# Lipopolysaccharide Responsive Beige-Like Anchor (LRBA) Protein Deficiency in a 12-year-old Female with Failure to Thrive

Kyndra Liburd, MD, Christopher Chang, MD, PhD
Division of Pediatric Immunology and Allergy, Joe DiMaggio Children's Hospital, Hollywood, FL

## Background

- LRBA protein upregulates the function of CTLA4.
- CTLA4 is an immune system checkpoint which regulates T cell activation.
- LRBA deficiency leads to failure of the immune system checkpoint, leading to aberrant lymphoproliferation, autoimmunity, immunodeficiency, and recurrent infections.

## Case Report

- The patient is a 12-year-old previously healthy female with weight loss, growth deceleration, and cytopenia over a one-year period.
- Two months prior to diagnosis, she developed an upper respiratory infection manifested by cough, chest pain, night sweats, and intermittent fevers.
- She was found to have splenomegaly on exam.
- CT scan showed multiple nodular lesions (Figure 1).
- Lung biopsy was consistent with granulomatous and lymphocytic interstitial lung disease (GLILD).
- Laboratory work up revealed hypogammaglobinemia and low absolute CD3+, CD4+, CD8+, CD16+/56+ and CD19+ cells (Table 1).
- WBC count was 3.5, NK cell function and lymphocyte mitogen stimulation tests were within normal limits. LDH was 456 (ref range 100-325 units/L).
- Pulmonary function tests (PFTs) showed restrictive lung disease with decreased diffusion capacity.
- Gene sequencing revealed two variants of unknown significance in the *LRBA* gene not inherited maternally (Figure 2).
- **LRBA expression was decreased (Figure 3).**
- She has a 17-year old sister with failure to thrive at age 13 which resolved spontaneously, who has asymptomatic leukopenia and shares the same genetic variants.
- A 15-year old sister without the genetic variants is healthy.

## Imaging

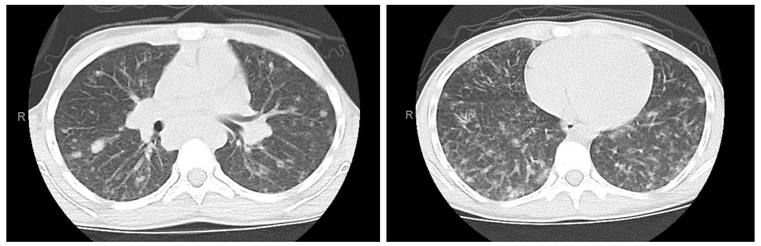


Figure 1: HRCT showing reticulonodular interstitial infiltrates with multiple superimposed pulmonary nodules

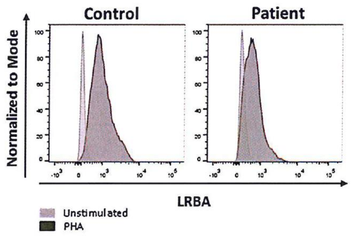
## Table 1: Immune Evaluation

| | Result | Reference Range |
|---|---|---|
| IgG | 136 | 647-1496 mg/dL |
| IgA | <8 | 53-237 mg/dL |
| IgM | <6 | 47-175 mg/dL |
| IgE | <4 | <200 IU/mL |
| CD3 | 628 | 850-3200 cells/μL |
| CD4 | 427 | 400-2100 cells/μL |
| CD8 | 175 | 300-1300 cells/μL |
| CD19 | 77 | 120-740 cells/μL |
| NK | 52 | 92-1200 cells/μL |
| B cell panel | Decreased absolute B cell number and % of isotype switched memory B cells | |
| Tetanus IgG Ab | <0.10 | Protective > 0.15 IU/mL |
| Diphtheria IgG Ab | <0.01 | Protective = or > 0.01 IU/mL |
| Varicella Zoster IgG Ab | <10 | Protective > 135 |
| Rubella IgG Ab | 25 | Protective > 10 IU/mL |
| *S. pneumoniae* 23 serotypes IgG Ab | All <0.3 | Protective = or >1.3 mcg/mL |

## Genetic Evaluation

| Gene | Variant | Zygosity | Variant Classification |
|---|---|---|---|
| LRBA | c.4263T>G (p.Ser1421Arg) | heterozygous | Uncertain Significance |
| LRBA | c.7291A>G (p.Lys2431Glu) | heterozygous | Uncertain Significance |
| The following genes were evaluated for sequence changes and exonic deletions/duplications: BLNK, BTK, CD27, CD79A, CD79B, CR2, CTLA4, DCLRE1C, GATA2, ICOS, IGLL1, IL21, IL21R, JAK3, LRBA, MOGS, NFKB2, PIK3CD, PIK3R1, PLCG2, PRKCD, RAC2, RAG1, SH2D1A, STAT3, STXBP2, TNFRSF13B, TNFRSF13C, TNFSF12, TRNT1, XIAP<br>Results are negative unless otherwise indicated | | | |

Figure 2: Variant of Uncertain Significance detected in the *LRBA* gene by Invitae PIDD panel, confirmed by Exome Sequencing




| Sample | MFI | Ratio |
|---|---|---|
| Travel control + PHA | 997 | 7.6 |
| Travel control unstimulated | 130 | |
| Patient CVID 1880-01 + PHA | 625 | 3.2 |
| Patient CVID 1880-01 unstimulated | 193 | |

MFI: Mean Fluorescence Intensity
Ratio: MFI of PHA-stimulated / MFI of unstimulated cells

Figure 3: LRBA functional testing showed decreased expression of LRBA compared to control

## Discussion and Conclusion

- This newly identified variant in *LRBA* is likely pathogenic, leading to low expression of LRBA protein.
- The patient was treated with IVIG and Rituximab.
- GLILD resolved completely, with almost complete normalization of DLCO.
- She experienced catch up growth and is free of infections while on monthly IVIG replacement.
- It is possible that this variant may lead to varying phenotypes depending on the level of deficiency.
- A CTLA-4 trans-endocytosis assay can further assess the functionality of LRBA.

## References

1. Warnatz, K., et al. Severe deficiency of switched memory B cells in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease, 2018.
2. Routes, JM., et al,. Use of combination chemotherapy for treatment of GLILD in Patients with CVID. J Clin Immunol. 2013 Jan; 33(1): 30–39.
3. Lopez-Herrera, G., et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am. J. Hum. Genet. 2012. 90, 986-1001.
4. Alkhairy, OK., et al. Spectrum of Phenotypes Associated with Mutations in LRBA. J Clin Immunol. 2016 Jan; 36(1): 33-45.