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ORIGINAL ARTICLE

A Novel Missense *LIG4* Mutation in a Patient With a Phenotype Mimicking Behçet's Disease

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Abstract

DNA ligase IV (LIG4) syndrome is a rare autosomal recessive disorder, manifesting with variable immune deficiency, growth failure, predisposition to malignancy, and cellular sensitivity to ionizing radiation. The facial features are subtle and variable, as well. Herein, we described an 18-year-old boy, the first child of consanguineous parents who presented with Behçet's disease (BD)-like phenotype, developmental delay, and dysembryoplastic neuroepithelial tumor (DNET). Whole-exome sequencing revealed a homozygous p.Arg871His (c.2612G > A) mutation in *LIG4*. To date, 35 cases have been reported with LIG4 syndrome. Peripheral blood mononuclear cells of the patient displayed notable sensitivity to ionizing radiation. Flow cytometric annexin V-propidium iodide (PI) and eFluor670 proliferation assays showed accelerated radiation-induced apoptosis and diminished proliferation, respectively. To our knowledge, this is the first case presenting with a BD-like phenotype. This case provides further evidence that rare monogenic defects could be the underlying cause of atypical presentations of some well-described disorders. Moreover, this clinical report further expands the phenotypical spectrum of LIG4 deficiency.

Keywords DNA ligase IV · LIG4 syndrome · Behçet's disease · whole exome sequencing

Introduction

DNA ligase IV (LIG4) syndrome (MIM 606593) is a rare autosomal recessive disorder, characterized by variable immune deficiency, variable growth failure, predisposition to malignancy, and cellular sensitivity to ionizing radiation caused by homozygous or compound heterozygous mutation in *LIG4* [1]. LIG4 and its interaction partner XRCC4 play an essential role in V(D)J recombination and repairing DNA double-strand breaks (DSB) by non-homologous end-joining (NHEJ) mechanism [1, 2]. XRCC4 and XLF act as a stabilizer for LIG4 and formation of XRCC4-XLF-LIG4 complex plays an essential role in NHEJ pathway [3]. Absence of either of these factors may lead to a molecular mechanism of impaired NHEJ. This complex is required for preventing mutagenesis and apoptosis, which can arise from DNA double-strand breaks caused by intracellular or extracellular events such as DNA replication or chemotherapeutic agents, reactive oxygen species, and ionizing radiation, respectively [4]. The first patient described with a *LIG4* mutation was a developmentally and clinically normal 14-year-old boy with acute lymphoblastic leukemia who died from radiation-induced encephalopathy after he received prophylactic cranial radiotherapy following chemotherapy [5]. Since this first patient, only 35 patients with LIG4 syndrome have been described to date with a range of presentations including variable immune

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deficiency, growth failure, predisposition to malignancy, and cellular sensitivity to ionizing radiation [5–20].

Herein, we present a new patient with *LIG4* mutation who presented with growth delay, dysembryoplastic neuroepithelial tumor (DNET), and a phenotype mimicking Behçet's disease (BD).

Case Report

An 18-year-old boy presented initially to our clinic with the complaints of fever, headache, and vomiting when he was 10 years old. His parents were first cousins (Fig. 1a). On neurological examination, neck stiffness along with Kernig's and Brudzinski's signs was positive. Fundus examination was normal. He was initially diagnosed with meningitis. His past medical history revealed four similar previous meningitis episodes during the last 3 years. However, no microbiologic agent could be isolated in any of these occasions. He was treated with intravenous antibiotics and complete recovery was achieved each time. In the last 2 years, he also suffered from intermittent attacks of non-erosive arthritis and recurrent oral and genital ulcers. He did not have mutations in the *MEFV* checked for familial Mediterranean fever (FMF). He had no history of trauma, otorrhea, rhinorrhea, or any history suggestive of chronic infection of parameningeal structures/spaces or immunosuppressive treatments. During subsequent hospitalizations with meningitis, primary or secondary immunodeficiencies were ruled out (Table 1). Computerized tomography (CT) cisternogram was normal.

