# Case Report: A Novel Homozygous LRBA Mutation in a Child with Episodes of Recurrent Infection and Hypogammaglobulinemia

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**Case Report: A Novel Homozygous *LRBA* Mutation in a Child with Episodes of Recurrent Infection and Hypogammaglobulinemia**

**Running title: Novel *LRBA* Mutation**

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**Key Clinical Message**

LPS-responsive beige-like anchor protein (LRBA) deficiency, classified as a disease of immune dysregulation due to regulatory T (Treg)-cell, is caused by autosomal recessive mutations in the *LRBA* gene. Since its first discovery in patients with Common Variable Immunodeficiency (CVID) in 2012, several other mutations in *LRBA* have been reported. Here, we introduce a 9-year-old female with childhood-onset arthritis and immunodeficiency, in whom we found a novel mutation in*LRBA* .

KEYWORDS

*LRBA* mutation; Primary Immunodeficiency Diseases; Common Variable Immunodeficiency; LPS-responsive beige-like anchor protein; Hypogammaglobulinemia; Child

**Main body**

## INTRODUCTION

One of the most common primary immunodeficiencies (PIDs) in children is Common Variable Immunodeficiency (CVID), which is a polygenic and heterogenous disorder characterized by recurrent infections, hypogammaglobulinemia (markedly reduced immunoglobulin (Ig)G serum concentration in combination with low levels of IgA and/or IgM), autoimmunity, poor antibody response to immunizations, and absence of any other defined immunodeficient state, which makes it a diagnosis of exclusion [1-4]. Only 5-25% of individuals with CVID have an affected relative, with most of them showing an autosomal dominant (AD) pattern of inheritance [5]. Biallelic mutations in several genes involved in B cell stimulation have been identified and shown to be associated with autosomal recessive (AR) hypogammaglobulinemia (*CD19* [6], *MS4A1*[7], *CD81* [8], *CR2*[9], and *TNFRSF13C* [10]). In 2012, Lopez-Herrera et al. discovered mutations in the *LRBA* gene associated with the clinical presentation of CVID for the first time, which is known as LPS-responsive beige-like anchor protein (LRBA) deficiency since [1]. According to the International Union of Immunological Societies, LRBA deficiency is classified as a disease of immune dysregulation due to regulatory T (Treg)-cell defects since 2018 [11].

LRBA is a cytosolic protein in the BEACH-WD40 protein family, which is expressed in several cell types and tissues [1,12,13]. LRBA participates in multiple cellular processes including cytoskeleton assembly, signal transduction, vesicular trafficking, transcriptional regulation, chromatin dynamics, and apoptosis, and has a role in maintaining intracellular stores of CTLA4 (cytotoxic T-lymphocyte-associated protein 4) in T-cells [12,14]. However, still little is known about the definitive role of LRBA in cellular function and human biology, which remains to be clarified[1,12,13].

Lopez-Herrera et al. managed to find four distinct homozygous mutations in the *LRBA* gene in five symptomatic individuals clinically diagnosed with CVID [1]. Since then, several novel mutations in the *LRBA* gene have been identified and shown in many case reports of PID as well as in other disorders without hypogammaglobulinemia [15-22]. Here, we report a novel mutation in *LRBA* in a patient with childhood-onset immunodeficiency presenting with CVID-like symptoms.

## CASE DESCRIPTION

Herein, we introduce a 9-year-old female patient who started to have symptoms at the age of 5, with arthritis being her first presenting condition. She was hospitalized with the impression of pneumonia and unclassified rheumatic disease at 7 years old due to cough, polyarthritis, and splenomegaly. Her laboratory tests (including CBC-DIFF, ESR, and FANA) and bone marrow aspiration were normal. Her bone scan suggested a systemic disease with multi-articular involvement. She was discharged with ibuprofen and methotrexate (MTX). She also received some courses of intra-articular corticosteroids.

At the age of 8, she developed pneumonia and was hospitalized again. Pulmonary consolidation with pleural effusion was reported on her chest X-ray at the time. On her chest HRCT scan, mediastinal and hilar lymphadenopathy was reported on the right side with a slight left-side deviation of the trachea and marked extrinsic compression upon the right middle lobe (RML) bronchus. RML collapse was noted with cylindrical bronchiectasis. Collapse-consolidation in the posterior and medial basal right lower lobe (RLL) was present. Some scattered bilateral ill-defined pulmonary nodules–mostly pleural-based–were seen.

The patient's parents were 1$^{st}$ cousins and other than the mother having a history of a single spontaneous abortion, the parents had no history of any kind of disease. Given the patient's condition and the severity of her presenting symptoms, the appropriate laboratory tests including the flow cytometric study of immunological CD markers were ordered. The results of these tests are represented in Table 1 in detail.

