UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
FIELD OF MEDICINE

SPECIFIC HLA ALLELE TYPING IN CHRONIC LYMPHOPROLIFERATIONS

SUMMARY OF THE DOCTORAL THESIS

PhD coordinator:
PROF. DR. CONSTANTINESCU ILEANA

PhD student:
TIZU (married IONESCU-LUPEANU) MARIA

2025

CONTENTS

List of published articles

Articles published in ISI indexed journals

1. **Tizu M**, Calenic B, Hârza M, Cristea BM, Maruntelu I, Caragea AM, Talangescu A, Dima A, Constantinescu AE, Constantinescu I. "HLA Gene Polymorphisms in Romanian Patients with Chronic Lymphocytic Leukemia". Genet Res (Camb). 2024 Feb 28;2024:8852876. doi: 10.1155/2024/8852876. PMID: 38449839; PMCID: PMC10917483.
   Impact Factor 1.4
   https://pubmed.ncbi.nlm.nih.gov/38449839/
   (Chapter 5, Subsection 5.1)

2. **Tizu M**, Calenic B, Constantinescu AE, Bratei AA, Stoia RA, Popa MC, Constantinescu I. "Cluster of Differentiation Markers and Human Leukocyte Antigen Expression in Chronic Lymphocytic Leukemia Patients: Correlations and Clinical Relevance". Curr Issues Mol Biol. 2024 Sep 11;46(9):10008-10025. doi: 10.3390/cimb46090598. PMID: 39329950; PMCID: PMC11430089.
   Impact Factor 2.8
   https://pubmed.ncbi.nlm.nih.gov/39329950/
   (Chapter 5, Subsection 5.2)

Articles published in PubMed indexed journals

1. **Tizu M**, Calenic B, Maruntelu I, Caragea AM, Talangescu A, Ursu L, Rotarescu C, Surugiu M, Constantinescu AE, Constantinescu I. "Immunogenetic Background of Chronic Lymphoproliferative Disorders in Romanian Patients-Case Control Study". Med Sci (Basel). 2024 Feb 23;12(1):14. doi: 10.3390/medsci12010014. PMID: 38535155; PMCID: PMC10972167.
   https://pubmed.ncbi.nlm.nih.gov/38535155/
   (Chapter 5, Subsection 5.3)

Introduction

Chronic lymphoproliferative diseases (CLPDs) are one of the component subcategories of lymphoproliferative diseases (LPDs). They are a diverse group of blood cancers characterized by heterogeneous manifestations and abnormal accumulation of mature lymphocytes [1]. They are distinguished from acute leukemias by the absence of terminal deoxynucleotidyl transferase, an enzyme usually found in young lymphocytes [2].

The CLPD group includes a multitude of conditions, such as: Chronic Lymphocytic Leukemia (CLL), Diffuse Large B-Cell Lymphoma (DLBCL), Burkitt Lymphoma (BL), Peripheral T-Cell Lymphoma Not Otherwise Specified (PTCL-NOS), etc [3]. Because these diseases are so different, diagnostic methods vary from one pathology to another. Thus, we recall that for CLL the diagnostic strategy involves altered leukocyte and lymphocyte values, followed by a peripheral blood smear [4] while in the case of Burkitt lymphoma the diagnosis requires the anatomo-pathological result of the biopsy..

Currently, in addition to these determinations, there is an increasing use of immunophenotypic profiling, which helps both in diagnosis and in subsequent monitoring [4]. Thus, the idea of performing a comprehensive immunological profile arises, which can serve as the basis for an early diagnosis of severe forms and can help in the development of personalized therapeutic strategies. In this endeavor, testing the human leukocyte antigen (HLA) genes, as disease markers, is of great help [5].

Currently, the best known associations between HLA and disease are: the link between HLA-B*27 and ankylosing spondylitis, the association of type 1 diabetes with HLA-DQB1 alleles, the influence of HLA-DQ2 and HLA-DQ8 in the occurrence of celiac disease [6–8] etc. Associations between chronic lymphoproliferative disorders and HLA genes have also been reported. The most important examples are the association of CLL with the following alleles: HLA-C*07:01, HLA-DRB1*04:01, HLA-DQB1*04:02, HLA-B*15:01 [9], alelele HLA- DQB1*05:01 și DRB1*01:01 which favors the occurrence of DLBCL [10], HLA-A*02, HLA-B*58 și HLA-DQA1*04:01 which are found in patients with Burkitt lymphoma [11,12] and the list goes on. These associations motivated us to search for possible links between HLA genes and CLPD in the Romanian population. At the same time, these data may contribute to establishing HLA alleles as new disease markers that could, in the future, serve both to diagnose certain pathologies and to determine the severity of the disease.

I. CURRENT STATE OF KNOWLEDGE

1. General data on chronic lymphoproliferations

1.1. Prevalence of chronic lymphoproliferations

Being a broad category of diseases, epidemiological data regarding the entire group of chronic lymphoproliferative disorders are lacking, preferring to report for each type of neoplasm. This trend can be observed not only in Romania but throughout the world.

In Europe, the incidence of CLL is 4.2 cases per 100,000 people each year [4] while in our country the incidence is 8 cases per 100,000 inhabitants per year [13]. Diffuse large B-cell lymphoma, on the other hand, has an estimated prevalence in Western Europe of approximately 45 cases per 100,000 inhabitants[14,15]. Mantle cell lymphoma is a type of B-cell LMNH with a prevalence for our continent of 1-9 new cases per 100,000 inhabitants [16]. In Europe 1 in 530,000 individuals under the age of 14 is diagnosed with Burkitt lymphoma, while for adolescents between 15 and 19 years it can occur in 1 in 670,000 people [17].

A rare type of cancer is PTCL-NOS [18]. This represents 35% of PTCL cases in Europe and North America [19]. Another equally aggressive pathology is Adult T-cell Leukemia/Lymphoma (ATLL) [20]. Although only 2-5% of carriers of this virus can speak of the occurrence of ATLL[21], a study conducted on the Romanian population shows a prevalence of 5.33 diagnosed infections per 10,000 potential stem cell donors[22].

1.2. Classification of chronic lymphoproliferative diseases

Chronic lymphoproliferative pathologies were first brought into discussion by the World Health Organization (WHO), which since 1956 has aimed to classify not only these pathologies but all types of tumors[23,24], having as a classification principle the location and histological appearance specific to tumors.

Chronic mature B-cell lymphoproliferations are divided into: preneoplastic and small neoplastic lymphocytic proliferations, splenic B-cell lymphomas and leukemias, lymphoplasmacytic lymphoma, marginal zone lymphoma, follicular lymphoma, cutaneous follicular center lymphoma, mantle cell lymphoma, transformations of indolent B-cell

lymphomas, large B-cell lymphomas, Burkitt lymphoma, KSHV/HHV8-associated B-cell lymphomas and lymphoid proliferations, proliferations and lymphomas associated with immune deficiency and dysregulation, and Hodgkin lymphoma [3]. Each of these categories in turn includes several pathologies, which can be seen in Appendix- Supplementary Table 1 taken from the WHO guideline [3].

Mature T-cell or NK-cell cancers are in turn divided into: mature T-cell or NK-cell leukemias, primary cutaneous T-cell lymphomas, intestinal T-cell and NK-cell lymphoid proliferations and lymphomas, hepatosplenic T-cell lymphoma, anaplastic large cell lymphoma[3]. Each of these categories brings together several types of neoplasms, as can be seen in Supplementary Appendix-Table 2, all of which are found in the WHO guidelines[3].

1.3. The diagnosis of chronic lymphoproliferations

In Romania, the 2021 Medical Practice Guide approved by Order no. 219 of February 23, 2021[4,25], provides the diagnostic criteria for CLL according in accordance with the European Society for Medical Oncology (ESMO) 2016 [4]. A lymphocyte count exceeding 5x109/L indicating monoclonal lymphocytosis is the first indication that raises suspicion of this diagnosis[4]. These changes correlate with the identification of small lymphocytes, scanty cytoplasm and dense chromatin nuclei on the peripheral blood smear[4]. In the diagnostic process, cytometry helps by identifying specific differentiation clusters (CDs) for the B lymphocyte lineage such as CD19, CD20, CD79b, CD5, etc. associated with low expression of kappa or lambda chains[4].

In the case of Burkitt lymphoma, anatomic-pathological analysis of the biopsy is necessary to establish the diagnosis [26], as is the case of peripheral T-cell lymphomas, which include PTCL-NOS[27]. The 2015 ESMO guidelines also establish that the gold standard in the diagnosis of DLBCL is also biopsy, which provides important information about the tumor architecture and the type of cells involved [28].

MCL is one of the malignancies for which the diagnosis will be made based on the anatomo-pathological examination [29], and for Lymphoma and T-cell leukemia in adults, the most useful diagnostic tests will aim to determine the morphology of T cells and their phenotype and biopsy the affected tissues in order to determine their histology [30].

2. The immune response in chronic lymphoproliferations

2.1. The role of HLA genes in the immune response

The major histocompatibility complex (MHC) is an essential component for the proper functioning of the adaptive immune system [31,32]. The importance of these molecules lies in their involvement in the process of antigen presentation to T lymphocytes, without which the activation of these immune cells would not be possible [32].

HLA and autoimmune diseases

Since MHC molecules play such an important role in the proper functioning of the immune response, specialized studies have concluded that certain variants of HLA genes may favor the occurrence of certain diseases [32].

One of the well-established links is between ankylosing spondylitis (AS) and the HLA-B*27 allele [6]. It is now thought that over 85% of AS patients carry this allele [33,34]. While HLA-B*27 remains the most prominent genetic risk factor, other HLA alleles, such as HLA-B*60, have also been implicated in increasing susceptibility to developing AS [6].

