

Cytotoxic T-cell lymphoma with muscle involvement and germline variants in inborn error of immunity-related genes: clinical and genetic insights from a case series

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of mature T-cell and natural killer cell neoplasms with aggressive clinical behavior and poor outcomes.^{1,2} Although recurrent somatic mutations involving epigenetic regulation and T-cell receptor signaling have been identified in PTCL,³ the molecular drivers and genetic susceptibility underlying disease development, particularly in young patients, remain incompletely understood.

Inborn errors of immunity are inherited disorders of immune development and function that predispose affected individuals to infections, immune dysregulation, and malignancies, particularly lymphomas.^{4–8} Accordingly, there is growing interest in identifying inborn errors of immunity in patients presenting with lymphoid malignancies, and current guidelines recommend genetic screening for pediatric and adolescent cancer patients to uncover underlying immune defects.

Here, we report six young adults with cytotoxic PTCL characterized by prominent skeletal muscle involvement. All patients underwent whole-exome sequencing (WES) using peripheral blood DNA, and peripheral blood smears showed no morphologic evidence of circulating lymphoma cells. Heterozygous variants in inborn error of immunity-related genes were identified in all six cases. Tumor samples from all cases underwent targeted next-generation sequencing (NGS) using a 413-gene panel covering recurrent lymphoma-related genes. We summarize their clinical, pathological, and genetic features and discuss potential links between immune dysregulation and this unusual disease presentation. The study was approved by the institutional review board of Peking Union Medical College Hospital and was done in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Case 1

A 19-year-old male presented with a 1-year history of tongue swelling and a 3-month history of right maxillofacial mass. Progressive tongue enlargement with ulceration and movement restriction was initially responsive to corticosteroids but relapsed after discontinuation. Lower lip biopsy showed dense lymphocytic aggregates in the submucosa. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma (Table 1), and supportive of PTCL not otherwise specified (PTCL-NOS). Clonal T-cell receptor (TCR) V β rearrangement was detected by polymerase chain reaction (PCR). Positron emission tomography/computed tomog-

raphy (PET/CT) revealed intense 18F-fluorodeoxyglucose (FDG) uptake in the oropharynx, cervical lymph nodes, and paraspinal muscles (Figure 1A). WES identified heterozygous *UNC13D* c.1352C>T and *STX11* c.401C>G variants. The patient was refractory to CHOP but achieved complete remission after etoposide-based therapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Case 2

A 22-year-old male presented with progressive swelling of the left face and forearm. Biopsies of the upper lip and masseter muscle demonstrated dense lymphocytic infiltration of skeletal muscle fibers, with immunophenotypic findings consistent with cytotoxic T-cell lymphoma. Clonal TCR rearrangement was detected by PCR. PET/CT showed multifocal muscular involvement (standardized maximum uptake value [SUV_{max}] 25.2; Figure 1B). WES revealed a heterozygous *IL7R* c.314G>A mutation. After failure of azacitidine, chidamide, and CHOP, the patient achieved symptom relief with golidocitinib and is scheduled for allo-HSCT.

Case 3

An 18-year-old male presented with eyelid and maxillofacial swelling, fever, and lower limb myalgia. Laboratory tests showed cytopenia. Bone marrow examination revealed hemophagocytosis. Biopsy of the right buccal mass demonstrated dense lymphocytic infiltration within skeletal muscle fibers with immunophenotypic findings consistent with cytotoxic T-cell lymphoma. Clonal TCR rearrangement was detected by PCR. PET/CT revealed extensive muscular and craniofacial lesions (SUV_{max} 19.6; Figure 1C). A heterozygous *IFIH1* c.229C>T variant was detected. Treatment with golidocitinib plus CHOP induced complete remission, followed by auto-HSCT, with sustained remission.