He was re-evaluated for recurrent meningitis in our hospital at the age of 10. Body weight was 21 kg (< 3rd percentile), body height was 119 cm (< 3rd percentile), and head circumference was 52 cm (50th percentile). He had high forehead, mild hypertelorism, malar hypoplasia, retrognathia, pes planus, and clinodactyly. The cerebrospinal fluid (CSF) examination showed pleocytosis (400 cell/mm^3; 96% lymphocytes), high protein level (44 mg/dL), and low glucose level (35 mg/dL; with a simultaneous blood glucose level of 106 mg/dL). Bacterial, tuberculosis, and fungal cultures were all negative. Endocrine tests were performed for growth delay. Serum insulin-like growth factor 1 (IGF-1) level, thyroid hormones, and the growth hormone stimulus test were all normal. In cranial magnetic resonance imaging (MRI), a lesion in the left temporal cortex consistent with dysembryoplastic neuroepithelial tumor (DNET) was detected (Fig. 2). Audiological assessment was normal. Pathergy test was negative and human leucocyte antigen (HLA)-B51 was positive. He was initially diagnosed with BD due to recurrent aseptic meningitis, oral, and genital aphthous lesions. Prednisolone (1 mg/kg/day) and colchicine were administered. He completely recovered after these treatments.

During the follow-up, prednisolone treatment was tapered and stopped after 6 months. Then, he was admitted to hospital with red-blurry eyes at the age of 12 years. Anterior uveitis was diagnosed and azathioprine (1.5 mg/kg/day) therapy was initiated.

The patient is currently 18 years old and is now stable on colchicine and azathioprine with intermittent flares of oral and genital ulcers. He did not have any further meningitis episodes. He underwent cranial MRI annually due to DNET; the lesion was stable. Thus, it was not resected.

Genomic DNA was extracted by standard phenol-chloroform protocol from peripheral blood of index case and family members after the receipt of the informed consent. Ion AmpliSeq™ Exome RDY Kit was used for amplification of the target regions. Emulsion PCR was performed on Ion OneTouch™ 2 instrument using the Ion PI Hi-Q OT2 200 Kit, and enrichment of Ion Sphere Particles (ISP) was performed using the One Touch™ ES module. Enriched ISPs were loaded on Ion PI chips then sequenced on Ion Proton™ platform according to the manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA, USA).

Exome sequencing was performed for index case. Torrent Mapping Alignment Program (TMAP) was used for aligning reads to the hg19/GRCh37 human reference genome. Raw sequence file was processed using the Torrent Suite software v5.0.5 for generating mapped reads, analyzing coverage data and variant calling. All variants that passed the quality score filters were annotated with the Ion Reporter™ 5.2 software. We applied variant filtration steps as stated in Fig. 1b. After filtering steps, 17 homozygous rare variants remained as candidate. We used AgileVCFMapper, a software that performs mapping of disease loci by SNP genotyping using VCF file obtained from exome sequence data, to identify the Runs of Homozygosity (ROH) in index cases [21]. All Human Gene Mutation Database/HGMD-linked mutations were ruled out with Ingenuity Variant Analysis software (IVA/QIAGEN Bioinformatics). Sanger sequencing was performed by using the BigDye Terminator v.3.1 Cycle Sequencing Kit and sequenced with ABI 3130 genetic analyzer (Thermo Fisher Scientific, Waltham, MA, USA). The primers used to amplify and sequence the target region are as follows: LIG4_3F:AAAGCCTGACCTGGAGAA–LIG4_3R:GCTTTCCTCACTAGGAAACC.

Through 17 homozygous candidate variants filtered from whole-exome sequencing data, one was located in X chromosome. That alteration was ruled out due to pedigree analysis. Only four genes were associated with a disease phenotype in OMIM database (*UROC1*, *CCDC39*, *FLT3*, and *LIG4*). Among them, variants in *UROC1*, *CCDC39*, and *LIG4* were classified as "disease causing" and "damaging" with three different variant effect prediction tools (MutationTaster, PolyPhen2, and SIFT). The p.Arg871His (c.2612G > A)