The results represent an immunodeficient state characterized by hypogammaglobulinemia with a normal number of circulating B cell lymphocytes. Also, a normal percentage of leukocyte adhesion markers was reported, and the total number of T cell lymphocytes as well as CD4+ and CD8+ T cells were in the normal range. This is suggestive of an immunodeficiency disorder affecting most prominently the function of B cells. Other findings in this patient include a low hemoglobulin level, thrombocytopenia, positive stool calprotectin

indicative of inflammation of the bowels, and a slight increase in liver enzymes.

Based on these results, appropriate treatment with a monthly dose of Intravenous Immunoglobulin (IVIG), and prophylactic antibiotic was begun and after one month, she had an IgG level in the normal range in combination with a negative CRP. On her follow-up chest CT scan performed after 4 months, multiple bilateral pulmonary nodules (innumerous) with a maximum diameter of 25 mm in both lungs were seen.

Nine months after the patient's last hospitalization with pneumonia, she was hospitalized again due to fever and chills, and a productive cough that had lasted for 2 weeks. On physical examination, she had splenomegaly and clubbing of the fingers. She was admitted to the COVID PICU with a positive COVID-19 PCR. On her Chest HRCT scan, patchy ground glass opacities with crazy pattern in both lungs was shown, which could be due to bronchopneumonia (suggestive of COVID-19 infection). She received vancomycin, meropenem, interferon beta 1-alpha, remdesivir, dexamethasone, IVIG, ganciclovir, ASA, and voriconazole. She was discharged from the COVID ward after 14 days with the treatment plan of monthly IVIG and a prophylactic dose of cefixime.

## DIAGNOSTIC ASSESSMENT

According to the episodes of recurrent infection, hypogammaglobulinemia (low levels of IgG in combination with low levels of IgA and IgM levels), poor response to immunizations, absence of profound T cell immunodeficiency and any other defined immunodeficiency state, CVID was suggested as the possible diagnosis. In order to find the gene responsible, whole exome sequencing (WES) was done approximately 6 months after initiating the treatment with IVIG (Table 2).

Two novel mutations in two different gene loci (*TCF3* and*LRBA* ) were reported as possible candidates responsible for the patient's condition. The missense variants reported in both of these genes were absent in population databases (ExAC, 1000G, and our local databases) and were not reported previously for pathogenicity. Predictions of computational tools were conflicting for both genes. Mutation Taster, CADD, and SIFT supported the deleterious effect of the heterozygous missense variant in the *TCF3* gene on the gene or gene product(s), while PolyPhen predicted it as benign. For the homozygous missense variant in the *LRBA* gene, Mutation Taster and CADD supported the deleterious effect of this variant on the gene or gene product(s), while SIFT and PolyPhen predicted it as tolerated or benign. Based on ACMG guidelines, both of these variants can be classified as Variant of Uncertain Significance (VUS) .

The timetable is depicted in Figure 1.

## DISCUSSION

A mutation in the *LRBA* gene that encodes LRBA protein causes an autosomal recessive monogenic disorder named LRBA deficiency. The individuals that Lopez-Herrera et al. investigated, presented variable symptoms and phenotypes including recurrent infections, hypogammaglobulinemia, lymphadenopathy and hepatosplenomegaly, lymphoid follicular hyperplasia, granulomatous infiltration of the brain, chronic lung disease with bronchiectasis and obstruction of the small airways, recurrent chronic diarrhea (IBD-like syndrome), autoimmunity (idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), hypothyroidism, myasthenia gravis, and autoimmune enteropathy), allergic and inflammatory diseases (such as allergic dermatitis, asthma, and arthritis) and growth retardation (failure to thrive). They demonstrated that individuals with homozygous *LRBA* mutations could not produce any LRBA. They had severe defects in B cell development and activation and in plasmablast formation, reduced counts of switched-memory B cells, impaired immunoglobulin secretion, low proliferative responses, increased susceptibility to apoptosis, and severe defects in autophagy. All of these characteristics are associated with a clinical phenotype of early-onset hypogammaglobulinemia (reduced levels of at least two immunoglobulin isotypes (IgM, IgG, or IgA)) accompanied by autoimmunity in homozygous individuals. All heterozygous individuals in this study were healthy. Accordingly, they proposed that LRBA has unanticipated functions in B cells, which are essential for normal development and humoral immune responses [1].

Several novel mutations in the *LRBA* gene have been identified and reported in many cases of PID as

well as in other disorders without hypogammaglobulinemia, since Lope-Herrera's study [15]. Liphaus et al. introduced a new *LRBA* mutation that was associated with Juvenile Systemic Lupus Erythematous (JSLE) [16]. In another study, LRBA deficiency was reported in a patient with Juvenile Idiopathic Arthritis (JIA) and immune dysregulation[17]. Charbonnier et al. identified a loss of function mutation in *LRBA* in a patient who presented with Immune dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX)-like syndrome, and Severe $T_R$ cell deficiency. They proposed that LRBA deficiency results in depressed suppressive function and increased apoptosis of $T_R$ cells [18]. Akarcan et al. also reported a novel LRBA mutation in two male siblings with IPEX syndrome [19]. Another study performed by Taylan et al. in 2020 revealed LRBA deficiency in a patient with end-stage renal disease [20]. Some other studies reported novel mutations in *LRBA* associated with Type 1 diabetes mellitus (T1DM) and immune dysregulation [21,22].

