

Patient's HLA Genotype Is Associated With the Risk of Central Nervous System Dissemination and Clinical Disease Presentation in Diffuse Large B-cell Lymphoma

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Abstract. *Background/Aim: Central nervous system (CNS) involvement in aggressive B-cell lymphoma, either as a primary or secondary event to systemic disease, portends a poor prognosis. This study sought to identify patients at high risk for CNS relapse by analyzing their human leukocyte antigen (HLA) genotypes. Patients and Methods: We retrospectively examined the HLA genotypes of 164 patients with systemic lymphoma, primary CNS lymphoma, and CNS relapse of systemic lymphoma. Patient records were analyzed, and HLA typing was performed by the Finnish Red Cross Blood Service. After excluding patients who received CNS prophylaxis, 131 patients were included in the final analysis. Results: A strong association was found between the HLA-A*31 genotype and CNS disease ($p=0.001$). Additionally, various HLA genotypes were linked to lactate dehydrogenase levels, extranodal disease, International Prognostic Index score, and disease stage. Conclusion: The patient's genetic constitution, rather than solely disease-related factors, plays a role in the tropism of lymphoma for the CNS. If confirmed in a larger study, defining the HLA genotype of a lymphoma patient could provide valuable information for predicting CNS relapse.*

Lymphomas encompass a diverse group of over 100 entities, as defined by the revised World Health Organization (WHO)-HAEM5 classification. Advancements in research have significantly broadened our understanding of lymphoma classification and biological underpinnings. An increasing body of evidence links specific tumor mutation profiles to distinct disease presentations (1).

However, the influence of *host-related* factors on disease presentation and prognosis has received less attention. Genome-wide association studies have identified several susceptibility loci for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, suggesting that patient genetics modulate the risk of lymphomagenesis (2, 3). Notably, variations in the human leukocyte antigen (HLA) genes are particularly relevant for susceptibility to lymphomas (4). Beyond influencing lymphoma etiology, specific HLA alleles have been linked to disease survival (5, 6) with increased HLA-A mutations correlating with an elevated risk of relapse in DLBCL (7).

Approximately five percent of patients with DLBCL experience a central nervous system (CNS) relapse. While high-dose intravenous methotrexate (HD-MTX) is offered as CNS prophylaxis for certain patients, its efficacy remains controversial. Current prophylaxis approaches are hampered by insufficient evidence and limited ability to accurately predict individual risk of CNS recurrence. Several studies have identified clinical factors associated with increased risk of CNS relapse, leading to the development of prognostic models. Recent research has explored combining biomarkers like cell of origin with clinical factors to refine CNS relapse prediction (8-10).

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Primary CNS lymphoma (PCNSL) is a rare disease, but Finland exhibits a high incidence rate compared to neighboring countries, with a potential explanation being the isolated gene pool of the Finnish population (11). This study examined the association between HLA genotype and CNS dissemination in patients with either primary or secondary CNS lymphoma.

Patients and Methods

The data set comprised 164 patients and was retrospectively collected from the Oulu University Hospital database. Between 1999 and 2022, HLA typing was performed as a standard procedure by the Finnish Red Cross Blood Service before high-dose therapy following autologous hematopoietic stem cell transplantation (ASCT). The cohort consisted of 50 patients with PCNSL, 18 patients with CNS relapse of systemic lymphoma (sCNSL), and 96 patients with systemic lymphoma without CNS involvement. Of these, 33 patients were excluded due to prior CNS prophylaxis, leaving 131 patients for the analysis.

This study was approved by the Ethics Committee of Oulu University Hospital (EETMK: 21/2018), and the ethical principles of the Declaration of Helsinki were followed. Informed consent was obtained from all subjects. Data analysis was conducted using IBM SPSS Statistics for Windows version 27 software (IBM Corp. Armonk, NY, USA). The chi-square and Fisher's exact tests were employed to assess the association between CNS involvement and various HLA genotypes.

Results

Patient demographics are presented in Table I. Our analysis revealed a significant association between HLA-A*31 genotype and CNS involvement ($p=0.001$). Among the 13 cases with this genotype, 12 (92.3%) presented with either PCNSL or sCNSL, while only one (7.7%) had systemic lymphoma.