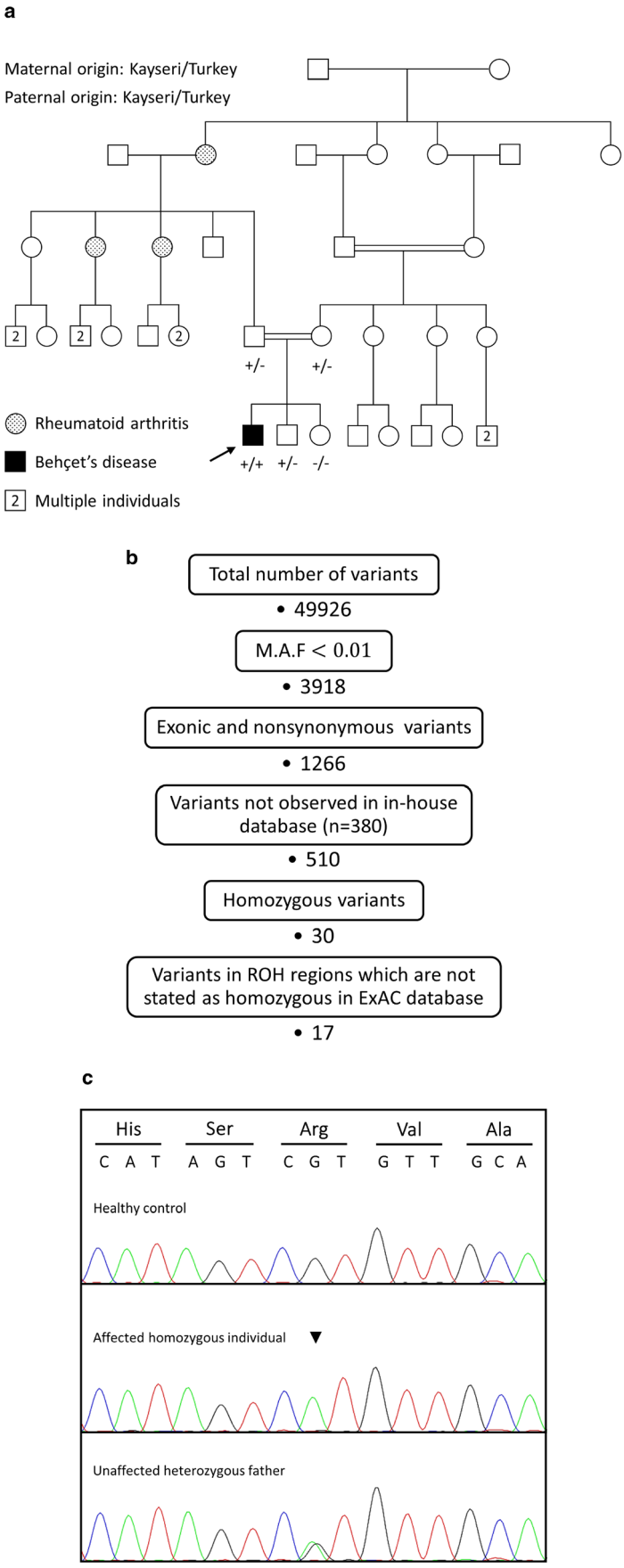

Fig. 1 **a** The pedigree of affected individual and segregation of the p.Arg871His variant in *LIG4*. Based on the pedigree size, we indicated multiple individuals as numbers. **b** Variant filtering strategy. After filtering steps, 17 functional candidate variants were selected for further analysis. **c** Sanger sequencing of p.Arg871His variant in *LIG4*. Healthy individual, homozygous patient and heterozygous carrier father from top to bottom

Table 1 Immunological analyses of the patient with *LIG4* mutation when he was 10 years old

Complete blood count	
Hemoglobin (g/dl)	13.2 (12.5–16.1)
White blood cell counts (10^3/mm^3)	9.3 (4–10.5)
Platelet (10^3/mm^3)	289 (150–400)
Absolute lymphocyte count (10^3/mm^3)	2.6 (1.5–3)
Absolute neutrophil count (10^3/mm^3)	5.9 (3–5.8)
Absolute eosinophil count (10^3/mm^3)	0.1 (0.5–2.5)
Immunglobulins (Ig)	
IgG[a] (mg/dL)	966 (608–1572)
IgM[a] (mg/dL)	78 (52–242)
IgA[a] (mg/dL)	113 (45–236)
Lymphocyte subgroups	
CD3$^+$ T cell (%)	79 (56–84)
CD4$^+$ (%)	30 (31–52)
CD8$^+$ (%)	44 (18–35)
CD19$^+$ (%)	10 (6–23)
CD16 + 56 (NK[a]) (%)	10 (3–22)
NBT[a] test (%) (compared with healthy control)	100
Anti-nuclear antibody	Negative
Anti-double-stranded DNA antibody	Negative
Antibodies to extractable nuclear antigens	Negative
Anticardiolipin and beta-2 glycoprotein antibody IgG and IgM	Negative

