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ORIGINAL ARTICLE

Successful Hematopoietic Stem Cell Transplantation in a Patient with LPS-Responsive Beige-Like Anchor (*LRBA*) Gene Mutation

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Abstract
Purpose Autosomal recessive mutations in *LRBA*, encoding for LPS-responsive beige-like anchor protein, were described in patients with a common variable immunodeficiency (CVID)-like disease characterized by hypogammaglobulinemia, autoimmune cytopenias, and enteropathy. Here, we detail the clinical, immunological, and genetic features of a patient with severe autoimmune manifestations.
Methods Whole exome sequencing was performed to establish a molecular diagnosis. Evaluation of lymphocyte subsets was performed for immunological characterization. Medical files were reviewed to collect clinical and immunological data.
Results A 7-year-old boy, born to consanguineous parents, presented with autoimmune hemolytic anemia, hepatosplenomegaly, autoimmune thyroiditis, and severe autoimmune gastrointestinal manifestations. Immunological investigations revealed low immunoglobulin levels and low numbers of B and NK cells. Treatment included immunoglobulin replacement and immunosuppressive therapy. Seven years after disease onset, the patient developed severe neurological symptoms resembling acute disseminated encephalomyelitis, prompting allogeneic hematopoietic stem cell transplantation (HSCT) with the HLA-identical mother as donor. Whole exome sequencing of the patient uncovered a homozygous 1 bp deletion in *LRBA* (c.7162delA:p.T2388Pfs*7). Importantly, during 2 years of follow-up post-HSCT, marked clinical improvement and recovery of immune function was observed.
Conclusions Our data suggest a beneficial effect of HSCT in patients with LRBA deficiency.

Keywords primary immunodeficiency · hematopoietic stem cell transplantation · common variable immune deficiency · enteropathy · acute disseminated encephalomyelitis · whole exome sequencing

Peter Priftakis and Fredrik Lindgren contributed equally to this work.

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Introduction

Common variable immunodeficiency (CVID) represents a heterogeneous group of disorders characterized by defective antibody production, recurrent sinopulmonary infections, and impaired functional antibody response with a prevalence of around 1:25–50,000 [1]. Additional clinical presentations of CVID include autoimmunity, splenomegaly, bronchiectasis, enteropathy, and malignancies [1]. Even though most cases of CVID are sporadic, some have a clear dominant or recessive inheritance pattern. During the last decade, several genes causative of different subgroups of CVID have been described [2]. However, the great majority of patients with CVID still have an unknown genetic etiology.

In 2012, autosomal recessive mutations in *LRBA*, encoding LPS-responsive beige-like anchor (LRBA) protein, were described as a cause of CVID-like disease [3]. LRBA is an intracellular protein belonging to the BEACH-WD40 protein family which also includes Nbea, Nbeal1, Nbeal2, FAN, and LYST [4]. The LRBA protein is widely expressed, with high expression observed in immune cells, particularly lymphocytes [3, 5]. Recently, LRBA was implicated in the regulation of lysosomal degradation of cytotoxic T lymphocytes antigen-4 (CTLA-4), an inhibitory checkpoint receptor on T cells [6]. LRBA deficiency results in increased CLTA4 degradation and clinical manifestations similar to CLTA4 haploinsufficient individuals [7, 8]. Moreover, decreased numbers and function of Treg cells have been reported in LRBA-deficient patients [9].

To date, 30 patients with LRBA deficiency from 20 different families have been reported. Chronic diarrhea and hypogammaglobulinemia are two common denominators of LRBA deficiency [3, 6, 9–14]. Autoimmune cytopenias, lymphadenopathy, lung disease, and recurrent and/or severe infections are frequently observed. Notably, five of the reported patients presented with severe enteropathy and type 1 diabetes, thus resembling immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome [6, 9, 12], and three patients were reported with a presentation resembling autoimmune lymphoproliferative syndrome (ALPS), including presence of elevated double negative T cells and impaired FAS-mediated apoptosis [14]. Thus, the clinical presentation of LRBA deficiency is variable and overlaps with different primary immunodeficiency syndromes. Reported treatment for the LRBA-deficient patient includes corticosteroids, intravenous immunoglobulins (IVIG), infliximab, rituximab, and azathioprine. Of interest, a patient with LRBA deficiency and long-term remission after hematopoietic stem cell transplantation (HSCT) was reported [10]. LRBA patients have also shown response to abatacept, a CTLA-4-Ig fusion protein [6].

Here we present the clinical, immunological, and genetic features of an LRBA-deficient patient with hypogammaglobulinemia, autoimmune cytopenias, endocrinopathy, autoimmune gastrointestinal manifestations, and neurological symptoms who underwent a HSCT with a clear clinical improvement, thus supporting a beneficial effect of HSCT in LRBA-deficient patients with severe disease.