Another pathology that has been extensively documented for possible association is type 1 diabetes mellitus (T1D), an autoimmune disease with a complex genetic basis [35]. Studies have shown that the HLA region, especially the HLA-DR and HLA-DQ genes, plays a crucial role in determining susceptibility to T1D [36,37].

HLA and transplantation

In recent years, significant progress has been made in understanding the impact of HLA mismatches on the outcomes of allogeneic hematopoietic stem cell transplantation (HSCT). HLA matching is a critical component of HSCT, ensuring compatibility between donor and recipient to prevent graft rejection and graft-versus-host disease (GVHD) [38].

Organ transplantation provides a life-saving treatment for many people with organ failure [39]. HLA matching is a critical factor in the success of organ transplantation, as it significantly reduces the risk of graft rejection and improves long-term outcomes [40].

2.2. Genetic aspects and mutations associated with chronic lymphoproliferations

Chronic lymphoproliferative disorders are a large group of diseases that bring together under the same umbrella some of the most well-known and common pathologies such as CLL, Burkitt lymphoma, PTLC-NOS, etc. [1]. However, due to the fact that these pathologies have different cellular involvement, different manifestations and overall are not similar in the way the disease evolves[1], we considered that they should be analyzed individually.

In the case of CLL, FISH technology has significantly contributed to the understanding of this disease [41]. Approximately 80% of CLL tumors have specific chromosomal abnormalities, including deletions of chromosomes 13 and 11, trisomy 12, and deletion of the short arm of chromosome 17 [41].

For DLBCL, the literature documents a variety of genetic alterations involved in the development of the disease. As DLBCL consists of two subcategories GCB-DLBCL (germinal center B-cell) and ABC-DLBCL (activated B-cell) [42]. Common mutations in GCB DLBCL included BCL2, GNA13, EZH2, TNFRSF14, BCL6, MYC and PTEN, while ABC DLBCL was frequently associated with mutations in TNFAIP3, MYD88, CDKN2A, BCL2, PRDM1, CD79A/B and CARD111 [42,43].

The hallmark of Burkitt lymphoma is, genetically, the aberrant expression of the c-MYC oncogene [44]. This overexpression is driven by chromosomal translocations fusing c-MYC to immunoglobulin genes [44]. The most common translocation, t(8;14), involves the immunoglobulin heavy chain gene, while t(2;8) and t(8;22) involve the immunoglobulin light chain genes [44].

One of the most common T-cell neoplasms, PTCL-NOS, also appears to have an important genetic component [45]. Gene expression analysis has revealed a molecular classification of PTCL-NOS based on the expression of one of the GATA3 or TBX21 genes [45].

All these genetic changes, found in both T-cell and B-cell pathologies, have important implications for the progression and treatment of the disease. The research and identification of these markers has brought answers about the mechanisms of action encountered in some neoplasms. Also, the identification of these changes is in some cases pathognomonic and helps to establish new disease markers.

II. PERSONAL CONTRIBUTIONS

3. Aim and objectives of the study

This research contributes to the deep understanding of chronic lymphoproliferations, providing valuable data for optimizing therapeutic strategies and improving patient prognosis. Through a detailed analysis of clinical and biological characteristics, the work aims to lay the foundation for new research directions and personalized therapeutic approaches..

Therefore, our study aims to complete the specific immunological picture of this vast category of diseases, represented by chronic lymphoproliferations. We also want to make a contribution in the fields of both immunology and hematology, with the potential to positively influence the clinical management of patients with chronic lymphoproliferations.

The following specific objectives have been formulated to achieve this goal:

1. Data collection from patients diagnosed with different types of chronic lymphoproliferation. The number of patients included in the study must exceed 100 patients for clinical relevance. The data considered are: gender, age, different genetic factors that can lead to the onset of the disease, associated comorbidities, the values of certain biochemical, hematological and immunophenotypic markers;
2. Investigation of potential associations between HLA genes and chronic lymphoproliferations, analyzed as a unitary group;
3. Investigation of potential associations between HLA genes and different types of chronic lymphoproliferations, analyzed individually;
4. Investigating potential associations between HLA genes and Chronic Lymphocytic Leukemia;
5. Investigating potential associations between HLA genes and Chronic Lymphocytic Leukemia, considering the gender of the patients;
6. Outlining the immunological profile for patients with Chronic Lymphocytic Leukemia taking into account both existing markers for this disease and the HLA genes identified specifically for this pathology.

4. Patients and Methods

4.1. Patient groups

This doctoral thesis aims to monitor a group of 41 women and 63 men, resulting in a total of 104 patients diagnosed with chronic lymphoproliferations, in the Hematology Clinic of the Fundeni Clinical Institute, who were compared with 100 healthy volunteers, who did not present hematological diseases, active acute or chronic infections or other types of neoplasia.

The present study focuses on the identification of HLA class I and II genes, which play a role in the occurrence of chronic lymphoproliferative disorders and may influence the prognosis and therapeutic management of patients diagnosed with one of the malignancies in this group of diseases. The associations between HLA class I and II gene polymorphisms and 7 types of chronic lymphoproliferative disorders were investigated: Chronic lymphocytic leukemia (CLL), Peripheral T-cell lymphoma - not otherwise specified (PTCL-NOS), Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, Adult T-cell lymphoma (ATLL), Cutaneous T-cell lymphoma, Mantle cell lymphoma (MCL).

Study inclusion criteria

Patients diagnosed with chronic lymphoproliferations who met the following eligibility criteria were included in the study: at least 18 years old, able to provide informed consent, no chromosomal abnormalities, no acute or chronic infections, no other associated cancers or diseases with a poor prognosis (less than 5 years), no autoimmune diseases, allergies, or mental disorders. In the case of women, an important criterion taken into account was the absence of pregnancy at the time of inclusion in the study and sample collection.

Study exclusion criteria

Patients who did not meet the inclusion criteria were excluded from the present study. Thus, out of a total of 164 patients who were initially recruited for the present study, 60 were excluded due to non-compliance with the inclusion criteria, resulting in the group of 104 participants that we studied..

All patients who participated in the study gave their consent for the use of biological samples by signing an informed consent form, respecting the ethical principles supported by the Declaration of Helsinki. The study was also approved by the Bioethics Committee of the Fundeni Clinical Institute in Romania (no. 41066).

4.2. Methods

4.2.1. Genomic DNA isolation

In order to analyze HLA genes, in a first step, genomic DNA was extracted from whole blood using the QIAamp DNA Blood Mini kit. The DNA was isolated from the blood using special columns with silica membranes.

The extraction process involves mixing a 200 µl volume of whole blood with protease and lysis solution in order to destroy cell membranes and release DNA from the nucleus, followed by the immediate passing the lysed blood through a tube with a silica membrane, a membrane to which the DNA will adhere, based on the charge difference. After the silica membrane is washed to remove any impurities, the elution solution will be added, which will cause the DNA to detach from the membrane.

4.2.2. HLA sequencing

For determiningof specific alleles, the genotyping method chosen was next-generation sequencing using Immucor reagents (Mia Fora NGS Flex, Norcross, United States) for the construction of the working library together with Illumina kits (San Diego, United States) for the actual sequencing. The kits help to sequence 11 of the HLA genes, namely HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DPA1, HLA-DQB1, HLA-DQA1, HLA-DRB1, HLA-DRB3, HLA-DRB4 and HLA-DRB5. The analysis of these genes was carried out in full, for each being sequenced all exons as well as all introns.

Although the technique yields a wealth of information, it involves multiple steps. The first step in constructing a sequencing library is to amplify the DNA by long-range PCR. After this amplification is complete, the sequencing library can be constructed or the PCR products can be safely stored for 4 days at -20°C.

The second step involves enzymatic cleavage of the amplification products, followed by repair of the ends of these fragments, with the assignment of an adenine nucleotide (A) at the 3' end, a process called A-tailing. After completion of this amplification, the amplification products cannot be stored, but it is mandatory to purify the amplicons using magnetic beads. Based on the charge difference, the DNA will bind to the beads. After removing the supernatant, the beads will be washed with 80% ethanol and then 10 mM Tris-HCl solution pH8.0 will be added to facilitate the detachment of the DNA from the beads.

The purified, fragmented, repaired amplification products, having an adenine at the 3' end, can proceed directly to the next step, that of ligation of the index adapter. Through this step, the DNA fragments will be identified according to the sample they come from and according to the gene they belong to. After the amplification is completed, the purification of the obtained products will be carried out immediately, also using magnetic beads.

Among the ligated and purified DNA fragments, those with a size between 500 and 900bp (base pairs) must be selected. The selection of fragments of the appropriate size is performed using the Pippin Prep method. This method is based on electrophoresis performed using a 1.5% agarose gel cassette). The eluate obtained through Pippin Prep selection undergoes a final amplification, followed by purification with magnetic beads, and at the end, the concentration of the working library will be measured using the Qubit fluorometer. Depending on the displayed concentration, the pre-sequencing library dilution will be performed. The library will be brought to a concentration of 1nm by successive dilutions after which it will be denatured with NaOH. Subsequently, the concentration will be reduced to 1.3pm using the special hybridization buffer from the Illumina kit. When the library is ready for amplification, it can be pipetted into the Illumina cartridge, which will then be inserted into the MiniSeq sequencer.

4.2.3. Cytomorphological analysis

To perform a complete blood count, using the SYSMEX XN-2000 analyzer, 5 mL of whole blood was collected from each patient.

4.2.4. Analysis of biochemical markers

For CRP determination, the ABBOTT ALINITY analyzer was used, while for LDH determination, the SIEMENS ATELLICA CH analyzer was used.

4.2.5. Flow cytometry

For the extensive analysis of the immunological profile of patients with CLL, immunophenotypic analysis of the differentiation clusters specific to this disease was performed, including: CD45, CD5, CD20, CD43, CD22, CD19, CD79b, CD23, CD81, CD38, CD11c, kappa and lambda light chains, FMC7 and CD200.