Additionally, the HLA genotype exhibited associations with various clinical disease presentations, as detailed in Table II. Notably, the HLA-A*11 genotype was linked to elevated lactate dehydrogenase (LDH) levels ($p=0.048$) and high International Prognostic Index (IPI) scores ($p=0.023$). Conversely, the HLA-B*57 genotype was associated with normal LDH levels ($p=0.020$). Furthermore, specific HLA genotypes manifested associations with disease stage: both B*13 and DRB1*03 were linked to limited-stage disease ($p=0.021$ and $p=0.019$, respectively), while HLA-DRB1*03 was associated with low IPI scores ($p=0.029$). Lastly, the HLA-DRB1*08 genotype exhibited connections with extranodal disease ($p=0.041$) and high IPI score ($p=0.040$).

Discussion

HLA genes appear to play a crucial role in lymphoma's tropism for the CNS. In this study, we discovered a strong association between the HLA-A*31 genotype and CNS dissemination in DLBCL. These findings highlight the patient's genetic constitution as a significant factor influencing the clinical disease presentation of lymphoma.

Recent years have witnessed a notable increase in genetic information for DLBCL, enabling its classification into genetically distinct subgroups on tumor characteristics. However, research remains limited on whether these subgroups demonstrate varying risks of CNS relapse. Ollila *et al.* found two genetic subgroups (MYD88/CD79B-mutated and double-hit/TP53-mutated) significantly enriched in patients with CNS recurrence. If confirmed in future trials, this finding could improve the accuracy of predicting CNS relapses (12, 13).

Intravenous HD-MTX has been used to prevent CNS relapse in DLBCL. However, considering the associated costs and potential toxicities, accurate predictive factors are crucial for patient selection. Schmitz *et al.* identified IPI factors (stage III/IV disease, age >60 years, elevated LDH, multiple extranodal sites, and WHO performance status >1), and renal/adrenal involvement, as independent risk factors for CNS relapse. Based on these risk factors, patients can be classified into low-, intermediate-, or high-risk groups of CNS recurrence. This allows for targeted prophylaxis for the high-risk group (8, 9).

Data on biological risk factors for CNS relapse are limited. High-grade B-cell lymphomas with MYC and BCL2 rearrangements are known for their aggressive behavior and higher risk of CNS relapse. Oki *et al.* found that patients with cytogenetic rearrangements exhibited a significantly increased risk of CNS relapse (13% cumulative involvement at three years) (1, 14). Additionally, dual expression of MYC and BCL2, as well as the non-germinal center (GC) phenotype, has been linked to an elevated risk of CNS relapse compared to non-dual expressers (9.7% vs. 2.2% as a two-year risk, respectively) and the GC phenotype (15). However, Klanova *et al.*'s recent prognostic model did not demonstrate an influence of BCL2/MYC dual-expression status on CNS relapse risk (10).

HLA class I and II molecules are expressed on the surface of B lymphocytes, where they present antigens to CD8⁺ and CD4⁺ T cells, respectively (5). Loss of HLA molecule expression has been proposed as a potential mechanism for immune escape and extranodal disease. Compared to nodal DLBCL, primary testicular and PCNSL demonstrate a significantly higher frequency of HLA class I molecule loss on the cell surface (60% vs. 10%, respectively) (16). Overall, HLA class I loss has been described in 40 to 60 % of DLBCL cases (17). The mechanisms regulating HLA class I expression on DLBCL cell surface are complex and not fully understood, but genome-wide screens have identified several potential regulators (18).

This study evaluated the frequencies of HLA-A, HLA-B (HLA class I), and HLA-DRB1 (HLA class II) among patients with aggressive lymphomas. At least one previous study has investigated HLA polymorphisms associated with extranodal DLBCL. This study found significantly higher frequencies of HLA class II alleles HLA-DRB1*15 and

Table I. Patient demographics.

