The Human Leukocyte Antigen Class I Region Is Associated with EBV-Positive Hodgkin's Lymphoma: *HLA-A* and *HLA Complex Group 9* Are Putative Candidate Genes

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Abstract

Various studies have indicated that the human leukocyte antigen (HLA) region is associated with Hodgkin's lymphoma. We recently showed a specific association of the HLA class I region with EBV-positive Hodgkin's lymphoma cases. One haplotype of two consecutive microsatellite markers (D6S265 and D6S510) was overrepresented in the patient group, whereas another haplotype was underrepresented. Here, we did fine mapping of this region of ~400 kb as a next step to find the causative single-nucleotide polymorphism(s) (SNP). To select candidate SNPs for screening the total study population, several known SNPs were determined by sequencing two individuals homozygous for either of the above-mentioned associated haplotypes. Seven SNPs displayed different alleles in these two individuals and were therefore analyzed in the total study population, including 238 Hodgkin's lymphoma patients and 365 family-based controls. All seven SNPs showed significant association with the EBV-positive patient group. Two of these SNPs were analyzed in a Scottish Hodgkin's lymphoma population and revealed significant associations as well. The associated SNPs are located nearby two putative candidate genes: *HLA-A* and *HLA complex group 9*. *HLA-A* represents the most interesting target because of its consistent expression in EBV-positive Hodgkin's lymphoma cases and its ability to present EBV-derived peptides to cytotoxic T cells. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2280–4)

Introduction

Hodgkin's lymphoma is characterized by an unusual phenotype because the malignant cells, the so-called Hodgkin/Reed-Sternberg cells, constitute only a minority of less than 1% to 2% of the total tumor mass. The majority of the tumor mass consists of an inflammatory infiltrate containing varying amounts of T ($CD4^+$ and $CD8^+$) and B lymphocytes, plasma cells, histiocytes, and eosinophilic granulocytes (1-4). The Hodgkin/Reed-Sternberg cells and their neighboring cells are able to cross-talk via a complex of cytokine and cell contact–dependent interactions, and these probably include proliferative and antiapoptotic signals favoring tumor cell survival and expansion (4, 5). This suggests that immunologic mechanisms contribute to Hodgkin's lymphoma pathogenesis. EBV is the most important environmental factor in the pathogenesis of Hodgkin's lymphoma, and its presence in Hodgkin/Reed-Sternberg cells is observed in about one third of Hodgkin's lymphoma cases in the Western world (6). EBV-associated Hodgkin's lymphoma cases have a clonal EBV infection in the Hodgkin/Reed-Sternberg cells (5), indicating that the EBV infection was an early step in transformation and is likely a causal event (1, 6, 7).

Literature on genetic predisposition in sporadic and familial Hodgkin's lymphoma cases includes a large number of significant associations with the human leukocyte antigen (HLA) region (8-13). We have recently analyzed DNA samples obtained from >200 Hodgkin's lymphoma patients and family-based controls with a set of microsatellite markers covering the entire HLA region (9). Effect was shown with three successive microsatellite markers D6S2704, D6S265, and D6S510 in EBV-positive Hodgkin's lymphoma cases but not in EBV-negative cases. The strongest effect was shown with D6S265 and D6S510. These markers are located in the HLA class I region. The distance between D6S2704 and D6S510 is ~250 kb, and the distance between the two flanking nonassociated markers, HL003 and D6S478, identified as the candidate region for an associated EBV-positive Hodgkin's lymphoma gene is ~400 kb. The risk haplotype carried the 126-bp allele of D6S265 and the 284-bp allele of D6S510 and was more prevalent in the patient subgroup with EBV-positive Hodgkin's lymphoma (46%) than in the control population (22%). A second, nonrisk haplotype is formed by the 130-bp allele of D6S265 and the 302-bp allele of D6S510 and was more prevalent in the control population than in the patient population, occurring in 27% of the controls and in 10% of the EBV-positive Hodgkin's lymphoma patients.

These findings warranted a more extensive mapping attempt using single-nucleotide polymorphisms (SNP). In this study, we aimed to identify SNPs that could discriminate between the risk and the nonrisk haplotype and that could reduce the associated region in size. The assumption underlying this approach is that the associated microsatellite alleles are not causal themselves but only in linkage disequilibrium with the susceptibility mutations. A disease-causing allele is therefore hypothesized to be present at the risk haplotype, whereas the nonrisk haplotype should carry the wild-type allele. Seven SNPs presenting different alleles for these two haplotypes were typed on the entire Dutch study population. Two of these SNPs were also tested on a Scottish Hodgkin's lymphoma cohort to minimize the probability of false-positive findings (14).

