Two Faces of LRBA Deficiency in Siblings: Hypogammaglobulinemia and Normal Immunoglobulin Levels

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LPS-responsive beige-like anchor protein (LRBA) deficiency is a novel primary immunodeficiency disorder (PID) caused by biallelic mutations in the *LRBA* gene that abolish its protein expression [1]. Similar to common variable immune deficiency, immune dysregulation as a consequence of LRBA deficiency leads to recurrent infections, autoimmunity, and enteropathy [1-7]. Affected individuals mainly show reduced levels of at least 2 Ig isotypes. We report on siblings from 2 different families with LRBA deficiency who were carrying the same mutation but had discordant serum Ig levels. Clinically, in both families, one sibling had hypogammaglobulinemia, whereas the other had normal Ig levels. Next-generation sequencing is a useful approach for molecular diagnosis of human diseases. The increasing availability of targeted next-generation sequencing panels, whole exome sequencing (WES), and whole genome sequencing, have facilitated identification of genetic defects in PID patients with the same mutation and variable clinical phenotypes [8].

Family 1

Patient 1 was the child of first cousins. At 3 years of age, she presented with growth retardation, upper respiratory tract infection, recurrent pneumonia, recurrent diarrhea, and hepatosplenomegaly. She was diagnosed with probable IgA deficiency (Table). At age 8, she developed autoimmune thyroiditis, and at age 13 she was diagnosed with bronchial asthma, atopic dermatitis, mucosal candidiasis, and refractory diarrhea. Laboratory evaluation revealed immune thrombocytopenia purpura and low serum Ig levels, indicating progression from IgA deficiency to hypogammaglobulinemia. Intravenous immunoglobulin (IVIG) therapy was started. She later developed autoimmune hemolytic anemia and underwent splenectomy at age 20 owing to hypersplenism. The patient also lost bone mineral density during the previous year and developed bronchiectasis. Gastrointestinal biopsy revealed chronic active gastritis-esophagitis and atrophic duodenal mucosa (villous atrophy). WES revealed a splice site mutation (c.4729 +2dupT) in the *LRBA* gene.

Patient 2 was a 20-year-old woman and sibling of patient 1 who developed autoimmune hemolytic anemia at 5 years of age. She also had upper respiratory tract infections and generalized lymphadenopathy and splenomegaly. Persistence of her anemia necessitated splenectomy at that time. She experienced severe viral meningitis at age 10. The immunological evaluation showed increased double-negative T-cell counts, low $CD8^+$ T-cell counts, and normal Ig levels. She developed immune thrombocytopenia purpura at age 11 and another episode of viral meningitis at age 12. A granuloma-like lesion coupled with a demyelinating process in the brain was reported. Immunomodulatory therapy with high-dose IVIG was started 2 years later owing to loss of vision in her left eye. From the age of 15 until now, the patient has had multiple episodes of sinusitis and otitis media. She also has low bone mineral density. Mutation analysis revealed the same mutation as her sister.

Family 2

Patient 3, the index case in family 2, was a 27-year-old man born to consanguineous parents. Symptoms first appeared at age 2 years, with respiratory tract infection. At age 10, he was diagnosed with hypogammaglobulinemia. His clinical records included several episodes of pneumonia, sinusitis, and chronic diarrhea. Other reported manifestations were arthritis, bronchiectasis, failure to thrive, and finger clubbing. Loss of bone mineral density and *Helicobacter pylori* infection were also detected. This patient was initially diagnosed with IgA deficiency, although further investigations revealed hypogammaglobulinemia and absent isohemagglutinins. IVIG therapy was started. WES analysis revealed a homozygous nonsense mutation (c.C4814G [p.S1605X, exon 30]), which was confirmed by Sanger sequencing.

Patient 4, the older brother of patient 3, was a 36-year-old man who had chronic sinusitis with no significant complications of immunodeficiency. The immunological evaluation revealed normal serum Ig and a specific antibody response to the vaccine. Lymphocyte subsets were also in the normal range. WES analysis revealed a homozygous nonsense mutation in the *LRBA* gene similar to that of his younger brother. Western blot analysis of both patients revealed absent LRBA expression.