NBT nitroblue tetrazolium, NA not available, NK natural killer

[a] Numbers in parenthesis are the reference values, and these values were tested when the patient was not under immunosuppressive therapy

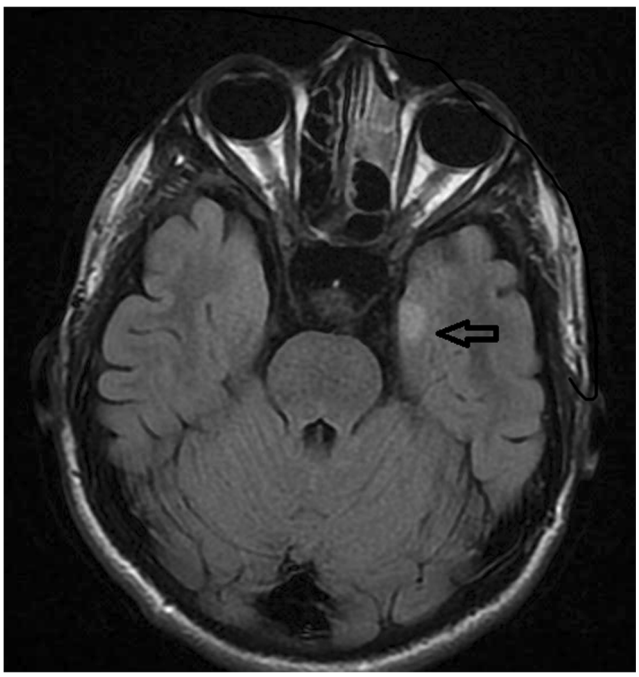

Fig. 2 Cranial magnetic resonance imaging. A lesion in the left temporal cortex consistent with dysembryoplastic neuroepithelial tumor (DNET)

variant in *LIG4* gave the highest CADD score (25.6) between these three variants (Supplementary Table 1). This p.Arg871His variant was observed in dbSNP with "rs183928755" ID, and ExAC database showed that four unrelated individuals were heterozygous carriers for that alteration with a low minor allele frequency (MAF 0.00003301). The p.Arg871His (c.2612G > A) variant in *LIG4* was further verified by conventional sequencing, and segregation within family members showed that father, mother, and the younger unaffected male sibling were all heterozygous carriers for this alteration (Fig. 1c). The youngest unaffected female sibling was not carrying p.Arg871His variant on both alleles. Besides, this genetic change was not present in our in-house database established within "Hacettepe Exome Project," which comprises 380 clinically unrelated Turkish individuals.

Since the increased sensitivity to ionizing radiation is a facet of LIG4 syndrome [1], the peripheral blood mononuclear cells (PMBCs) of the patient with missense *LIG4* mutation were irradiated. Flow cytometry (FACSAria II, Becton Dickinson, San Jose, CA, USA) was used to determine the percentage of the cells in early (annexin V$^+$PI$^-$) and late (annexin V$^+$PI$^+$) stages of apoptotic cell death (Annexin V Apoptosis Detection Kit, Biolegend, San Diego, CA, USA). Moreover, the proliferation capacities of irradiated PBMCs were also tested with eFluor670-based flow cytometric assay (eBioscience, San Diego, CA, USA). Lymphocytes were stimulated in vitro with anti-CD3 monoclonal antibody (mAb; HIT3a, eBioscience) and recombinant human IL-2 (rhIL-2, Biolegend) for 72 h, and the percentage of proliferated cells were determined according to the dilution of eFluor670 fluorescence. PBMCs from two individuals were used as controls and the experiments were run in duplicates. Apoptotic cell death was accelerated among the lymphoid cells obtained from the LIG4 patient compared to the samples of control individuals (Fig. 3a, b). Flow cytometric analysis revealed a significant sub-population with annexin V and PI positivity at 24 h that accumulated in the late stage of apoptosis (annexin V$^+$PI$^+$ cells following 5-Gy radiation: LIG4 syndrome patient, 26.8%; control individuals 13.7–14.7%) (Fig. 3a). Moreover, a proliferation block was observed in the irradiated lymphocytes of the LIG4 syndrome patient. The cells with missense *LIG4* mutation were less responsive to the anti-CD3 mAb and rhIL-2 proliferation stimuli (proliferated cells, 36.2%) than those from the controls (proliferated cells, 50.4–66.2%) (Fig. 3c).

