

Review

**Genetic Associations in Classical Hodgkin Lymphoma:
A Systematic Review and Insights into Susceptibility
Mechanisms**Kushi Kushekhar¹, Anke van den Berg¹, Ilja Nolte², Bouke Hepkema³, Lydia Visser¹, and Arjan Diepstra¹**Abstract**

Both targeted and genome-wide studies have revealed genetic associations for susceptibility, prognosis, and treatment-induced secondary malignancies and toxicities in classical Hodgkin lymphoma (cHL). This review gives a systematic and comprehensive overview of significant associations and places them into a biologic context. The strongest susceptibility polymorphisms have been found for the human leukocyte antigen (HLA) genes. These associations are specific for cHL overall or for subgroups based on tumor cell Epstein–Barr virus (EBV) status. These findings strongly suggest that EBV-specific immune responses influence cHL susceptibility in EBV⁺ cHL and that immune responses targeting other tumor-associated antigens are important in EBV⁻ cHL. Accordingly, most of the numerous other susceptibility loci map to genes that affect functionality of the immune system, underscoring the crucial role of the immune system in cHL development. The number of association studies on cHL prognosis is limited with one consistent association for the drug-metabolizing *UGT1A1* gene. *PRDM1* is associated with radiation-induced secondary malignancies and a small number of genes are associated with treatment-related toxicities. In conclusion, most loci showing genetic associations in cHL harbor genes with a potential functional relevance for cHL susceptibility. *Cancer Epidemiol Biomarkers Prev*; 23(12); 2737–47. ©2014 AACR.

Introduction

Classical Hodgkin lymphoma (cHL) is a B-cell malignancy that is characterized by a minority of large, sporadically binucleated tumor cells, called Hodgkin Reed–Sternberg (HRS) cells. Reactive infiltrating cells, especially T cells, usually make up at least 99% of the cells in the tumor mass (1). On the basis of the background architecture and the composition of the microenvironment, cHL can be subdivided into four histologically defined subgroups, with nodular sclerosis (NS) being the most common subtype representing approximately 70% to 80% of all cases. The mixed cellularity (MC) subtype is the second most common subtype accounting for 15% of all cases, while the lymphocyte rich and lymphocyte depleted

subtypes are less common (2). Epstein–Barr virus (EBV) is present in the tumor cells in a variable proportion of cases depending on geographic area and ethnicity. In the Western world, EBV can be found in 30% to 40% of the cHL cases, whereas the percentage of EBV positivity is up to 80% in South America (3, 4). EBV is observed at higher frequencies in children and elderly cHL patients with the MC subtype, whereas young adult patients with cHL usually are diagnosed with EBV⁻ NS subtype (5). This typical age- and EBV-dependent incidence pattern varies between different ethnic populations and geographic locations and reflects a complex disease etiology. Inherited susceptibility to cHL is strongly supported by the 3- to 9-fold increased risk observed in first-degree relatives of patients with cHL (6) and the 100-fold increased risk of cHL concordance in monozygotic twins compared with dizygotic twins (7). The estimated heritability of cHL in Caucasians is close to 30% (8). Genetic-association studies based on segregation and linkage analysis in HL families have resulted in identification of susceptibility loci in the human leukocyte antigen (HLA) region (reviewed in ref. 9). More recent data also suggest contribution of non-HLA genes to the inherited susceptibility of familial cHL (10, 11). In addition, a recent exome sequencing and linkage analysis in one family identified two genes on 3p (*FAM107A*, *ALS2CL*) as causative candidates (12). Together, these studies support the presence of inherited components contributing to the risk of cHL. Current treatment strategies in cHL result in a 5-year disease-free survival of

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65% to 90% depending on stage and clinical risk factors (1). However, long-term survivors frequently suffer from treatment-related adverse effects, such as cardiac disease and secondary malignancies (13).

Numerous studies have been carried out to find genetic cHL susceptibility associations, as well as associations with cHL prognosis and risk of treatment-related late adverse effects. In this article, we critically review these studies and comment on the possible biologic relevance of reported findings.

Materials and Methods

Literature search and study selection strategy

We performed a systematic literature search in PubMed for publications concerning the influence of genetic polymorphisms in cHL susceptibility, prognosis, secondary malignancies, and toxicities up to June 2014. Restricting to English publications, we obtained a total of 112 articles (Supplementary Fig. S1). We excluded studies with less than 100 cases ($n = 50$), included duplicate studies that reanalyzed the same SNPs in the same patient cohort as a single study ($n = 5$) and filtered out studies that were off topic ($n = 12$). In total, we reviewed 45 individual studies.

Evaluation of studies

Data were extracted and documented in a spread sheet (Supplementary Tables S1–S5). If the same SNP was analyzed in multiple studies, we looked for consistency of the results. If different SNPs in the same genetic region were studied, we evaluated the consistency by linkage disequilibrium (LD) analysis between the SNPs and by coinherence of alleles based on haplotype analysis (using Haploview 4.2 and SNP allele frequency data retrieved from the International HapMap project; ref. 14). For genome-wide association studies (GWAS), only results with genome-wide significance in the primary study cohort were considered. We also evaluated whether SNPs that were found to be associated in targeted gene approach studies were analyzed and associated in our recent GWAS study (15). In case the published SNP was not present in our GWAS, we identified linked SNPs and checked for presence and P values of those linked SNPs.