Methods

Genetic Analyses

Blood samples from the patient, prior to the HSCT, and his parents were obtained with informed consent according to the Declaration of Helsinki. Whole exome enrichment and sequencing were performed using the Agilent SureSelect v5 51Mb kit and an Illumina HiSeq2000 sequencer, respectively. Sequencing reads were aligned to the human genome build GRCh37 with BWA/0.7.4 [15], while variant calling and annotation were performed with haplotype caller from the Genome Analysis Toolkit (GATK) (v.3) [16] and variant effector predictor (VEP) (version 75) [17], respectively. Variant filtering was performed using GEMINI (v0.11.0a) [18]. The *LRBA* mutation was Sanger validated using the following primers: 5′-GAGTGATGGATGATGGGACA-3′ as forward primer and 5′-CAGCTTTGTCCAGAAGAGCA-3′ as reverse primer.

Immunological Analyses

Antibodies against CD3 (clone S4.1), CD4 (S3.5), CD8 (3B5), CD20 (2H7), and CD56 (NCAM16.2) were added into absolute counting tubes (Trucount, BD) together with 50 μl heparinized whole blood within 3 h of venipuncture. Red blood cells were then lysed with FACS lysing solution (BD) and the cells evaluated on a cell analyzer (BD LSRFortessa). Absolute numbers of each cell population were determined. Evaluation of lymphocyte cytotoxicity and cytotoxic T cell and natural killer (NK) cell degranulation were performed on bulk PBMC, gated on NK cell (CD56dimCD3-) or cytotoxic T lymphocytes (CD3+CD8+CD57+) as previously described [19].

Results

Clinical Presentation Pre-HSCT

A previously healthy boy, born to consanguineous healthy parents of Turkish origin, presented at the age of 7 years with severe autoimmune hemolytic anemia (AIHA) (Fig. 1a, d) with positive direct Coombs test, hepatosplenomegaly, autoimmune thyroiditis with high titers of TPO-antibodies, and low levels of immunoglobulin G (IgG), M (IgM), and A

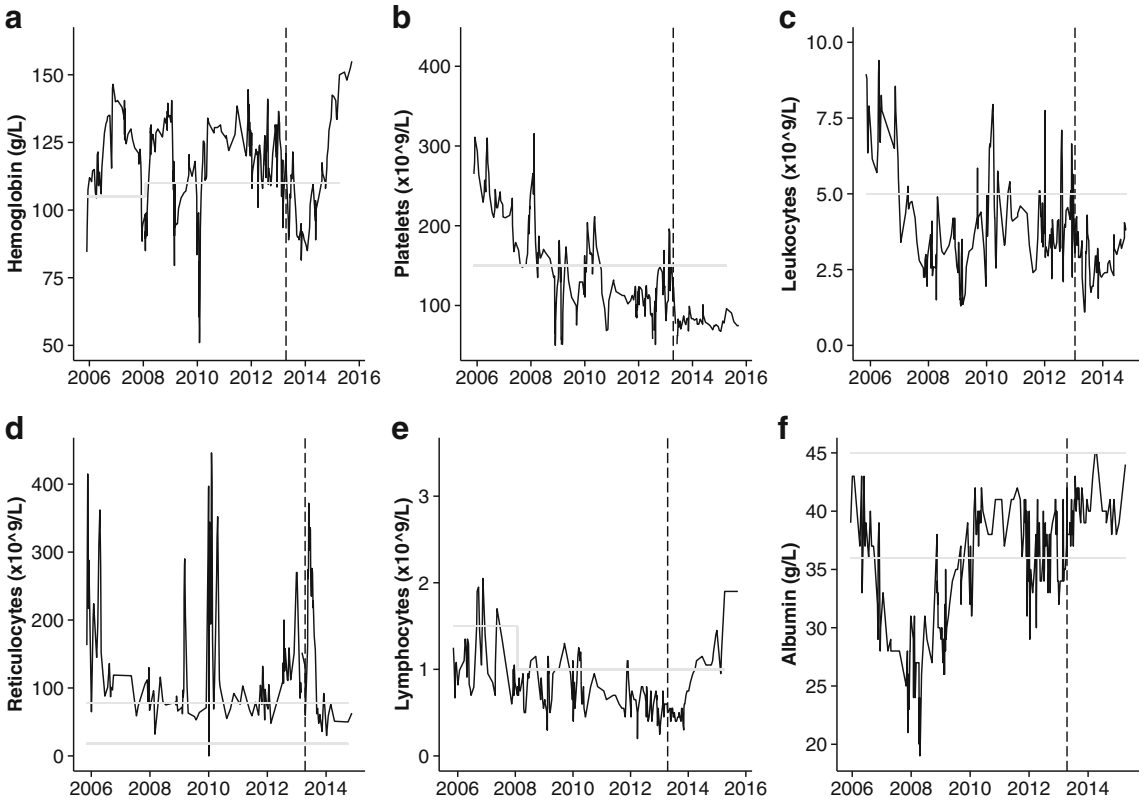

Fig. 1 Laboratory values from diagnosis to 2 years post-HSCT. **a** Values of hemoglobin [reference values: 7–10 years 105–150 g/L, 11–17 years 110–160 g/L]; **b** platelets [reference values: 1–17 years 150–400 × 10^9/L]; **c** leukocytes [reference values: 7–17 years 5–13 × 10^9/L]; **d** reticulocytes [reference values: 18–78 × 10^9/L]; **e** lymphocytes [reference values: 7–11 years 1.5–6.5 × 10^9/L, 11–16 years 1–5.5 × 10^9/L]; **f** and serum albumin [reference values: 0–40 years 36–48 g/L] over time are shown. Laboratory values (except reticulocytes and albumin) are displayed as rolling average of three consecutive values. A *vertical dashed line* represents the time of HSCT

(IgA) (Table 1). In addition to several episodes of AIHA, the patient also displayed recurrent immune thrombocytopenia (ITP) after the age of 10 years (Fig. 1b). The patient was initially treated with oral prednisolone as well as isolated high dose IVIG. The patient also received regular weekly subcutaneous immunoglobulin replacement. Of note, retrospective review of the patient's growth chart revealed failure to thrive from 4.5 years of age.

