Case Report

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CVID-8 in a Compound Heterozygous LRBA Mutation Carrier Presenting as Refractory ITP in a Pediatric Patient

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Abstract

Background: Common Variable Immunodeficiency (CVID), a heterogeneous syndrome characterized by hypogammaglobulinemia and defective humoral immunity, is the most prevalent symptomatic primary immunodeficiency. CVID-8 is a monogenic variant due to bi-allelic mutation in the LRBA gene. Individuals carrying a single mutated LRBA allele are considered phenotypically healthy. However, immune dysregulation may arise in certain heterozygous carriers likely via haploinsufficiency or dominant-negative activity. LRBA critically regulates CTLA-4 recycling, directly linking this deficiency to immune checkpoint biology. **Case Presentation**: We report a 7-year-old female, born to consanguineous Lebanese parents, with a family history of thrombocytopenia, presented with chronic refractory ITP first diagnosed at age 2. The patient was resistant to multiple sequential therapeutic interventions including immunosuppressive agents and splenectomy. Whole exome sequencing (WES) detected compound heterozygous LRBA variants c.7937T>G (p.Ile2646Ser) and c.7046T>A p.Leu2349*, the former is pathogenic associated with CVID-8. Immunological assessment revealed hypogammaglobulinemia with suppressed IgG1, IgG3, IgA and IgM levels. Her latest hospitalization was marked by abdominal pain, impaired consciousness, acute liver injury, coagulopathy, peripheral leukocytosis, and lung infiltrates on imaging, suggesting autoimmune enteropathy complicated by infection. **Conclusion**: This report raises important questions regarding the clinical impact of heterozygous LRBA variant. It highlights the diagnostic value of WES in refractory cytopenias and inherited immune deficiencies. Abatacept, a CTLA-4-Ig fusion protein, is a promising targeted therapy for LRBA deficiency cases; yet its unavailability in Lebanon impeded its use, emphasizing the critical gap in access to targeted biologics in the MENA region.

Keywords: LRBA deficiency; Common Variable Immunodeficiency; pediatric ITP; compound heterozygosity; CVID-8

1. Introduction

Common Variable Immunodeficiency (CVID) is considered the leading symptomatic primary immunodeficiency disorder with an estimated incidence of approximately 1 in 25,000 to 50,000 individuals, but the actual prevalence is likely higher due to reported diagnostic delays by an average of 5-10 years (Cunningham-Rundles & Maglione, 2012). CVID is not a single condition, but rather a clinically heterogeneous syndrome characterized by hypogammaglobulinemia and defective humoral immunity. Of these complications, autoimmune cytopenia especially immune

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thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia, are the most documented findings.

CVID-8, a monogenic variant ascribable to bi-allelic mutations in the LRBA gene (Lipopolysaccharide-Responsive Beige-like Anchor protein), is known to be phenotypically defined and notably severe subtype within the CVID spectrum. This condition was first recognized by Lopez-Herrera et al. (2012) using genetic linkage analysis in families with known consanguinity, showing an association between homozygous mutations in LRBA and pediatric onset of hypogammaglobulinemia and autoimmune manifestations. In contrast, carriers of one mutated copy of the gene did not exhibit disease phenotypes. The underlying molecular mechanisms of LRBA deficiency was further clarified by Lo et al. (2015) who revealed that LRBA is required to regulate intracellular transport and cell surface display of CTLA-4, a key immunoregulatory molecule found on regulatory T cells (Tregs). Deficiency of functional LRBA results in premature lysosomal turnover and degradation of CTLA-4 protein consequently leading to unchecked T cell activation and development of wide-ranging autoimmune pathology (Lo et al., 2015).

The clinical presentation of LRBA deficiency is characterized by a wide and heterogeneous phenotypic expression. Through a systematic review of published cases, Habibi et al. (2019) found that autoimmunity, chronic gastrointestinal disturbances, hypogammaglobulinemia, and recurrent infections are the predominant reported clinical findings with a median age at symptom onset of 1.8 years. Autoimmune involvement associated with LRBA deficiency encompasses multiple organ systems including but not limited to ITP, inflammatory bowel diseases, autoimmune enteropathy, and insulin-dependent type 1 diabetes mellitus (Lo et al., 2015).