Received 6/12/06; revised 8/9/06; accepted 9/13/06.

Grant support: Dutch Cancer Society, Koningin Wilhelmina Fonds grant RUG 2000-2315.

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doi:10.1158/1055-9965.EPI-06-0476

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Materials and Methods

Patient and Control Total Study Population. The Dutch study sample consisted of 211 Hodgkin's lymphoma patients and 365 family-based controls, recruited from the Caucasian population of the northern Netherlands and has been described previously (9). To enlarge our number of EBV-positive Hodgkin's lymphoma cases, 27 additional cases were included in the present study and genotyped for microsatellite markers D6S265 and D6S510. The total percentage of EBV-positive cases were 34%. The United Kingdom study sample is derived from the previously described Scotland and Newcastle Epidemiological Study of Hodgkin's Disease (15). Germ-line DNA samples from cases of known EBV status were available for 341 cases, representing 60% of this population-based series. All subjects (patients and controls) had given written informed consent. The protocol was approved by the medical ethics board of the University Medical Center Groningen.

SNP Determination. Twelve primer sets were used to amplify and sequence in total 24 known SNPs in the previously identified candidate region. SNPs located nearby the strongest associated microsatellite markers were selected based on a minor allele frequency above 10% (Table 1; Fig. 1). The PCR product of primer set 8 contained eight SNPs and primer set 9 contained six SNPs. Some of these SNPs have unknown minor allele frequency, but all SNPs were analyzed. The SNPs were derived from the SNP bank (National Center for Biotechnology Information build 35.1), and primer sequences flanking the SNPs were selected from National Center for Biotechnology Information sequence files (http://www.ncbi.nlm.nih.gov/genomes/sts; available on request).

PCRs were carried out in a final volume of 50 μL containing ~125 ng DNA and 2.5 units Taq DNA polymerase (Amersham Pharmacia Biotech, Uppsala, Sweden). Reaction mixtures contained 10 mmol/L Tris-HCl (pH 9.0), 50 mmol/L KCl, 2.5 mmol/L $MgCl_2$, 0.2 mmol/L deoxynucleotide triphosphate (Roche Diagnostics, Mannheim, Germany), and 0.25 μmol/L of each primer (Sigma, Malden, the Netherlands). Thermal cycling was done on a PTC-225 Thermal cycler (MJ Research, Waltham, MA). PCR started with incubation of 5 minutes at 95°C followed by 32 cycles of 30 seconds at 94°C, 30 seconds at the primer-specific annealing temperature, and 1 minute at 72°C. The final cycle ended with 5 minutes at 72°C. The quality and the length of the PCR products were checked on a 1% agarose gel containing ethidium bromide. The PCR products were purified either directly using QIA spin columns or, after isolating the appropriate product out of the gel, with an agarose gel extraction kit (Qiagen, Venlo, the Netherlands). The PCR products were sequenced directly using the amplification primers or in case the SNPs were too close to the primer binding sites after cloning using a TOPO TA cloning kit (Invitrogen, Breda, the Netherlands). After verification of the insert, plasmids were multiplied using TempliPhi (Amersham Pharmacia Biotech) and sequenced using M13 primers (Invitrogen) following the standard protocol recommended for the MegaBACE 1000 capillary sequencer (Amersham Pharmacia Biotech). The SNPs were identified by careful inspection of the sequences from PCR products using SeqMan (DNA Star, Inc., Madison, WI).

SNP Selection for Analysis on the Dutch Study Population. Two individuals were analyzed, one EBV-positive Hodgkin's lymphoma patient homozygous for the risk haplotype and one control homozygous for the nonrisk haplotype. Twelve SNPs had different alleles for the patient and the control haplotypes, and seven of them were screened in the Dutch study population. The other five SNPs could not readily be analyzed with restriction fragment length polymorphism (absence of restriction enzyme sites) or Taqman probes (failure to design discriminating probes due to closely flanking SNP sites) and were omitted. As a control for our SNP selection design, one SNP (rs2523969) that did not differ between the risk and the nonrisk haplotype was also typed in the total population. For rs2530388, rs3823352, rs2523969, rs6457110, and rs2517749, Taqman probes were used (Assays-on-Demand/Design, Applied Biosystems, Niewerkerk Alden Ÿssel, the Netherlands). Three different restriction enzymes were selected to discriminate between the two different alleles for rs2523972, rs4713276, and rs2256543. For these three SNPs, the DNA region, including the SNPs, could be amplified in a single PCR (primer set 9). Amplification was carried out in 10 μL volume containing ~25 ng genomic DNA and 0.5 units Taq DNA polymerase. Three independent amplifications were carried