Shortly after the first episode of AIHA, the patient developed chronic non-bloody, non-mucous diarrhea. Calprotectin in feces was elevated (900–2400 mg/kg). The patient was diagnosed with an inflammatory bowel disease (IBD)-like colitis, but subsequent evaluations rather resembled lymphocytic colitis (Supplementary Fig. 4A–C). Moreover, gastroscopy revealed acute and chronic inflammation and atrophy resembling autoimmune gastritis (Fig. 2a, c). Several polyps in the stomach were noted and later categorized as tubular adenoma with low-grade dysplasia (Fig. 2a). Resembling celiac disease, subtotal villus atrophy was found in the duodenum with increased numbers of lymphocytes as well as macroscopic nodularity (Fig. 2e, g). IgA anti-tissue transglutaminase as well as IgA and IgG anti-deamidated gliadin were negative, possibly reflecting the generally low immunoglobulin level. No disease remission was seen with a gluten-free diet. However, a minor improvement was seen with immunosuppressive therapy, including prednisolone (varying doses), as well as azathioprine. Of note, the diarrhea episodes were more profound at the beginning and improved after the age of 12 years, correlating to increasing levels of serum albumin (Fig. 1f), whereas the patient continued to suffer from stomach pain, bad appetite, and failure to thrive. The patient received both enteral and parenteral nutritional support, the latter with better results. Although a primary growth hormone (GH)-deficiency was not likely, GH was administered. At the age of 14 years, the patient also experienced an episode of pancreatitis with abdominal pain and elevated pancreatic enzymes. The ultrasound scan was compatible with pancreatitis, which we presume was autoimmune mediated (Supplementary Fig. 1A).

The patient suffered from repeated infections, including *Candida albicans* esophagitis (Supplementary Fig. 4E), several *Clostridium difficile* infections, herpes zoster, and infections in the subcutaneous venous port, and therefore repeatedly received broad-spectrum antibiotics iv. During respiratory tract infections, chest X-rays showed bilateral diffuse consolidation and progress of peribronchial cuffing. Later, more nodular opacity was seen by computer tomography (CT) scan and X-rays of the chest (Supplementary Fig. 2A-C). These finding

Table 1 Cellular and serological parameters pre- and post-HSCT

	Pre-HSCT[a]		Post-HSCT (1 year follow-up)		Post-HSCT (2.5 years follow-up)	
Lymphocyte subsets	Absolute ($\times 10^9$/L)	Relative (%)	Absolute ($\times 10^9$/L)	Relative (%)	Absolute ($\times 10^9$/L)	Relative (%)
$CD3^+$	0.92 (0.8–3.5)	*92* (52–78)	*0.63* (0.8–2.1)	71 (63–83)	1.07 (0.8–2.1)	64 (52–78)
$CD3^+CD4^+$	0.65 (0.4–2.1)	*65* (25–48)	*0.41* (0.5–1.3)	46 (35–59)	0.71 (0.5–1.3)	40 (25–48)
$CD3^+CD8^+$	0.23 (0.2–1.2)	23 (9–35)	*0.18* (0.1–0.8)	20 (14–36)	0.30 (0.1–0.8)	19 (9–35)
$CD19^+$	*0.02* (0.2–0.6)	*2* (8–24)	0.14 (0.1–0.4)	15 (9–24)	*0.47* (0.1–0.4)	23 (8–24)
$CD16^+CD56^+$	*0.05* (0.07–1.2)	*5* (6–27)	0.1 (0.07–0.4)	11 (4–17)	0.16 (0.07–0.4)	8 (6–27)
$CD3^+CD4^+CD45RA^+$ (% of $CD3^+CD4^+$)	39		52		ND	
$CD3^+CD4^+CD45RO^+$ (% of $CD3^+CD4^+$)	55		33		ND	
TCR α/β + TCR $D3^+CD4^-CD8^-$ (% of total $CD3^+$)	ND		1.4 (>2)		ND	
CD4/CD8 ratio	2.81 (0.9–3.4)		2.3 (1.13–3.93)		2.4 (1.13–3.93)	
Serum immunoglobulin						
IgG (g/L)	*2.6* (6.1–14.5)[b]		6.5 (6.1–14.5)		7.0 (6.1–14.5)[c]	
IgM (g/L)	*0.2* (0.27–2.1)[b]		*0.20* (0.27–2.1)		0.61 (0.27–2.1)[c]	
IgA (g/L)	*0* (0.7–3.65)[b]		*<0.08* (0.7–3.65)		*0.24* (0.7–3.65)[c]	
Mitogen proliferation assay						
PHA, ConA, PWM	Normal		ND		ND	
Donor chimerism						
CD33 (% donor cells)	NA		98.4		97[c]	
CD3 (% donor cells)	NA		98.6		96.9[c]	
CD19 (% donor cells)	NA		98.8		97[c]	