The long-term prognosis of LRBA deficiency is associated with significant clinical difficulties. As evidenced by Habibi et al. (2019), only 11.6% of patients managed without transplantation, were able to withdraw from immuno-suppressive treatment, reinforcing the chronic nature of this disorder. The use of targeted therapeutic agents such as the CTLA-4-Fc fusion protein (abatacept) and sirolimus have demonstrated clinical efficacy. However, hematopoietic stem cell transplantation (HSCT) remains the only definitive cure (Alkhairy et al., 2016). From a genetic standpoint, LRBA deficiency is inherited in an autosomal recessive manner with all molecularly confirmed cases reported in literature, carry biallelic mutations either in homozygous or heterozygous form (Lopez-Herrera et al., 2012; Soler-Palacín et al., 2018). Individuals carrying a single mutated LRBA allele are considered phenotypically healthy. However, growing evidence indicates that immune dysregulation may arise in certain heterozygous carriers due to potential mechanisms such as haploinsufficiency or dominant-negative activity, an aspect that has yet to be addressed in literature (Alkhairy et al., 2016).

We report a case of a 7-year-old female found to carry a confirmed heterozygous mutation in LRBA gene, presenting with a clinical presentation consistent with a CVID-8 phenotype, and characterized by treatment-resistant ITP necessitating splenectomy, repeated episodes of auto-immune cytopenias, and an acute presentation suggestive of autoimmune enteropathy. This case contributes to the emerging evidence that heterozygous carriers of LRBA mutation can present as clinically significant phenotype.

2. Case Presentation

We present the case of a 7-year-old female, born to Lebanese consanguineous parents (first degree cousins), with a family history notable for deceased sibling at 6 months of age (cause unknown) and a cousin with thrombocytopenia (Figure 1). She presented with chronic refractory ITP first diagnosed at age 2. Her condition course was notable for non-responsiveness to sequential escalating therapies including corticosteroids, intravenous immunoglobulin (IVIG), and azathioprine, ultimately undergoing total splenectomy in July 2023, after which having a baseline drop of platelets (4 x 109 /L). Thereafter, 4 cycles of Rituximab (375 mg/m2 /dose) were administered. Importantly, information regarding post-splenectomy vaccination for encapsulated organisms remains unknown, as the surgery was performed abroad.

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Physical examination over the course of her management was remarkable for stunted growth (101 cm), rounded facies and increased body weight (27 kg), a cushingoid appearance consistent with her prolonged corticosteroid exposure. A bone marrow aspiration was carried out on April 16th, 2024, following her first hospital admission for persistently severe thrombocytopenia (6,000/μL on first presentation in 2021, and 11,000/μL on day of admission), along with a planned rituximab course (375 mg/m2 diluted in 250mL normal saline). Given a family history of low platelet counts in her cousin, hereditary thrombocytopenia, along with thrombocytopenic purpura and medullary dysplasia were to be ruled out. The bone marrow showed a cellular marrow with trilineage hematopoiesis and mildly atypical megakaryocytes with eosinophilia and no malignant cells identified. Hemoglobin electrophoresis yielded no pathological findings.

The patient's blood tests also revealed persistent anemia (9.3 g/dL on first presentation in 2021, 9.5 g/dL on day of admission), hence a hemoglobin electrophoresis was performed to rule out possible hemoglobinopathy as cause of anemia and it yielded no pathological findings.

A targeted Next Generation Sequencing panel (NGS) encompassing 86-platelet- related genes conducted in January 2024 detected no deleterious variants. Considering the significant familial history, and the refractory course despite immune regulatory treatment, whole exome sequencing (WES) was done where it identified biallelic heterozygous mutations affecting the LRBA genes, one categorized as pathogenic (c.7937T>G (p.Ile2646Ser) linked to CVID-8 and a second variant classified as likely pathogenic c.7046T>A p.Leu2349* expected to introduce a premature stop codon resulting in a structurally incomplete protein or non-sense mediated mRNA decay with consequent loss of LRBA protein function (Table 1). Parental testing was recommended to confirm the segregation of LRBA variants in trans; however, it was not performed.