Case 4

A 20-year-old male had a 5-year history of episodic forearm swelling and fever, followed by progressive facial involvement. He was initially diagnosed with focal myositis and treated with immunosuppressive therapy, with temporary relief. The disease later progressed to involve the orbit, eyelids, and lips, causing swelling, erosion, and trismus. Lip mucosal biopsy showed dense lymphocytic aggregates in the submucosa with a perivascular growth pattern and angioinvasion. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma and supportive of PTCL-NOS. PET/CT showed diffuse muscular and subcu-

Table 1. Clinical characteristics, immune-related features, treatment, and outcomes of the patients.

Patient	Sex/age, years	Major clinical symptom	BM and PB	Prior immune disorders	Key lab findings	Pathology features	TCR rearrangement	PIT score	Treatment and response	Status at last follow-up	Follow-up, months
Case 1	M/19	Painful swelling of the tongue, facial mass	Unremarkable	None	Unremarkable	CD3 ⁺ , CD5 ⁺ , CD7 ⁺ , CD8 ⁺ , granzyme B ⁺ , TIA-1 ⁺ , EBER-ISH ⁺ , Ki-67 80%	Clonal	1	CHOP→SD→allo-HSCT	Alive, ongoing CR	36
Case 2	M/22	Left facial and forearm swelling	Unremarkable	None	Unremarkable	Cytotoxic T-cell phenotype, EBER-ISH ⁺ , Ki-67 60%	Clonal	2	Azacitidine and chidamide plus CHOP→SD→golidocitinib	Alive, scheduled for allo-HSCT	25
Case 3	M/18	Eyelid and maxillofacial swelling, fever, lower limb myalgia	HLH and leukopenia	None	Low IgM	Cytotoxic T-cell phenotype, EBER-ISH ⁺ , Ki-67 80%	Clonal	1	Golidocitinib plus CHOP→CR→auto-HSCT	Alive, ongoing CR	18
Case 4	M/20	Recurrent fever, forearm swelling, facial/lip swelling	Unremarkable	Focal myositis (5 years earlier)	Elevated CK	Cytotoxic T-cell phenotype, EBER-ISH ⁺ , Ki-67 60%	NA	1	CHOP→not evaluated	Alive, supportive care	9
Case 5	M/16	Progressive lip swelling	Unremarkable	Inflammatory myopathy (3 years earlier)	Elevated CK	Cytotoxic T-cell phenotype, EBER-ISH ⁺ , Ki-67 60%	Clonal	1	Chidamide plus CHOP→CR→allo-HSCT	Alive, ongoing CR	9
Case 6	M/19	Mandibular/orbital swelling, fever, diffuse myalgia	Unremarkable	Autoimmune encephalitis (1 year earlier)	Low IgA, IgM, IgG, and elevated CK	Cytotoxic T-cell phenotype, EBER-ISH ⁺ , Ki-67 60%	NA	1	Golidocitinib plus CHOP→CR	Alive, on treatment	6

allo-HSCT: allogeneic hematopoietic stem cell transplantation; auto-HSCT: autologous hematopoietic stem cell transplantation; BM: bone marrow; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CK: creatine kinase; CR: complete remission; EBER-ISH: Epstein–Barr virus–encoded RNA *in situ* hybridization; F: female; HLH: hemophagocytic lymphohistiocytosis; lab: laboratory; M: male; NA: not available; PB: peripheral blood; PIT: prognostic index for PTCL-NOS; SD: stable disease; TCR: T-cell receptor.

taneous lesions (SUV_{max} 35.9; Figure 1D). WES identified a heterozygous *LRBA* c.1570G>A mutation. CHOP resulted in partial symptomatic improvement, and he subsequently received supportive treatment.

Case 5

A 16-year-old male presented with progressive lip swelling. Four years earlier, he had been diagnosed with inflammatory myopathy which improved after corticosteroids and immunosuppressive therapy. At the current presentation, he developed bilateral lip swelling. Laboratory tests revealed elevated creatine kinase (CK). Biopsy of the lip mucosa demonstrated focal submucosal lymphocytic infiltration with neurovascular involvement. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma, and clonal TCR rearrangement was detected by PCR. PET/CT showed diffuse skeletal muscle involvement (SUV_{max} 30.8; Figure 1E). A heterozygous *PRF1* c.1429C>A mutation was detected. The patient achieved complete remission after chidamide plus CHOP and underwent allo-HSCT, remaining in remission.