PHA phytohemagglutinin, *ConA* concanavalin A, *PWM* pokeweed-mitogen, *ND* no data, *NA* not applicable

[a] The data before HSCT is shown at 11 years of age unless specified

[b] At initial diagnosis, 7 years old

[c] At 2 years post-HSCT

Italic was used to highlight values outside the reference range

improved after treatment with corticosteroids. However, a fiberoptic bronchoscopy with bronchoalveolar lavage was normal. Spirometric investigations also yielded normal results.

At the age of 14 years, the patient was admitted to the hospital with a 2-week history of headache and episodes of vertigo, nausea, and vomiting. CT and a magnetic resonance imaging (MRI) revealed multiple lesions resembling acute disseminated encephalomyelitis (ADEM) (Fig. 3a, c). Hemophagocytic lymphohistiocytosis was radiologically considered as a differential diagnosis. No infectious agents were identified in blood and cerebrospinal fluid (CSF). After 10 days, the patient deteriorated with signs of increased intracranial pressure and received a catheter for drainage of CSF. Methylprednisolone pulses were given, followed by tapering doses of prednisolone. The patient also received 2 days of high dose IVIG (1 g/kg), with improvement (Fig. 3b, d). Another similar episode with vertigo and headache occurred 4 months later and new suspected ADEM lesions were seen in the juxtacortical (Fig. 3e, g) and supratentorial region and in the spinal cord. Again, he received 2 days of IVIG. Of note, the patient was hospitalized once before at the age of 10 years for headache and at the age of 13 years he developed pain over his right eye and ear, and a right-sided paresis of the facial nerve.

HSCT

Due to the cumulating severe CVID-related clinical problems, a HSCT was performed at the age of 15 years with bone marrow stem cells (3.2×10^8 total nucleated cells/kg and 3.2×10^6 CD34+ cells/kg) from his human leukocyte antigen (HLA)-identical mother after a reduced intensity conditioning regimen including fludarabin (30 mg/m^2/day −6 to −2) and treosulfan (14 g/m^2/day −6 to −4). ATG was given day −5 to −1 as GVHD prophylaxis. Engraftment, defined as neutrophils more than 0.2×10^9 for more than 2 days, was reached day +13.

Immunological Analyses

Repeated immunological investigations pre-HSCT revealed low total lymphocyte numbers (Fig. 1c, e) with consistently low numbers of B cells as well as NK cells and with time, also reduced numbers of T cells

