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Polymorphic variation in *NFKB1* and other aspirin-related genes and risk of Hodgkin lymphoma

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Abstract

We found that regular use of aspirin may reduce the risk of Hodgkin lymphoma (HL), a common cancer of adolescents and young adults in the US. To explore possible biological mechanisms underlying this association, we investigated whether polymorphic variation in genes involved in nuclear factor (NF)-κB activation and inhibition, other inflammatory pathways, and aspirin metabolism influences HL risk. Twenty single nucleotide polymorphisms (SNPs) in seven genes were genotyped in DNA from 473 classical HL cases and 373 controls enrolled between 1997 and 2000 in a population-based case-control study in the Boston, Massachusetts, metropolitan area and the state of Connecticut. We selected target genes and SNPs primarily using a candidate-SNP approach and estimated haplotypes using the expectation-maximization algorithm. We used multivariable logistic regression to estimate odds ratios (ORs) for associations with HL risk. HL risk was significantly associated with rs1585215 in *NFKB1* (AG vs. AA: OR=2.1, 95% confidence interval [CI]=1.5–2.9; GG vs. AA: OR=3.5, 95% CI=2.2–5.7, $P_{trend}=1.7\times10^{-8}$) and with *NFKB1* haplotypes ($P_{global}=6.0\times10^{-21}$). Similar associations were apparent across categories of age, sex, tumor Epstein-Barr virus status, tumor histology, and regular aspirin use, although statistical power was limited for stratified analyses. Nominally significant associations with HL risk were detected for SNPs in *NFKBIA* and *CYP2C9*. HL risk was not associated with SNPs in *IKKA/CHUK*, *PTGS2/COX2*, *UDP1A6*, or *LTC4S*. In conclusion, genetic variation in the NF-κB pathway appears to influence risk of HL. Pooled studies are needed to detect any heterogeneity in the association with NF-κB across HL subgroups, including aspirin users and non-users.

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Keywords

Hodgkin lymphoma; genetic polymorphism; nuclear factor kappa B; NFKB1 protein; aspirin; case-control

Introduction

Hodgkin lymphoma (HL) is a relatively rare malignancy whose etiology is complex and poorly understood. Because HL is one of the most common cancers of children and young adults, it ranks third in average years of life lost to a malignancy (1). While the probability of survival from HL is high in young people, survival is associated with substantial treatment-related health risks later in life (2,3). Therefore, research into risk factors for HL, with the ultimate aim of primary prevention, is an important public health strategy for reducing the occurrence of both HL and its long-term complications.

At present, there are few established HL risk factors, especially ones that are easily amenable to change. There is consistent evidence that a family history of hematopoietic malignancy, a sheltered childhood social environment (for young-adult HL) or a crowded childhood social environment (for childhood and older-adult HL), and certain immunodeficiency syndromes are associated with increased risk of HL (4). Epstein-Barr virus (EBV) proteins and RNA are also detected in 20–50% of HL tumors (5), and certain characteristics—including male sex, older age, non-White race, low socioeconomic position (6), and infectious mononucleosis (7)—are associated with increased risk of EBV-positive HL in particular.

Our recent discovery of a significant inverse association between regular aspirin use and risk of HL (8) raises the possibility that aspirin use may have potential for primary prevention of HL. Furthermore, the lack of an association between HL risk and non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin in our study suggests that properties unique to aspirin may explain its inverse relationship with HL risk. Unlike most other NSAIDs, aspirin inhibits the activation of the transcription factor nuclear factor (NF)-κB (9,10), a regulator of immune activation, inflammation, cell growth, and apoptosis, and a necessary survival factor that is constitutively activated in malignant HL cells (11). As the NF-κB pathway appears critical to HL development, its inhibition by aspirin may help prevent disease onset. Other inflammatory mediators blocked by aspirin, such as cyclooxygenases, and metabolism of aspirin itself may also affect HL risk.

The observed inverse association with regular aspirin use points to several biological pathways that could be involved in the etiology of HL. To further explore the potential importance of these routes in HL development, we genotyped single nucleotide polymorphisms (SNPs) in three genes involved in NF-κB activation and inhibition, two genes involved in other inflammatory pathways affected by aspirin, and two genes involved in aspirin metabolism, using DNA from participants in a population-based case-control study of HL. Our goal was to examine whether polymorphic variation in these genes is associated with risk of HL, and whether any such associations are modified by age group, tumor EBV status, or regular aspirin use.