A study in 2015 showed LRBA's interaction with the cytoplasmic tail of CTLA4 that protects and prevents CTLA4 from being degraded by the lysosomes [14]. Therefore, a deficit in LRBA leads to a deficit in CTLA4. In addition, an autosomal dominant disorder caused by a heterozygote mutation in the *CTLA4* gene called CTLA4 Haploinsufficiency with Autoimmune Infiltration (CHAI) has similar symptoms with LRBA deficiency, but LRBA deficiency causes lower levels of CTLA4, earlier onset of the disease and more severity than CHAI[23]. Different clinical and immunological characteristics have been found in more than 70 patients with LRBA deficiency, including hypogammaglobulinemia, autoimmune disorders, chronic diarrhea, recurrent infection, and organomegaly[1,13,15].

Pulmonary manifestations of CTLA4 haploinsufficiency and LRBA deficiency have been compared. LRBA deficiency has been shown to be associated with more severe forms of pulmonary disease in terms of pulmonary symptoms, radiological findings and pulmonary function test (PFT)s. Cough was the most common respiratory symptom and more common in LRBA deficiency. Also, abnormalities in PFT and CT scan findings (mediastinal lymphadenopathy, bronchiectasis, and ground-glass opacification) were more frequent in LRBA deficiency [24].

In patients with LRBA deficiency, a history of infectious complications (with pneumonia and respiratory tract infections being the most common), autoimmunity (mostly autoimmune cytopenia) with early-onset hypogammaglobulinemia, and enteropathy must be considered. The mean age at which the first symptoms present and the time until diagnosis in LRBA deficiency cases is variable. In this study, we introduced a patient with the first manifestation of the disease and final diagnosis at the age of 5 and 9 years old, respectively. This patient presented with arthritis at first and then she developed pneumonia at the age of 8 with pulmonary consolidation on her chest X-ray at the time. In laboratory tests, low levels of Hb and also low levels of IgG, IgM, and IgA were found, which is suggestive of CVID. WES was ordered and DNA was extracted from whole blood. Analysis of exome data showed *TCF3*and *LRBA* as possible candidates that could explain the clinical history mentioned above.

The *TCF3* gene has been reported to be associated with agammaglobulinemia in previous studies, whereas the *LRBA* gene was shown to be related to CVID with autoimmunity. Based on the clinical and paraclinical data in this patient, which is most compatible with CVID, the *LRBA* variant seems to be the responsible gene causing symptoms in this patient. However, further analysis including parental genotyping of the variant detected in *TCF3* is essential in order to make a definitive conclusion. The presence of this variant in the asymptomatic parent(s) strongly supports the benign nature of the variant while confirming a *de novo* nature is in favor of its pathogenicity, which should be followed by further investigation.

Regarding the presence of hypogammaglobulinemia despite the normal number of total circulating B cells (CD19+), further analysis of memory B cells with flow cytometry could elaborate on whether hypogammaglobulinemia in this patient is due to a defect in isotype-switching (reduction of class-switched CD27+IgM-IgD- memory B cells) of memory B cells or not.

**Limitations**

For this patient, only genes that were associated with reported clinical features were analyzed. Therefore, this study cannot exclude the possibility of mutations in genes not related to the given phenotype. Also,

the reported variants were only seen in exome data. Therefore, validation of detected variants by another molecular method, such as PCR-Sanger sequencing, is recommended. It is of value to note that the *TCF3* gene has a pseudogene ( *TCF3P1* ) with a high degree of sequence similarity. Therefore, it is very important to validate this variant by another molecular method before any clinical decision-making.

It should be kept in mind that there are still many limitations in using NGS itself and also in the interpretation of the obtained data. Among them is the possibility of pathologic variants present in the genome that are not detected by the technique. Also, Large duplications and deletions, balanced translocations, inversions, ploidy changes, uniparental disomies, and methylation alterations cannot be detected by this method.