Susceptibility Loci

cHL was one of the first diseases to be associated with specific HLA serotypes in 1967 (16). Subsequent studies reported additional associations, but did not always confirm these initial associations probably due to the heterogeneous nature of the disease. These earlier studies were generally focused on the entire cHL patient group, whereas more recent studies stratified cases by EBV and histologic subtype, resulting in more consistent subgroup-specific associations. In the past few years, several GWAS confirmed that the most dominant risk and protective polymorphisms in cHL are indeed located in the HLA region.

Targeted gene approaches

HLA gene loci. The HLA region on 6p21.3 is the most polymorphic region of the human genome. It spans approximately 1.8 Mb and can be subdivided into the HLA class I, II, and III subregions. The HLA class I region includes among others the classical *HLA-A*, *HLA-B*, and *HLA-C* gene loci. The HLA class II region includes the classical *HLA-DP*, *HLA-DQ*, and *HLA-DR* gene loci. The HLA class III region is located in between the HLA class I and class II regions and harbors genes coding for complement system proteins and cytokines. Each of the classical HLA genes comprises a large number of alleles. Traditional serologic HLA typing methods are based on specificity of antibody binding to the expressed HLA protein, while DNA-based typing methods allow a genetic and more detailed identification of each individual allele (17, 18). The WHO Nomenclature Committee for Factors of the HLA System is responsible for the naming of HLA genes and allele sequences. The current HLA nomenclature designates DNA-typed HLA alleles based on the locus name (e.g., *HLA-A*), followed by an asterisk (*) and a unique number corresponding to up to four sets of digits separated by colons (e.g., *HLA-A*01:01*). The digits before the first colon describe the type, which often corresponds to the serologic antigen and the next set of digits are used to list the subtypes. Serologically typed HLA antigens are named by the gene followed by the antigen number, for example, HLA-A1 (19).

Ethnic background is an important factor that should be taken into account in HLA association studies as common well-documented (CWD) allele frequencies show marked differences between populations. For instance, *HLA-A*01* is common in Caucasians, but rare in the Chinese population. *HLA-A*02* is common in both Caucasians and Chinese, but >95% of the Caucasian *HLA-A*02* alleles are *HLA-A*02:01*, whereas there are multiple CWD allelic variants in Chinese (i.e., *A*02:01*, *A*02:03*, *A*02:06*, *A*02:07*, and *A*02:10*; ref. 20). These differences in HLA allele distribution might lead to different associations in different ethnic groups.

Another factor to consider in HLA association studies is the strong LD in the HLA region. LD is the nonrandom coinherence of specific combinations of alleles at two or more loci. Multiple well-known coinherited HLA alleles have been described, for example, *HLA-A*01-B*08-DRB1*03-DQB1*02* in approximately 15%, *HLA-A*03-B*07-DRB1*15* in approximately 7%, and *HLA-A*02-B*44-DRB1*04* in approximately 5% of Caucasians (21, 22).

In 2005, we reviewed the literature on genetic susceptibility in cHL for the HLA region, mostly concerning serologic typing and including most studies on familial cHL (9). We here focus on studies using a DNA-based HLA typing approach or using microsatellite markers. Eleven studies have been published including 79 alleles of six classical HLA class I and II genes and two microsatellite markers mapping to the HLA class I region (Supplementary Table S1). The total number of patients ranged from 100 to 900 and control groups ranged from 59 to

Table 1. Risk and protective HLA associations in cHL

HLA gene	Allele	Association	Population ^a	Reference
HLA-A	A*01	Risk	EBV ⁺ cHL	(24–26)
	A*02	Protective	EBV ⁺ cHL	(24–26)
	A*02:07	Risk	Chinese, EBV ⁺ cHL	(27)
	A*02:07	Protective	Chinese, EBV ⁻ cHL	(27)
HLA-B	B*05	Risk	cHL overall	(26)
	B*37	Risk	EBV ⁺ cHL	(26)
HLA-DRB1	DRB1*04:04	Protective	NS cHL	(25)
	DRB1*07:01	Protective	cHL overall, NS cHL	(26, 29, 30)
	DRB1*10	Risk	EBV ⁺ cHL	(26)
	DRB1*11:04	Risk	NS cHL	(25)
	DRB1*11/12 (DR5)	Risk	EBV ⁻ cHL	(26)
	DRB1*15:01	Risk	cHL overall, NS cHL	(29, 30)
	DRB1*15/16 (DR2)	Risk	EBV ⁻ cHL	(26)
HLA-DQA1	DQA1*02:01	Protective	cHL overall, NS cHL	(29, 30)
HLA-DQB1	DQB1*03:03	Protective	cHL overall, NS cHL	(29, 30)
	DQB1*06:02	Risk	cHL overall, NS cHL	(29, 30)
HLA-DPB1	DPB1*03:01	Risk	cHL overall, Females, NS cHL	(29, 31–33)
	DPB1*11:01	Protective	NS cHL	(29, 31)
	DPB1*34:01	Risk	Males-MC cHL	(31)

^aAll the case and control populations are of Caucasian ethnicity unless otherwise specified.

>7,000 individuals. A limited number of alleles were studied either in more than one study or in a single study with significant associations after applying appropriate statistical tests (Table 1).