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Table 1. SNPs tested on risk and control haplotype

No.	SNP name	Chromosome position	Primer sets	Polymorphism alleles	Minor allele frequency, if available (%)	Alleles different for 2 haplotypes [yes (+); no (−)]
1	rs9261268	30138036	1	G/A	6	−
2	rs259919	30133482	2	C/T	17	−
3	rs259930	30112165	3	C/G	14	−
4	rs165256	30094663	4	A/G	17	−
5	rs2530388*	30075107	5	T/A	29	+
6	rs3823352*	30050012	6	C/G	36	+
7	rs2523969*	30046756	7	T/A	18	−
8	rs2523971	30046237	8	C/A		+
9	rs6916451	30046153	8	C/T		+
10	rs6916422	30046089	8	C/T	19	+
11	rs6457116	30046004	8	A/G		−
12	rs2517671	30045956	8	A/G	40	+
13	rs6939037	30045950	8	T/C		−
14	rs1061535	30045903	8	T/C	25	−
15	rs3202637	30045875	8	T/C	26	−
16	rs2256543*	30045812	9	T/C	44	+
17	rs1061536	30045805	9	T/C		−
18	rs1061537	30045774	9	C/T	31	+
19	rs4713276*	30045773	9	G/C	43	+
20	rs6911940	30045769	9	T/C		−
21	rs2523972*	30045763	9	A/G	50	+
22	rs6457110*	30041860	10	A/T	43	+
23	rs7745413	30023448	11	C/T	36	−
24	rs2517749*	30005238	12	A/T	29	+

*Tested on total study population.

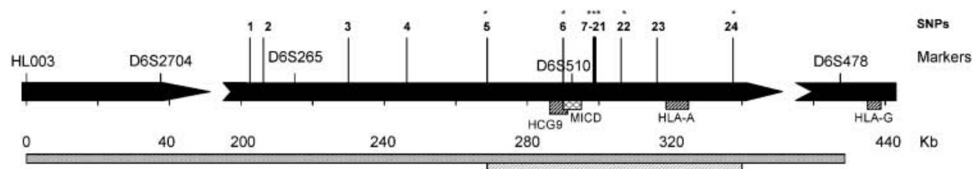

Figure 1. ▒, previously identified candidate region (13) associated markers D6S2704, D6S265, and D6S510 and flanking nonassociated markers HL003 and D6S478. ▨, present region with associated SNP(s) marked by *asterisks*.

out using one 5′ 6-FAM-labeled primer (Sigma) followed by restriction enzyme digestion for 2 hours at 37°C with 1 unit enzyme. SNP rs2523972 was detected by *Bgl*I, rs4713276 by *Hae*III (Roche Diagnostics), and rs2256543 by *Nsi*I (New England Biolabs, Herts, United Kingdom). The digested PCR products were visualized on a MegaBACE sequencer according to the manufacturer's protocol. Undigested PCR product was 185 bp, and after digestion, fragments of 159, 154, and 114 bp were obtained for rs2523972, rs4713276, and rs2256543, respectively. Results were analyzed using Genetic Profiler version 2.0 (Amersham Pharmacia Biotech).

Detection of Polymorphisms in the United Kingdom Study Population. Samples derived from the Scotland and Newcastle Epidemiological Study of Hodgkin's Disease study were analyzed using assays for two SNPs, which showed Hardy-Weinberg equilibrium and flanked the associated haplotype rs2530388 and rs6457110 15. The frequency of genotypes and alleles at these two SNPs was compared in the EBV-positive and EBV-negative cases.

Statistical Analysis. Each of the SNPs was first tested for Hardy-Weinberg equilibrium among healthy unrelated controls as a quality check for the genotyping assays. Next, the set of alleles present in the patients and the controls was identified. The nontransmitted alleles of the parents (n = 192, of which 28 from a single parent) and the alleles of the spouse of the patient (n = 70) served as control alleles. An additional 30 control alleles were reconstructed from siblings or children of the patients. Observed genotype frequencies were compared with the ones expected based on the allele frequencies by means of a χ^2 test with 1 degree of freedom.

Allele and genotype association analyses were done by comparison of the frequencies of the different alleles and genotypes in Hodgkin's lymphoma patients and controls using χ^2 tests to assess significant differences. Haplotype frequencies were estimated by means of an expectation-maximization algorithm after first assigning haplotype phase based on available family information. The resulting frequencies were compared using a likelihood ratio test. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated by logistic regression analysis. In addition to the entire patient group, patients were also stratified according to EBV status and compared with each other and with a control group.