**Conclusion**

Joint involvement and recurrent infections with hypogammaglobulinemia are variable in LRBA deficiency, hence it should always be kept in mind as a differential diagnosis for a patient with these conditions. In this case, arthritis was the first presenting condition followed by pneumonia, and according to the episodes of recurrent infection, hypogammaglobulinemia, and poor response to immunizations, CVID was suggested as the possible diagnosis. Fecal calprotectin level was increased during bacterial infection and as disease severity increased. This being considered, fecal calprotectin level may be a useful marker for application in children with LRBA deficiency during infectious diarrhea. In this patient, we found two novel mutations in two different gene loci ( *TCF3* and *LRBA* ) which were both classified as *Variant of Uncertain Significance (VUS)* . Validation of these detected variants by another molecular method such as PCR-Sanger sequencing is recommended. Also, more effort should be made to resolve VUS classification as pathogenic or benign. This can be achieved by investigating and functional analysis of these variants in a sufficient number of families. Based on this analysis, a more accurate classification of variants could be reached.

## AUTHOR CONTRIBUTIONS

**Elahe Radmehr:** Data collection and interpretation; writing – original draft; writing – review and editing; visualization, investigation. **Izat Mohammad Khawajah:** Writing – original draft; writing – review and editing, investigation. **Sima Shamshiri Khamene:** Writing – original draft; visualization.**Maryam Heydar Azadzadeh:** Resources. **Maryam Asarehzadegan Dezfouli:** Resources. **Seyed Alireza Mahdaviani:**Conceptualization; Supervision.


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## CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Institutional review board approval for a case report is not required at our institution. To keep ethical principles and protect the subject's rights, the name of the patient was not pointed out in the paper.

## CONSENT STATEMENT

Written informed consent was obtained from the patient's family for participation in this study and for the publication of any potentially identifiable data included in this article.

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**Tables**

**TABLE 1** Result of Laboratory Tests

| Test | Result | Unit | Reference Range | |
|---|---|---|---|---|
| WBC | 5.66 | 10^3/micL | | |
| RBC | 3.92 | 10^6/micL | | |
| Hemoglobin | 10 | 10^3/micL | | |
| Platelets | 159 | 10^3/micL | | |
| ESR 1 hrs | 38 | mm/hr | 1-20 | High |
| CRP | 32.4 | mg/L | Up to 6 | High |
| FANA | <1:100 | | Negative <1:100 | |
| Anti-CCP | 0.81 | RU/mL | Negative <12 | |
| RF (latex) | Negative | | | |
| Stool Calprotectin | Positive | micg/gr stool | | |

| Test | Result | Unit | Reference Range | |
|---|---|---|---|---|
| IgG | <17 | mg/dL | 600-1300 | Low |
| IgA | <3 | mg/dL | 51-297 | Low |
| IgM | 8 | mg/dL | 40-150 | Low |
| IgE | 1 | IU/mL | up to 115 | |
| Diphtera Ab IgG | 0.031 | IU/mL | | booster vaccination recommende |
| Tetanus Ab IgG | 0.237 | IU/mL | | To be Controlled after 2-4 years |
| Anti-pneumococcus IgG | 7.6 | mg/L | 3.3 - 270 | |
| Total lymphocyte count | 960 | cell/micL | | |
| CD3 | 75.5 | % | 50-90 | |
| CD4 | 64.8 | % | 20-65 | |
| CD8 | 7.54 | % | 5-40 | |
| CD4:CD8 | 8.59 | | 1-3 | High |
| CD19 | 5.89 | % | 3-40 | |
| Total Granulocyte Count | 4290 | cell/micL | | |
| CD18 | 99.8 | % | 90-100 | |
| CD11a | 99.7 | % | 60-100 | |
| Serum protein electrophoresis | | | | |
| Albumin | 2.7 | g/dL | | Low |
| Alpha 1 globulin | 0.7 | g/dL | | High |
| Alpha 2 globulin | 1.2 | g/dL | | High |
| Beta 1 and 2 globulin | Normal | | | |
| Gamma globulin | 0 | g/dL | | |
| Lymphocyte transformation test (LTT) | | | | |
| PHA | 3.8 | | | |
| Candida | 1 | | | |
| BCG | 1 | | | |

**TABLE 2** Whole Exome Sequencing (WES) results

| Gene/Transcript | Variant Location | Variant | Chromosome Position (GRCh37) | Zygosity | Related Phenotypes | OMIM number | Inheritance Pattern | Variant Classification |
|---|---|---|---|---|---|---|---|---|
| *TCF3* ENST00000262965.5 NM_003200 | Exon 13 | c.1069G>C p.V357L | Chr19: 1,620,991 | Het | Agammaglobulinemia-8 | 616941 | AD | VUS |
| *LRBA* ENST00000357115.3 NM_006726 | Exon 53 | c.7742T>A p.M2581K | Chr4: 151,231,521 | Hom | Common variable immunodeficiency-8 with autoimmunity | 614700 | AR | VUS |

VUS Variant of Insignificant Importance, Het Heterozygous, Hom Homozygous, AD Autosomal Dominant, AR Autosomal Recessive

**Figure Legends**

FIGURE 1 Timeline of clinical events and treatment of the patient.