Case 6

A 19-year-old male presented with mandibular and orbital

swelling, fever, and generalized myalgia. One year earlier, he had been diagnosed with autoimmune encephalitis because of recurrent seizures. Laboratory tests revealed elevated lactate dehydrogenase and CK levels. Biopsy of the right upper arm muscle demonstrated extensive infiltration by medium-sized lymphocytes with irregular nuclei and mitotic figures within skeletal muscle fibers. Immunophenotypic findings were consistent with cytotoxic T-cell lymphoma, and the pathologic findings supported PTCL-NOS. PET/CT demonstrated diffuse muscular involvement, including the diaphragm (SUV_{max} 18.3; Figure 1F). WES revealed heterozygous *PRF1* c.1153C>T and *UNC13D* c.2588G>A mutations. Treatment with golidocitinib plus CHOP resulted in interim complete remission, and therapy is ongoing. This case series describes a distinctive subset of young patients with cytotoxic phenotype PTCL characterized by predominant skeletal muscle involvement and heterozygous germline variants in inborn error of immunity-related genes. The association between inborn errors of immunity and lymphoid malignancies has been increasingly recognized, with reported cancer risks ranging from 10% to 25%.^{7,9} While B-cell lymphomas are the most commonly reported malignancies in the inborn error of immunity population,

