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# Novel compound heterozygous LRBA deletions in a 6-month-old with neonatal diabetes

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## Abstract

We report a 6-month-old boy with antibody-positive insulin-dependent diabetes mellitus. Sequencing identified compound heterozygous deletions of exon 5 and exons 36–37 in *LRBA*. At three years, he has yet to exhibit any other immune symptoms. Genetic testing of *LRBA* is warranted in patients with neonatal diabetes, even without immune dysregulation.

### Keywords

Type 1 diabetes; Monogenic; Autoimmunity; Next generation sequencing; Copy number variants

## 1. Introduction

A clinical presentation of autoimmune type 1 diabetes is exceedingly rare before the age of 6 months [1,2] and is commonly due to pathogenic variants genes related to immune function (such as *FOXP3*, *STAT3*, and *IL2RA*) [3–5]. Recently, bi-allelic pathogenic loss of function (LOF) variants in lipopolysaccharide-responsive beige-like anchor gene (*LRBA*) have been reported in several probands with onset of insulin-dependent diabetes before one year of age [6–9]. LRBA deficiency was previously reported to be associated with immune dysregulation, with affected individuals presenting with a wide spectrum

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Contributions of the authors

May Sanyoura and Erika Lundgrin wrote the manuscript and participated in the discussion. Min Yu, Priscilla Sodadasi, and Hari Prasanna Subramanian processed and analyzed the data. May Sanyoura and Daniela del Gaudio interpreted the genetics results. Daniela del Gaudio, Siri Atma W. Greeley, and Sarah MacLeish participated in writing and editing the final version. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

of phenotypes including chronic diarrhea, hypogammaglobulinemia, recurrent infections, pneumonitis, organomegaly, lymphoproliferative disease, and autoimmune disorders such as type 1 diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia [10–14]. In this report, we present a case of isolated autoimmune neonatal diabetes due to novel compound heterozygous intragenic deletions in *LRBA*.

## 2. Case presentation

A previously healthy 6-month-old boy presented with severe diabetic ketoacidosis. Initial lab work was consistent with type 1 diabetes, including elevated hemoglobin A1c (7.5%, 58 mmol/mol), undetectable serum insulin, low C peptide (0.5 ng/mL), and elevated anti-insulin antibody (0.83 nmol/L; reference ≤ 0.02). IA-2 antibodies were negative, and GAD-65 antibody was not tested due to insufficient sample.

A comprehensive genetic evaluation included a targeted next generation sequencing (NGS) neonatal diabetes gene panel for detection of single nucleotide variants and intragenic deletions/duplications in genes associated with neonatal diabetes [15]. Copy number analysis from NGS data identified two heterozygous deletions in *LRBA* (NM_006726.4): one involving exon 5 and the other involving exons 36–37. This finding was confirmed by a custom designed array-comparative genomic hybridization assay:

exon 5, NC_000004.11:g.(151844060_151842691)_(151841716 _151841229)del and exons 36–37, NC_000004.11:g.(151665290_151658057)_(151589391_151564275)del (Fig. 1). Both exonic deletions are predicted to preserve the reading frame. These deletions were not previously reported in the literature or in public genomic databases. Carrier status was confirmed in the parents.

The patient had normal T-cell/B-cell distributions and immunoglobulin levels. He developed iron deficiency anemia and chronic diarrhea around one year of age; upper and lower endoscopies with biopsies performed at 18 months old revealed candida esophagitis but no other pathology. MRI enterography performed at 21 months old showed no active or chronic inflammatory changes. Our now 3-year-old patient has not developed any other autoimmune conditions and has exhibited overall normal growth and development. He continues to be monitored for immune dysregulation with periodic laboratory assessments and is undergoing preparation for a stem cell transplant.

## 3. Discussion

To our knowledge, this is the first report of compound heterozygous exon deletions in *LRBA* leading to an initial presentation of neonatal diabetes. LRBA plays a fundamental role in the normal function and regulation of the immune system by interacting with CTLA-4 within recycling endo-somes, preventing it from being sorted to lysosomes for degradation. Loss of LRBA results in increased CTLA-4 degradation, reducing inhibition of T cell activation, which results in uncontrolled activation of the immune response [16]. More than 70 cases of LRBA deficiency have been reported with highly variable clinical and immunologic presentations and no clear genotype-phenotype correlation [17,18].

Bi-allelic pathogenic variants in *LRBA* have been associated with neonatal diabetes diagnosed as early as 6 weeks old [6]. However, the majority of reported cases of infancy-onset diabetes were due to truncating LOF variants in *LRBA*. Furthermore, most of these variants were homozygous and in the setting of parental consanguinity [6–8,13]. One report described autoimmune diabetes diagnosed in infancy related to a homozygous LOF variant due to uniparental disomy (UPD) [9]. Our patient has compound heterozygous *LRBA* deletions involving exon 5 and exons 36–37, both of which are predicted to preserve the reading frame. Exon 5 (aa 184–215) lies within the ConA-like domain, whereas exons 36–37 (aa 1882–1974) lie within the highly conserved domain of unknown function 1088 (DUF1088); both are known to play a role in normal protein function. LRBA interacts with CTLA-4 through its ConA-like and PH-BEACH domains [16], while the DUF1088 was identified as a nuclear localization signal [19]. An abridged LRBA protein may retain much of its function, but in light of our case, the loss a portion of the ConA-like domain and DUF1088 appear to have a detrimental impact protein function.