5. Results and Discussions

5.1. HLA gene expression in Romanian patients with Chronic Lymphocytic Leukemia

5.1.1. Results

Of the patients included in the study group, 66 were diagnosed with CLL. Of these, 38 are men and 28 are women. In order to analyze the possible associations between this pathology and HLA genes, a control group of 100 healthy volunteers was chosen. Since each person presents two alleles for each of the analyzed HLA genes, a total of 132 alleles were analyzed among the patients with CLL and 200 alleles for the subjects in the control group. The demographic data for these patients are mentioned in Table 5.1[46]. For these patients, 11 of the HLA genes were analyzed by next-generation sequencing as mentioned in Chapter4.

Analysis of HLA allele frequencies (at the 6-digit level) revealed four protective and two predisposing alleles associated with chronic lymphocytic leukemia (CLL). Despite the lower representation of HLA class I genes, a strong protective effect was observed for HLA-A*24:02:01. In addition, the HLA-DQA1*05:05:01 allele ($p = 0.01$, $OR = 0.56$) and the HLA-DQB1*03:02:01 allele ($p = 0.03$, $OR = 0.4$) were also identified as protective. Among the HLA-DRB3/4/5 genes, HLA-DRB4*01:03:01 ($p = 0.03$, $OR = 0.54$) was particularly prominent, showing low expression in the patient group but was identified in most of the control volunteers. Last but not least, we were able to highlight the importance of HLA-DRB1 genes in the development of chronic lymphocytic leukemia (CLL), by identifying a positive association between the HLA-DRB1*04:02:01 allele and CLL ($p = 0.009$, $OR = 1.03$). The HLA-DRB3*02:01:01 allele also demonstrated a statistically significant association with CLL ($p = 0.009$).

HLA allele frequencies for CLL patients were also analyzed, taking into account gender. The group of female CLL patients (n=28, 56 alleles) was compared with the group of female controls (n=45, 90 alleles). In women with CLL, HLA-B*39:01:01 ($p=0.019$, $OR=1.077$) and HLA-DRB3*02:01:01 ($p=0.019$, $OR=1.077$) were associated with the disease, while HLA-A*03:01:01 ($p=0.03$, $OR=0.365$), HLA-B*35:01:01 ($p=0.021$, $OR=0.228$) and HLA-DQA1*05:05:01 ($p=0.036$, $OR=0.487$) were protective. In men, only the HLA-DRB1*04:02:01 allele ($p = 0.011$, $OR = 1.070$) was significantly associated with CLL.

5.1.2. Discussions

Numerous studies conducted by Romanian research teams have managed to demonstrate the existence of several associations between HLA genes and certain diseases, for our population. Thus, to date, the existence of a link between Type 1 Diabetes Mellitus and HLA-DQB1 has been established [7]. Also, predisposing alleles that favor the occurrence of Chronic Renal Failure have been discovered, such as HLA-B*40, HLA-C*12 and HLA-DRB1*14 [47]. In addition to these discoveries, perhaps one of the most important studies is the one conducted by Marunțelu et al. [48] which speaks of the causal relationship between the presence of the HLA-DQA1*05:01, HLA-DQB1*02:01 and HLA-DQB1*02:02 alleles and the occurrence of celiac disease.

Perhaps the most relevant result of this study concerns the identification of the predisposing role of the HLA-DRB1*04:02:01 allele (p=0.001, OR of 1.05) in the onset of the disease.[46]. The result was conclusive for the entire group of patients with CLL, but also separately for the men in the study group (p=0.011, OR=1.070) [46]. The same conclusion was reached by the team led by Gragert et al [9] who recorded the involvement of this allele in the onset of CLL for the Jewish population of the United States of America but also for the American population. In another study, HLA-DRB1*04:02 is mentioned by Scally et al. for its strong protective role in rheumatoid arthritis [49].

Another positive association we found was between HLA-DRB3*02:01:01 and CLL (p = 0.009, OR = 1.03). This association was also particularly identified for the group of women with CLL (p = 0.019, OR = 1.077). Several reports focus on the HLA-DRB3 genes and their involvement and association with different pathologies, although their exact role has not yet been established. For example, Mueller et al.[50] found a high expression of the HLA-DRB3*01:01 allele among women with CLL. Furthermore, Le et al. [51] discussed the involvement of HLA-DRB3*02:02 in the occurrence of PLA2R-associated membranous nephropathy.

The first protective HLA allele we identified was HLA-A*24:02:01. This finding is similar to that of the group led by Cuttner et al. [52] who suggested that HLA-A24 alleles are positively associated with CLL in the Ashkenazi Jewish population. Although their hypothesis was not statistically supported, our study was able to confirm this premise. A similar scenario was observed in a subsequent study that observed a higher incidence of HLA-A24 alleles among CLL patients, but the association was not statistically

significant[53]. Several studies have identified HLA-A*01:01 as a strong protective allele against CLL [54]. In addition, a strong association between the HLA-A*02:01 allele and CLL has been widely reported [9,55].

Gragert et al. [9] have highlighted the association between the presence of HLA-DQB1*03:02:01 and an increased risk of developing CLL, an association also reported in German patients with CLL [56]. Other reports indicate an increased risk of progression from monoclonal high-number B-cell lymphocytosis to CLL in patients with IGHV and HLA-DQB1*03 mutations [53]. However, our study showed a high frequency of HLA-DQB1*03:02:01 in the control group, which leads us to attribute a protective role to this allele. These findings are supported by the protective role of the same allele in acute lymphoblastic leukemia [57].

Another link discovered by Machulla et al. [56] is the predisposition to develop CLL given by the presence of HLA-DRB4*01:03 among CLL patients. This finding is reconfirmed by the same team, in a subsequent study detailing the link between HLA-DRB4*01:03 and the disease, regardless of the age and sex of the patients [50]. In addition to these associations, Zhao et al. mention the positive association between this allele and diabetes mellitus [58]. Despite these findings, our results indicate a strong protective role offered by HLA-DRB4*01:03:01 against the occurrence of CLL. Our research also shows that the presence of this allele is accompanied by the presence of HLA-DQB1*03:02:01, in a manner similar to that of previous studies.

Another statistically significant association identified by our team was between HLA-DQA1*05:05:01 and CLL. This result should be analyzed in close connection with another result of the study, namely, the protective role that this allele has among the female population. Several studies have stipulated its involvement in the occurrence of certain pathologies regarding this variant of the HLA-DQA1 gene. A relevant example is the study conducted by Wang et al.[59] who, investigating the factors influencing the occurrence and evolution of squamous cell carcinoma of the skin, identified the HLA-DQA1*05:05 allele as being responsible for the occurrence of the disease. Also, Schwarm et al.[60] observed a positive association between bullous pemphigoid occurring among the German population and HLA-DQA1*05:05, and Nowak et al.[61] identified a strong link between the presence of HLA-DQA1*05 and extensive ulcerative colitis found in children.

All the results listed above, having statistical significance, were accompanied by a series of other findings in terms of HLA alleles, which although not exceeding the limit of statistical significance should be taken into account for studies conducted on larger cohorts. Among these alleles we mention: HLA -DPA1*02:02:02, HLA-DRB1*11:01:01, HLA-A*03:02:01 and HLA-DQA1*01:02:01. Also, another important allele that did not exceed the limit of statistical significance for the entire group of patients with CLL is HLA-B*35:01:01 (p = 0.057). However, we identified this allele for its protective role among the female population with CLL. Regarding the HLA-B35 antigen, a study conducted in 1994 first reported the high incidence of this antigen among European Jews and also among Caucasians with CLL [52]. In our case, the HLA-B allele that has a strong predisposing role among women is HLA-B∗39:01:01. This result is congruent with the discovery of Hojjat-Farsangi et al. [54] who identified two HLA-B alleles (HLA-B*53:01 and HLA-B*65:01) with a protective role among men and the HLA-B*35:01 allele with a high incidence in patients with CLL, regardless of gender.

Approaching the limit of statistical significance, HLA-DRB1*11:01:01 (p = 0.057) is one of the important results obtained. This result is congruent with the identification of the link between HLA-DRB1*11:01 and CLL by DiBernardo et al. [55] although, as in our case, without statistical relevance. The role that HLA-DRB1*11:01 has in the occurrence of various types of cancer has been mentioned in numerous studies. For example, Aureli et al.[62] reported that the aforementioned allele is a potential risk factor for breast cancer. Arons et al.[63] speaks about the importance of HLA-DRB1*11:01 in the occurrence of hairy cell leukemia. At the same time, Rossman et al.[64] documented an increased incidence of sarcoidosis in patients with this allele. One of the few studies that speaks of the protective role of HLA-DRB1*11:01 is the one conducted by Rezaieyazdi et al.[65], who in juvenile idiopathic arthritis identified this allele in an increased percentage in healthy patients, which gives it a protective valence.

Subchapter 5.1. represents a translation, adaptation and extension of the results and discussions previously published by the doctoral student in the article "*HLA Gene Polymorphisms in Romanian Patients with Chronic Lymphocytic Leukemia*"[46] as a partial requirement for the fulfillment of the doctoral thesis..

5.2. The correlation of the expression of differentiation clusters and HLA genes in Romanian patients with Chronic Lymphocytic Leukemia

5.2.1. Results

For our group of patients with CLL, we wanted to see if the association of HLA genes could be correlated with other pre-existing markers. Thus, we looked for associations between HLA genes and CDs commonly tested for these diseases. We also analyzed: PCR (C-reactive protein), LDH and complete blood count [66].

