clin Endocrinol Diabetes* 2018;126:612-8.
- E28. Vairo FP, Boczek NJ, Cousin MA, Kaiwar C, Blackburn PR, Conboy E, et al. The prevalence of diseases caused by lysosome-related genes in a cohort of undiagnosed patients. *Mol Genet Metab Rep* 2017;13:46-51.
- E29. Fang M, Abolhassani H, Lim CK, Zhang J, Hammarstrom L. Next generation sequencing data analysis in primary immunodeficiency disorders—future directions. *J Clin Immunol* 2016;36:68-75.
- E30. Azizi G, Abolhassani H, Yazdani R, Mohammadikhajehdehi S, Parvaneh N, Negahdari B, et al. New therapeutic approach by sirolimus for enteropathy treatment in patients with LRBA deficiency. *Eur Ann Allergy Clin Immunol* 2017;49:235-9.
- E31. Al-Mayouf SM, Naji H, Alismail K, Alazami AM, Sheikh F, Conca W, et al. Evolving spectrum of LRBA deficiency-associated chronic arthritis: is there a causative role in juvenile idiopathic arthritis? *Clin Exp Rheumatol* 2017;35:327-9.
- E32. Seidel MG, Hirschmugl T, Gamez-Diaz L, Schwinger W, Serwas N, Deutschmann A, et al. Long-term remission after allogeneic hematopoietic stem cell transplantation in LPS-responsive beige-like anchor (LRBA) deficiency. *J Allergy Clin Immunol* 2015;135:1384-90.
- E33. Shamriz O, Shadur B, NaserEddin A, Zaidman I, Simanovsky N, Elpeleg O, et al. Respiratory manifestations in LPS-responsive beige-like anchor (LRBA) protein-deficient patients. *Eur J Pediatr* 2018;177:1163-72.
- E34. Güven A, Jonhson M, De Franco E. A diabetic infant with homozygous LRBA mutation: the youngest patient reported. *J Clin Res Pediatr Endocrinol* 2016;8:16-7.
- E35. Sharapova SO, Haapaniemi E, Sakovich IS, Rojas J, Gamez-Diaz L, Mareika YE, et al. Novel LRBA mutation and possible germinal mosaicism in a Slavic family. *J Clin Immunol* 2018;38:471-4.
- E36. Azizi G, Abolhassani H, Habibi S, Rahamooz T, Mohammadi H, Jafarnejhad-Ansariha F, et al. Two faces of LRBA deficiency in siblings: hypogammaglobulinemia and normal immunoglobulin levels. *J Investig Allergol Clin Immunol* 2018;28:48-50.
- E37. Azizi G, Abolhassani H, Zaki-Dizaji M, Habibi S, Mohammadi H, Shaghghi M, et al. Polyautoimmunity in patients with LPS-responsive beige-like anchor (LRBA) deficiency. *Immunol Invest* 2018;47:457-67.
- E38. De Bruyne M, Bogaert DJ, Venken K, Van den Bossche L, Bonroy C, Roels L, et al. A novel LPS-responsive beige-like anchor protein (LRBA) mutation presents with normal cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and overactive TH17 immunity. *J Allergy Clin Immunol* 2018;142:1968-71.
- E39. Rajpurkar M, Buck S, Lafferty J, Wakeling E, Ravindranath Y, Savasan S. Acquired pure red cell aplasia and acquired amegakaryocytic thrombocytopenia associated with clonal expansion of T-cell large granular lymphocytes in a patient with lipopolysaccharide-responsive beige-like anchor (LRBA) protein deficiency [published online ahead of print September 4, 2018]. *J Pediatr Hematol Oncol*. <https://doi.org/10.1097/MPH.0000000000001292>.
- E40. Soler-Palacin P, Garcia-Prat M, Martin-Nalda A, Franco-Jarava C, Riviere JG, Plaja A, et al. LRBA deficiency in a patient with a novel homozygous mutation due to chromosome 4 segmental uniparental isodisomy. *Front Immunol* 2018;9:e2397.
- E41. Eren Akarcan S, Edeer Karaca N, Aksu G, Aykut A, Yilmaz Karapinar D, Cetin F, et al. Two male siblings with a novel LRBA mutation presenting with different findings of IPEX syndrome. *JMM Case Rep* 2018;5:e005167.
- E42. Li R, Zheng Y, Li Y, Zhang R, Wang F, Yang D, et al. Common variable immunodeficiency with genetic defects identified by whole exome sequencing. *Biomed Res Int* 2018;2018:3724630.
- E43. Fernandez KS, Antony R, Kumar A. Patients with “ALPS-like phenotype” diagnosed with immune dysregulation due to LRBA deficiency. *Pediatr Blood Cancer* 2019;66:e27558.
- E44. Tafaroji J, Salami F, Mahdavian S, Shirvani A, Chavoshzadeh Z. Gastrointestinal manifestations of Iranian patients with LRBA deficiency. *Immunol Genet J* 2018;1:93-102.
- E45. Mozdarani H, Kiaee F, Fekrvand S, Azizi G, Yazdani R, Zaki-Dizaji M, et al. G2-lymphocyte chromosomal radiosensitivity in patients with LPS responsive beige-like anchor protein (LRBA) deficiency. *Int J Radiat Biol* 2019;95:680-90.