Scholar: Pilot and Validation Studies ISSN: 2689-7644
Volume 3 Issue 2 Pages: 1 – 3 DOI:10.32778/SPVS.71366.2022.27

Heterozygous deletion of LRBA associated with humoral immunodeficiency, chronic diarrhea and autoimmune thyroiditis

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Keywords: LRBA, Lipopolysaccharide-responsive and beige-like anchor protein, common variable immunodeficiency, antibody deficiency, heterozygous deletion, hypogammaglobulinemia

Article History: Date received: 06/06/2022 Date revised: 12/15/2022 Date accepted: 12/19/2022
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Introduction:

Lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency is an autosomal recessive primary immunodeficiency characterized by common variable immunodeficiency (CVID)-like presentation with hypogammaglobulinemia and autoimmunity.[1,2] Deficiencies in the LRBA protein impairs expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) resulting in immune dysregulation.[3] Clinical manifestations of this disorder are variable but commonly include recurrent infections, chronic diarrhea, organomegaly, and autoimmune dysfunction.[4-8] Although various mutations have been reported, we describe a patient with novel compound heterozygote mutations in the LRBA gene associated with humoral deficiency as well as autoimmune thyroiditis and nonspecific chronic diarrhea.

Case description:

We present a 68-year-old male with a past medical history of asthma, chronic rhinitis, and recurrent episodes of sinopulmonary infections. The patient had an extensive history of recurrent sinusitis and numerous episodes of pneumonia starting in childhood as well as chronic lymphadenopathy and diarrhea. At the age of 18, the patient was diagnosed with a humoral immunodeficiency after his immunoglobulin serology revealed low IgG (718 mg/dL; normal: 747 – 1470 mg/dL), IgA (64 mg/dL; normal: 79 – 396 mg/dL), IgM (50 mg/dL; normal: 56 – 352 mg/dL) and had inadequate response to vaccinations in addition to his recurrent infections. Lymphocyte subsets and proliferation studies were unremarkable (It is important to note these studies, antibody responses and lymphocyte studies, were performed over 50 years ago and were only reported in immunologist consultation letters. The original studies have not been located). Further evaluation with colonoscopy and lymph node biopsy was unremarkable with nonspecific changes. His autoimmune history was significant for Hashimoto thyroiditis. Initially the patient was trialed on prophylactic antibiotics without significant improvement. He began receiving intramuscular immunoglobulin replacement therapy at the time of his diagnosis and is presently maintained on intravenous immunoglobulin therapy every three weeks.

He had significant clinical improvement after starting immunoglobulin replacement therapy with only one hospitalization at the age of 45 for scrotal cellulitis. A genetic evaluation was performed using the primary immunodeficiency panel through Invitae Corp. Next-generation sequencing was performed for full-gene sequencing and deletion/duplication analysis. A pathogenic mutation (LRBA c.6352del, p.Ile2118Serfs*46) and a variant of uncertain significance (LRBA c.6315A>T, p.Lys2117Asn) were identified in the LRBA gene. Both variations were located on the same chromosome in exon 41. Another heterozygous pathogenic deletion in exon 1 was identified in the HPS3 gene. This gene is associated with the autosomal recessive Hermansky Pudlak syndrome 3; however, the patient did not express any features of this disease.

Discussion

LRBA deficient patients present with a broad spectrum of clinical phenotypes.[8] The major clinical manifestations include immune dysfunction, organomegaly, recurrent infections and hypogammaglobulinemia.[6] In addition, most LRBA deficient patients present with early-onset chronic diarrhea and develop one or more autoimmune disorders.[1,7] We describe a patient presenting with features of humoral immunodeficiency akin to CVID in clinical severity, including recurrent infections as well as nonspecific chronic diarrhea and autoimmune thyroiditis with two mutations in the LRBA gene. Despite the patient's history of chronic diarrhea, there was no histologic evidence to suggest an autoimmune etiology. Autoimmune thyroiditis has been reported in cases of LRBA deficiency, however our patient has no other associated autoimmune conditions.[5,7,8]

Conclusion:

The LRBA gene is located on locus 4q31.3 and is expressed in many tissues, albeit highly in lymphocytes. Various mutations have been reported in LRBA without clear genotype-phenotype correlations. Our patient presented with a novel frameshift (predicted deleterious) and missense (variant of undetermined significance) mutation in exon 41 of the LRBA gene. This pathogenic frameshift mutation may lead to a truncated protein that is unstable and rapidly degraded; however, no further studies were performed to show a decreased cellular expression of LRBA in this patient. The complete role of the LRBA protein is not fully understood, but it has known functions in vesicle trafficking; whereas LRBA deficiency leads to decreased turnover of CTLA-4 on T regulatory cells resulting in immune dysfunction.

The genotype-phenotype correlation for LRBA deficiency has yet to be completely elucidated. This novel mutation and clinical presentation may expand the genotype-phenotype relationship between LRBA mutations and clinical disease.

Author Contributions:

All authors provided substantial contributions to conception and design, acquisition of data, or analysis, interpretation of data, manuscript preparation and review.

Funding Sources: None.

Potential Conflicts of Interest Disclosures:

The authors disclose that there were no conflicts of interest or financial support in the development of this project. All data is authentic and accurate.

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