Discussion

We describe a patient with a novel missense mutation in *LIG4*, presenting with a BD-like phenotype. However, it is difficult to distinguish whether BD is related with LIG4 syndrome or it is a coexistence of two different diseases. LIG4 syndrome is a

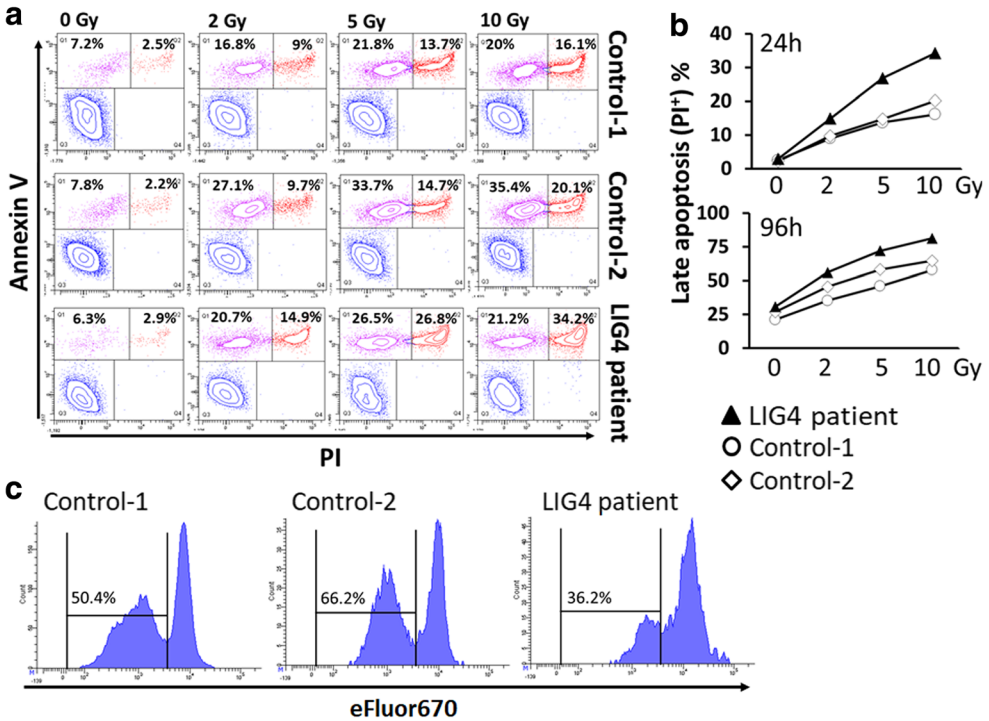

Fig. 3 **a** The peripheral blood mononuclear cells (PBMCs) were irradiated (0, 2, 5, and 10 Gy) and apoptotic cell death was analyzed at 24 h with annexin V-propidium iodide (PI) staining. Representative flow cytometry plots are given together with the results of two control samples. Annexin V^+PI^- early apoptotic cell (in purple) and annexin V^+PI^+ late apoptotic cell (in red) populations can be seen in the upper left and the upper right quadrants of the contour plots, respectively. **b** The percentages of lymphoid cells that accumulated in late apoptosis phase at 24 h and 96 h are shown. **c** The irradiated (10 Gy) PBMCs were labeled with eFluor670 proliferation tracer and stimulated for 72 h in the presence of anti-CD3 monoclonal antibodies and recombinant IL-2. The percentage of proliferated cells was determined according to eFluor670 dilution under the viability gate