Immunophenotyping studies looked into immunoglobulin levels including IgA (1.32 g/L), IgG along with its subclasses, IgM (0.67 g/L) and IgE, and found that all were below the normal limits, except for IgG2 and IgG4. These studies, however, did not look into T-cell subsets (CD4/CD8 counts, naive and memory cells, or Treg cell counts), nor B-cell subsets despite memory B cells being a diagnostic criterion for CVID. Moreover, the CTLA-4 expression on the surface of Treg cells was not assessed. This comes as a limitation to our study as these analyses would have helped link our patient's genotypic findings to the proposed molecular and phenotypical features. Treatment with Eltrombopag was thus initiated and subsequently dose increased to 50mg, resulting in transient platelets responses.

Her hospitalization on November 2025 was marked by critically low platelet count (5 x 103) with polymicrobial infections including a wound culture positive for Staphylococcus aureus and urinary culture growing Escherichia Coli for which intravenous immunoglobulin (IVIG 1g/Kg) and antibiotics were administered for which she was discharged with continued Eltrombopage 50 mg once daily. An additional admission was recorded on February 4, 2026, presenting under emergency circumstances with reduced alertness, marked fatigue, frontal headache, diffuse abdominal pain, blurry vision and recurrent emesis with blood observed in the last two episodes. On clinical assessment, she appeared jaundiced, pale and had generalized abdominal tenderness on palpation. The patient's platelet count on admission was markedly elevated at 692,000/μL, with elevated liver function tests (ALT= 509 U/L; AST= 573 U/L). The patient's jaundice, coagulopathy problems, and acute liver injury raised concern for acute liver failure.

Laboratory workup revealed marked leukocytosis (WBC 41.38 x 109/ L, acute hepatocellular injury (ALT 509 U/L. AST 573 U/L), elevated LDH (597 U/L), coagulopathy (Pt 24.6 seconds, INR 2.23), low serum sodium and hypoglycemia. Additionally. A plain chest X-ray showed micronodular infiltrates in the right lower lobe with prominent broncho-vascular markings consistent with a pulmonary infection for which antibiotic coverage with clarithromycin commenced. Viral serology panels including COVID-19, RSV, Influenzas A and B were negative, and abdominal ultrasound ruled out cholecystitis and cholelithiasis.

This pattern of progressive immune dysregulation resulted in a subsequent hospitalization in April 2026 marked by a refractory systemic hyperinflammation and a decline in clinical trajectory despite the ongoing supportive interventions. Serial hematological monitoring showed persistent

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markedly elevated leukocytes of 54.54 x 109/L and worsening microcytic hypochromic anemia (Hgb declining from 8.7 g/dL on entry to 7.7 g/dL in few days). A significant ongoing eosinophilia (eosinophils 12%) suggests the possibility of an additional immune-mediated or parasitic process. Further investigation of hemolysis showed a negative direct antiglobulin test (DAT) demonstrating critically decreased haptoglobin (<10 mg/dL) with low reticulocyte count (22 x 109/L), a pattern more consistent with hepatic haptoglobin consumption due to acute hepatocellular injury than with hemolytic anemia; the direct antiglobulin test (DAT) was negative. ALT and AST were maximally elevated upon admission (509 U/L and 573 U/L) respectively, partially improving on the 4th day of admission (131 U/L and 110 U/L) while alkaline phosphatase remained above the upper limit (604-618 U/L), indicating ongoing cholestatic or infiltrative liver disease. Amylase was also elevated at 137 U/L suggesting associated pancreatic involvement.

Such combination of clinical and laboratory findings including leukocytosis with eosinophilia, anemia, acute hepatic injury with improving transaminasemia, clotting impairment, pulmonary infiltrates layered upon an underlying diagnosis of LRBA deficiency was consistent with autoimmune enteropathy and systemic immune dysregulation.