In a hallmark study on HLA associations, two microsatellite markers located in the HLA class I region were found to be associated with EBV⁺ cHL in Caucasians (23). Subsequent studies have consistently shown that *HLA-A*01* is a risk allele and *HLA-A*02* is a protective allele for developing EBV⁺ cHL (24–26). The *HLA-B*37* and *HLA-DRB1*10* alleles are also associated with an increased risk of EBV⁺ cHL (26). These associations might be attributed to the strong LD between these alleles and *HLA-A*01*, because *HLA-A*01-B*37-C*06-DRB1*10* is a common haplotype in Caucasians (21). In a Northern Chinese population, no associations were observed for *HLA-A*01* and *HLA-A*02* in EBV⁺ cHL (Supplementary Table S1; ref. 27). For *HLA-A*01*, this might be due to the low-allele frequency in the Chinese population. For *HLA-A*02*, additional sequence-based typing of the CWD alleles indicated that *HLA-A*02:07* is a predisposing allele for EBV⁺ cHL, whereas it is a protective allele for EBV⁻ cHL (27). The predisposing *HLA-A*02:07* allele has also been associated with EBV-associated undifferentiated nasopharyngeal carcinoma, which is characterized by the same type of latent EBV infection as EBV⁺ cHL and is common in Eastern Asia (28).

Several HLA class II alleles have been associated with cHL susceptibility in different EBV, histology, and sex-stratified subgroups. *HLA-DRB1*04:04* and *HLA-DRB1*07:01* are protective, whereas *HLA-DRB1*11:04* and

*HLA-DRB1*15:01* are risk allele for cHL overall and/or NS cHL (26, 29, 30). *HLA-DRB1*11/12* (DR5) and *HLA-DRB1*15/16* (DR2) are associated with an increased risk for EBV⁻ cHL (26). The *HLA-DQA1*02:01* and *HLA-DQB1*03:03* alleles are protective, whereas *HLA-DQB1*06:02* is a risk allele for cHL overall and NS cHL (29, 30). For *HLA-DQB1*06:02*, this might be due to LD with *HLA-DRB1*15:01*. The *HLA-DPB1*11:01* is a protective allele for NS cHL (30, 31), whereas *HLA-DPB1*03:01* and *HLA-DPB1*34:01* were risk alleles for cHL overall, NS cHL, cHL in females and MC cHL in males, respectively (30–33).

In summary, these studies clearly show a strong effect of certain HLA alleles with cHL susceptibility overall or with specific subgroups. The HLA class I alleles are strongly associated with EBV⁺ cHL, whereas HLA class II alleles are mainly associated with EBV⁻ cHL.

Non-HLA gene loci. Nineteen targeted gene approach studies have been published on 82 gene loci including a total of 323 SNPs (Supplementary Table S2). In most of these studies, cHL cases were not stratified by EBV status, histology, sex, or age. The total number of patients in the study cohorts ranged from 100 to 500. Thirty nine gene loci were analyzed for a single SNP with significant associations found for eight genes. Forty-three gene loci were studied for multiple SNPs. Consistent and significant associations were found for 15 of the 43 gene loci. In total, significant results have been observed for 32 SNPs mapping to 23 gene loci with an immune function for the vast majority of these associated genes (Table 2).

The Fc fragment of IgG low-affinity IIa receptor (FCGR2A or CD32) locus is associated with EBV⁺ cHL

Table 2. Non-HLA genes/SNPs associated with Hodgkin lymphoma susceptibility

Gene	SNP	Allele comparison	Association	Population ^a	Reference
<i>BMF</i>	rs1540686	GG vs. AA	Protective	cHL overall	(36)
	rs648289	GG vs. AA	Protective	cHL overall	(36)
<i>CASP6</i>	rs1800627	AG/GG vs. AA	Risk	cHL overall	(36)
<i>CYP2C9</i>	rs1799853	CT/TT vs. CC	Risk	cHL overall, <50 y, EBV ⁻ cHL	(40)
<i>ERCC1</i>	rs3212986	TG/GG vs. TT	Protective	cHL overall	(41)
<i>FCGR2A</i>	rs1801274	G vs. A	Risk	EBV ⁺ cHL	(34)
<i>IFNG</i>	rs2069718	AA vs. GG	Risk	cHL overall	(36)
	rs6581795	AG/GG vs. AA	Risk	cHL overall	(36)
<i>IL8</i>	rs4073	AT/TT vs. AA	Protective	cHL overall	(37)
<i>IL10RA</i>	rs3135932	AG/GG vs. AA	Protective	cHL overall	(39)
<i>IL12p40</i>	rs3212227	AC/CC vs. AA	Risk	cHL overall	(38)
<i>IL18</i>	rs187238	GC/CC vs. GG	Protective	cHL overall	(37)
<i>IL4RA</i>	rs1801275	GG vs. AA	Risk	cHL overall	(37)
<i>IRF4</i>	rs872071	GG vs. AA	Risk	cHL overall	(35)
<i>MDR1</i>	rs1045642	T vs. C	Risk	cHL overall	(43)
<i>MTHFR</i>	rs1801133	T vs. C	Protective	cHL overall	(42)
<i>NFKBIA</i>	rs1050851	CT/TT vs. CC	Protective	cHL overall, >50 y, EBV ⁻ cHL	(40)
	rs696	GA/AA vs. GG	Risk	cHL overall, <50 y, EBV ⁻ cHL	(40)
	rs8904	CT/TT vs. CC	Risk	cHL overall, <50 y	(40)
<i>STAT3</i>	rs4103200	GC/CC vs. GG	Protective	cHL overall	(36)
	rs9912773	CG/GG vs. CC	Protective	cHL overall	(36)
<i>STAT4</i>	rs4853546	GA/AA vs. GG	Protective	cHL overall	(36)
<i>STAT6</i>	rs324011	GA/AA vs. GG	Protective	cHL overall	(36)
	rs703817	GA/AA vs. GG	Protective	cHL overall	(36)
<i>TLR4</i>	rs1554973	CT/TT vs. CC	Protective	cHL overall	(37)
	rs4986790	AG/GG vs. AA	Risk	cHL overall	(39)
<i>TLR7</i>	rs179008	AT/TT vs. AA	Protective	cHL overall	(37)
<i>TP63</i>	rs6790068	GG vs. AA	Risk	cHL overall	(36)
	rs9681004	GG vs. AA	Risk	cHL overall	(36)
<i>XPC</i>	rs2228000	CT/TT vs. CC	Risk	cHL overall	(41)
<i>XRCC1</i>	rs1799782	CT/TT vs. CC	Protective	cHL overall	(41)
	rs25487	AG/AA vs. GG	Risk	cHL overall	(41)

^aAll the case and control populations are of Caucasian ethnicity unless otherwise specified.