rare disorder with only 35 patients described so far in the literature [5–20]. Previously described five mutations that located in XRCC4 binding domain of the LIG4 which cause DNA ligase IV syndrome were loss-of-function non-sense mutations or small INDELs [14, 15, 22]. The p.Arg871His missense variant reported in this manuscript is also located in XRCC4 binding domain of DNA ligase IV, and we hypothesized that this novel variant can possibly disrupt the LIG4-XRCC4 interaction and affect NHEJ mechanism. Different phenotypic findings represented in this manuscript can arise from indicated novel rare missense variant which might cause a partially functional LIG4 protein product in contrast with previously described truncating mutations. The p.Arg871His alteration may affect the LIG4-XRCC4 interaction and the function of XRCC4-XLF-LIG4 complex. Less severe growth failure observed for this patient may arise from indicated novel rare missense variant located in the XRCC4 binding domain of LIG4. The p.Arg871His alteration could possibly have a minor effect on LIG4-XRCC4 binding while previously reported truncating mutations completely or partially removes

Table 2 Comparison of the clinical features of the LIG4 syndrome patients reported so far ($n = 35$) and the present patient

Clinical findings	Number of patients, *n* (%) [35]	The present patient
Microcephaly	33 (94.3)	No
Growth delay	33 (94.3)	Yes
Facial dysmorphology	15 (42.8)	Yes
Bone abnormalities	11 (21.4)	Yes
Delayed puberty	3 (8.8)	Yes
Skin lesions	10 (29.5)	No
Immunodeficiency	25 (73.5)	No
Autoimmunity	1 (2.9)	No
Malignancy	9 (25.7)	DNET

DNET dysembryoplastic neuroepithelial tumor

this domain. Individuals with mutations in XRCC4 may present without any overt symptoms of immunodeficiency [3]. Moreover, the increased sensitivity of the patient's blood cells to radiation-induced apoptosis and proliferation block was regarded as a functional evidence for LIG4 syndrome.

LIG4 syndrome has a broad spectrum of phenotype, including variable immune deficiency, variable growth failure, malignancy predisposition, and cellular sensitivity to ionizing radiation [1]. Additional features include bony deformations, skin features, and susceptibility to malignancy [1]. Although it is classified as a primary immunodeficiency syndrome, the finding of immunodeficiency may not be present in every patient. Some patients may present with malignancy or severe growth delay as initial findings [5, 14, 20]. The clinical severity of LIG4 have presented with leukemia, LIG4 syndrome, Dubowitz syndrome, Omenn syndrome, and radiosensitive severe combined immunodeficiency (Table 2). A case with autoimmune hemolytic anemia was also reported [1]. This is the first patient with a *LIG4* mutation presenting with a BD-mimic. BD is a variable vessel vasculitis, characterized by multi-system involvements [23]. According to the pediatric BD [PEDBD] group criteria, our patient was classified as having BD with the presence of recurrent oral and genital aphthosis, uveitis, and neurologic involvement [23]. Although previous studies have demonstrated an association between systemic vasculitides and primary immunodeficiency such as Wiskott-Aldrich syndrome (WAS) and interleukin-12 receptor beta-1 (IL-12Rβ1) deficiency [24, 25].

Although not universal, one of the most common findings of LIG4 syndrome is congenital non-progressive microcephaly. Interestingly, the patient described here does not have microcephaly. However, he had a postnatal onset of growth delay.

There is no standard treatment of LIG4 syndrome. The main therapy is conservative, including antibiotic prophylaxis, immunoglobulin replacement, and providing support for bone marrow hypoplasia. In addition, patients should be warned to avoid ionizing radiation. Hematopoietic stem cell transplantation (HSCT) may be a curative treatment of choice. However, outcomes of HSCT in these patients are restricted by sensitivity of radiation and alkylating agents. Thus, conditioning regimes should be personalized in these patients. For instance, O'Driscoll M et al. have demonstrated that CsA may result to increase levels of DNA double-strand break in LIG4 syndrome [26]. Until now, ten patients have been treated with HSCT [7–11, 13, 15, 17, 27] among whom four died because of the complications such as multi-organ failure, Epstein-Barr virus-driven lymphoproliferative disease, and hepatic veno-occlusive disease.

In conclusion, LIG4 syndrome is a rare disease with a broad spectrum of presentations. The finding of BD-like phenotype might further expand the phenotypic spectrum of this rare entity.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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