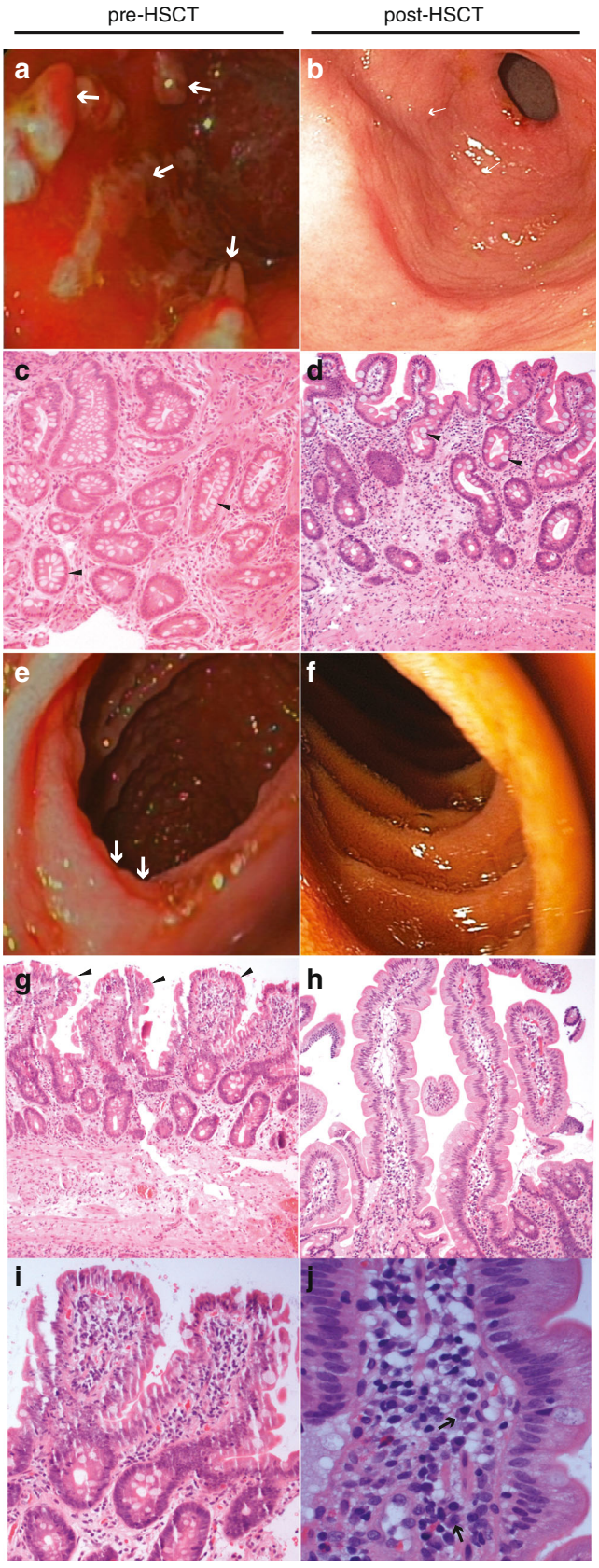

Fig. 2 Endoscopic and histological evaluations of the gastrointestinal tract pre- and post-HSCT. **a** Gastric erythema, loss of vascular pattern, and multiple ulcerated polyps (indicated by *arrows*) 2.5 years after onset of symptoms and 1 year after introduction of gluten-free diet. **b** Normalized signs of vascular pattern and no gastric erythema 21 months post-HSCT, 3 months after introduction of normal diet, and 14 months after last immunosuppressive therapy (prednisolone). **c** Corpus mucosa of the stomach shows chronic active gastritis, total atrophy of specialized parietal-cell containing glands, and extensive intestinal metaplasia (goblet cells indicated by *arrowheads*) (×100 H&E stain). **d** No improvement in the histological appearance of corpus mucosa of the stomach is seen post-HSCT (×100 H&E stain), despite the improvement noted by endoscopy. **e** Swollen mucosa in duodenum with typical scalloping, as indicated by *arrows*, resembling celiac disease pre-HSCT 2.5 years after onset of symptoms and 1 year after introduction of gluten-free diet. **f** Normalized macroscopic findings in duodenum 21 months post-HSCT at the age of 17 years, 3 months after introduction of normal diet. **g**, **i** Duodenal mucosa shows blunt villi (indicated by *arrows*), resembling celiac disease, but lacking plasma cells and therefore suggesting CVID (×100 and ×200 H&E stain). **h** Duodenal mucosa with normalized mucosal architecture (×100 H&E stain) and **j** a normal quantity of plasma cells in the lamina propria (×400 H&E stain)

(Table 1, Supplementary Fig. 3A). Moreover, no antibodies against tetanus were found following vaccination. The T cells demonstrated normal proliferative responses upon stimulation (Table 1). The cytotoxic lymphocyte function and NK cell degranulation against K562 cells were defective on several occasions whereas cytotoxic T cell degranulation was normal (Supplementary Fig. 3B, 3C). Post-HSCT, a recovery has been observed in terms of cell numbers, immunoglobulin levels, and NK cell function (Table 1, Supplementary Fig. 3A–C). Antibody response to re-vaccination post-HSCT against pertussis and polio was seen (response against tetanus has not been tested).

Clinical Recovery Post-HSCT

Tacrolimus was given as graft-versus-host disease (GVHD)-prophylaxis until 19 months post-HSCT. There were no signs of GVHD. Donor/recipient DNA chimerism was analyzed using real-time PCR on a peripheral blood sample. An almost full donor chimerism was detected in all analyzed fractions (1 year post-HSCT CD19 98.8 %, CD3 98.6 %, CD33 98.4 % donor cells; 2 years post-HSCT CD19 97 %, CD3 96.9 %, CD33 97 % donor cells). He received prednisolone and IVIG replacement therapy until, respectively, 6 and 5 months post-HSCT.

A transient episode of hemolysis with increased reticulocytes occurred during the first month post-HSCT (Fig. 1a). Besides this, he has not suffered from further episodes of autoimmune cytopenias. Platelet count has stabilized, although below the reference value (Fig. 1b). He still has mild splenomegaly and still continues thyroid hormone