Mutations affecting different domains of LRBA result in diminished expression and a spectrum of clinical phenotypes that includes hypogammaglobulinemia, enteropathy, autoimmune disorders, respiratory infections,

Table. Immunologic Characteristics of Patients With LRBA Deficiency

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Normal Range
IgG, mg/dL[a]	765	1207	360	1237	503-1719
IgG1, mg/dL[a]	480	NA	236	NA	280-1030
IgG2, mg/dL[a]	72	NA	31	NA	66-502
IgG3, mg/dL[a]	163	NA	40	NA	11.5-106
IgG4, mg/dL[a]	41	NA	0.8	NA	1.0-121
IgM, mg/dL[a]	69	17	44	121	34-255
IgA, mg/dL[a]	5	67	0	255	86-320
IgE, IU/mL[a]	0.3	0	NA	1	< 46
Specific antibody response[a]	Positive	Positive	Negative	Positive	Positive
White blood cell count, cell/μL[a]	8730	3300	14400	6030	4000-11 000
Lymphocytes, cell/μL[a]	2095	2145	2016	2412	1000-5300
$CD3^+$, cell/μL[a]	1739	1625	1492	1761	800-3500
$CD4^+$, cell/μL[a]	649	643	363	769	400-2100
$CD8^+$, cell/μL[a]	670	558	1109	1066	200-1200
$CD16\text{-}56^+$, cell/μL[a]	98		201	NA	70-1200
$CD19^+$, cell/μL[a]	147	493	121	193	200-600
Transitional, % of B lymphocytes	0.7	0	0	NA	3-5.9
Naïve, % of B lymphocytes	50	32	55	NA	65.6-79.6
Marginal zone, % of B lymphocytes	0	0	0	NA	7.4-13.9
Switched memory, % of B lymphocytes	3.6	2.1	4.1	NA	7.2-12.7
Plasmablasts, % of B lymphocytes	0	0	0	NA	0.6-1.6
$CD21^{low}$, % of B lymphocytes)	45	65	36	NA	0.9-3.6
Regulatory T-cells, % of $CD4^+$ T cells	0.17	0.1	1.1	2.8	1.2-3.1
Hemoglobin, g/dL	7	4.6	13	13	12-16
Platelet, $\times 10^3$	226	458	182	138	150-400
IgG anti-IgA antibody	2.3	NA	1.2	NA	Negative
Thyroid peroxidase antibody, IU/mL	535	NA	NA	NA	< 35
Thyroglobulin antibody, IU/mL	>5000	NA	NA	NA	<20
Direct Coombs test	Positive	Positive	NA	NA	Negative
Indirect Coombs test	Positive	NA	NA	NA	Negative

Abbreviation: NA, not available.
[a]Values were obtained at the time of diagnosis of immunodeficiency.

and combinations of these phenotypes. There is no apparent genotype–phenotype correlation, as patients with the same mutation in *LRBA* may present different clinical phenotypes or even be asymptomatic [8]. Incomplete penetrance was reported in 3 Palestinian brothers with the same variation in *LRBA*, 2 of whom had organomegaly and autoimmune disease, while another was symptom-free [8]. We report 2 immunologic phenotypes of LRBA deficiency in 2 female siblings, including hypogammaglobulinemia and normal Ig levels with autoimmunity. Moreover, we report 2 male siblings with LRBA deficiency with the same mutation and discordant clinical and immunological presentations. The index patient had severe clinical complications, including chronic diarrhea, organomegaly, respiratory tract infection, and hypogammaglobulinemia, whereas his brother had no clinical complications and normal serum Ig and specific antibody levels.

Therefore, our findings are consistent with those of a report confirming that the same genetic mutation in the *LRBA* gene can manifest with a broad phenotypic spectrum and no genotype–phenotype correlation. In most cases where a particular genotype is inherited, it is not fully known why the same allele can cause subtle or profound differences in phenotypes. A disease phenotype may be modulated by genetic

and nongenetic modifiers, including modifier genes, allelic variation, environmental factors, and complex genetic and environmental interactions. In some cases, there is genetic evidence that modifier genes influence phenotypic variation. The correlation between genotype and phenotype is a statistical relationship that predicts a physiological trait in a healthy individual or an abnormality in a patient with a given mutation or a group of similar mutations. Modifier genes can affect penetrance, dominance, and expressivity. A genetic modifier, when expressed, is able to alter the expression of another gene. Modifier genes can affect transcription and alter immediate gene transcript expression, or they can affect phenotypes at the cellular or organismal level [9,10]. Further studies are required to define the exact role of genetic and nongenetic parameters in the penetrance of LRBA deficiency.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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