Knowing that both the blood count and immunophenotyping show specific patterns in patients with this pathology, we associated these markers and analyzed them simultaneously. We thus identified that in patients in whom CD38 is positive, the number of leukocytes generally exceeds 55,000/µl (p=0.019, OR=4.1). Also, CD79b is more frequently positive in patients who have over 27,000/µl of leukocytes (p=0.1965, OR=2.23). Another important marker is CD81 which, when positive, is associated with increases in leukocytes up to 18,500/µl (p=0.1144, OR=2.75). Positive CD38 also correlates with lymphocyte values exceeding 45,000/µl (p=0.0087, OR=7). In a similar manner, the presence of CD22 is most often accompanied by lymphocyte values above the normal limit but not exceeding 6500/ µl (p=0.171, OR=4.05). LDH values exceeded 470 U/L for patients with CD23 negative, while in patients with CD43 strongly positive, LDH levels exceeded 360 U/L (OR=3.48). It was also observed that CD22 positive patients more frequently presented CRP values > 5 mg/L (p=0.074, OR=4.643).

These associations are supplemented by the correlation of HLA gene expression with the immunophenotypic profile. Thus, we observed that 50% of patients with strong CD20 expression also have one of the HLA-DRB1*11:04:01 or HLA-B*49:01:01 alleles present. On the other hand, HLA DRB1*15:02:01 is associated with a diminished expression of CD20.

CD79b expression is positively correlated with HLA-DPA1*02:01:02 and HLA-B*08:01:01, as 57.14% of strongly positive CD79b patients associated at least one of the two alleles. Among the four alleles that were positively correlated with CD22 expression (HLA-B*49:01:01, HLA-C*07:01:01, HLA-DPB1*02:01:02 and HLA-DRB1*11:01:01), it was observed that 85.71% of patients with strong CD22 expression associated at least two of the four HLA variants.

Regarding CD81 expression, it was observed that 57.14% of patients with negative or weak CD81 expression associate at least one of the two alleles (HLA-DPB1*04:02:01 and HLA-DRB4*01:03:01). In comparison, none of the patients with strong CD81 expression present these variants of the mentioned HLA genes.

5.2.2. Discussions

One of the markers considered is CD22, which is associated particularly with acute lymphoblastic leukemia [67] but which is also present in CLL, especially in atypical forms[68] and in forms with significant involvement of secondary lymphoid tissue, with the appearance of lymphadenopathy and splenomegaly in patients in whom it is identified[69]. In our group of patients, CD22 was associated with the following alleles HLA-B*49:01:01, HLA-C*07:01:01, HLA-DPB1*02:01:02 and HLA-DRB1*07: 01:01. These alleles have previously been found to be involved in the development of various pathologies: HLA-C*07 increases the risk of acute myeloid leukemia[70], HLA-B*49:01:01 has been shown to be present in individuals with aplastic anemia[71], and HLA-DPB1*02:01 is frequently found in children with common acute lymphoblastic leukemia[72].

Also known as common lymphocyte antigen, CD45 is one of the distinctive markers of leukocytes and is specific for multiple myeloma and acute lymphoblastic leukemia [73]. The presence of this marker in chronic lymphoproliferative diseases was to distinguish between typical and atypical forms of CLL [74,75]. After performing statistical tests, we concluded that between CD45 and HLA-DQA1*05:01:01, HLA-C*07:01:01 and HLA-DQA1*01:02:02 we have statistically significant correlations. Studies show that among these alleles HLA-C*07:01[9] intervenes in the occurrence of CLL, while HLA-DQA1*01:02:01 was close to the limit of statistical significance [46] also in the case of patients with CLL.

One of the most important surface markers present on B lymphocytes is CD20 [76], which is one of the target antigens for which various therapies have been developed [77–79]. In most cases of CLL, the expression of the CD20 antigen is reduced or absent[80], according to the literature and reinforced by our observations. CD43 has been associated with other hematological disorders such as CLL or myeloid lineage pathologies[81–84]. CD43 is one of the markers considered in CLL due to its positivity especially in atypical forms of this disease [85]. Our observations indicate CD43 positivity in few patients, in

which, moreover, it was accompanied by the presence of the HLA-DRB1*15:01:01 allele indicating atypical forms of CLL.

CD23 helps in differentiating SLL/CLL from MALT lymphoma [86,87]. This marker was statistically significantly associated with the HLA-A*11:01:01 and HLA-B*39:01:01 alleles. Although the majority of our patients showed CD23 expression, the fact that HLA-B*39:01:01 and HLA-A*11:01:01 alleles were found mainly in patients with reduced CD23 expression in our cohort, despite the high prevalence of CD23, highlights the need for further studies to better understand the role of these markers in CLL.

Having a structural role at the level of the antigen receptor present on the surface of B lymphocytes, CD79 is composed of two subunits: CD79a and CD79b[88], of which CD79b is specific to patients with CLL. We observed an association between the absence of CD79b expression and the presence of the HLA-A*32:01:01 allele, as well as an association between CD79b expression and the HLA-DPA1*02:01:02 allele in our patient cohort. The literature indicates an unfavorable evolution of patients with strongly positive CD79b [89,90], a conclusion reproducible also for our patients who fulfill this condition.

A useful marker due to its property to distinguish lymphocytic from myeloid pathology is CD81 [91,92]. For the group of patients with CLL, we found a statistically significant association between CD81 and HLA-DRB1*14:01:01, HLA-DQA1*01:04:01, HLA-DPB1*04:02:01 and HLA-DQB1*05:03:01. Regarding HLA-DRB1*14:01:01, the literature documents its presence in patients with ALL [93], and HLA-DQB1*05 confers protection against the occurrence of Hodgkin lymphoma together with HLA-DPB1*04:01 [94,95]. Similar to the results obtained by our team, other studies confirm the presence of CD38 positivity in aggressive cases of CLL [96,97]. Our results indicate a significantly higher risk of rapid disease progression in CD38+ patients with a leukocyte count above 55,000/µl (p=0.0193, OR=4.1) and a lymphocyte count above 45,000/µl (p=0.0087, OR=7). These patients could benefit from earlier initiation of treatment.

Subchapter 5.2. represents a translation, adaptation and extension of the results and discussions previously published by the doctoral student in the article "*Cluster of Differentiation Markers and Human Leukocyte Antigen Expression in Chronic Lymphocytic Leukemia Patients: Correlations and Clinical Relevance*"[66] as a partial requirement in the fulfillment of the doctoral thesis.

5.3. HLA gene expression in Romanian patients with Chronic Lymphoproliferative Disorders

5.3.1. Results

In addition to studying the association between HLA and CLL, we also wanted to analyze the potential association between other types of chronic lymphoproliferative disorders and HLA genes. We therefore considered the following malignancies: DLBCL, MCL, primary cutaneous T-cell lymphoma, Burkitt lymphoma, PTLCL-NOS, and ATLL [98]. For the 38 patients diagnosed with other types of chronic lymphoproliferative disorders, we observed the expression of the 6 most important HLA genes. The data from these patients were compared with the results of 50 healthy patients out of a total of 100 in the control group. We considered it necessary to adapt the number of patients in the control group so that the statistical results would be conclusive. Thus, we analyzed a number of 76 alleles in the patient group and 100 alleles in the control group.

The samples of these patients were genotyped and analyzed by two different methods. In a first stage, sequencing was performed using the SSP (Sequence-Specific Primers) method. Reporting was performed at 4 digits and the data were analyzed and published in the author's article entitled “Immunogenetic Background of Chronic Lymphoproliferative Disorders in Romanian Patients-Case Control Study”[98]. Later, we chose to use the NGS technique, and analyze the same data at 6 digits to provide unity to the results of this doctoral research. After increasing the resolution, we noted that all the associations reported at 4 digits were also preserved in the case of reporting at 6 digits, but in addition to these, we also identified new associations.

By evaluating allele frequencies at the four-digit level, we identified six protective alleles (HLA-A*11:01 - p = 0.010, HLA-B*35:02 - p = 0.037, HLA-B*81:01 - p = 0.037, HLA-C*07:02 - p = 0.036, HLA-DRB1*11:01 - p = 0.021 and HLA-DRB1*13:02 - p = 0.03,) and two predisposing alleles (HLA-C*02:02 - p = 0.002 and HLA-C*12:02 - p = 0.002) for the entire group of patients with chronic lymphoproliferative disorders.

At the same time, we evaluated the HLA alleles for each of the pathologies in the study group. For the PTLC-NOS population, two important associations were established, HLA-C*12:02 (p = 0.0001, OR = 1.231) was positively associated with the disease, while HLA-A* 11:01 (p = 0.009, OR = 0.128) has a protective role. In the case of DLBCL, we established the protective role of HLA-B*39:01 (p = 0.003, OR = 0.06). For patients with

Burkitt lymphoma, we discovered the following allele also with a protective role, HLA-C*06:02 (p = 0.047, OR = 0.233). For the rest of the pathologies, no statistically significant associations were reported.

Following NGS sequencing, in PTLC-NOS patients, the two alleles found in the 4-digit resolution analysis were identified. These are HLA-A*11:01:01 (p=0.009, OR=0.128) with a protective role and HLA-C*12:02:01 (p=0.000, OR=1.231) with a predisposing role. In addition, a new allele was noted for the protection it offers to patients, namely HLA-DRB1*11:01:01 (p=0.03, OR=0.160). For patients with DLBCL, the HLA-B*39:01 allele retained its protective role even after analysis at the 6-digit level, HLA-B*39:01:01 (p=0.03, OR=0.060). An additional allele with a protective role was also identified, HLA-B*38:01:01 (p=0.03, OR=0.060).

In the case of Burkitt Lymphoma, another allele with statistical significance was identified in addition to the HLA-C*06:02:01 allele (p=0.047, OR=0.233). This is HLA-DQA1* 04:01:01 (p=0.023, OR=0.250) with a protective role. ATLL patients were highlighted for the association of the disease with HLA-A*11:01:01 (p=0.027, OR= 0.08) which in this case has an important protective role.