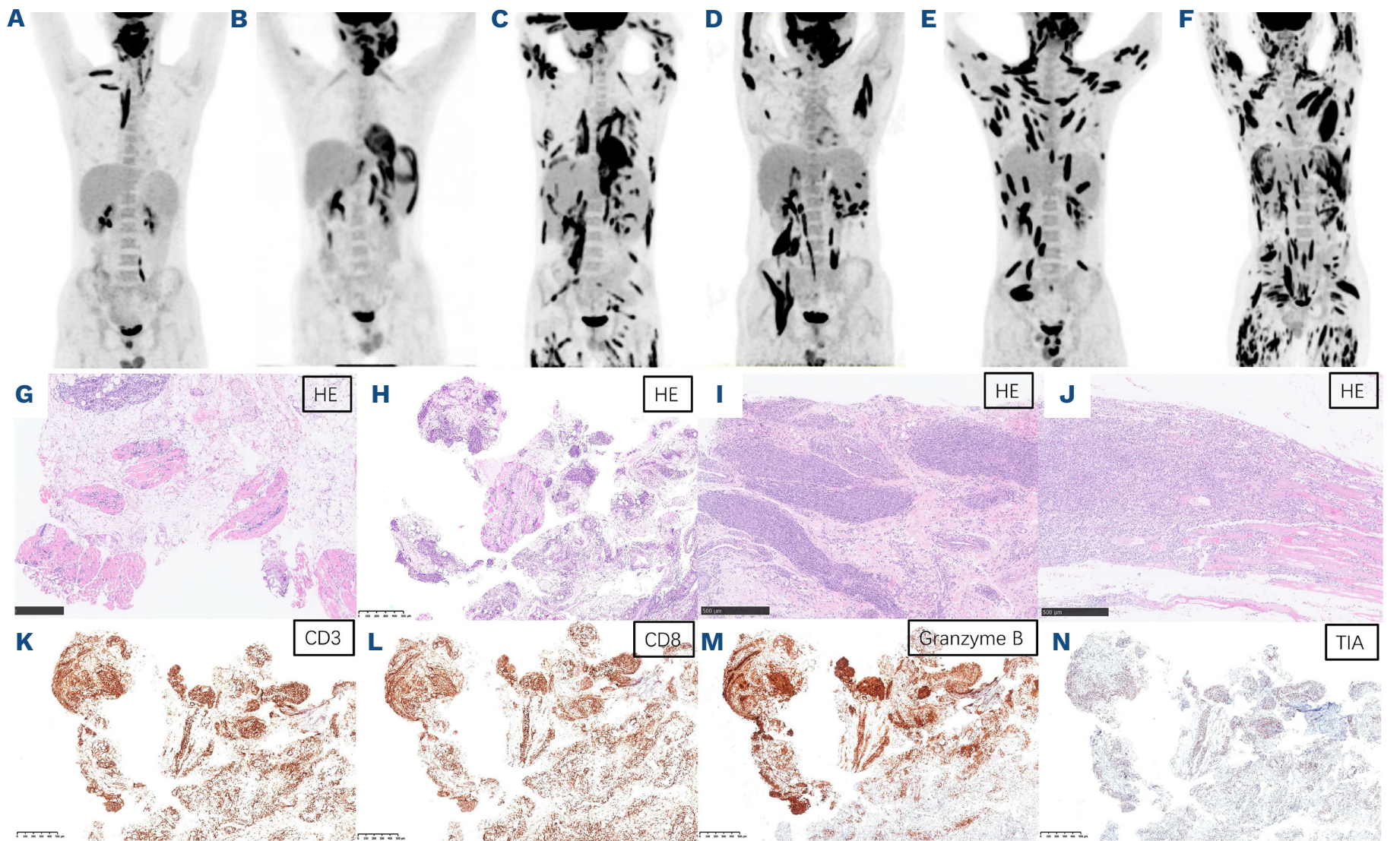


Figure 1. Representative imaging and histopathologic findings of the cohort. (A–F) Positron emission tomography/computed tomography (PET/CT) images of cases 1–6, respectively. (G) Hematoxylin and eosin (H&E) staining of the right buccal mass biopsy from case 3. (H, I) H&E staining of lip biopsies from cases 4 and 5, respectively. (J) H&E staining of the right upper arm muscle biopsy from case 6. (K–N) Immunohistochemical staining of the lesion from case 4 showing positivity for CD3 (K), CD8 (L), granzyme B (M), and TIA-1 (N) (original magnification, ×400). Scale bar =500 μm.

Table 2. Variant details and clinical significance.

Patient	IEI-related germline mutation	Gene	cDNA/protein change	VAF	Associated IEI condition	ACMG interpretation	SIFT prediction	Somatic mutations in tumor	Somatic mutation types
Case 1	UNC13D and STX11 heterozygous mutations	UNC13D	c.1352C>T, p.Thr451Ile	NA	FHL type 3	Uncertain significance	Damaging	ND	
		STX11	c.401C>G, p.Ala134Gly	NA	FHL type 4	Uncertain significance	Tolerated		
Case 2	IL7R heterozygous mutation	IL7R	c.314G>A, p.Ser105Asn	47%	IL7R deficiency	Uncertain significance	Tolerated	ND	
Case 3	IFIH1 heterozygous mutation	IFIH1	c.229C>T, p.Arg77Trp	48%	MDA5 deficiency	Uncertain significance	Damaging	ARID1A c.3458C[2>1]	Frameshift mutation
								ATRX c.2812A>G	Missense mutation
Case 4	LRBA heterozygous mutation	LRBA	c.1570G>A, p.Gly524Ser	42%	LRBA deficiency	Likely benign	Damaging	ND	
Case 5	PRF1 heterozygous mutation	PRF1	c.1429C>A, p.Pro477Thr	53%	FHL type 2	Uncertain significance	Tolerated	ND	
Case 6	PRF1 and UNC13D heterozygous mutations	PRF1	c.1153C>T, p.Arg385Trp	46%	FHL type 2	Uncertain significance	Damaging	STAT5A c.2252_2262delAATTCGACCTG	Frameshift mutation
		UNC13D	c.2588G>A, p.Gly863Asp	50%	FHL type 3	Uncertain significance	Damaging		

ACMG: American College of Medical Genetics and Genomics; FHL: familial hemophagocytic lymphohistiocytosis; IEI: Inborn errors of immunity; IL7R: interleukin 7 receptor; LRBA: LPS-responsive beige-like anchor protein; MDA5: melanoma differentiation-associated protein 5; NA: not available; ND: not detected; SIFT: sorting intolerant from tolerant; VAF: variant allele frequency.