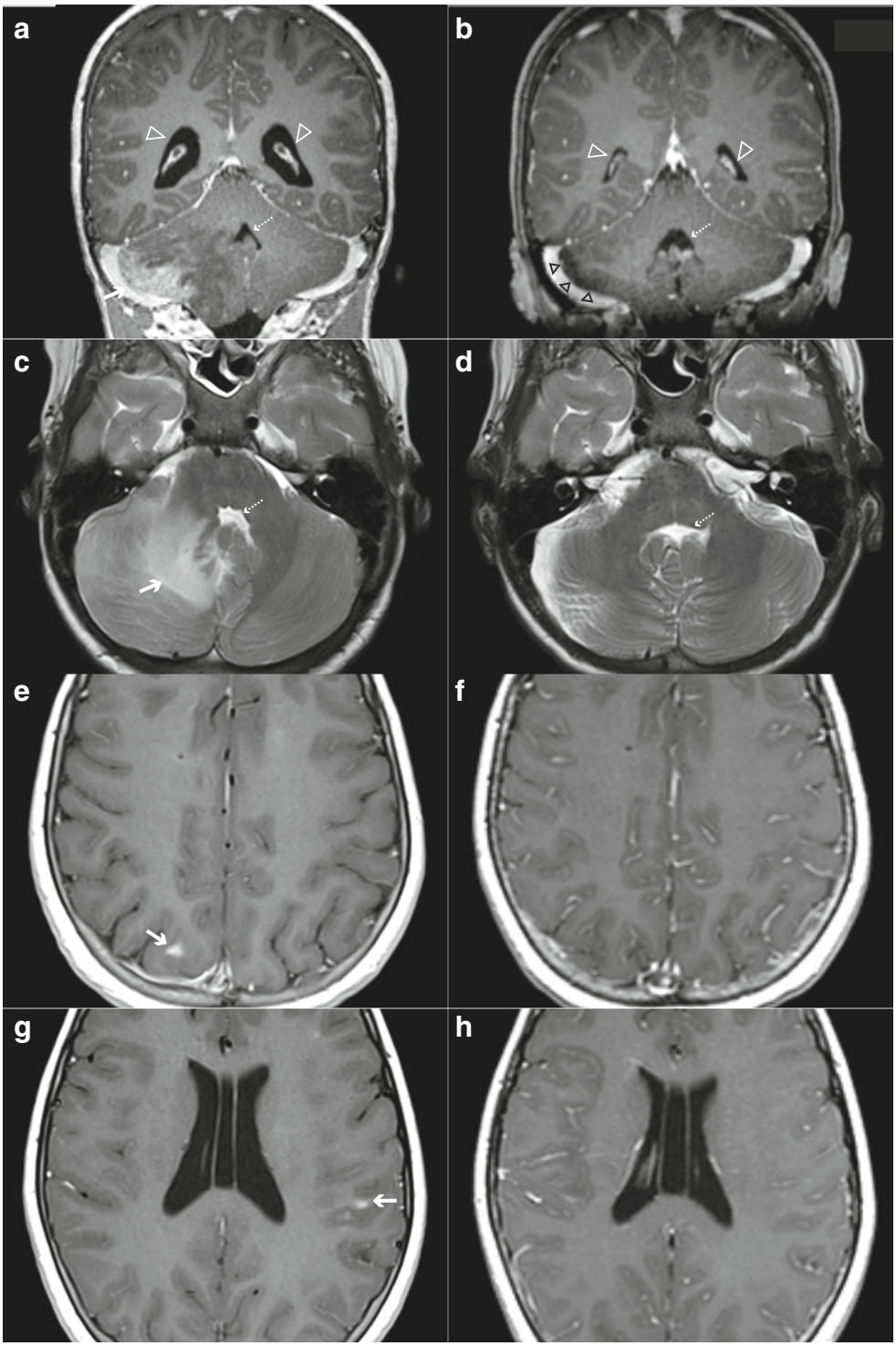

Fig. 3 MRI of the brain. Coronal T1-weighted images after intravenous administration of gadolinium-based contrast medium **(a**, **b)** and axial T2-weighted images **(c**, **d)**. A large lesion (*white arrow*) which exhibited contrast enhancement **(a)** and perifocal edema **(c)** in the right cerebellar hemisphere with compression of the fourth ventricle (*white dashed arrow*) and hydrocephalus (*white arrow heads*) was considered a manifestation of ADEM. The findings resolved after treatment with IVIG and steroids and CSF decompression **(b**, **d)**. After treatment, low signal-intensity **(b)** corresponds to areas of gliosis (*black arrowheads*). Axial T1-weighted images after the intravenous administration of gadolinium-based contrast medium obtained pre- **(e**, **g)** and post-HSCT **(f**, **h)**. In **e** and **g**, two juxtacortical lesions shows contrast enhancement (*white arrows*) and were considered (along with other not shown supratentorial lesions) as further manifestations of ADEM. Post-HSCT therapy both lesions disappeared **(f**, **h)**

replacement therapy. Based on the previous severe growth failure, with short stature, the patient is treated with growth hormone even though he has not been diagnosed with a primary GH-deficiency. A catch-up in length has been observed, without gluten-free diet, with continuing growth.

Post-HSCT, he has not suffered from colitis but was once hospitalized due to a concomitant adeno- and rotavirus infection. Ileocolonoscopy post-HSCT has been completely normal on several occasions (Supplementary Fig. 4D, G). Examinations have shown macroscopic and histological normalization in duodenum (Fig. 2f, h, Supplementary Fig. 4G). The esophagitis has also resolved (Supplementary Fig. 4F). Moreover, autoimmune gastritis has improved, although histological signs are still present (Fig. 2b, d). Some residual

polyps remain and are planned for excision. Pancreatic MRI/MR cholangiopancreatography (MRCP) post-HSCT showed signs equivocal of chronic pancreatitis according to both Cambridge and M-ANNHEIM classification, but no gland atrophy (Supplementary Fig. 1B–F). The patient did not show signs of exocrine or endocrine pancreatic insufficiency.

