Human Leukocyte antigen and classical Hodgkin lymphoma
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Age dependent HLA associations in classical Hodgkin lymphoma

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In preparation
ABSTRACT
Classical Hodgkin lymphoma (cHL) is characterized by a bimodal age incidence curve. In the western world, the first prominent peak in young adults (15-35 years) is generally associated with tumors that are Epstein Barr virus (EBV) negative and with nodular sclerosis subtype. In contrast, the second peak after 50 years of age is more often associated with EBV positivity and mixed cellularity subtype. Human leukocyte antigen (HLA) typing studies have identified multiple alleles associated with risk of cHL overall and of EBV stratified cHL subgroups.

In this study we tested for differences in HLA allele frequency between cHL patient subgroups stratified for age at diagnosis in a cohort of 1,378 West European Caucasians. We used moving 10-15 year wide age-bins to compare HLA allele frequencies between each individual age-bin and all other age-bins combined. Statistical significance was based on 2,500 permutations. Frequencies of significant alleles were subsequently compared to allele frequencies in control populations to establish risk or protective effects.

Allele frequencies of HLA-B*08 and HLA-DRB1*03 were significantly increased in older age-bins (p<0.0015), whereas allele frequencies of HLA-DQB1*06 and HLA-DRB1*15 were significantly increased in the younger age-bins. These first analyses suggested the most relevant cut-off for age at diagnosis to be at 45 years. Subsequent comparison of allele frequencies of HLA-B*08, HLA-DRB1*03, and the frequency of putative haplotype B*08-DRB1*03 in a dichotomous analysis of cHL using the age cut-off of 45 years confirmed a significant increase of both allele and haplotype frequencies in older (>45 years) cHL and within older cHL EBV+/non-NS cHL patients as compared to the controls. The allele frequencies of HLA-DQB1*06, HLA-DRB1*15, and the putative DQB1*06-DRB1*15 haplotype frequency were significantly increased in younger (≤45 years) patients. Within the younger cHL group the association was restricted to EBV-/NS cHL patients and absent in EBV+ cHL.

In this novel unbiased age-stratification approach we identified four HLA alleles belonging to two common Caucasian haplotypes that confine risk specifically to young or older cHL patients. This suggests that age and most likely age related differences of the immune function contribute to the etiology of cHL.
INTRODUCTION

Classical Hodgkin lymphoma (cHL) is a B cell malignancy derived from pre-apoptotic germinal center B cells (1). A unique characteristic of cHL is the presence of <1% of tumor cells, called Hodgkin-Reed Sternberg (HRS) cells, in a large background of reactive infiltrating cells (2,3). Based on histology and the composition of the tumor microenvironment cHL has been classified into nodular sclerosis (NS), mixed cellularity (MC), lymphocyte rich (LR) and lymphocyte depleted (LD) subtypes (4). In up to 35% of cHL cases in the western population the HRS cells are carry Epstein Barr virus (EBV) (5).

The etiology of cHL includes both genetic and environmental risk factors. Unlike most diseases, which show increasing incidence with increasing age, cHL has a bimodal age incidence pattern in affluent countries in the West. The first more pronounced peak can be found in young adults (15-35 years) and the second peak is seen above 50 years (6). Cases in the two age peaks might have different etiologies based on EBV and histological subtype (7). EBV+ cHL is more common in children, older adults, and the MC subtype (8). The young adult cases are usually EBV- and of NS subtype. The age and EBV specific incidence pattern implicates the functionality of the immune system in cHL pathogenesis. Indeed, several studies show that the immune system in children is not fully developed, whereas the immune system in the elderly has diminished functionality as compared to young adults (9–11).

HLA was the first genetic risk factor to be associated with cHL susceptibility (12). Current HLA genotyping studies clearly indicate strong associations with HLA class I alleles being associated with EBV+ cHL and HLA class II alleles being associated with cHL overall or with EBV- cHL (13–16). Recent genome wide associations studies (GWAS) have consistently shown log additive effects of single nucleotide polymorphisms (SNPs) mapping to the HLA region, also within EBV, subtype or age defined subgroups (17–21). However, the number of studies focusing on the possible effect of age on HLA allele associations in cHL is limited.

The aim of the current multicenter study is to investigate HLA associations in cHL patients stratified based on their age at diagnosis. As the most optimal age cut-off is not known and most studies use different pre-defined age groups, we applied a novel and unbiased moving average approach to establish if the distribution of HLA alleles varies with age.