(34). Several cytokine and cytokine receptor gene loci as well as innate immunity-related Toll-like receptor (*TLR*) gene loci are associated with cHL overall [interferon- γ (*IFNG*), IFNG response factor 4 (*IRF4*), interleukin-8 (*IL8*), p40 subunit of IL12 (*IL12p40*), *IL18*, interleukin receptor 4 α (*IL4RA*), *IL10RA*, *TLR4*, and *TLR7*; refs. 35–39]. In a single study, Janus kinase and signal transducer and activator of transcription (JAK-STAT) signaling pathway gene loci and some loci-harboring genes related to apoptosis were associated with risk of cHL overall [*STAT3*, *STAT4*, *STAT6*, Bcl2-modifying factor (*BMF*), caspase-6 (*CASP6*), and tumor protein 63 (*TP63*); ref. 36]. Nuclear factor of κ light polypeptide gene enhancer in B cells inhibitor α (*NFKBIA*) SNPs associate either with cHL overall or cHL-stratified on the basis of age and EBV status (40). Gene loci related to DNA repair and DNA integrity associate with cHL overall [excision repair cross-complementing rodent repair deficiency, complementa-

tion group 1 (*ERCC1*), methylenetetrahydrofolate reductase (NAD(P)H) (*MTHFR*), xeroderma pigmentosum, complementation group C (*XPC*), and X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*); refs. 41, 42]. Two gene loci involved in drug metabolism are associated with cHL overall or cHL-stratified on the basis of age and EBV status [cytochrome P450, family 2, subfamily C, polypeptide 9 (*CYP2C9*) and multidrug resistance gene 1 (*MDR1*); refs. 40, 43].

Despite the high number of non-HLA gene loci studied, only a limited number of significant associations have been reported to date and independent validation studies are generally missing.

Genome-wide association studies

To date, five GWAS publications totaling 3,159 unique cases have been published (Table 3 and Supplementary Table S3; refs. 15, 44–47). Three of these studies were

Table 3. Overview of GWAS

	Gene locus	Gene candidate	SNP	Minor allele	Association	Population ^a	Reference
HLA region	6p21.32	<i>HLA-DRA</i>	rs6903608	G	Risk	cHL overall, NS cHL, YANS cHL, EBV ⁻ cHL	(15, 44–47)
	6p21.32	<i>HLA-DRA</i>	rs9268542	G	Risk	NS cHL	(45)
	6p21.32	<i>HLA-DRA</i>	rs2395185	T	Protective	cHL overall	(15)
	6p21.32	<i>HLA-DRB1</i>	rs2858870	G	Protective	NS cHL	(45)
	6p21.32	<i>PRRT1</i>	rs204999	G	Protective	cHL overall, NS cHL, YANS cHL, EBV ⁻ cHL	(45, 47)
	6p21.33	<i>MICB</i>	rs2248462	A	Protective	cHL overall	(15)
	6p22.1	<i>HLA-A</i>	rs2734986	C	Risk	EBV ⁺ cHL, MC cHL	(15, 47)
	6p22.1	<i>HCG9</i>	rs6904029	A	Protective	EBV ⁺ cHL, MC cHL	(15, 47)
Non-HLA region	2p16.1	<i>REL</i>	rs1432295	G	Risk	cHL overall, EBV ⁻ cHL	(44, 46)
	3p24.1	<i>EOMES</i>	rs3806624	G	Risk	cHL overall, <40 yrs	(46)
	5q31	<i>IL13</i>	rs20541	A	Risk	cHL overall, NS cHL, YANS cHL, EBV ⁻ cHL	(15, 47)
			rs2069757	A	Risk	cHL overall, NS cHL, YANS cHL, EBV ⁻ cHL	(47)
	6q23.3	<i>HBS1L-MYB</i>	rs7745098	G	Risk	cHL overall	(46)
	8q24.21	<i>PVT1</i>	rs2608053	G	Risk	cHL overall, EBV ⁻ cHL	(44, 46)
			rs2019960	G	Risk	cHL overall, NS cHL, YANS cHL, EBV ⁻ cHL	(44, 46, 47)
	10p14	<i>GATA3</i>	rs485411	A	Risk	cHL overall	(44)
			rs501764	C	Risk	cHL overall	(44, 46)
	19p13.3	<i>TCF3</i>	rs1860661	G	Protective	cHL overall	(47)

Abbreviation: YANS cHL, young adult NS cHL.

^aAll the case and control populations are of Caucasian ethnicity.

performed in independent patient cohorts, while in one study, a new patient cohort was combined with GWAS data of a previous study (44, 46). The GWAS meta-analysis study (47) was performed on study cohorts of two previous studies (15, 45) combined with a GWAS cohort used to study associations related to secondary malignancies after cHL treatment (48). The validation cohorts used in these studies included at least, in part, the screening cohorts of one or more of the other studies. All patients and controls were of Caucasian ethnicity with cHL patient cohorts from the Czech Republic, Denmark, France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. Four studies conducted subgroup analyses based on age, EBV, and subtype (15, 44, 46, 47), whereas one study specifically included young adult NS subtype cHL cases (45).