Repeated follow-up brain MRI post-HSCT revealed regression of the lesions in both brain (Fig. 3f, h) and spinal cord. Sixteen months post-HSCT, he was diagnosed with a left-side paresis of the facial nerve. He improved during antibiotic treatment against borrelia, despite a negative serology. All lung lesions have disappeared post-HSCT (Supplementary Fig. 2D–F). Of unknown etiology, a malformation of the chest close to the sternum as well as in the vertebrae has been noted on CT and MRI examination.

Genetic Analyses

Advancements in sequencing technologies have enabled unbiased genome-wide genetic analyses. Whole exome sequencing (WES) was performed on genomic DNA from the patient, obtained prior to the HSCT, as well as from the parents. Considering the parental consanguinity and lack of disease in the parents, we hypothesized an autosomal recessive inheritance. Trio analysis identified 615 likely damaging variants fitting with an autosomal recessive model, for which the patient was homozygous non-reference and the parents were heterozygous carriers. Having filtered out variants present in the general population, using data from the 1000 Genomes Project and the Exome Aggregation Consortium (ExAC), we were left with eight homozygous variants (Supplementary Table 1). Among these, a 1-bp homozygous deletion in *LRBA* (c.7162delA, p.T2388Pfs*7) causing a stop codon in the BEACH domain of the LRBA protein was identified. The mutation was validated by Sanger sequencing (Fig. 4). The same mutation was recently reported in two siblings with LRBA deficiency [13]. Considering the phenotypic overlap with the previously reported LRBA-deficient patient with the same mutation and other LRBA-deficient patients, the *LRBA* mutation was deemed disease-causing.

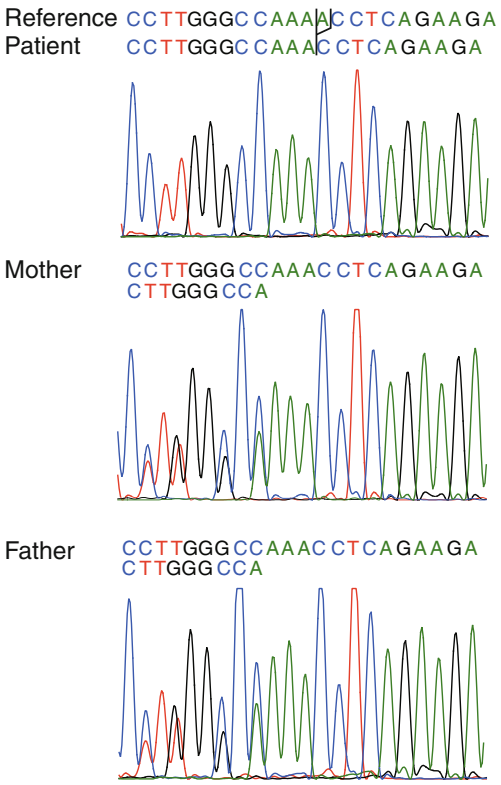

Fig. 4 Results of genetic investigations. Sanger traces for the *LRBA* mutation in the patient, parents, and an unrelated control

Discussion

The 30 LRBA-deficient patients reported to date displayed diverse clinical presentations, with autoimmune cytopenias, enteropathy and hypogammaglobulinemia representing common denominators [3, 6, 9–14]. Consistent with a frameshift mutation causing nonsense mediated decay [13], our patient was severely affected in many organ systems, with AIHA, autoimmune thyroiditis, hypogammaglobulinemia, and a severe enteropathy as initial clinical manifestations. In addition to previously described features of LRBA deficiency, our patient later also developed severe neurological manifestations. Importantly, allogeneic HSCT had a favorable effect, with resolution of majority of the disease manifestations during 2 years of follow-up.

Gastrointestinal investigations during the course of disease revealed autoimmune gastritis, IBD/lymphocytic colitis, pancreatitis, and enteropathy with duodenal histology and macroscopical findings similar to celiac disease. Autoimmune enteropathy and CVID-associated enteropathy may be histologically indistinguishable [20], complicating the diagnostic process like in our case. Autoimmune enteropathy more commonly associates with other gastrointestinal autoimmune disorders and often presents in infancy [20]. Histologic features of celiac disease have been reported in about 30 % of CVID patients with gastrointestinal symptoms or anemia [21] as well as in six LRBA-deficient patients [3, 6, 10–12]. Similarly to previous reports in CVID patients [22], no improvement was seen on a gluten-free diet. Not reported before in other LRBA-deficient patients, our patient had several polyps in the stomach, classified as small tubular adenoma with low-grade dysplasia (Fig. 2a). Of note, these were present prior to GH replacement therapy and treatment with omeprazole. In patients with CVID, nodular lymphoid hyperplasia as well as colorectal polyps, whereof some classified as tubular adenoma with low-grade dysplasia, have been described [23]. A 10-fold increase in stomach cancer has been seen among patients with CVID [24]. Post-HSCT, endoscopic investigation showed complete regression of inflammation and enteropathy in the duodenal mucosa, and inflammation in colon, but persistence of

autoimmune gastritis and dysplastic polyps. Nonetheless, our patient recovered from the gastrointestinal symptoms with marked improvements in appetite and growth.