MATERIALS AND METHODS
Chapter 4

Patient cohort

Data on a total of 1,378 Caucasian cHL patients were retrieved from three West European studies, including Denmark (n=212), Sweden (n=293) (13), the Netherlands (n=370) (14) and the United Kingdom (UK) (n=503) (Johnson et al., submitted). In brief, the SCALE study was carried out in Denmark and Sweden between 1999 and 2002 and included 586 patients with classical HL (participation rate, 91%) (13). The Dutch patients from the northern region of the Netherlands were diagnosed between 1987 and 2010 at the University Medical Center Groningen. The UK cases were from the YHHCCS (n=41) and SNEHD (n=282) case control studies and a case series from Scotland and the Northern region on England (n=180). For all patients, data on age at diagnosis, sex, EBV status, and histology were available. Study designs were approved by relevant human subject protection committees and all patients gave written informed consent in accordance with the Declaration of Helsinki.

HLA genotyping

HLA genotyping data of SCALE (13) and Dutch case series (14) have been published previously. HLA-A genotyping data of the UK case series have been published previously (13) and the complete data have been submitted for publication (Johnson et al.). In the SCALE case series, intermediate resolution of only the HLA-A and HLA-B loci were available. In the Scale study HLA-A, HLA-B and HLA-DR alleles were typed. In the Dutch and Scottish cohorts all classical HLA class I and II alleles were defined with the exception of HLA-DQA1, which was available typed only in the UK case series. The allele typing was converted to 2-digit DNA-based alleles for all cases. The nomenclature of the HLA alleles was done according to the WHO Nomenclature Committee for Factors of the HLA System (22). In case of ambiguous results, the allele combination of common and well-documented alleles was used (23). For HLA-DPB1 one ambiguity remained (DPB1*04:02/105:01) which was analyzed as one group of alleles together with DPB1*04.

Statistical analysis

Differences in sex, age, EBV status, and histology between the different patient cohorts and between age defined patient subgroups were analyzed using either the chi-square test (sex, EBV status, and histology) or a non-parametric Kruskal-Wallis test (age).

We designed a moving-average approach to compare HLA allele frequencies between different age groups. For each allele a series of consecutive overlapping year age-bins were made by moving each age-bin by one year, e. g. 10-20, 11-21, 12-22, etc.
for 10 year age-bins. For all 37 alleles (with a frequency ≥ 5% in the combined cohort), the allele frequency in each age-bin was compared to the frequencies in all other age-bins using a chi-square test. The number of nominal significant differences (p<0.05) was counted for each HLA allele. Its significance was next determined from 2,500 permutations of ages across all patients by calculating the proportion of permutations in which the number of nominal significant differences between age-bins was larger than the observed number. A p-value of less than 0.0015 (multiple testing correction for 37 alleles) was considered as significant, whereas a p-value less than 0.005 was considered as suggestive for significance. The size of the age-bins was chosen based on the number of patients typed for each HLA locus. Thus, the cHL patients were grouped into age-bins of 10 years for HLA-A (n=1,371) and HLA-B (n=1,269) or 15 years for HLA-Cw (n=858), HLA-DPB1 (n=615), HLA-DQA1 (n=253), HLA-DQB1 (n=613) and HLA-DRB1 (n=837).

In a second phase, significant allele frequencies and their putative haplotype frequencies were compared between age defined cHL patients subgroups and stratified based sex and on tumor EBV status and histological subtype status with the frequencies in the geographically matched controls obtained from a publicly available database (allelefrequency.net) (24). We used a chi-square test with p<0.015 considered significant and p<0.045 considered suggestive for significance in order to account for multiple testing for 4 alleles in linkage disequilibrium and 2 derived haplotypes.