T-cell lymphomas occur less frequently. A recent systematic review identified 534 cases of B- and T-cell lymphomas among patients with inborn errors of immunity, of which 74 (13.9%) were T-cell lymphomas.¹⁰

In our cohort, all detected variants were heterozygous and classified as variants of uncertain significance or likely benign, whereas the corresponding syndromes, including familial hemophagocytic lymphohistiocytosis (FHL), interleukin 7 receptor (IL7R) deficiency, and LPS-responsive beige-like anchor protein (LRBA) deficiency, typically follow an autosomal recessive inheritance pattern and require biallelic mutations for full disease penetrance. Although none of the patients fulfilled diagnostic criteria for a defined syndrome of inborn errors of immunity, several showed clinical or laboratory features suggestive of underlying immune dysregulation, including HLH, hypogammaglobulinemia, prior autoimmune encephalitis, and a prolonged inflammatory/myositis-like course with partial responsiveness to immunosuppressive therapy. These findings support a background of immune dysregulation in this cohort. Because WES was performed on peripheral blood DNA rather than a definitive non-hematopoietic germline source, occult tumor-related contamination cannot be excluded, and the identified variants should therefore be interpreted cautiously. Targeted NGS of tumor samples identified somatic alterations in a subset of cases, including *ARID1A*, *ATRX*, and *STAT5A*. Among these, *ARID1A* and *ATRX* are involved in chromatin remodeling, whereas *STAT5A* is involved in the JAK-STAT signaling pathway. Notably, we did not observe the recurrent epigenetic mutations commonly reported in PTCL, and the overall number of somatic alterations was relatively limited across the cohort, suggesting that this subset may differ from more typical molecular patterns of PTCL.

According to the 2024 International Union of Immunological Societies classification, the inborn error of immunity-related genes identified in our cohort span multiple immunological categories, including familial hemophagocytic lymphohistiocytosis-related genes (*UNC13D*, *STX11*), severe combined immunodeficiency (*IL7R*), and immune dysregulation with autoimmunity due to impaired CTLA-4 trafficking (*LRBA*)^{11,12}. Notably, *IFIH1* gain-of-function mutations have been associated with inflammatory myopathies, further supporting a possible link between immune dysregulation and muscle involvement.¹³ A striking feature of this series is the predominant involvement of skeletal muscle, an uncommon site for PTCL infiltration. Skeletal muscle has been proposed as a relatively immune-privileged tissue with limited lymphatic drainage and specialized antigen-presenting capacity. In the context of impaired immune regulation, this microenvironment may permit persistent cytotoxic T-cell activation and clonal expansion, thereby providing a niche for lymphomagenesis.

These cases should also be interpreted in the context of the differential diagnosis and the emerging biolog-

ic heterogeneity of cytotoxic PTCL. Recent studies have identified biologically distinct subsets of cytotoxic PTCL, including a subgroup characterized by loss of *SMARCB1/INI1* expression.¹⁴ Notably, our cases share several features with that subgroup, including young age at onset and cytotoxic phenotype. However, no *SMARCB1* mutations or copy number loss were detected by targeted NGS-based analysis, although *SMARCB1/INI1* expression was not evaluated. Therefore, overlap cannot be fully excluded. At the same time, our cases appear distinct from the more typical Epstein-Barr virus (EBV)-associated lymphoproliferative disorders described in the setting of FHL-related defects, as all lesions in this cohort were EBV-negative by EBER *in situ* hybridization. Another important differential diagnosis is reactive or atypical cytotoxic T-cell proliferation associated with immune dysregulation, because restricted or oligoclonal lymphoid expansions may occur in inborn error of immunity and can complicate interpretation. In our cohort, clonal TCR rearrangement was demonstrated in four cases. The diagnosis was therefore based on integrated clinicopathologic assessment, including morphology, immunophenotype, clonality findings when available, multifocal PET-avid disease, and clinical course. Taken together, these findings suggest that our cohort may represent a distinct clinicopathologic pattern rather than fitting neatly into currently recognized categories.