Methods

Study population

The source population for the population-based case-control study included the greater Boston, Massachusetts, metropolitan area and the state of Connecticut, as described previously (8). Briefly, eligible cases were individuals diagnosed with HL at ages 15 to 79 years between

August 1, 1997, and December 31, 2000, living within the described geographic area, and without evidence of human immunodeficiency virus (HIV) infection. Of 735 eligible HL cases, permission for patient contact was granted by the treating physician for 677 (92%); 567 (77%) participated in the study interview.

Population-based controls were frequency matched to the expected distribution of the cases by 5-year age group, sex, and state of residence. From the Boston region, controls were randomly identified from the current "Town Books" identifying all town or city residents aged 17 years and older in the 132 cities and towns within the study area (12). Of the 720 potential controls with valid contact information, 346 (48%) refused or did not respond to invitations to participate, 4 had a language barrier, 2 were incapacitated, 1 was deceased, and 367 (51%) consented to complete the interview.

In Connecticut, controls between 18 and 65 years of age were identified by random digit dialing (RDD), while those between ages 66 and 79 years were randomly selected from Medicare files. Among 450 eligible Connecticut residents identified by RDD (from 5,632 telephone numbers attempted), 170 (38%) refused or did not respond to invitations to participate, 4 (1%) were incapacitated, and 276 (61%) consented to complete the interview. Of 69 eligible Medicare members, 31 (45%) refused or did not respond to invitations to participate, 2 (3%) were incapacitated, and 36 (52%) consented to complete the interview. In total, 679 controls participated by completing the study interview.

All study participants granted written informed consent (or, if younger than 18 years, assent) at the time of enrollment in the study. The research protocol was approved by the Institutional Review Boards (IRBs) of the Harvard School of Public Health, the Yale University School of Medicine, the Johns Hopkins Medical School, all 68 participating hospitals, the Massachusetts Cancer Registry, and the Connecticut Department of Public Health Human Investigation Committee. The current analysis was also approved by the IRB of the Northern California Cancer Center.

Histopathology

The study pathologists reviewed all available pathology material to verify the diagnosis of HL (8). Among the 463 cases with information on histologic subtype, 354 (76%) were nodular sclerosis, 64 (14%) were mixed cellularity, 14 (3%) were interfollicular variant, 11 (2%) were lymphocyte rich, 4 (1%) were lymphocyte depleted, and 16 (3%) were nodular lymphocyte predominant (NLP). Cases with NLP HL were excluded from this analysis, as it is considered a separate disease entity from classical HL (13).

The presence of EBV in HL tissue was determined by *in situ* hybridization for EBV-encoded RNA transcripts and/or by immunohistochemical assay for the viral latency membrane protein 1 in the malignant HL cells, as described previously (5,8). Among the cases with informative EBV results, 312 (76%) were EBV-negative and 97 (24%) were EBV-positive.

Exposure assessment

Following the receipt of an introductory letter, participants completed a structured telephone interview (or an abbreviated mailed questionnaire, for 2 cases and 29 controls) assessing known and suspected risk factors for HL. Data on median household income in census tract and percentage of census tract below poverty level were obtained based on participants' residential street address (14).

DNA collection

Among the participants who completed the interview, 466 cases (85% of 551 cases, excluding NLP HL) provided a blood specimen and 373 controls (55%) provided a buccal cell specimen. In addition, 7 eligible cases who did not complete the interview, but with basic demographic information, provided a blood specimen. Participants who donated a biospecimen were older, more highly educated, and more likely to be of White race than those who did not.[1] Buccal cell specimens were self-collected by participants using a mailed kit with commercial mouthwash. Initial DNA extraction from buccal cells was performed by using the Puregene kit (Gentra Systems, Inc., Minneapolis, MN). DNA from the buccal and buffy coat specimens was subsequently extracted by using the QIAamp DNA blood kit (Qiagen GmbH, Hilden, Germany).