Our analysis revealed a significant association between Cutaneous Lymphoma and the alleles HLA-A*26:01:01 (p=0.043, OR=0.120), HLA-C*07:02:01 (p=0.013, OR=0.133) HLA-C*15:02:01 (p=0.027, OR=0.080) and HLA-DRB1*16:01:01 (p=0.025, OR=0.187) suggesting that these alleles offer protection. The genetic profile of MCL patients is characterized by the predisposition to develop the disease, given by HLA-C*02:02:02 (p=0.003, OR=1.500) but also by the protection conferred by HLA-DPB1*13:01:01 (p=0.008, OR=0.030).

5.3.2. Discussions

Currently, in the specialized literature we find many references to the association between chronic lymphoproliferative disorders and HLA genes, to our knowledge, no such studies have been performed for the Romanian population to date [99–102]. Thus, the basis of our decision to investigate these associations is the need to establish results for the autochthonous population.

One of the most promising results is represented by HLA-C*02:02 and HLA-C*12:02, alleles positively associated with the lymphoproliferative disorders studied by us.

Of these, HLA-C*12:02 is responsible for the occurrence of PTLC-NOS, while HLA-C*06:02 has a protective role against the development of Burkitt lymphoma. Not surprisingly, when typing to 6 digits, by NGS, these results are preserved (HLA-C*06:02:01 and HLA-C*12:02:01) and moreover, in addition to them, the protective alleles HLA-C*07:02:01 and HLA-C*15:02:01 for patients with cutaneous lymphoma and the allele HLA-C*02:02:02 that predisposes to the occurrence of MCL were also identified. The literature mentions an allele from the HLA-C*12 group involved in the occurrence of DLBCL in the Caucasian population, belonging to the haplotype HLA-A*2601~C*1203~B*3801~DRB1*0402~ DQB1*0302 [99].

Other alleles with a protective role for all patients with lymphoproliferations are HLA-B*35:02 and HLA-B*81:01, to which is added the protective effect of HLA-B* 39:01:01 and HLA-B* 38:01:01 only for patients with DLBCL. This protective role of HLA-B*35 has been recalled over time by several studies, such as the one developed by Wang et al. [103] which speaks about the fact that the HLA-B*35:03 allele is associated with a low risk of developing LMNH. These data are not confirmed, however, by Brazzelli et al. [101] who associate the presence of HLA-B*35 with mycosis fungoides. Of course, pathologies have also been identified for which alleles from this group increase the risk of developing certain pathologies, as is the case of HLA-B*35:01, found predominantly in patients with chronic lymphocytic leukemia (13). Also for patients with HLA-B*35 present, Benencio et al. [104], report an increased risk of developing myelopathy/tropical spastic paraparesis for patients who are also infected with HTLV-1. We have also identified studies that come with a different opinion from the findings of our team, this is HLA-C*07:02 identified by us for its protective role, a finding contradicted by the identification of alleles from the HLA-C*07 group for the increased susceptibility of ATLL for the carrier population [104]. Other studies talk about the protective role offered by HLA-Cw*08, in patients with myelopathy and positive HTLV-1 (93), and Wang et al. [105] identifies the HLA-C*07:02 allele as being involved in the progression of multiple myeloma.

An increased expression of HLA-A*11:01 in the control group associated with a decreased expression of this allele in patients with PTLC-NOS indicated the protective role of this genetic variant. The association remains valid even at 6-digit resolution (HLA-A*11:01:01) and following NGS typing other statistically significant results appear. Among these, we mention the protective role offered by the same HLA-A*11:01:01 allele in patients with ATLL and the protection given by HLA-A*26:01:01 in people diagnosed with

cutaneous lymphoma. The serological variant of this allele, HLA-A11, has also been reported to be protective, but this time in patients with Hodgkin lymphoma [10,106]. Gavioli et al. [107] talk about the importance of HLA-A*11 in decreasing the expression of Burkitt lymphoma. Also, alleles in the HLA-A*11 group are remembered for the protection they offer to the Korean population against the development of DLBCL [108].

The HLA-DRB1*13:02 ($p = 0.037$, $OR = 0.940$) and HLA-DRB1*11:01 ($p = 0.021$, $OR = 0.190$) alleles were also identified for their increased expression in the control group, indicating a protective effect against the development of lymphoproliferations. Following NGS typing, these alleles are added to the HLA-DRB1*11:01:01 alleles that provide protection in those diagnosed with PTLC-NOS and HLA-DRB1*16:01:01, identified for protection in cutaneous lymphoma. These results are similar to those of Wang et al. [103] who in the case of follicular lymphoma found protection offered by HLA-DRB1*13 among carriers.

Last but not least, HLA-DRB1*13 and HLA-DQB1*03 protect against both Hodgkin and non-Hodgkin lymphoma, according to the study conducted by Galleze et al. [109] Similar results have been reproduced for hepatitis B viral infection in patients from Iran [110] for Finnish multiple sclerosis [111] and also in the rheumatoid arthritis population [112,113]. Another documentation is for HLA-DRB1*04:01 which protects against the occurrence of DLBCL [103].

Two other alleles identified by NGS sequencing are HLA-DQA1* 04:01:01 with a protective role in Burkitt lymphoma and HLA-DPB1*13:01:01 which offers protection to patients with MCL. Even though the aforementioned association between HLA-DPB1 and MCL is not mentioned in the literature to date, it seems that the HLA-DPB1*13:01:01 allele has been identified in patients infected with SARS-CoV-2 because it prevents the onset of severe forms of the disease [114], thus proving its protective role. In the case of the HLA-DQA1* 04:01:01 allele, it has been mentioned in the literature for increasing the risk of Burkitt lymphoma in children [115].

Subchapter 5.3. represents a translation, adaptation and extension of the results and discussions previously published by the doctoral student in the article "*Immunogenetic Background of Chronic Lymphoproliferative Disorders in Romanian Patients-Case Control Study*" [98] as a partial requirement in the fulfillment of the doctoral thesis.

6. Conclusions and personal contributions

The present work is among the only ones that analyzes the involvement of HLA genes in chronic lymphoproliferative diseases, internationally. Also, to our knowledge, no other similar study has been conducted for the Romanian population to date.

Moreover, to study HLA genes in this group of pathologies, we used the most advanced sequencing method currently used, namely NGS. Thus, we performed high-resolution genotyping with reporting of results at the 6-digit level. In this way, we obtained detailed information about the genes involved both in the process of protection against the occurrence of one of the chronic lymphoproliferations, and about the genes that increase the risk of these pathologies.

Moreover, for some of the patients, we performed high-resolution sequencing using two methods and were able to report the data at 4-digit level and 6-digit level. This gave us the opportunity to discover three very important aspects: 1) there are differences between reporting at 4-digit and 6-digit levels; 2) by testing 6 of the HLA genes using both methods, we identified several statistically significant associations for NGS-typed patients, with results reported at 6-digit resolution; 3) by genotyping several HLA genes using NGS, we identified new associations between the disease and previously untested genes.

For patients with CLL, who represented the largest proportion of our group, we tried to create an immunological profile that would include already known and used markers such as immunophenotypic markers, leukocyte and lymphocyte values, LDH and CRP values, as well as potential new disease markers such as HLA alleles. All these data helped us to draw a broad immunological picture for our patients and we managed to pinpoint the defining paraclinical features of patients with atypical CLL. This represents a premiere that may open new horizons towards a different therapeutic approach in the future.

Chronic lymphoproliferative disorders are a heterogeneous group of diseases, therefore there is a need for a better characterization of this group of pathologies in order to develop effective therapeutic strategies. The present work represents only a first step in achieving a complex immunological picture, introducing for the first time the HLA genes as a disease marker and the HLA-CD association indicating atypical forms of CLL, for a better characterization of patients with this disease.

Bibliography

[1] Vaillant AAJ, Stang CM. Lymphoproliferative Disorders. Lanzkowsky's Manual of Pediatric Hematology and Oncology 2023:334–47. https://doi.org/10.1016/B978-0-12-801368-7.00016-8.

[2] Faber J, Kantarjian H, Roberts WM, Keating M, Freireich E, Albitar M. Terminal deoxynucleotidyl transferase-negative acute lymphoblastic leukemia. Arch Pathol Lab Med 2000;124:92–7. https://doi.org/10.5858/2000-124-0092-TDTNAL.

[3] Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB de O, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720–48. https://doi.org/10.1038/S41375-022-01620-2.

[4] Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021;32:23–33. https://doi.org/10.1016/J.ANNONC.2020.09.019.

[5] Trabace S. HLA and disease association. The Journal of Headache and Pain 2000 1:2 2000;1:S109–13. https://doi.org/10.1007/S101940070003.

[6] Hanson A, Brown MA. Genetics and the causes of ankylosing spondylitis. Rheum Dis Clin North Am 2017;43:401. https://doi.org/10.1016/J.RDC.2017.04.006.

[7] Guja C, Guja L, Nutland S, Rance H, Sebastien M, Todd JA, et al. Type 1 diabetes genetic susceptibility encoded by HLA DQB1 genes in Romania. J Cell Mol Med 2004;8:249. https://doi.org/10.1111/J.1582-4934.2004.TB00280.X.

[8] Brown NK, Guandalini S, Semrad C, Kupfer SS. A clinician's guide to celiac disease HLA genetics. American Journal of Gastroenterology 2019;114:1587–92. https://doi.org/10.14309/AJG.0000000000000310.

[9] Gragert L, Fingerson S, Albrecht M, Maiers M, Kalaycio M, Hill BT. Fine-mapping of HLA associations with chronic lymphocytic leukemia in US populations. Blood 2014;124:2657–65. https://doi.org/10.1182/BLOOD-2014-02-558767.

[10] Zhong C, Cozen W, Bolanos R, Song J, Wang SS. The role of HLA variation in lymphoma aetiology and survival. J Intern Med 2019;286:154–80. https://doi.org/10.1111/JOIM.12911.