Results

SNP Determination and Selection. Sequence analysis of the PCR products and comparison of alleles in the two individuals homozygous for the risk and the nonrisk haplotype revealed different alleles for 12 SNPs. These SNPs were all located nearby the genes HLA complex group 9 (*HCG9*) and *HLA-A* (Fig. 1). The other 12 SNPs had identical alleles (Table 1).

Screening the Dutch Study Population. A total of 238 patients and 365 family members of the Caucasian population of the northern Netherlands participated in this study. All

Table 2. Allele and genotype frequencies of microsatellite markers and SNPs in the Dutch Hodgkin's lymphoma population

Marker/SNP	Allele	Controls (n = 292)*	EBV-positive Hodgkin's lymphoma (n = 162)*		EBV-negative Hodgkin's lymphoma (n = 292)*	
		Frequency (%)	Frequency (%)	P	Frequency (%)	P
D6S265	126	26	50	2.62×10^{-6}	28	0.24
rs2530388	A	31	52	9.34×10^{-6}	31	0.39
rs3823352	G	61	84	3.70×10^{-6}	67	0.08
D6S510	284	26	48	1.07×10^{-5}	29	0.19
rs2523969	T	89	90	0.15	86	0.73
rs2256543	T	44	65	2.02×10^{-5}	42	0.27
rs4713276	G	57	80	1.71×10^{-6}	63	0.09
rs2523972	A	50	75	2.83×10^{-7}	49	0.4
rs6457110	T	52	76	1.38×10^{-6}	56	0.16
rs2517749	T	58	69	0.03	58	0.49

Marker/SNP	Genotype	Controls (n = 117)	EBV-positive Hodgkin's lymphoma cases (n = 81)			
		Frequency (%)	Frequency (%)	P	OR	95% CI
D6S265	126/126	7	28	2.32×10^{-4}	8.57	2.55-28.84
rs2530388	A/A	10	26	4.0×10^{-3}	6.18	2.53-15.10
rs3823352	G/G	37	69	2.1×10^{-6}	19	1.8-201
D6S510	284/284	5	23	9.11×10^{-4}	6.07	1.67-22.12
rs2523969	T/T	79	82	0.25	—	—
rs2256543	T/T	18	41	3.90×10^{-4}	6.38	2.60-15.65
rs4713276	G/G	32	63	6.58×10^{-6}	9.78	2.74-34.89
rs2523972	A/A	26	56	1.13×10^{-5}	9.28	3.27-26.37
rs6457110	T/T	26	57	6.23×10^{-6}	7.70	2.68-22.11
rs2517749	T/T	32	51	0.02	1.85	0.67-5.09

*Number of alleles taken into account in the analyses.

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SNPs, except rs2517749, were in Hardy-Weinberg equilibrium. The percentage of missing alleles were 2.5%, and the number of inheritance errors was 6 (0.3%) for the seven SNPs combined. The additional 27 EBV-positive cases used in this study were also analyzed for the two associated microsatellites and increased significances for D6S265 with a *P* from 6.1×10^{-5} to 2.6×10^{-6} and for D6S510 from 5.1×10^{-4} to 1.1×10^{-5}.

Seven SNPs were selected based on presence of different alleles between the risk and the nonrisk haplotypes. All SNPs showed significant differences in allele frequencies for EBV-positive Hodgkin's lymphoma patients versus controls or versus EBV-negative Hodgkin's lymphoma patients (Table 2; Fig. 1). Although SNP rs2514779 was not in Hardy-Weinberg equilibrium, it showed a significant association with EBV-positive Hodgkin's lymphoma ($P = 0.03$). As expected, rs2523969, a control for our SNP selection design, did not show a significant difference between EBV-positive Hodgkin's lymphoma patients, EBV-negative Hodgkin's lymphoma patients, and controls. The allele frequencies differed most for rs3823352, rs4713276, rs2523972, and rs6457110 (*P*s = 2.83×10^{-7} to 3.7×10^{-6}). Individuals homozygous for the risk allele of rs4713276 had an OR of developing EBV-positive Hodgkin's lymphoma of 9.78 (95% CI, 2.74-34.89; Table 2), whereas the OR for heterozygotes was 3.39 (95% CI, 0.94-12.27). Individuals homozygous for the risk allele of rs3823352 had an OR of developing EBV-positive Hodgkin's lymphoma of 19 (95% CI, 1.8-201; Table 2), whereas the OR for heterozygotes was 6 (95% CI, 0.76-48.12). The haplotype formed by subsequent markers D6S265, rs2530388, rs3823352, D6S510, rs2256543, rs4713276, rs2523972, and rs647110 with allele combination 126-A-G-284-T-G-A-T was overrepresented in the EBV-positive patients (45%) versus controls (23%), with a *P* of 7.5×10^{-6}. The nonrisk haplotype with allele combination 130-T-C-302-C-C-G-A-A was present in 9% of the patients versus 28% of the controls.