RESULTS

Patient characteristics

An overview of patient characteristics in terms of sex, age, EBV status and histology in all cohorts included in this study is given in Table 1. The distribution of sex, EBV status, and histology did not differ significantly between the four case series. Overall, a slightly higher percentage of cases were male (50.1%-55.2%) compared to female (44.8%-49.9%). The percentage of cases with EBV+ cHL varied from 25.7% to 30.8%. The percentage of NS subtype ranged from 68.4% to 75.7%. The age distribution was significantly different between the cohorts, with the median age of the Danish cHL cohort (i.e. 38 years) being slightly higher than the median ages of the other cohorts. Presumably this is related to the lower age limit for study recruitment rather than any biological difference.
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Denmark n=212</th>
<th>Netherlands n=370</th>
<th>UK n=503</th>
<th>Sweden n=293</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>115 (54.2)</td>
<td>196 (53.0)</td>
<td>278 (55.2)</td>
<td>147 (50.1)</td>
<td>ns(^a)</td>
</tr>
<tr>
<td>Female</td>
<td>97 (45.8)</td>
<td>174 (47.0)</td>
<td>225 (44.8)</td>
<td>146 (49.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td>&lt;0.0001(^b)</td>
</tr>
<tr>
<td>Range</td>
<td>19-75</td>
<td>12-89</td>
<td>15-80</td>
<td>18-75</td>
<td></td>
</tr>
<tr>
<td><strong>EBV status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV pos.</td>
<td>54 (30.5)</td>
<td>86 (25.7)</td>
<td>155 (30.8)</td>
<td>69 (27.2)</td>
<td>ns(^a)</td>
</tr>
<tr>
<td>EBV neg.</td>
<td>123 (69.5)</td>
<td>249 (74.3)</td>
<td>348 (69.2)</td>
<td>184 (72.8)</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>35</td>
<td>43</td>
<td>0</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>Histology n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>145 (68.4)</td>
<td>280 (75.7)</td>
<td>353 (70.2)</td>
<td>205 (70.0)</td>
<td>ns(^a)</td>
</tr>
<tr>
<td>Non-NS</td>
<td>67 (31.6)</td>
<td>90 (24.3)</td>
<td>150 (29.8)</td>
<td>88 (30.0)</td>
<td></td>
</tr>
</tbody>
</table>

Percentages are in parentheses, \(^a\)Chi-square test, \(^b\)Kruskal-Wallis test. Abbreviations: EBV=Epstein-Barr virus, NS=Nodular sclerosis. n.a.=Not available.

**Age effects on HLA associations**

Our analysis using moving average age bins revealed significant differences in the association with cHL by age for four alleles (Figure 1). HLA-B*08 and HLA-DRB1*03 allele frequencies were significantly increased in cHL patients from the older age-bins compared to those from the younger age-bins. These two alleles together with HLA-A*01 form a haplotype that is common in Caucasians, but HLA-A*01 frequencies were not different over age bins (p=0.069). Allele frequencies of HLA-DQB1*06 and HLA-DRB1*15 were significantly increased in cHL patients from the younger age-bins compared to those from the older age-bins. The HLA-B*07 allele, which is part of a common haplotype that also includes the HLA-DQB1*06 and HLA-DRB1*15 alleles, showed a borderline significant variation in frequency across age bins with a pattern similar to that of DQB1*06 and HLA-DRB1*15 (p=0.0016).
Age dependent HLA associations in cHL

Figure 1. Age association of HLA alleles. HLA allele frequencies in each 10 year (HLA-B*08) or 15 year (HLA-DRB1*03, HLA-DQB1*06 and HLA-DRB1*15) age-bin are plotted. The average allele frequency in cHL patients overall is indicated as a horizontal line. The size of the dots indicates the level of significance. P-values (<0.0015) indicate significant differences between younger and older age-bins.
**Chapter 4**

Differences in the HLA allele/haplotype frequencies between young and old cHL cases and controls

To establish if the identified HLA alleles confer risk or protective effects for the development of cHL, we next determined if the allele and haplotype frequencies were significantly different from the control frequencies. Based on Figure 1, we selected an age at onset cut-off of 45 years for these analyses. We first compared patient characteristics of cHL ≤45 years at the time of diagnosis to cHL patients aged >45 years at diagnosis. This revealed significant differences in the distribution of sex, EBV, and subtype by age (Table 2). Female sex, EBV- and NS subtype were significantly overrepresented in cHL patients with an age at diagnosis ≤45 years compared to cHL patients with an age at diagnosis >45 years. Based on these differences we decided to perform association analyses of EBV status, subtype, and sex with the associated alleles and haplotypes as well.

The allele frequencies of HLA-B*08 (25.2% vs. 13.3%, p=1.1x10^{-10}) and HLA-DRB1*03 (23.9% vs. 13.9%, p=3.0x10^{-6}) were significantly increased in cHL patients with an age at diagnosis of >45 years compared to controls (Table 3). The frequency of patients carrying both HLA-B*08 and HLA-DRB1*03, which is an indication of patients carrying the common B*08-DRB1*03 haplotype, was as expected also significantly increased in cHL patients >45 years compared to controls (20.9% vs. 10.4%, p=3.4x10^{-13}). There were no significant differences between cHL patients with an age at diagnosis ≤45 years and controls for HLA-B*08, HLA-DRB1*03, and the corresponding haplotype. Analysis of putative confounders revealed that the associations of HLA-B*08, HLA-DRB1*03, and the B*08-DRB1*03 haplotype were most pronounced in the EBV+, non-NS and female subgroups of older age, but the associations were not significantly different between males and females in either age subgroup (Figure 2). In addition, young EBV+ or non-NS cases and old EBV- or NS cases with a HLA-B*08 or HLA-DRB1*03 allele or corresponding haplotype were at equal risk for cHL, whereas the associations were clearly absent in EBV- or NS cHL patients ≤45 years of age at time of diagnosis.