[11] Kirimunda S, Verboom M, Otim I, Ssennono M, Legason ID, Nabalende H, et al. Variation in the human leukocyte antigen (HLA) system and risk for endemic Burkitt Lymphoma in Northern Uganda. Br J Haematol 2020;189:489. https://doi.org/10.1111/BJH.16398.

[12] Liu Z, Luo Y, Kirimunda S, Verboom M, Onabajo OO, Gouveia MH, et al. Human Leukocyte Antigen Contributes to Childhood Endemic Burkitt Lymphoma in Eastern Africa: A Case-Control Association Study. Blood 2022;140:9233–5. https://doi.org/10.1182/BLOOD-2022-169911.

[13] Leucemia limfocitară cronică – cel mai frecvent tip de leucemie n.d. https://cancer-plan.ro/leucemia-limfocitara-conica-cel-mai-frecvent-tip-de-leucemie/ (accessed October 28, 2024).

[14] Kanas G, Ge W, Quek RGW, Keeven K, Nersesyan K, Arnason JEA. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe: population-level projections for 2020-2025. Leuk Lymphoma 2022;63:54–63. https://doi.org/10.1080/10428194.2021.1975188.

[15] Pacis S, Bolzani A, Heuck A, Gossens K, Kruse M, Fritz B, et al. Epidemiology and Real-World Treatment of Incident Diffuse Large B-cell Lymphoma (DLBCL): A German Claims Data Analysis. Oncol Ther 2024;12:293–309. https://doi.org/10.1007/S40487-024-00265-8/FIGURES/3.

[16] Orphanet: Mantle cell lymphoma n.d. https://www.orpha.net/en/disease/detail/52416 (accessed November 3, 2024).

[17] Orphanet: Burkitt lymphoma n.d. https://www.orpha.net/en/disease/detail/543 (accessed November 2, 2024).

[18] Weiss J, Reneau J, Wilcox RA. PTCL, NOS: An update on classification, risk-stratification, and treatment. Front Oncol 2023;13. https://doi.org/10.3389/FONC.2023.1101441.

[19] Oluwasanjo A, Kartan S, Johnson W, Alpdogan O, Gru A, Mishra A, et al. Peripheral T-Cell Lymphoma, not Otherwise Specified (PTCL-NOS). Cancer Treat Res 2019;176:83–98. https://doi.org/10.1007/978-3-319-99716-2_4.

[20] Marchi E, O'Connor OA. The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management. CA Cancer J Clin 2020;70:47–70. https://doi.org/10.3322/CAAC.21589.

[21] Shah UA, Shah N, Qiao B, Acuna-Villaorduna A, Pradhan K, Adrianzen Herrera D, et al. Epidemiology and survival trend of adult T-cell leukemia/lymphoma in the United States. Cancer 2020;126:567–74. https://doi.org/10.1002/CNCR.32556.

[22] Tanase AD, Colita A, Craciun OG, Lipan L, Varady Z, Stefan L, et al. Allogeneic Stem Cell Transplantation for Adult T-Cell Leukemia/Lymphoma—Romanian Experience. Journal of Clinical Medicine 2020, Vol 9, Page 2417 2020;9:2417. https://doi.org/10.3390/JCM9082417.

[23] WCT: Objective and Historical perspective n.d. https://whobluebooks.iarc.who.int/about/objective-and-historical-perspective/ (accessed October 20, 2024).

[24] Attygalle AD, Chan JKC, Coupland SE, Du MQ, Ferry JA, Jong D de, et al. The 5th edition of the World Health Organization Classification of mature lymphoid and stromal tumors – an overview and update. Leuk Lymphoma 2024;65:413–29. https://doi.org/10.1080/10428194.2023.2297939.

[25] GHID 23/02/2021 - Portal Legislativ n.d. https://legislatie.just.ro/public/DetaliiDocument/238478 (accessed November 4, 2024).

[26] Graham BS, Lynch DT. Burkitt Lymphoma. StatPearls 2023.

[27] d'Amore F, Gaulard P, Trümper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015;26:v108–15. https://doi.org/10.1093/ANNONC/MDV201.

[28] Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015;26:vii78–82. https://doi.org/10.1093/ANNONC/MDV304.

[29] Dreyling M, Campo E, Hermine O, Jerkeman M, Le Gouill S, Rule S, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017;28:iv62–71. https://doi.org/10.1093/ANNONC/MDX223.

[30] Ishitsuka K. Diagnosis and management of adult T-cell leukemia/lymphoma. Semin Hematol 2021;58:114–22. https://doi.org/10.1053/J.SEMINHEMATOL.2021.02.005.

[31] Cruz-Tapias P, Castiblanco J, Anaya J-M. Major histocompatibility complex: Antigen processing and presentation 2013.

[32] Mosaad YM. Clinical Role of Human Leukocyte Antigen in Health and Disease. Scand J Immunol 2015;82:283–306. https://doi.org/10.1111/SJI.12329.

[33] Ankylosing spondylitis: MedlinePlus Genetics n.d. https://medlineplus.gov/genetics/condition/ankylosing-spondylitis/#references (accessed November 16, 2024).

[34] Paladini F, Fiorillo MT, Tedeschi V, Cauli A, Mathieu A, Sorrentino R. Ankylosing spondylitis: A trade off of HLA-B27, ERAP, and pathogen interconnections? Focus on Sardinia. Front Immunol 2019;10:435127. https://doi.org/10.3389/FIMMU.2019.00035/BIBTEX.

[35] Sticht J, Álvaro-Benito M, Konigorski S. Type 1 Diabetes and the HLA Region: Genetic Association Besides Classical HLA Class II Genes. Front Genet 2021;12:683946. https://doi.org/10.3389/FGENE.2021.683946/BIBTEX.

[36] Nguyen C, Varney MD, Harrison LC, Morahan G. Definition of High-Risk Type 1 Diabetes HLA-DR and HLA-DQ Types Using Only Three Single Nucleotide Polymorphisms. Diabetes 2013;62:2135–40. https://doi.org/10.2337/DB12-1398.

[37] Noble JA, Valdes AM. Genetics of the HLA Region in the Prediction of Type 1 Diabetes. Curr Diab Rep 2011;11:533. https://doi.org/10.1007/S11892-011-0223-X.

[38] Geo JA, Ameen R, Al Shemmari S, Thomas J. Advancements in HLA Typing Techniques and Their Impact on Transplantation Medicine. Medical Principles and Practice 2024;33:215–31. https://doi.org/10.1159/000538176.

[39] Mahdil B mutar. A glow of HLA typing in organ transplantation. Clin Transl Med 2013;2:6. https://doi.org/10.1186/2001-1326-2-6.

[40] Zachary AA, Leffell MS. HLA mismatching strategies for solid organ transplantation - a balancing act. Front Immunol 2016;7:221588. https://doi.org/10.3389/FIMMU.2016.00575/BIBTEX.

[41] Montague AM, Pathak S. Chronic Lymphocytic Leukemia With Variant Genetics. StatPearls 2023.

[42] Pasqualucci L, Dalla-Favera R. Genetics of diffuse large B-cell lymphoma. Blood 2018;131:2307–19. https://doi.org/10.1182/BLOOD-2017-11-764332.

[43] Bakhshi TJ, Georgel PT. Genetic and epigenetic determinants of diffuse large B-cell lymphoma. Blood Cancer J 2020;10. https://doi.org/10.1038/S41408-020-00389-W.

[44] Jamil A, Mukkamalla SKR. Lymphoma. Essential Paediatric Surgery: A Practical Guide 2023:344–7. https://doi.org/10.1201/9781003182290-64.

[45] Sandell RF, Boddicker RL, Feldman AL. Genetic Landscape and Classification of Peripheral T Cell Lymphomas. Curr Oncol Rep 2017;19:28. https://doi.org/10.1007/S11912-017-0582-9.

[46] Tizu M, Calenic B, Hârza M, Cristea BM, Maruntelu I, Caragea AM, et al. HLA Gene Polymorphisms in Romanian Patients with Chronic Lymphocytic Leukemia. Genet Res (Camb) 2024;2024:8852876. https://doi.org/10.1155/2024/8852876.

[47] Mărunţelu I, Cristea BM, Omer S, Preda CM, Constantinescu I. Relevance of HLA gene polymorphisms in Romanian patients with chronic renal insufficiency undergoing renal transplantation. J Clin Lab Anal 2021;35:e24075. https://doi.org/10.1002/JCLA.24075.

[48] Maruntelu I, Preda CM, Sandra I, Istratescu D, Chifulescu AE, Manuc M, et al. HLA Genotyping in Romanian Adult Patients with Celiac Disease, their First-degree Relatives and Healthy Persons. J Gastrointestin Liver Dis 2022;31:191–7. https://doi.org/10.15403/JGLD-4187.

[49] Scally SW, Petersen J, Law SC, Dudek NL, Nel HJ, Loh KL, et al. A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. J Exp Med 2013;210:2569–82. https://doi.org/10.1084/JEM.20131241.

[50] Mueller LP, Machulla HKG. Increased frequency of homozygosity for HLA class II loci in female patients with chronic lymphocytic leukemia. Leuk Lymphoma 2002;43:1013–9. https://doi.org/10.1080/10428190290021588.

[51] Le WB, Shi JS, Zhang T, Liu L, Qin HZ, Liang S, et al. HLA-DRB1∗15:01 and HLA-DRB3∗02:02 in PLA2R-related membranous nephropathy. Journal of the American Society of Nephrology 2017;28:1642–50. https://doi.org/10.1681/ASN.2016060644.

[52] Cuttner J, Skerrett D, Rosina O, Troy KM, Wallenstein S, Spivack M. Increased incidence of HLA antigen B35 in patients with chronic lymphocytic leukemia. Leuk Res 1994;18:565–7. https://doi.org/10.1016/0145-2126(94)90037-X.