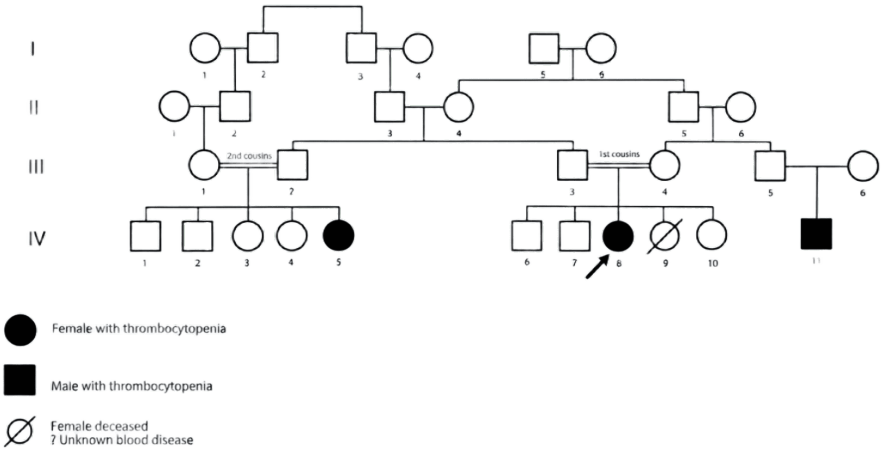

Figure 1. Family Pedigree demonstrating consanguinity and inheritance pattern.

Table 1. Genetic variants identified in the LRBA gene by whole exome sequencing.

Gene	cDNA	Protein	Zygosity	ACMG Classification	Predicted Effect
LRBA	c.7937T>G	p.Ile2646Ser	Heterozygous	Pathogenic	Missense, disrupt CTLA-4 trafficking, previously reported in CVID-8
LRBA	c.7046T>A	p.Leu2349*	Heterozygous	Likely Pathogenic	Nonsense, premature stop codon, loss of LRBA function

Table 2. Timeline of disease course with key laboratory parameters and therapeutic intervention.

Date	Event	Platelets	Key Other Labs	Treatment	Outcome
2021	Initial ITP diagnosis (age 2)	6 x 10^3	Severe thrombocytopenia	Corticosteroids, IVIG	No sustained response

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July 2023	Total Splenectomy	4 x 10^3	Persistent severe ITP	Surgery, Azathioprine, Rituximab recommended	No response
April-May 2024	Admission	11 x 10^3	BMA: trilineage, atypical megakaryocytes, eosinophilia, Electrophoresis normal	Rituximab 4 doses (375 mg/m^2 each)	Transient response
Nov 2025	Admission	5 x 10^3	Infection + ITP	IVIG 1g/kg + Antibiotics + Eltrombopag 50 mg	Temporary improvement
Dec 2025	Admission	674 x 10^3	Rebound thrombocytosis	IVIG 1g/kg, Eltrombopag 50 mg	Relapse
Feb 2026	Admission	27 x 10^3	Liver injury (ALT 509, AST 573, ALP 604, LDH 597) + INR 2.23 + GI symptoms + CXR: RLL infiltrates	Steroids, IVIG 1g/kg, broad spectrum antibiotics (clarithromycin)	Partial stabilization
April 2026	Admission	410 x 10^3	Leukocytosis, Eosinophilia, Amylase 137, ALP elevated	IVIG 1g/kg, antimicrobials	Partial stabilization

3. Discussion

3.1. CVID-8 Molecular Mechanism

While the primary cause of CVID remains undetermined, its etiology is considered heterogeneous and multifactorial, encompassing genetic, epigenetic, and environmental factors. In fact, the cause behind the disorder remains unknown in most patients (Pescador Ruschel & Penney, 2026).

Less than 20% of cases are now attributed to monogenic defects, with many genes involved in immune cell development, activation, and survival, being associated with the disease. Monogenic causes therefore constitute only a small fraction of cases, and may result in defects of receptors and ligands, activating and co-stimulatory molecules, and intracellular signaling molecules. These genetic variants ultimately translate to altered antigen presentation, antibody class switch recombination (CSR), antibody affinity maturation, and somatic hypermutation (SHM).

Furthermore, mutations in LRBA (lipopolysaccharide-responsive and beige-like anchor protein) have been linked to both CVID and CVID-like immune dysregulation syndromes. LRBA mutations are often truncating (nonsense or frameshift variants) at exon 4 of the gene that disrupt the BEACH domain, a highly conserved domain. Rather than abolishing the CTLA-4 protein production the LRBA deficiency leads to impaired intracellular trafficking and recycling of CTLA-4, which results in its increased lysosomal degradation and hence its reduced intracellular and surface expression, particularly in regulatory T (Treg) cells. The loss of CTLA-4 impairs Treg-mediated suppression of antigen-presenting cells, allowing for a persistent CD28-mediated T-cell activation and chronic immune stimulation (Lo et al., 2015). The centrality of CTLA-4 in this process is further supported by

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Kiykim et al., which reported abatacept (CTLA4-Ig fusion protein) as restorative of suppression and immune regulation in LRBA-deficient patients (Kiykim et al., 2019).