Gene and SNP selection

The target genes and SNPs in this study were selected based primarily on a candidate-SNP approach, using a combination of database and literature searches. We searched the PubMed database[2] to identify association studies of polymorphisms in genes on the NF-κB pathway (e.g., *NFKB1*, *NFKB2*, *NFKB3/RELA*, *NFKBIA*, *NFKBIB*, *NFKBIE*, *IKKA/CHUK*, *IKKB*, and *IKKE*), those involved in aspirin metabolism (e.g., *CYP2C9*, *CYP3A4*, *CYP2E1*, *GSTP1*, and *UGT1A6*), and those involved in susceptibility to aspirin-intolerant asthma (e.g., *CysLTR1*, *FCER1B*, and *LTC4S*), as well as *PTGS2/COX2*. In addition, we searched the SNP database[3] and the Ensembl database[4] and used the bioinformatics tool SNPSelector[5] to identify validated SNPs in coding regions or, secondarily, in untranslated regions of these genes. We limited the list to SNPs known to have a minor allele frequency >5% in Europeans or Caucasians, who comprise 89% of the study population. Genes without qualifying SNPs or previously published association studies were excluded from the target gene list, leaving seven genes: NF-κB subunit 1 (*NFKB1*), NF-κB inhibitor α (*NFKBIA*), inhibitor of NF-kB α/conserved helix-loop-helix ubiquitous kinase (*IKKA*/*CHUK*), prostaglandin-endoperoxide synthase 2/cyclooxygenase-2 (*PTGS2*/*COX2*), cytochrome p450, family 2, subfamily C, polypeptide 9 (*CYP2C9*), UDP glucuronosyltransferase 1 family, polypeptide A6 (*UDP1A6*), and leukotriene C4 synthase (*LTC4S*). We genotyped 20 SNPs in these genes, prioritizing 1) SNPs in coding regions, 2) SNPs previously found to be associated with risk of other disorders, 3) SNPs in untranslated regions or locus regions (15), and 4) haplotype-tagging SNPs (htSNPs), and favoring genes in the NF-κB pathway. The selected SNPs were as follows: *NFKB1* rs1585215, rs1599961, rs1609993, rs3774936, rs3774937, and rs3774938; *NFKBIA* rs696, rs8904, rs1050851, and rs1957106; *IKKA*/*CHUK* rs2230804; *PTGS2* rs5272, rs5277, rs20417, and rs689466; *CYP2C9* rs1057910 and rs1799853; *UDP1A6* rs1105879 and rs2070959; and *LTC4S* rs730012.

Genotyping

Genotyping was performed at the High-Throughput Polymorphism Detection Core of the Dana-Farber/Harvard Cancer Center. All samples were genotyped using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The 5′ nuclease assay (TaqMan®) was used to distinguish the two alleles of each gene. Polymerase chain reaction (PCR) amplification was carried out on 5–20 ng DNA. TaqMan® primers and probes were designed using the Primer Express® Oligo Design software v2.0 (ABI PRISM) or using the ABI Assays-By-Design service. In each assay, 10–12 blinded quality control (QC) samples (5–6 sets of 2 replicate DNAs each) were included. The concordance rate in QC samples that

[1] Bandell C and Mueller NE, personal communication
[2] http://www.ncbi.nlm.nih.gov/pubmed/
[3] http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp
[4] http://www.ensembl.org/Homo_sapiens/Info/Index
[5] http://www.ama-assn.org/ama/pub/category/1736.html

yielded a non-missing call was 100% in each assay. Among HL cases, the call rate ranged between 94% (for *NFKB1* rs1585215) and 99% (for *CYP2C9* rs1799853), and was 97% overall. Among controls, the call rate ranged between 94% (for *NFKB1* rs3774938) and 99% (for *NFKB1* rs1609993 and *CYP2C9* rs1057910), and was 97% overall.

Statistical analysis

Tests of Hardy-Weinberg equilibrium were performed among controls for all loci, with no significant departures. Each SNP was included separately in a logistic regression model, with genotype as a categorical variable, to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for associations with HL risk, controlling for 5-year age group, sex, state of residence, and race/ethnicity (White, Black, Hispanic, Asian, or other/mixed/unknown). If there were fewer than 10 cases and controls with the homozygous variant genotype, then the homozygous variant and heterozygous genotypes were combined. Tests for trend were performed with genotypes coded according to the number of variant alleles. Likelihood ratio tests were used to evaluate the statistical significance of gene-environment interactions. Heterogeneity by tumor EBV status or histology was examined by using case-case comparisons in logistic regression models controlling for 5-year age group and sex.