Screening the United Kingdom Population. The genotype and allele frequencies of the rs2530388 and rs6457110 SNPs were determined for 94 EBV-positive and 247 EBV-negative cases from the Scotland and Newcastle Epidemiological Study of Hodgkin's Disease study. Significant differences in allele frequency were observed with *P*s of 7.40×10^{-6} and 3.55×10^{-4} (Table 3).

Discussion

This study not only confirms the results of Diepstra et al. (9) but also strengthens the previously found association of the HLA class I region with EBV-positive Hodgkin's lymphoma. Strong positive associations were observed with seven SNP markers, rs2530388, rs3823352, rs2256543, rs4713276, rs2523972, rs6457110, and rs2517749, and their haplotypes. These SNPs were all located in a region of 80 kb, and three of these SNPs showed more significant results than the microsatellite markers in our previous study. Although SNP rs2517749 was not in Hardy-Weinberg equilibrium, it also showed significant association with EBV-positive Hodgkin's lymphoma like the other SNPs. We observed too many individuals with a homozygous T allele, which might be caused by presence of additional previously unrecognized SNPs, causing unreliable detection with the SNP assay. rs4713276 and rs2523972 showed ORs of 9 for developing EBV-positive Hodgkin's lymphoma for individuals with homozygous risk alleles, whereas individuals with heterozygous alleles showed ORs of 3, which suggest a codominant effect. rs3823352 had an OR of 19; however, the 95% CI was very large, 1.8 to 201. Two SNPs flanking the associated haplotype were analyzed in the Scottish Hodgkin's lymphoma cohort and showed the same association. This supports the conclusion that these SNPs are indeed associated with EBV-positive Hodgkin's lymphoma and that this finding is not specific to the Dutch population nor a false-positive result. As there is strong linkage disequilibrium in the entire HLA region (16-20), it is possible that the associated SNPs do not have causal or modifying effects but are associated due to linkage disequilibrium with a nearby causal SNP.

Table 3. Allele frequencies of SNPs in Scottish Hodgkin's lymphoma population

Marker/SNP	Allele	EBV-positive Hodgkin's lymphoma (n = 188)	EBV-negative Hodgkin's lymphoma (n = 494)	*P*
		Frequency (%)	Frequency (%)	
rs2530388	A	53	34	7.40×10^{-6}
rs6457110	T	74	60	3.55×10^{-4}

NOTE: Number of alleles taken into account in the analyses.

The risk haplotype comprises a region with nine pseudogenes, which are therefore unlikely to be causative, the protein coding *HCG9* gene, and the *HLA-A* gene. Moreover, there are no known microRNAs located in this region. HCG9 belongs to a multigene family (HCG) whose members are dispersed throughout the HLA class I region and are closely associated with members of another multigene family designated PERB11 (otherwise known as MIC). These two families form a cluster that have been dispersed together throughout the telomeric part of the HLA region and have been involved in the genesis of this human class I region (21). Two members of the PERB11 family, PERB11.1 (MICA) and PERB11.2 (MICB), seem to be functional as stress-induced antigens that are broadly recognized by natural killer cells, $CD8^+$ $\alpha\beta^-$ T cells, and $\gamma\delta^-$ T cells, which express the NKG2D receptor (22, 23). Although the *PERB11* and *HCG* genes form a cluster, their functional relation is unknown. The start sequence of the *HCG9* gene corresponds with part of the PERB11.4 (MICD) sequence. MICD is suggested to be a pseudogene, whereas HCG9 is expressed (21, 24). The *HLA-A* gene is a HLA class I gene, which is involved in foreign peptide antigen presentation, including EBV-derived peptides. Antigenic presentation of EBV-derived peptides presented in the context of certain HLA class I alleles can induce $CD8^+$ cytolytic T-cell responses. This would be unfavorable for Hodgkin/Reed-Sternberg cells, which frequently express HLA class I in EBV-positive Hodgkin's lymphoma cases (25-27). Association of HLA-A with EBV-positive Hodgkin's lymphoma might be associated with low affinity for the most immunogenic EBV-derived peptides precluding an effective immune response.

Although, the *HCG9* and *HLA-A* genes are both strong candidates for the causal gene, we cannot exclude other disease-influencing variations in the associated region.

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