Additionally, when looking at LRBA-deficient patients, Charbonnier et al. found an association between LRBA deficiency and decreased numbers and aberrant phenotypes of Treg cells, characterized by absent key markers (Helios, CD25, FOXP3), leading to decreased suppression of T cells. Treg cells also exhibited impaired mTOR signaling and increased apoptosis. Moreover, LRBA-deficient subjects had increased autoantibodies, reflecting defective peripheral tolerance. Collectively, these findings help explain the chronic immune activation observed in these patients (Charbonnier et al., 2015).

3.2. Heterozygous Mutations and Compound Heterozygosity

Despite LRBA deficiency being first described as an autosomal recessive disorder secondary to biallelic mutations in the LRBA gene (OMIM #614700), an increasing number of heterozygous cases with variable clinical presentations have been reported (Yao et al., 2022). Heterozygous individuals are generally asymptomatic compared to those with biallelic mutations, which typically present with hypogammaglobulinemia and autoimmunity. Conversely, a subset of heterozygous individuals develops refractory thrombocytopenia, autoimmune polyglandular disease, and recurrent infections amongst other features. The discrepancy in phenotypical presentation could be a reflection of compound heterozygous variations and different variation locations, with functional domains including BEACH, DUF4704, and LamG being the main ones reported (Yao et al., 2022).

Phenotypical presentation in heterozygous LRBA-deficiency has also been reported in prior literature as CVID-like characterized by autoimmune cytopenias, similar to the presented case. Likewise, compound heterozygosity is believed to cause such a phenotype, with an undetected second pathogenic variant in trans on the other allele (Sandhu et al., 2019).

This mechanism of inheritance is further proven as parents of compound heterozygous patients (missense and nonsense mutations) carried only one of the 2 variants, yet didn't possess any sign of immune dysregulation (Gámez-Díaz et al., 2016).

Additionally, CVID remains a genetically heterogeneous disease for which digenic combinations is increasingly recognized (Szczawińska-Popłonyk et al., 2024). In fact, the digenic etiologies associated with CVID phenotypes with antibody production deficiencies, autoimmunity, thrombocytopenia, and hemolytic anemia included concomitant variants in genes LRBA and NEIL3 (Nei-Like DNA Glycosylase 3), both of which were proven essential in establishing peripheral B cell tolerance (Massaad et al., 2016).

Beyond the previously mentioned mechanisms, additional etiologies described in primary immunodeficiencies and CVID may contribute to incomplete penetrance and phenotypic variability, including polygenic inheritance and epigenetic modifications such as DNA methylation and chromatin accessibility changes (Rodríguez-Ubreva et al., 2022); (Ranjbarnejad et al., 2025).

Collectively, these findings suggest a more complex genetic basis underlying CVID-like presentations in patients with heterozygous LRBA variants, in which additional genetic factors, including digenic interactions and compound heterogeneity, may contribute to disease expression. Our patient's compound heterozygous variants: c.7937T>G (p.Ile2646Ser, Pathogenic) and c.7046T>A (p.Leu2349*, likely pathogenic) phenotypically match with the compound heterozygous case described by Yao et al. (2022).

3.3. Refractory ITP, Autoimmune Enteropathy, Type 1 Diabetes Association, and Splenectomy Indications and Post-Splenectomy Risks

Our patient presented with immune thrombocytopenic purpura (ITP) that was refractory to all conventional first line treatments including high dose corticosteroids and rituximab and also refractory to splenectomy. This clinical course is similar to what is reported in literature (Gámez-Díaz & Grimbacher, 2016) with autoimmune cytopenias in LRBA deficiency being resistant to multiple first line medications as a result of the loss of CTLA-4 mediated immune checkpoints. This refractory nature is often the presenting feature and diagnostic hallmark for monogenic immune dysregulation

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as well as a major cause of morbidity in these patients. According to Pacillo et al. (2022), the failure of cytopenias to respond to standard treatment should raise the suspicion of a primary immunodeficiency (PID) like LRBA deficiency, similar to the progression of our case.