In conclusion, we describe a distinctive clinicopathologic pattern of young-onset cytotoxic PTCL with prominent skeletal muscle involvement and inborn error of immunity-related variants. These findings expand the spectrum of PTCL associated with immune dysregulation and suggest that a subset of cases previously regarded as sporadic may arise in the context of subtle inherited immune dysfunction.

Authors

Chong Wei,¹ Danqing Zhao,¹ Congwei Jia,² Kaini Shen,¹ Wei Zhang¹ and Daobin Zhou¹

¹Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and ²Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Correspondence:

W. ZHANG - vv1223@vip.sina.com

<https://doi.org/10.3324/haematol.2026.300669>

Received: February 6, 2026.

Accepted: May 27, 2026.

Early view: June 4, 2026.

Disclosures

No conflicts of interest to disclose.

Contributions

CW, WZ, and DBZ designed the study. CW, DQZ, CWJ, and KNS analyzed all the data. CW wrote the main manuscript. All authors

approved the final manuscript.

Funding

The study was funded by the National High Level Hospital Clinical Research Funding (2025-PUMCH-A-183).

Data-sharing statement

The data generated in this study are available upon request from the corresponding author.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.

2. Liu W, Ji X, Song Y, et al. Improving survival of 3760 patients with lymphoma: Experience of an academic center over two decades. *Cancer Med*. 2020;9(11):3765-3774.

3. Watatani Y, Sato Y, Miyoshi H, et al. Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. *Leukemia*. 2019;33(12):2867-2883.

4. Poli MC, Aksentijevich I, Bousfiha A, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. *J Hum Immun*. 2025;1(1):e20250003.

5. Baris S, Kolukisa B. Immune dysfunction in inborn errors of immunity causing malignancies. *Expert Rev Clin Immunol*. 2021;17(7):695-699.

6. Mitchell MR, Urdinez L, Bernasconi AR, et al. Cancer prevalence in children with inborn errors of immunity: report from a single institution. *J Clin Immunol*. 2024;44(6):138.

7. Fekrvand S, Abolhassani H, Esfahani ZH, et al. Cancer trends in inborn errors of immunity: a systematic review and meta-analysis. *J Clin Immunol*. 2024;45(1):34.

8. Costagliola G, De Marco E, Consonni F, et al. Inborn errors of immunity presenting with lymphoproliferation: lessons from a case series. *Ann Hematol*. 2025;104(6):3117-3127.

9. Bomken S, van der Werff Ten Bosch J, Attarbaschi A, et al. Current understanding and future research priorities in malignancy associated with inborn errors of immunity and DNA repair disorders: the perspective of an Interdisciplinary Working Group. *Front Immunol*. 2018;9:2912.

10. Riaz IB, Faridi W, Patnaik MM, Abraham RS. A systematic review on predisposition to lymphoid (B and T cell) neoplasias in patients with primary immunodeficiencies and immune dysregulatory disorders (Inborn Errors of Immunity). *Front Immunol*. 2019;10:777.

11. Winer H, Rodrigues GOL, Hixon JA, et al. IL-7: Comprehensive review. *Cytokine*. 2022;160:156049.

12. Taghizade N, Babayeva R, Kara A, et al. Therapeutic modalities and clinical outcomes in a large cohort with LRBA deficiency and CTLA4 insufficiency. *J Allergy Clin Immunol*. 2023;152(6):1634-1645.

13. Nakashima R, Imura Y, Kobayashi S, et al. The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. *Rheumatology (Oxford)*. 2010;49(3):433-440.

14. Fischer A, Albert TK, Moreno N, et al. Lack of SMARCB1 expression characterizes a subset of human and murine peripheral T-cell lymphomas. *Nat Commun*. 2024;15(1):8571.