[53] María GÁ, Miguel A, Miriam LP, Noemí P, Alicia A, Ana B, et al. HLA specificities are associated with prognosis in IGHV-mutated CLL-like high-count monoclonal B cell lymphocytosis. PLoS One 2017;12. https://doi.org/10.1371/JOURNAL.PONE.0172978.

[54] Hojjat-Farsangi M, Razavi SM, Sharifian RA, Shokri F. Frequency analysis of HLA class I alleles in Iranian patients with progressive and non-progressive chronic lymphocytic leukemia. Hum Immunol 2014;75:170–5. https://doi.org/10.1016/J.HUMIMM.2013.11.003.

[55] Di Bernardo MC, Broderick P, Harris S, Dyer MJS, Matutes E, Dearden C, et al. Risk of developing chronic lymphocytic leukemia is influenced by HLA-A class I variation. Leukemia 2013;27:255. https://doi.org/10.1038/LEU.2012.173.

[56] Association of chronic lymphocytic leukemia with specific alleles of the HLA-DR4:DR53:DQ8 haplotype in German patients - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/11291046/ (accessed August 10, 2024).

[57] Abdul-Rahman MT, Al-Ammar NS, Kreyenberg H. HLA-DQA1 and -DQB1 Alleles as Risk Factors for Acute Lymphoblastic Leukemia. Iranian Journal of War and Public Health 2022;14:185–95. https://doi.org/10.29252/IJWPH.14.2.189.

[58] Zhao LP, Alshiekh S, Zhao M, Carlsson A, Larsson HE, Forsander G, et al. Next-Generation Sequencing Reveals That HLA-DRB3, -DRB4, and -DRB5 May Be Associated With Islet

Autoantibodies and Risk for Childhood Type 1 Diabetes. Diabetes 2016;65:710–8. https://doi.org/10.2337/DB15-1115.

[59] Wang W, Ollila HM, Whittemore AS, Demehri S, Ioannidis NM, Jorgenson E, et al. Genetic variants in the HLA class II region associated with risk of cutaneous squamous cell carcinoma. Cancer Immunol Immunother 2018;67:1123–33. https://doi.org/10.1007/S00262-018-2168-2.

[60] Schwarm C, Gola D, Holtsche MM, Dieterich A, Bhandari A, Freitag M, et al. Identification of two novel bullous pemphigoid- associated alleles, HLA-DQA1*05:05 and -DRB1*07:01, in Germans. Orphanet J Rare Dis 2021;16. https://doi.org/10.1186/S13023-021-01863-9.

[61] Nowak JK, Glapa-Nowak A, Banaszkiewicz A, Iwańczak B, Kwiecień J, Szaflarska-Popławska A, et al. Hla-dqa1*05 associates with extensive ulcerative colitis at diagnosis: An observational study in children. Genes (Basel) 2021;12. https://doi.org/10.3390/GENES12121934.

[62] Aureli A, Canossi A, Del Beato T, Buonomo O, Rossi P, Roselli M, et al. Breast Cancer Is Associated with Increased HLA-DRB1*11:01 and HLA-DRB1*10:01 Allele Frequency in a Population of Patients from Central Italy. Immunol Invest 2020;49:489–97. https://doi.org/10.1080/08820139.2020.1737539.

[63] Arons E, Adams S, Venzon DJ, Pastan I, Kreitman RJ. Class II human leucocyte antigen DRB1*11 in hairy cell leukaemia patients with and without haemolytic uraemic syndrome. Br J Haematol 2014;166:729–38. https://doi.org/10.1111/BJH.12956.

[64] Rossman MD, Thompson B, Frederick M, Maliarik M, Iannuzzi MC, Rybicki BA, et al. HLA-DRB1*1101: a significant risk factor for sarcoidosis in blacks and whites. Am J Hum Genet 2003;73:720–35. https://doi.org/10.1086/378097.

[65] Rezaieyazdi Z, Kochakzadeh M, Hatef MR, Esmaily H, Malek A, Valizadeh N, et al. Protective role of HLA-DRB1*11 against juvenile idiopathic arthritis living in North Eastern Iran. Iran J Basic Med Sci 2018;21:564–8. https://doi.org/10.22038/IJBMS.2018.25022.6215.

[66] Tizu M, Calenic B, Constantinescu AE, Bratei AA, Stoia RA, Popa MCG, et al. Cluster of Differentiation Markers and Human Leukocyte Antigen Expression in Chronic Lymphocytic Leukemia Patients: Correlations and Clinical Relevance. Curr Issues Mol Biol 2024;46:10008–25. https://doi.org/10.3390/CIMB46090598.

[67] Lanza F, Maffini E, Rondoni M, Massari E, Faini AC, Malavasi F. CD22 Expression in B-Cell Acute Lymphoblastic Leukemia: Biological Significance and Implications for Inotuzumab Therapy in Adults. Cancers (Basel) 2020;12. https://doi.org/10.3390/CANCERS12020303.

[68] Robak T, Krawczyńska A, Cebula-Obrzut B, Urbaniak M, Iskierka-Jażdżewska E, Robak P. Atypical Chronic Lymphocytic Leukemia—The Current Status. Cancers 2023, Vol 15, Page 4427 2023;15:4427. https://doi.org/10.3390/CANCERS15184427.

[69] Kimby E, Mellstedt H, Björkholm M, Holm G. Clonal cell surface structures related to differentiation, activation and homing in B-cell chronic lymphocytic leukemia and monoclonal lymphocytosis of undetermined significance. Eur J Haematol 1989;43:452–9. https://doi.org/10.1111/J.1600-0609.1989.TB00335.X.

[70] Solanki H, Mishra V, Tiwari A, Kakkar N, Vashisht N, Raina V, et al. Human leukocyte antigen associations with acute leukemia: An indian perspective. Indian Journal of Medical and Paediatric Oncology 2020;41:850–8. https://doi.org/10.4103/IJMPO.IJMPO_195_20.

[71] Olson TS, Frost BF, Duke JL, Dribus M, Xie HM, Prudowsky ZD, et al. Pathogenicity and impact of HLA class I alleles in aplastic anemia patients of different ethnicities. JCI Insight 2022;7. https://doi.org/10.1172/JCI.INSIGHT.163040.

[72] Malcolm Taylor G, Dearden S, Ravetto P, Ayres M, Watson P, Hussain A, et al. Genetic susceptibility to childhood common acute lymphoblastic leukaemia is associated with polymorphic peptide-binding pocket profiles in HLA-DPB1*0201. Hum Mol Genet 2002;11:1585–97. https://doi.org/10.1093/HMG/11.14.1585.

[73] Tchilian EZ, Wallace DL, Wells RS, Flower DR, Morgan G, Beverley PCL. A deletion in the gene encoding the CD45 antigen in a patient with SCID. J Immunol 2001;166:1308–13. https://doi.org/10.4049/JIMMUNOL.166.2.1308.

[74] Rizzo D, Lotay A, Gachard N, Marfak I, Faucher JL, Trimoreau F, et al. Very low levels of surface CD45 reflect CLL cell fragility, are inversely correlated with trisomy 12 and are associated with increased treatment-free survival. Am J Hematol 2013;88:747–53. https://doi.org/10.1002/AJH.23494.

[75] Usefulness of CD45 density in the diagnosis of B-cell chronic lymphoproliferative disorders - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/15985726/ (accessed August 27, 2024).

[76] Kaminski DA, Wei C, Qian Y, Rosenberg AF, Sanz I. Advances in human B cell phenotypic profiling. Front Immunol 2012;3. https://doi.org/10.3389/FIMMU.2012.00302.

[77] Maeshima AM, Taniguchi H, Fujino T, Saito Y, Ito Y, Hatta S, et al. Immunohistochemical CD20-negative change in B-cell non-Hodgkin lymphomas after rituximab-containing therapy. Ann Hematol 2020;99:2141–8. https://doi.org/10.1007/S00277-019-03853-1.

[78] Katchi T, Liu D. Diagnosis and treatment of CD20 negative B cell lymphomas. Biomark Res 2017;5. https://doi.org/10.1186/S40364-017-0088-5.

[79] Dinner S, Liedtke M. Antibody-based therapies in patients with acute lymphoblastic leukemia. Hematology 2018;2018:9–15. https://doi.org/10.1182/ASHEDUCATION-2018.1.9.

[80] Zhang X, Aguilera N. New immunohistochemistry for B-cell lymphoma and Hodgkin lymphoma. Arch Pathol Lab Med 2014;138:1666–72. https://doi.org/10.5858/ARPA.2014-0058-RA.

[81] Fuhlbrigge RC, King SL, Sackstein R, Kupper TS. CD43 is a ligand for E-selectin on CLA+ human T cells. Blood 2006;107:1421–6. https://doi.org/10.1182/BLOOD-2005-05-2112.

[82] Gillissen MA, De Jong G, Kedde M, Yasuda E, Levie SE, Moiset G, et al. Patient-derived antibody recognizes a unique CD43 epitope expressed on all AML and has antileukemia activity in mice. Blood Adv 2017;1:1551. https://doi.org/10.1182/BLOODADVANCES.2017008342.

[83] Hsieh YC, Lin CL, Tsao CJ, Hsieh PP, Tzeng CC, Chuang SS. Aberrant expression of CD19 and CD43 in a patient with therapy-related acute myeloid leukemia and a history of mantle cell lymphoma. Kaohsiung J Med Sci 2009;25:389–94. https://doi.org/10.1016/S1607-551X(09)70532-7.

[84] Kurtin PJ, Hobday KS, Ziesmer S, Caron BL. Demonstration of distinct antigenic profiles of small B-cell lymphomas by paraffin section immunohistochemistry. Am J Clin Pathol 1999;112:319–29. https://doi.org/10.1093/AJCP/112.3.319.