The most pronounced associations in all five studies were observed in the HLA region (6p21.32 to 6p22.1) and confirmed the results of previous studies focusing on the classical HLA gene loci. The rs6903608 (6p21.32) SNP located in the HLA class II region is consistently associated with cHL and this association is primarily driven by EBV⁻ cHL and NS cHL (15, 44–47). In addition, several other HLA class II SNPs are associated with cHL (15, 45). SNPs in the HLA class I region (6p22.1) are mainly associated with EBV⁺ cHL or MC cHL with rs2734986 mapping close to the *HLA-A* gene and rs6904029 mapping close to HLA complex group 9 (non-protein coding; *HCG9*; refs. 15, 47). These two SNPs are in LD with *HLA-A*01* ($r^2 = 0.98$) and *HLA-A*02* ($r^2 = 0.88$), respec-

tively, reconfirming the previously reported HLA-A associations to EBV⁺ cHL. Two haplotypes comprising five SNPs represent the strongest overall risk predictor in NS cHL. One haplotype explains 70% of the increased risk, whereas the second haplotype explains 60% of the decreased risk. All individuals that carry the protective haplotype also carry the *HLA-DRB1*07:01* allele (45). This is in line with HLA typing studies that showed that *HLA-DRB1*07:01* is a protective allele for developing NS cHL (26, 29, 30). Two SNPs mapping to nonclassical HLA genes in the HLA region, that is, MHC class I polypeptide-related sequence B (*MICB*) (6p21.33) and proline-rich transmembrane protein 1 (*PRRT1*) (6p21.32) are associated with cHL overall, NS cHL, or EBV⁻ cHL (15, 45, 47).

In addition to HLA, several non-HLA susceptibility loci have been identified in one or multiple GWAS. Three studies have consistently identified and confirmed the association of Pvt1 oncogene (non-protein coding; *PVT1*) at 8q24.21 for NS cHL, young adult NS cHL, or EBV⁻ cHL (44, 46, 47). The V-Rel avian reticuloendotheliosis viral oncogene homolog (*REL*) gene locus at 2p16.1 and the GATA binding protein 3, (*GATA3*) at 10p14 were identified and confirmed in two studies mainly for EBV⁻ cHL (44, 46); in a third study, these associations were noted as suggestive for significance (47). The association with *IL13* at 5q31 was identified in one study and confirmed in the meta-analysis for NS cHL, young adult NS cHL, and EBV⁻ cHL (15, 47). The association of eomesodermin (*EOMES*) at 3p24.1 and Hsp70 subfamily B suppressor 1-like protein/avian myeloblastosis viral oncogene

homolog (*HBSIL-MYB*) at 6q23.3 was reported in one study with *P* values close to genome-wide significance in the screening cohort and significant findings in the validation cohort in cHL overall and patients diagnosed before the age of 40 years (46). In the meta-analysis study, these associations were also noted but did not reach significance (47). One novel locus at 19p13.3 was identified and validated in the meta-analysis for cHL overall, mapping close to the transcription factor 3 (*TCF3*; ref. 47). Differences in associations between the five studies might at least, in part, be explained by subgroup specific analysis performed in three of the five studies (15, 44, 45) and differences in patient cohorts, being more than 90% females in one study (44) and young adult NS cHL in another study (45). None of the non-HLA gene loci identified in the above described targeted studies were found in the GWAS studies (see "Non-HLA gene loci").

Susceptibility mechanisms

On the basis of current association studies it is evident that HLA alleles and/or SNPs in the HLA region impart a hereditary susceptibility to cHL. Given the strong LD in the HLA region, each of the HLA region associations has to be interpreted with care, as other strongly linked variants/alleles might actually represent the true causative variant. In addition, several loci outside the HLA region are associated with cHL susceptibility, although these associations are in general less pronounced. Of the 42 associated SNPs mapping outside the HLA region, 13 result in an amino acid change and 14 may have an effect on the gene expression level (Supplementary Table S6). For the remaining 15 SNPs, putative functional differences between the two allelic variants remain unknown. On the basis of $P < 0.05$ in the GWAS dataset (Supplementary Table S6; ref. 15) and the known functionality of the associated gene variants, several susceptibility mechanisms can be anticipated. In Fig. 1, we give a schematic overview of the most likely susceptibility mechanisms.

SNPs mapping to growth/proliferation-associated gene loci, that is, *IL13*, *IL4RA*, *STAT6*, *TCF3*, *REL*, *NFKBIA*, and *STAT3*, might affect cHL susceptibility by providing survival signals for HRS precursor cells during and after malignant transformation (49, 50). *IL13* is a growth factor for B cells and signals through *IL4RA* and *STAT6*. The risk-associated 110Q *IL13* variant is more effective in enhancing *STAT6* phosphorylation (51) and the 576R *IL4RA* risk variant has a gain of function (52). The risk-associated *STAT6* rs703817 G-allele is associated with increased *STAT6* expression levels (53). All these signals can thus lead to enhanced proliferative capacity of HRS precursor cells. The protective allele of the *TCF3* gene locus is associated with higher *TCF3* expression levels (47). This might induce an enhanced retention of the B-cell phenotype in HRS precursor cells and confer a protective effect via increased sensitivity of the precursor cell to apoptosis. The risk allele of the *REL* gene locus is associated with an increased expression level of *REL* (53). Similarly, it might be expected that also the *NFKBIA* SNPs