Autoimmune enteropathy in patients with LRBA mutations typically presents as chronic diarrhea that leads to severe malabsorption and weight loss with no response to dietary modifications and other treatments (Azizi et al., 2017). While it is one of the most common presentations of LRBA, reported to be 62% in a study done by Gamez Díaz & Grimbacher (2016), our patient did not present primarily with gastrointestinal symptoms. However, her acute presentation, in February 2026, characterized by diffused abdominal pain, hematemesis and acute hepatocellular injury, may represent a late-onset systemic GI and hepatic manifestations of LRBA-associated immune dysregulation. This highlights the extent of phenotypic variability in LRBA deficiency, which aligns with the findings of Gamez-Diaz and Grimbacher (2016) who observed that although the molecular defect is constant, the clinical "penetrance" can vary widely. Therefore, lack or delay of gastrointestinal system involvement does not rule out LRBA deficiency in pediatric patients and emphasizes the role of genetic screening in any case of refractory ITP.

In addition to hematologic and gastrointestinal manifestations, LRBA deficiency has also been associated with endocrine autoimmunity, including type 1 diabetes mellitus (T1DM). Although less common than autoimmune cytopenias, T1DM has been reported in several cases as part of the LRBA-associated autoimmune spectrum, with affected children presenting with hyperglycemia, including early-onset disease in infancy (Johnson et al., 2017; Kardelen et al., 2021). Consistent with this immune dysregulation, impaired trafficking and recycling of CTLA-4 leads to loss of peripheral tolerance and activation of autoreactive T cells, which may contribute to pancreatic β-cell destruction (Lo et al., 2015). However, our patient did not exhibit features of endocrine autoimmunity. Given the risk of evolving autoimmune disease, periodic screening for T1DM should be considered, including assessment for symptoms of hyperglycemia, measurement of blood glucose and HbA1c, and evaluation of diabetes-associated autoantibodies such as GAD65, IA-2, and ZnT8 (American Diabetes Association, 2025; Moore et al., 2024).

Splenectomy remains a second-line therapeutic option in refractory immune thrombocytopenia (ITP) following failure of first-line treatments, including corticosteroids, IVIG, and rituximab (Neunert et al., 2019). However, in the context of autoimmune dysregulation and primary immunodeficiencies (PIDs), splenectomy may provide only transient hematologic improvement and often fails to achieve sustained remission (Pincez et al., 2022). Consistently, Egg et al. (2022) reported that only 25% of patients experienced improved outcomes following splenectomy. Moreover, splenectomy is generally discouraged in PIDs due to an increased risk of severe infectious complications, including overwhelming post-splenectomy infection (OPSI) (Pacillo et al., 2022; Sinwar, 2014). Patients with underlying immune dysregulation are particularly susceptible to OPSI, which may rapidly progress to fulminant sepsis and death. Asplenic individuals are especially vulnerable to infections caused by encapsulated organisms, including Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis, with S. pneumoniae accounting for the highest mortality rates (Sinwar, 2014).

Preventive strategies are therefore essential following splenectomy. Immunization against Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type b, and influenza is strongly recommended, ideally administered at least two weeks prior to elective surgery or delayed until at least two weeks after emergency procedures (Bonanni et al., 2017). In our case, vaccination was not performed due to the urgency of the procedure, compounded by socioeconomic constraints and limited access to pre-operative immunological counseling. In addition, daily antibiotic prophylaxis, most commonly with penicillin, is recommended following splenectomy; while the optimal duration remains uncertain, lifelong prophylaxis is advised for high-risk individuals, whereas shorter courses (1–3 years) may be appropriate based on age, immune status, and guideline recommendations (Lee, 2020).

Reactive thrombocytosis is another well-recognized complication of splenectomy and was observed in our patient (Harshita et al., 2024). Platelet counts increased to 692 $\times 10^9$/L, consistent with

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post-splenectomy thrombocytosis, which may confer an increased risk of thromboembolic events, including pulmonary embolism, deep vein thrombosis, and portal vein thrombosis (Khan et al., 2009)

3.4. Treatment Landscape and Access Disparities

The treatment framework for immune thrombocytopenia (ITP) in pediatrics has classically been guided by a structured step-up approach of protocol-driven immune suppression. Initial therapeutic agents including corticosteroids and intravenous immunoglobulins (IVIG) yield temporary thrombocyte recovery in most patients yet; lasting disease-free status is recorded in relatively few patients with refractory disease. Second-line-interventions such as Rituximab, chimeric monoclonal antibody selectively eliminating CD20 expressing B lymphocytes, produce inconsistent response rates and are frequently complicated by subsequent relapses. Thrombopoietin receptor agonists (TPO-RAs) including Eltrombopag and Romiplostim reflect a significant evolution in treatment via enhancement of platelet precursor development, yet, they offer symptom control rather than cure and they requires adequate bone marrow function.