Autoimmune cytopenias have been seen in approximately 50 % of LRBA-deficient patients [3, 9–14]. Our patient suffered from AIHA and thrombocytopenia. The clinical management of the cytopenic episodes included increased dose of corticosteroids, IVIG, and/or azathioprine. Two years post-HSCT, our patient shows no signs of AIHA and platelets have stabilized, albeit below reference values, indicating at least partial correction of such autoimmune manifestations.

As the most severe presentation, prompting HSCT, our patient developed a severe neurological disease diagnosed as ADEM. Neurological symptoms, including strabismus, abducens nerve palsy, hemiplegia, and seizures, have been described in two other patients with LRBA deficiency. In both patients, radiological examinations revealed granuloma [3]. In an additional patient, inflammatory brain lesions in the form of lymphohistiocytic infiltrates and poorly formed granulomas were reported [6]. Although not commonly associated with immunodeficiencies, ADEM has been described in one patient with CVID and inflammatory brain lesions were reported in CTLA4-haploinsufficient patients [7, 25]. LRBA belongs to the same protein family as LYST. Mutations in *LYST* are associated with Chediak-Higashi syndrome (CHS), a primary immunodeficiency syndrome where progressive neurological symptoms are a feature of the disease regardless of HSCT. Such manifestations likely reflect neuronal expression and function of LYST [26]. Remarkably, post-HSCT, our patient has not suffered from any ADEM-like symptoms. Moreover, follow-up MRI revealed regress of ADEM-like lesions, suggesting a favorable outcome after HSCT also on the neurological involvement of the disease.

Low B cell and NK cell numbers as well as hypogammaglobulinemia were a consistent feature in our patient. While hypogammaglobulinemia and low B cell numbers are common in LRBA-deficient patients, low NK cell numbers have previously been observed only in two patients with LRBA deficiency [4, 7]. Systematic investigations of NK cell function are required to determine if our results reflect an intrinsic NK cell defect in LRBA-deficient patients. Post-HSCT, lymphocyte numbers recovered. Moreover, immunoglobulin levels have normalized and IVIG replacement therapy has thus been discontinued. The resolution of disease manifestations therefore appear directly linked to the recovery from the immunological defects.

Hematopoietic stem cell transplantation, first performed in 1968 in a patient with severe combined immunodeficiency, has become a standard approach for long-term resolution of severe primary immunodeficiencies [27] and has cured IPEX patients [28, 29]. In contrast, the clinical management of CVID is mainly based on IgG replacement therapy, control of symptomatology, and prevention of complications [2]. In CVID, HSCT is indicated upon diagnosis of cancer or in cases of therapy-refractory severe complications [2, 30]. Recently, a LRBA-deficient patient with the same mutation as the one identified in our patient was treated by HSCT [13]. Both that patient and our patient had a beneficial effect of HSCT. However, the previously reported patient suffered from ITP and progressing vitiligo post-HSCT. Similarly, our patient has had persistently low platelets. Furthermore, he still requires thyroid hormone replacement therapy. Of note, anti-platelets antibodies have recently been identified in our patient. The remaining symptoms in these patients could speculatively be related to the HSCT or the fact that both patients received a HSCT with their mothers, heterozygous carriers of the mutation, as donors. Although disease manifestations have not been reported in heterozygous carriers of *LRBA* mutations, the remaining manifestations could represent a phenomenon elicited in the context of immune dysregulation. Another possible explanation would be that HSCT stabilizes but does not cure the disease. However, the great majority of the disease manifestations in our patient have completely disappeared post-HSCT. HSCT was performed on an additional LRBA-deficient patient, but no information concerning outcome was provided [6]. Considering the results from these two cases, HSCT appears as a possible strategy for cure, or at least control, of disease. Nonetheless, the risk of complications following HSCT should be weighed against the clinical presentation in each case and more reports, including patients with other *LRBA* mutations, are needed in order to establish appropriate guidelines for the clinical management of LRBA-deficient patients.

Our patient did not receive a molecular diagnosis until after HSCT. The diagnosis of LRBA deficiency was achieved with the use of WES, thus confirming once more the power of this high throughput sequencing application for the study of patients with suspected primary immunodeficiency.

Conclusions

We report a boy with LRBA deficiency diagnosed by WES. From the age of 7 years, he suffered from hypogammaglobulinemia, severe gastrointestinal disorders, and autoimmune manifestations including cytopenias and a life-threatening ADEM-like disease. Within a 2-year follow-up after HSCT, performed at the age of 15 years, a striking recovery from all major disease manifestations, growth, and overall improvement in quality of life has been observed. Thus, we conclude that HSCT should be considered in patients with LRBA deficiency.

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Author Contributions B.T. performed genetic analyses, interpreted results, and wrote the manuscript; P.P. and F.L. cared for the patient and provided clinical data; S.C.C.C. performed immunological analyses and analyzed data; N.K performed radiological investigations and interpreted results; A.L performed genetic analyses and analyzed data; E.L. performed histopathology investigations and interpreted results; J-I.H. analyzed data; J.W cared for the patient and provided clinical data; Y.T.B. designed research, analyzed data, interpreted results, and contributed to drafting the manuscript; M.M. conceived the study, designed research, analyzed data, interpreted results, and wrote the manuscript. All the authors reviewed and approved the final manuscript.

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