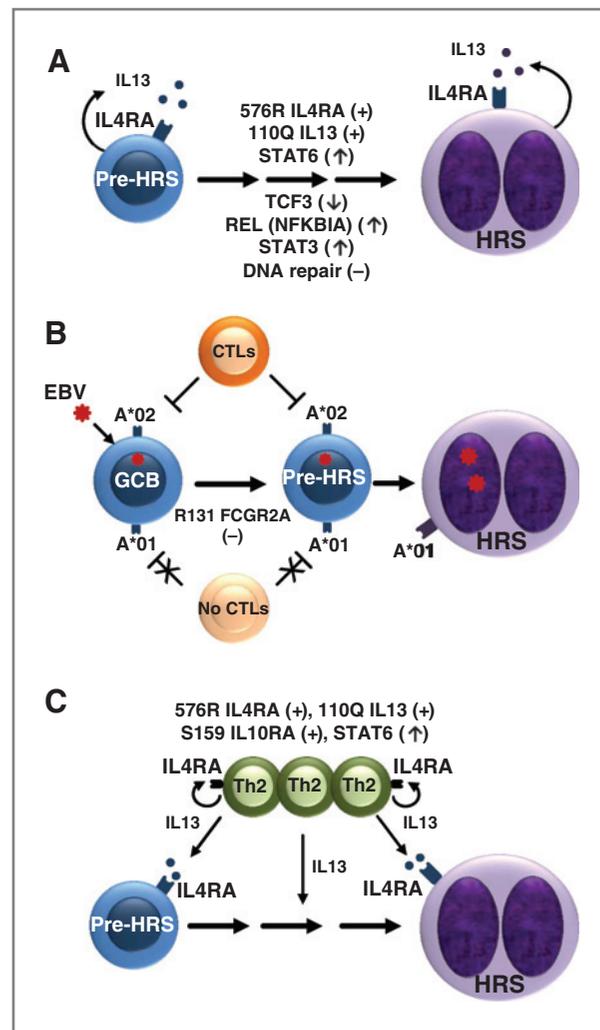


Figure 1. Putative susceptibility mechanisms of genetic associations in cHL. **A**, enhanced survival signals for precursor HRS cells (pre-HRS). The variants associated with hyperactivity (110Q *IL13* and 576R *IL4RA*), decreased expression of B-cell lineage commitment or differentiation factors (*TCF3*), increased transcriptional activity [*REL* (*NFKBIA*), *STAT3*, *STAT6*], and decreased DNA-repair capacity, and provide enhanced growth and survival signals for the pre-HRS cell. In addition, *IL13* and *IL4RA* polymorphisms can contribute to growth and survival of pre-HRS cells. **B**, EBV-associated malignant transformation of pre-HRS cells. HLA-A*02 carriers can effectively induce EBV-specific CTLs and control the number of EBV⁺ pre-HRS cells throughout the malignant transformation process. HLA-A*01 carriers cannot mount EBV-specific CTL responses to the latency type II infection pattern in pre-HRS cells. In addition, EBV⁺ B cells in R131 *FCGR2A* carriers are less effectively cleared by CTLs. **C**, Th2-based microenvironment and cHL susceptibility mechanisms. The autocrine growth signaling mediated by hyperactive 110Q *IL13*, 576R *IL4RA*, and S159 *IL10RA*, and increased expression of *STAT6* can enhance Th2 differentiation and subsequent secretion of *IL13*, providing growth and stimulation signals throughout the transformation process of pre-HRS cells. GCB, germinal center B cell.

contribute to enhanced activity of nuclear factor of κ light polypeptide gene enhancer in B cells (NF- κ B), which is advantageous for HRS precursor cells. Both *STAT3* protective alleles are associated with reduced expression of

STAT3 (53) and presumably lead to a diminished activation of NF- κ B (Fig. 1A).

The protective variants of DNA-repair genes 194W XRCC1, 222V MTHFR, and the ERCC1 G-allele are associated with increased DNA-repair capacity, whereas the 399Q XRCC1 risk variant is associated with a reduced DNA-repair capacity (54–57). Hence, these associations may all facilitate accumulation of mutations in HRS precursor cells and thereby contribute to the malignant transformation (Fig. 1A). However, the 499V XPC risk variant has a higher nucleotide excision repair capacity compared with the A499 variant (58), which does not match with the above proposed mechanism.

The association of HLA alleles with cHL susceptibility is most likely related to their differential binding affinity of tumor cell-specific antigenic peptides and the subsequent nature and efficiency of T-cell responses. This fits very well with the functionality of many of the non-HLA associations that map to genes with functions related to the immune response. For *HLA-A*, the association with EBV⁺ cHL is most likely driven by the effectiveness of different HLA-A alleles to present antigenic EBV-derived peptides to CD8⁺ cytotoxic T cells (CTL). The *HLA-A*01* allele has a low or no affinity for EBV latency type II-derived antigenic peptides (59), whereas the *HLA-A*02* allele can induce effective CTL responses against EBV latent peptides in a large proportion of individuals (60, 61). Thus, the EBV-specific CTL pool of individuals carrying *HLA-A*02* may more tightly control the number of circulating EBV⁺ B cells and as such reduce the risk of malignant transformation as compared with *HLA-A*01* individuals. In addition or alternatively, *HLA-A*02* carrying individuals are expected to have a constantly more effective CTL response against EBV⁺ HRS precursor cells reducing the change of reaching a fully malignant transformed phenotype. The R131 FCGR2A risk variant is also associated with poor control of EBV latent infection and may affect susceptibility in a similar manner (Fig. 1B; refs. 62, 63).