The allele frequencies of HLA-DQB1*06 (38.1% vs. 26.9%, p=3.4x10^{-7}) and HLA-DRB1*15 (25.2% vs. 16.7%, p=9.5x10^{-6}) were significantly increased in cHL patients with an age at diagnosis ≤45 years compared to controls. The putative haplotype frequency, based on HLA-DQB1*06 and HLA-DRB1*15 carriers, was as expected also significantly increased in this subgroup of cHL patients compared to controls (24.6% vs. 14.9%, p=1.9x10^{-14}). In the cHL patient group of >45 years no significant differences were observed for HLA-DQB1*06, HLA-DRB1*15, and the haplotype frequencies in comparison to the controls. In the analyses of putative confounders the associations of
both HLA-DQB1*06, HLA-DRB1*15 alleles, and the haplotype seemed to be restricted to EBV- or NS subtype cHL with an age at diagnosis \( \leq 45 \) years (Figure 2). In cHL patients with an age at diagnosis >45 years EBV status or subtype was not associated with HLA-DQB1*06, HLA-DRB1*15 alleles or haplotype frequencies. Sex differences were observed in neither the younger nor the older cHL patients.

**Table 3. Differences in HLA allele/haplotype frequencies between age-defined subgroups of cHL and controls.**

<table>
<thead>
<tr>
<th>HLA alleles /haplotypes</th>
<th>Allele/haplotype frequencies (%)</th>
<th>Controls vs. cHL ≤45y</th>
<th>Controls vs. cHL &gt;45y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=2096)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cHL ≤45y (n=1196)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cHL &gt;45y (n=472)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B*08</td>
<td>279 (13.3)</td>
<td>184 (15.4)</td>
<td>119 (25.2)</td>
</tr>
<tr>
<td>DRB1*03</td>
<td>132 (13.9)</td>
<td>185 (15.5)</td>
<td>113 (23.9)</td>
</tr>
<tr>
<td>B<em>08-DRB1</em>03</td>
<td>1330 (10.4)</td>
<td>139 (11.6)</td>
<td>99 (20.9)</td>
</tr>
<tr>
<td>DQB1*06</td>
<td>254 (26.9)</td>
<td>333 (38.1)</td>
<td>89 (27.3)</td>
</tr>
<tr>
<td>DRB1*15</td>
<td>158 (16.7)</td>
<td>220 (25.2)</td>
<td>54 (16.6)</td>
</tr>
<tr>
<td>DQB1<em>06-DRB1</em>15</td>
<td>1906 (14.9)</td>
<td>215 (24.6)</td>
<td>53 (16.2)</td>
</tr>
</tbody>
</table>

\(^a\)HLA allele frequencies are obtained from allelefrequencies.net (24) and are a weighted average of frequencies of HLA-B, HLA-DRB1 and HLA-DQB1 alleles from the populations from Germany (n=174) and England (n=298) and of HLA-B from Norway (n=576). \(^b\)Haplotype frequencies of European Americans (2N=12,790)(28). \(^c\)Chi-square test with significance level of p<0.01.

**DISCUSSION**

Several etiologically distinct cHL age incidence models have been proposed in conjunction with EBV and histology (8). Although there are clear incidence peaks in young adults and in patients over 55 years of age, there is no consensus on the precise age of diagnosis cut-off to separate these groups. In this multicenter study we used an unbiased moving average approach to investigate age dependency of HLA associations in cHL. We identified several age dependent associations with HLA alleles that belong to two common ancestral Caucasian haplotypes DQB1*06-DRB1*15 and B*08-DRB1*03, which are affected by EBV status and subtype.
Table 2. Comparison between young and older cHL patients.

<table>
<thead>
<tr>
<th></th>
<th>cHL ≤45 years</th>
<th>cHL &gt;45 years</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=966 (%)</td>
<td>n=412 (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>498 (51.5)</td>
<td>238 (57.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>468 (48.5)</td>
<td>174 (42.2)</td>
<td></td>
</tr>
<tr>
<td>EBV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV pos.</td>
<td>224 (25.0)</td>
<td>140 (37.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EBV neg.</td>
<td>671 (75.0)</td>
<td>233 (62.5)</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>71</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>738 (76.4)</td>
<td>245 (59.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-NS</td>
<td>228 (23.6)</td>
<td>167 (40.5)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Chi-square test. Abbreviations: EBV=Epstein Barr virus, NS=Nodular sclerosis, n.a.=Not available.