In the setting of monogenic immune dysregulation as in this case of LRBA deficiency, this classical management approach is often limited. Cytopenias in such patients represent a systemic immunoregulators failure and not merely an isolated autoimmune thrombocytopenic process. Therefore, treatments aimed at peripheral mechanisms including B-cell targeted monoclonal therapy or TPO-receptor mediated platelet production are unable to resolve the core immunological dysfunction as evidenced by the refractory clinical pattern in the present case.

LRBA deficiency interferes with intracellular trafficking of CTLA-4, an immune checkpoint surface protein, thereby resulting in defective immune checkpoint control and dysregulated T lymphocyte activation. This pathogenic mechanism establishes a therapeutic basis for molecularly guided therapy. Abatacept, CTLA-4 immunoglobulin fusion therapy, reactivates inhibitory signaling and has proven effective in managing immune-mediated manifestations notably cytopenias in patients with LRBA deficiency. It is currently regarded as the recommended molecularly guided treatment in this clinical context. Sirolimus, via inhibiting mTOR pathway activity and promoting regulatory T-lymphocyte activity, potentially serving as a second-line option or co-administered treatment modality. Hematopoietic stem cell transplantation stands as the only curative intervention for patients with severe or refractory immune disorders yet carries considerable transplant-related complications. In this case, although she shows progressive multi-system involvement, her clinical instability, compound heterozygous LRBA variants, and refractory ITP unresponsive to traditional therapies, the timing and candidacy of HSCT remains complex issue calling for personalized multidisciplinary evaluation including HLA typing of available family members particularly the affected cousin (Figure 1). Adjunctive therapeutic measures including immunoglobulin replacement and prophylactic antibiotic/antifungal coverage remain as significant pillars of management. Importantly, the reported case highlights a critical gap between diagnostic advancement and treatment accessibility. Despite genomic identification of molecularly defined immunological disorder, the lack of access to Abatacept in our resource-limiting setting hindered the use of such targeted treatment underscoring disparities in caring for patients with rare immunological disorders.

4. Conclusions

The reported case highlights the classic phenotypic spectrum of LRBA- associated immunological dysfunction and questions the classical perception that heterozygous mutations lead to no clinical manifestations. The development of severe refractory ITP in early childhood accompanied by subsequent systemic involvement stressing the necessity to consider underlying inherited primary immunodeficiency in atypical presentations or refractory cases. Recognizing compound biallelic LRBA mutations through WES demonstrates the essential role of genome based-diagnostic approaches in facilitating the diagnostic process in complex immune dysregulatory conditions. Given the consanguineous background and the presence of thrombocytopenia in the family history, family genetic testing and counselling are strongly recommended to detect any additional at-risk individuals. Moreover, this patient's clinical progression exemplifies the limitations

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of standard immunosuppressive regimens when the underlying pathology is not resolved. Targeted therapies like Abatacept provide a clinically promising management option for this disease yet the inaccessibility of such treatment in a resource limited setting, like Lebanon, exposes a critical disparity between precision diagnostic workup and equitable access to biologic treatment. Overall, this report reaffirms the necessity of early detection of primary immune dysregulatory disorders in pediatric patients and advocates for enhanced availability to targeted therapies especially in low-and middle-income countries, to improve clinical prognosis.

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Institutional Review Board Statement: The Institutional Review Board of Lebanese American University has determined that this work is exempt from IRB review, as the data is deidentified and constitutes a case report with a small number of patients (1). Written informed consent from the family has been obtained for the genetic studies and the publication of this case.

Informed Consent Statement: Written informed consent and assent were obtained from the patient's parent for publication of this case report in de-identified form.

Data Availability Statement: No datasets were generated or analyzed during the current study.

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Conflicts of Interest: The authors declare no competing interests.

Abbreviations

The following abbreviations are used in this manuscript:

CVID-8	Common Variable Immunodeficiency-8
ITP	Immune thrombocytopenia
WES	Whole Exome Sequencing
MENA	Middle East and North Africa

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