Most of the HLA class II allele associations are observed for either cHL overall or the EBV⁻/NS cHL subgroups. The susceptibility mechanisms of HLA class II risk and protective alleles might be related to their differential capacity of presenting tumor-associated antigens to CD4⁺ T helper (Th) cells.

Besides tumor (precursor) cell-specific susceptibility mechanisms, genetic associations in cHL are likely to affect the functionality of T cells in the microenvironment. Depending upon the cytokine milieu, CD4⁺ Th cells differentiate into either Th1 or Th2 type. An immune response orchestrated by Th1 cells is central to tumor eradication, whereas Th2 responses support tumor cell growth in cHL (64). Thus, a reduced Th1 and/or an increased Th2 polarization is expected to enhance the survival of precursor HRS cells. A number of risk and protective alleles appear to be involved in regulating the balance between Th1 and Th2. The most striking associations involve polarization to Th2. Several risk alleles favor

Th2 polarization, whereas several protective alleles suppress Th2 polarization. The 110Q IL13 and 576R IL4RA risk variants, both show enhanced signaling activity (51, 52) and support Th2 polarization (65). The protective 159G IL10RA variant with its reduced IL10-binding capacity and the *STAT6* rs703817 A-allele with its reduced expression level suppress Th2 responses (53, 66). The susceptibility effects of all these variants increase Th2 polarization, which is beneficial for survival of HRS precursor cells (Fig. 1C).

Intriguingly, risk alleles that favor Th1 or protective alleles that suppress Th1 polarization have also been identified. On the basis of the functionality and GWAS *P* values, the two most convincing candidates are *EOMES* and *TLR7*. The risk allele of *EOMES* is associated with increased expression levels of *EOMES* (53) and potentially supports Th1 differentiation. The protective 11L *TLR7* variant is less responsive to IFN α stimulation (67) and this could potentially result in a diminished Th1 differentiation potential. These findings are contradictory to the mechanism proposed in Fig. 1C. Current knowledge on cHL biology fits with a Th2 environment especially for the T cells in the close vicinity of the HRS cells at the time of diagnosis. It is unknown whether Th1 immune responses are involved in earlier stages of cHL development.

The protective *MICB* A-allele is associated with a decreased level of *MICB* (53). Reduced expression of the *MICB* on HRS cells might diminish the efficiency of activating natural killer (NK) cells via the NKG2D receptor, but it is unclear how this will provide a protective effect.

In summary, based on the functional roles of the associated gene variants several susceptibility mechanisms can be proposed. Besides the association with certain HLA alleles, the *IL4RA* and *IL13* missense SNPs seem to be strong candidates not only by supporting B-cell survival, but also by skewing the T-cell response toward a Th2 type microenvironment.

Genetic Variants Associated with cHL Prognosis and Treatment Response

Fifteen targeted gene approach studies have been published for cHL including a total of 41 SNPs mapping to 28 gene loci (Supplementary Table S4). The total number of patients varied from 100 to 301. Twenty-three gene loci studied for a single SNP yielded significant associations for three of them (Table 4). All of the five gene loci that were studied for multiple SNPs revealed inconsistent or nonsignificant results.

The UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) polymorphism affects the length of the TA repeat in the promoter region. In two studies with considerable cohort sizes (>200 cases, >60% patients treated with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD)), the patients with homozygous TA6/6 cHL have an adverse prognosis compared with TA7/7 patients, and this effect was independent of other known

Table 4. Genes/SNPs associated with cHL prognosis, treatment-related secondary malignancies and toxicities

Genes	SNP	Allele comparison	Treatment	Associations	Reference
<i>UGT1A1</i>	TA repeat	TA6/6 vs. TA6/7/TA7/7	ABVD/ChIVPP (70%), BEACOPP (11%), CHOP/COP/CHOEP (19%) + RT	Adverse OS	(69)
	TA repeat	TA6/6 vs. TA6/7/TA7/7	ABVD (66%), EBVP (22%), BEACOPP (12%)	Adverse FFP/OS/FFTF	(68)
<i>TRBP</i>	rs784567	TT/TC vs. CC	ABVD (52%), MOPPABVD (38%)	Adverse DFS	(71)
<i>XPO5</i>	rs11077	AA/CC vs. AC	ABVD (52%), MOPPABVD (38%)	Adverse DFS	(71)
<i>PRDM1</i>	rs4946728	A vs. C	RT/CHT (55%), RT only (41%), NA (4%)	Risk of any malignancy	(48)
	rs1040411	G vs. A	RT/CHT (55%), RT only (41%), NA (4%)	Risk of any malignancy	(48)
<i>GSTM1</i>	Deletion	Deletion vs. present	RT/CHT (63%), RT only (37%)	Risk of any malignancy/ cancer within radiation field	(72)
<i>KRT81</i>	rs3660	CC vs. GG	ABVD (52%), MOPPABVD (38%)	Risk of neurologic toxicity	(71)
<i>XPO5</i>	rs11077	AC vs. AA/CC	ABVD (52%), MOPPABVD (38%)	Risk of pulmonary toxicity	(71)

Abbreviations: BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, procarbazine; C(H)O(E)P: cyclophosphamide, (doxorubicin), vincristine, (etoposide), prednisolone; ChIVPP: chlorambucil, vinblastine, prednisolone, procarbazine; CHT, chemotherapy; DFS, disease-free survival; FFP, free from progression; FFS, failure-free survival; FFTF, freedom from treatment failure; MOPP, mustargen, oncovin, procarbazine, prednisone; NA, not available; OS, overall survival; RT, radiotherapy.

prognostic factors (68, 69). TA7/7 individuals have a 70% reduction in *UGT1A1* expression levels compared with TA6/6 individuals (70). Another study with 141 cases treated with ABVD alone or in combination with MOPP identified two SNPs mapping to genes related to miRNA biogenesis, that is, rs11077 at the exportin 5 (*XPO5*) locus and rs784567 mapping at the TAR (HIV-1) RNA-binding protein (*TRBP*) locus are both associated with adverse cHL prognosis (71). The *XPO5* association was independent of age, subtype, β -2-microglobulin levels, B symptoms, and stage of the disease, whereas the association of the *TRBP* SNP has not been tested for independency.