Overall, our patient's phenotype has been milder than most cases described. He presented at 6 months with insulin-dependent diabetes and anti-insulin antibodies, often the earliest antibody detected in infants who go on to develop type 1 diabetes [20,21]. Autoimmunity may be missed if anti-insulin antibodies are not evaluated; 5/6 LRBA-deficient patients with reported antibody-negative diabetes were screened only for GAD-65, IA2, and ZnT8 antibodies [6]. Our patient has yet to exhibit other features of immune dysregulation. In comparison, 5/9 patients with diabetes diagnosed prior to 12 months old presented with recurrent infections, and seven had at least one other autoimmune disorder [6]. Likewise, the case of LRBA deficiency due to UPD presented at 8 months with type 1 diabetes, psoriasis, and hepatosplenomegaly, followed by recurrent severe infections [9]. In-frame exon deletions may result in an abnormal, partially functional LRBA protein, and in the compound heterozygous state there may be partial functional rescue, which could explain his milder presentation. In support of this theory, a longitudinal study of 76 patients with LRBA deficiency found that residual protein expression was associated with better outcome and decreased disease burden [22]. Nevertheless, our patient may still develop additional immune features in the future.

Given the rarity of type 1 diabetes in infants and the opportunity for early targeted therapy, patients diagnosed with autoimmune diabetes prior to a year of age would benefit from prompt genetic testing for monogenic forms of diabetes. Genetic evaluation of *LRBA* should be considered in all patients presenting with neonatal diabetes, with or without evidence of other immune features.

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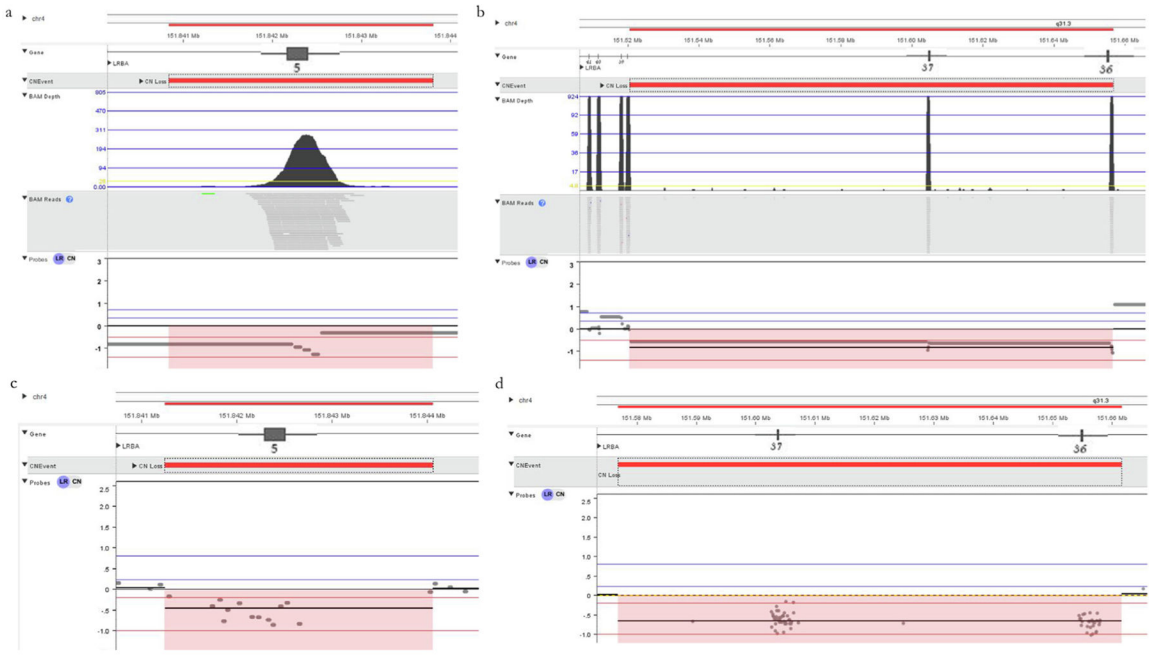

**Fig. 1 –.**

NGS and Array CGH results. (a,b) Copy number variants from NGS data were called using NxClinical 5.0 (BioDiscovery Inc.): heterozygous loss of exon 5 and heterozygous loss of exon 36–37 (NM_006726.4) (c,d) Confirmation of the LRBA exon deletions using a high resolution, custom-designed, exon targeted array CGH platform (Agilent Technologies, Santa Clara, CA).