[85] Falay M, Öztürk BA, Güneş K, Kalpakçı Y, Dağdaş S, Ceran F, et al. The Role of CD200 and CD43 Expression in Differential Diagnosis between Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma. Turkish Journal of Hematology 2018;35:94. https://doi.org/10.4274/TJH.2017.0085.

[86] Naeim F, Rao PN, Song SX, Phan RT. Principles of Immunophenotyping. Atlas of Hematopathology: Morphology, Immunophenotype, Cytogenetics, and Molecular Approaches, Second Edition 2018:29–56. https://doi.org/10.1016/B978-0-12-809843-1.00002-4.

[87] Dorfman DM, Shahsafaei A, Alonso MA. Utility of CD200 immunostaining in the diagnosis of primary mediastinal large B cell lymphoma: comparison with MAL, CD23, and other markers. Mod Pathol 2012;25:1637–43. https://doi.org/10.1038/MODPATHOL.2012.129.

[88] Tkachenko A, Kupcova K, Havranek O. B-Cell Receptor Signaling and Beyond: The Role of Igα (CD79a)/Igβ (CD79b) in Normal and Malignant B Cells. Int J Mol Sci 2024;25. https://doi.org/10.3390/IJMS25010010.

[89] Poeta G Del, Principe MI Del, Zucchetto A, Buccisano F, Simotti C, Maurillo L, et al. High CD79b Expression Predicts a Poor Outcome in B-Cell Chronic Lymphocytic Leukemia (B-CLL). Blood 2008;112:1054–1054. https://doi.org/10.1182/BLOOD.V112.11.1054.1054.

[90] Allan JN, Bhavsar EB, Vaisitti T, Sarno V, Liu Y, Arruga F, et al. CD79b Expression in Richter's Transformation. Blood 2019;134:4279–4279. https://doi.org/10.1182/BLOOD-2019-128305.

[91] Falay M, Serdar MA, Dalgali H, Uçar MA, Dagdaş S, Özet G. Which Markers Should the used for Diagnostic Chronic Lymphocytic Leukemia Immunophenotyping Scoring System by Flow Cytometry? Clin Lab 2019;65:2049–55. https://doi.org/10.7754/CLIN.LAB.2019.190316.

[92] Afacan-Öztürk HB, Falay M, Albayrak M, Yıldız A, Öztürk Çiğdem P, Maral S, et al. CD81 Expression in the Differential Diagnosis of Chronic Lymphocytic Leukemia. Clin Lab 2019;65. https://doi.org/10.7754/CLIN.LAB.2018.180802.

[93] Zhou M, Qiu H, Chen T, Xiao R, Yang J, Cen L, et al. Human leukocyte antigen (HLA)-DRB1*14 is associated with a high incidence of acute lymphocytic leukemia. Onkologie 2012;35:268–71. https://doi.org/10.1159/000338480.

[94] Kazemi MH, Momeni-Varposhti Z, Roshandel E, Sankanian G, Hosseini Rouzbahani N, Ghorban K, et al. Association of HLA alleles with hematologic malignancies. Gene Rep 2021;25:101346. https://doi.org/10.1016/J.GENREP.2021.101346.

[95] A clinical and epidemiological study of human leukocyte antigen-DPB alleles in Hodgkin's disease - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/7923125/ (accessed August 11, 2024).

[96] Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, Allen SL, et al. Ig V Gene Mutation Status and CD38 Expression As Novel Prognostic Indicators in Chronic Lymphocytic Leukemia. Blood 1999;94:1840–7. https://doi.org/10.1182/BLOOD.V94.6.1840.

[97] Hamblin TJ, Orchard JA, Ibbotson RE, Davis Z, Thomas PW, Stevenson FK, et al. CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Blood 2002;99:1023–9. https://doi.org/10.1182/BLOOD.V99.3.1023.

[98] Tizu M, Calenic B, Maruntelu I, Caragea AM, Talangescu A, Ursu L, et al. Immunogenetic Background of Chronic Lymphoproliferative Disorders in Romanian Patients-Case Control Study. Med Sci (Basel) 2024;12:14. https://doi.org/10.3390/MEDSCI12010014/S1.

[99] Zhong C, Gragert L, Maiers M, Hill BT, Garcia-Gomez J, Gendzekhadze K, et al. The association between HLA and non-Hodgkin lymphoma subtypes, among a transplant-indicated population. Leuk Lymphoma 2019;60:2899–908. https://doi.org/10.1080/10428194.2019.1617858.

[100] Jeffery KJM, Siddiqui AA, Bunce M, Lloyd AL, Vine AM, Witkover AD, et al. The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. J Immunol 2000;165:7278–84. https://doi.org/10.4049/JIMMUNOL.165.12.7278.

[101] Brazzelli V, Rivetti N, Badulli C, Carugno A, Grasso V, De Silvestri A, et al. Immunogenetic factors in mycosis fungoides: can the HLA system influence the susceptibility and prognosis of the disease? Long-term follow-up study of 46 patients. J Eur Acad Dermatol Venereol 2014;28:1732–7. https://doi.org/10.1111/JDV.12391.

[102] Lin WY, Fordham SE, Sunter N, Elstob C, Rahman T, Willmore E, et al. Genome-wide association study identifies risk loci for progressive chronic lymphocytic leukemia. Nature Communications 2021 12:1 2021;12:1–8. https://doi.org/10.1038/s41467-020-20822-9.

[103] Wang SS, Abdou AM, Morton LM, Thomas R, Cerhan JR, Gao X, et al. Human leukocyte antigen class I and II alleles in non-Hodgkin lymphoma etiology. Blood 2010;115:4820–3. https://doi.org/10.1182/BLOOD-2010-01-266775.

[104] Benencio P, Fraile Gonzalez SA, Ducasa N, Page K, Berini CA, Biglione MM. HLA-B*35 as a new marker for susceptibility to human T-cell lymphotropic virus type 1 (HTLV-1) Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) in patients living in Argentina. Retrovirology 2020;17. https://doi.org/10.1186/S12977-020-00536-Y.

[105] Wang X, An G, Wang J, Zhang Y, Li Q, Wei H, et al. The association of HLA-C alleles with multiple myeloma in Chinese patients. Exp Hematol Oncol 2018;7:19. https://doi.org/10.1186/S40164-018-0112-Y.

[106] Svejgaard A, Ryder LP. HLA and disease associations: detecting the strongest association. Tissue Antigens 1994;43:18–27. https://doi.org/10.1111/J.1399-0039.1994.TB02291.X.

[107] Gavioli R, De Campos-Lima PO, Kurilla MG, Kieff E, Klein G, Masucci MG. Recognition of the Epstein-Barr virus-encoded nuclear antigens EBNA-4 and EBNA-6 by HLA-A11-restricted cytotoxic T lymphocytes: implications for down-regulation of HLA-A11 in Burkitt lymphoma. Proc Natl Acad Sci U S A 1992;89:5862. https://doi.org/10.1073/PNAS.89.13.5862.

[108] Choi HB, Roh SY, Choi EJ, Yoon HY, Kim SY, Hong YS, et al. Association of HLA alleles with non-Hodgkin's lymphoma in Korean population. Int J Hematol 2008;87:203–9. https://doi.org/10.1007/S12185-008-0040-4.

[109] Galleze A, Raache R, Amroun H, Cherif N, Fadli M, Meçabih F, et al. HLA Polymorphism in Algerian Children With Lymphomas. J Pediatr Hematol Oncol 2015;37:e458–61. https://doi.org/10.1097/MPH.0000000000000419.

[110] Ramezani A, Hasanjani Roshan MR, Kalantar E, Eslamifar A, Banifazl M, Taeb J, et al. Association of human leukocyte antigen polymorphism with outcomes of hepatitis B virus infection. J Gastroenterol Hepatol 2008;23:1716–21. https://doi.org/10.1111/J.1440-1746.2008.05482.X.

[111] Laaksonen M, Pastinen T, Sjöroos M, Kuokkanen S, Ruutiainen J, Sumelahti ML, et al. HLA class II associated risk and protection against multiple sclerosis - A Finnish family study. J Neuroimmunol 2002;122:140–5. https://doi.org/10.1016/S0165-5728(01)00456-8.

[112] Van Der Woude D, Lie BA, Lundström E, Balsa A, Feitsma AL, Houwing-Duistermaat JJ, et al. Protection Against Anti-Citrullinated Protein Antibody-Positive Rheumatoid Arthritis Is Predominantly Associated With HLA-DRB1*1301 A Meta-Analysis of HLA-DRB1 Associations With Anti-Citrullinated Protein Antibody-Positive and Anti-Citrullinated Protein Antibody-Negative Rheumatoid Arthritis in Four European Populations. Arthritis Rheum 2010;62:1236–45. https://doi.org/10.1002/art.27366.

[113] Wysocki T, Olesińska M, Paradowska-Gorycka A. Current Understanding of an Emerging Role of HLA-DRB1 Gene in Rheumatoid Arthritis-From Research to Clinical Practice. Cells 2020;9. https://doi.org/10.3390/CELLS9051127.

[114] Farias TDJ, Brugiapaglia S, Croci S, Magistroni P, Curcio C, Zguro K, et al. HLA-DPB1*13:01 associates with enhanced, and KIR2DS4*001 with diminished protection from developing severe COVID-19. HLA 2024;103. https://doi.org/10.1111/TAN.15251.

[115] Liu Z, Luo Y, Kirimunda S, Verboom M, Onabajo OO, Gouveia MH, et al. Human leukocyte antigen-DQA1*04:01 and rs2040406 variants are associated with elevated risk of childhood Burkitt lymphoma. Communications Biology 2024 7:1 2024;7:1–9. https://doi.org/10.1038/s42003-023-05701-5.