The associations with HLA-B*08 and HLA-DRB1*03 in cHL >45 years of age at diagnosis are novel. As the number of elderly patients is limited in most cHL cohort studies and studies focusing specifically on cHL in elderly are scarce, this might have precluded identification of these two alleles in previous studies. Our patient cohort included 412 cHL cases with an age of onset >45 years, which is substantially more than the number of elderly patients in previous studies (14,25–27). Moreover, our analyses of putative confounders indicated that this association is absent in the young EBV- or NS cHL subgroup, which in general are the largest subsets of patients. This may explain why this association has not been noticed previously. The association of HLA-DQB1*06 and HLA-DRB1*15 with cHL susceptibility has been reported earlier (14,25,26). Both HLA-DQB1*06 and HLA-DRB1*15 alleles and the haplotype consisting of these two alleles have been reported to be associated with risk of NS cHL in a patient cohort with an age range of 9-62 years (25). We previously found a risk association of HLA-DRB1*15, but not HLA-DQB1*06 with EBV- cHL in a study that consisted of the same patients as in the current study but that did not stratify by age (14). We now show that the association of these two alleles with cHL is present for patients with an age at diagnosis of ≤45 years.
Figure 2. Forest plot of odds ratios (ORs) and 99% confidence intervals (CI) of the allele frequencies. The upper panels of the forest plot of each allele or haplotype shows the ORs for controls and cHL patients with an age at diagnosis of ≤45 years and with an age at diagnosis >45 years. The lower panels show the ORs and CI for age groups stratified by sex, EBV and subtype.
Analysis of confounders indicated that the association is most pronounced in EBV-NS cHL patients ≤45 years. Our findings confirm those of a previous study in which HLA-DQB1*06 and HLA-DRB1*15 were associated with cHL in patients <35 years of age (26). A recent GWAS showed associations of five SNPs mapping to HLA class II loci with cHL age at diagnosis <46 years (18). These SNPs map to a region with more than 200 genes including HLA-DQB1 and HLA-DRB1. The haplotype that includes these five SNPs was linked to multiple haplotypes consisting of HLA class II alleles, with one of them being the HLA-DQB1*06 allele (19). We observed a similar age association pattern for HLA-B*07, although this did not reach significance. The association with this allele can be explained by its strong linkage with HLA-DQB1*06 and HLA-DRB1*15, on the B*07-DQB1*06-DRB1*15 haplotype which is common in Caucasians (28).

The HLA-A*01 and HLA-A*02 alleles that were shown to be associated with EBV+ cHL in multiple studies (12-14), did not show significant associations with age at diagnosis. This indicates that HLA-A*01 and HLA-A*02 alleles are associated with EBV+ cHL independent of age of onset. This is quite remarkable as HLA-A*01 is part of the common A*01-B*08-DRB1*03 haplotype (7.8% in Caucasians) and HLA-A*02 is part of the common A*02-B*07-DQB1*06-DRB1*15 haplotype (2.4% in Caucasians) (28). Our data point to independent mechanisms for these HLA associations.

The HLA alleles shown in this study to be associated with cHL, have also been associated with several autoimmune diseases (29–31). A number of genes within the extended haplotype (HLA-A*01, Cw*07, B*08, TNFAB*a2b3, TNFN*S, C2*C, Bf*s, C4A*Q0, C4B*1, DRB1*03:01, DRB3*01:01, DQA1*05:01, DQB1*02:01) have been linked to modulation of the immune responsiveness and may affect multiple immunopathological diseases (32). The DQB1*06-DRB1*15 haplotype is associated with increased risk of multiple sclerosis in young patients (33,34). Both cHL and multiple sclerosis show common etiological features, for example both diseases are associated with developed countries, such as predominance in males and association with EBV, and there are reports of co-occurrence of multiple sclerosis and cHL (35,36). It has also been shown that presence of HLA-B*07 and HLA-DR*15 is associated with dysfunctional NK cell activity and antibody mediated cytotoxicity in multiple sclerosis (37). This might indicate that the association of this allele with cHL ≤45 years is related to an altered functionality of the innate immune system.

In conclusion, this is the largest study on HLA allele associations with age in a Caucasian cHL population. Novel findings in this study are the association of HLA-DQB1*06 and HLA-DRB1*15 specifically with EBV- cHL patients with an age at diagnosis ≤45 years. In addition, two novel HLA associations have been identified with HLA-B*08 and HLA-DRB1*03 and cHL with an age of onset >45 years.
REFERENCES


Chapter 4