Overall, only one gene locus yielded consistent results in two studies and two additional gene loci were identified in a single study. It is evident that more studies are required to validate these findings and to further explore the possible clinical use of genetic markers for the prediction of treatment outcome.

Genetic Polymorphisms Associated with cHL Treatment-Related Secondary Malignancies and Toxicities

Two targeted gene approach studies and a single GWAS studied genetic associations with treatment-induced toxicity and secondary malignancies after treatment of cHL (Supplementary Table S5 and Table 4). A total of 11 SNPs mapping to 11 gene loci were analyzed in the two targeted gene approach studies including 141 patients treated with ABVD alone or in combination with MOPP and 645 patients treated with radiotherapy or radiotherapy in combination with chemotherapy, respectively (71, 72). After multivariate analysis, the G-allele of

the rs3660 mapping to the keratin 81 (*KRT81*) gene locus was associated with increased risk for neurologic toxicity and the heterozygous rs11077 genotype mapping to the *XPO5* locus is associated with a reduced risk for pulmonary toxicity (71). Individuals with the deletion variant of the glutathione S-transferase mu 1 (*GSTM1*) gene are at risk of any subsequent malignancy or cancer within the radiation field (72). In the GWAS, 189 survivors of cHL treated with radiotherapy in childhood were included. Two SNPs near the PR domain containing 1 with ZNF domain (*PRDM1*, also known as *BLIMP1*) (6q21) gene locus are associated with an increased likelihood of developing any secondary malignancy after radiotherapy for cHL (48). Functional studies on lymphoblastoid cell lines derived from individuals carrying the risk alleles of these SNPs revealed lower endogenous *PRDM1* expression levels and a failure to effectively induce *PRDM1* expression upon exposure to radiation (48). *PRDM1* is also known to negatively regulate the expression of oncogene *MYC*, suggesting a role as radiation-responsive tumor-suppressor gene. The putative relevance of the *PRDM1* gene with respect to the risk on secondary malignancies was further supported by the higher frequency of 6q21 loss in breast cancer after radiotherapy for cHL as compared with sporadic breast cancer (73).

In summary, two gene loci are associated with treatment-induced toxicity after cHL treatment and two gene loci are associated with risk of secondary malignancies. Additional studies are required to replicate these findings and to further elucidate the genetic variants that can identify patients who are less likely to respond to treatment or develop secondary cancers after treatment for cHL.

Conclusions and Implications

Many genetic polymorphisms have been described in patients with cHL, mostly in association to susceptibility. However, when comparing different studies, many of these associations have not been confirmed, are inconsistent between independent studies, or are sometimes even contradictory. For susceptibility, results from large GWAS show that many associations found in targeted studies do not replicate. For prognosis and treatment-related secondary malignancies and toxicities, more studies are needed for screening and to validate candidate SNPs, preferably in GWAS approaches. Overall, reported inconsistencies may originate from suboptimal study design, or to some level reflect the heterogeneous nature of cHL in terms of age, sex, tumor cell EBV status, and ethnic background. In addition, differences in cHL treatment may influence associations in prognostic and late sequelae studies.

HLA alleles constitute the strongest risk and protective polymorphisms in cHL susceptibility, implying that antigen presentation and the function of the immune system is critically important in the etiology of cHL. This is corroborated by genetic associations of immune system-regulatory genes *IL13*, *IL4RA*, and *STAT6*, which are all in the same pathway and associated with a Th2-based immune response. It is generally accepted that a Th2-based immune response in cHL drives HRS cell maintenance and proliferation. Interestingly, the IL13 pathway has previously been shown to have oncogenic effects within the HRS cells as well. A striking observation is that many of the associations that may favor survival of HRS precursor cells also have a potential effect on the function of T cells and may thus contribute to cHL susceptibility by complementary mechanisms. Some other susceptibility associations, for example, in DNA-repair genes are probably also involved in HRS cell biology, but these associations are somewhat less pronounced.

Interestingly, many of the gene loci associated with susceptibility have already been causally linked to the pathogenesis of cHL in targeted studies, by altered expression levels or specific mutations (1, 74, 75). We recently performed a whole-exome sequencing (WES) study of five cHL cell lines and found mutations in several of the associated genes, including *HLA*, *B2M*, *NFKBIA*, *STAT3*, and *STAT6* (76), again indicating that antigen presentation and the IL13 pathway are critically important in cHL pathogenesis. WES studies in primary cHL could strengthen this indication, but are challenging, because of the difficulty of acquiring pure HRS cell DNA from primary cHL tissue.

To date, clinical factors such as stage, B symptoms, laboratory values, etc., are used as prognostic factors to guide cHL treatment (77). These represent disease burden but not disease pathogenesis and may have limited value in understanding lymphomagenesis and disease progression. The identified gene loci that underlie immunologic mechanisms and treatment response or toxicity, may help to improve prognostic models, individualize cancer treatment (increase efficacy and decrease toxicity), and indicate novel treatment targets or approaches.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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