	Systemic lymphoma n (%)	sCNSL n (%)	PCNSL n (%)
Number	96 (58.5%)	18 (11.0%)	50 (30.5%)
Lymphoma subtype			
DLBCL	84 (87.5%)	10 (55.5%)	50 (100%)
T-cell/histiocyte-rich large B-cell lymphoma	7 (7.3%)	2 (11.1%)	
Burkitt lymphoma	2 (2.1%)	4 (22.2%)	
High-grade B-cell lymphoma	2 (2.1%)	1 (5.6%)	
Primary mediastinal large B-cell lymphoma	0 (0%)	1 (5.6%)	
Missing	1 (1.0%)	0 (0%)	
Stage			
I-II	29 (30.2%)	3 (16.7%)	
III-IV	64 (66.7%)	14 (83.3%)	
Missing	3 (3.1%)	0 (0%)	
Extranodal sites			
0-1	67 (69.8%)	4 (22.2%)	
>1	24 (25.0%)	12 (66.7%)	
Missing	5 (5.2%)	2 (11.1%)	
LDH levels			
Normal	18 (18.7%)	0 (0%)	25 (50.0%)
Elevated	66 (68.8%)	17 (94.4%)	13 (26.0%)
Missing	12 (12.5%)	1 (5.6%)	12 (24.0%)
IPI			
0-2	39 (40.6%)	3 (16.7%)	
3-5	39 (40.6%)	9 (50.0%)	
Missing	18 (18.8%)	6 (33.3%)	
COO type			
GC	31 (36.9%)	3 (30.0%)	5 (10.0%)
Non-GC	28 (33.3%)	5 (50.0%)	27 (54.0%)
Missing	25 (29.8%)	2 (20.0%)	18 (36.0%)
CNS prophylaxis			
Yes	27 (28.1%)	6 (33.3%)	
No	69 (71.9%)	12 (66.7%)	
HLA-A*31 genotype	1 (7.7%)	3 (23.1%)	9 (69.2%)

sCNSL: Secondary central nervous system lymphoma; PCNSL: primary central nervous system lymphoma; DLBCL: diffuse large B-cell lymphoma; LDH: lactate dehydrogenase; IPI: International Prognostic Index; COO: cell of origin; GC: germinal center; CNS: central nervous system; HLA: human leukocyte antigen.

HLA-DRB1*12 in testicular lymphoma patients than healthy controls ($p < 0.013$ and $p = 0.043$, respectively) (19).

In our study, the observed frequency of HLA-A*31 (9.1%) aligns with previous reports of its prevalence in Finland (7.9%). Sirén *et al.* found minimal variation in HLA-A frequency within the Finnish people compared to broader international populations (20). Notably, the frequency of HLA-A*31 among patients with PCNSL in our study was significantly higher, at 18.0%. This elevated frequency could potentially be linked to increased incidence rates of PCNSL observed in Finland.

Interestingly, we also analyzed the 33 patients who received CNS prophylaxis. Among them, two patients possessed the HLA-A*31 genotype, and neither experienced CNS relapse. While the data is insufficient to draw any definitive conclusions due to the small size and lack of statistical significance, it raises the intriguing question of whether CNS prophylaxis could effectively prevent CNS relapse within this specific patient population.

Table II. Association of HLA genotype with clinical disease presentation.

	A*11	B*13	B*57	DRB1*03	DRB1*08
Elevated LDH	↑		↓		
Extranodal sites >1					↑
IPI 3-5	↑			↓	↑
Stage III-IV		↓		↓	

The associations were determined using a two-sided chi-square test. All p -values were < 0.05 . ↑ : positive association; ↓ : negative association; LDH: lactate dehydrogenase; IPI: International Prognostic Index.

Our findings suggest that, in addition to disease-related risk factors, *host-related* factors may also play a crucial role in future considerations. However, these results should be viewed as preliminary observations with the potential to

inform future hypotheses. Replicating this study with a significantly larger sample size is necessary. While our sample size of 131 patients might be adequate for some studies, the inherent high biological variability of HLA genotypes necessitates a considerably larger population to draw definitive conclusions. Additionally, our data collection focusing on patients undergoing ASCT introduced a bias towards individuals with relapsed disease.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, H.K., T.K. and O.K.; Methodology, K.P.; Validation, R.K.O. and K.P.; Formal Analysis, R.K.O., M.E.L.K., T.K. and O.K.; Investigation, R.K.O., A.S., K.P., K-M.H. and O.K.; Resources, T.T-H., H.K. and O.K.; Data Curation, R.K.O.; Writing – Original Draft Preparation, R.K.O., A.S., T.T-H., H.K., M.E.L.K., T.K. and O.K.; Writing – Review & Editing, All Authors; Visualization, R.K.O., M.E.L.K., T.K. and O.K.; Supervision, O.K.; Project Administration, R.K.O., M.E.L.K. and O.K.; Funding Acquisition, T.T-H., H.K., M.E.L.K. and O.K.

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