Haplotype frequencies were estimated by using the estimation maximization algorithm as implemented in PROC HAPLOTYPE in SAS/GENETICS (SAS Institute, Cary, NC). The most common haplotype served as the reference group. Omnibus tests of haplotype associations with HL risk were performed by using global likelihood ratio tests. Haplotypes with frequency below 0.05% were excluded from the analysis, and those with frequency below 5% were pooled for score calculation. Haplotype-specific ORs were estimated by using the most common haplotype as the reference group. Omnibus tests of haplotype interactions with age group, sex, or regular aspirin use were performed by using likelihood ratio tests as implemented in the HAPPY SAS macro[6](16). To adjust conservatively for multiple testing, we interpreted the statistical significance of our results using a more stringent *P*-value cutoff with Bonferroni correction for as many as 500 tests, i.e., $P \leq 0.05/500$ or $\leq 10^{-4}$). *P*-values described as "nominally" significant were those between 10^{-4} and 0.05. All analyses were performed by using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

In this analysis, the HL cases were somewhat younger and had less formal education than controls, but had a similar distribution of sex, race/ethnicity, state of residence, and area-level indicators of socioeconomic position (Table 1). The distribution of genotypes among HL cases and controls is shown in Table 2.

As shown in Table 2, HL risk was significantly associated with *NFKB1* rs1585215, even after Bonferroni correction for multiple testing ($P_{trend}=1.7\times10^{-8}$). The OR for rs1585215 AG vs. AA was 2.1 (95% CI=0.9–5.2) among regular aspirin users (≥2 times/week) and 2.4 (95% CI=1.6–3.4) among non-regular aspirin users (<2 times/week); and the OR for GG vs. AA was 2.4 (0.6–10.5) among regular aspirin users and 3.8 (95% CI=2.2–6.4) among non-regular users ($P_{heterogeneity}=0.89$). Conversely, the OR for regular vs. non-regular aspirin use was 1.0 (95% CI=0.4–2.5) for those with rs1585215 AA; 0.5 (95% CI=0.3–0.9) for AG; and 0.4 (95% CI=0.1–1.6) for GG.

Risk of HL was nominally associated with *NFKBIA* rs696, rs8904, rs1050851, and rs1957106, and *CYP2C9* rs1799853 (Table 2). There were no apparent risk associations with SNPs in

[6]http://www.hsph.harvard.edu/faculty/kraft/softetc/happy.sas

PTGS2, *IKKA*, *UGT1A6*, or *LTC4S*. These results did not change substantially after additional adjustment for race/ethnicity, education, socioeconomic position, or regular aspirin use, nor when analyses were limited only to Whites or cases with histopathologically confirmed HL (data not shown). Although HapMap data show that *NFKB1* rs1585215 is in a region of high linkage disequilibrium (LD) (17), rs1585215 was not in the same haplotype block as the other five SNPs in *NFKB1* in our study population, either overall or among only Whites (18).

In exploratory stratified analyses by age group, *NFKBIA* rs696, rs8904, and rs1957106 and *CYP2C9* rs179953 were nominally associated with HL risk only among young adults, although there were no statistically significant interactions between genotype and age group (Table 3). Similarly, there were no statistically significant interactions between genotype and tumor EBV status, although *NFKBIA* rs1957106 was nominally associated only with risk of EBV-positive HL, whereas *PTGS2* rs20417 was nominally associated only with risk of EBV-negative HL (Table 4). There were no noteworthy differences in genotype associations with HL risk by sex, tumor histology (nodular sclerosis vs. mixed cellularity), or regular aspirin use (data not shown).

The distribution of estimated haplotypes with frequency of more than 5% is shown in Table 5. The results of the haplotype analysis were qualitatively similar to those of the SNP analysis. There was a significant global association of haplotypes in *NFKB1* with HL risk, including after adjustment for multiple testing ($P_{global}=6.0\times10^{-21}$), driven by the association with rs1585215. Haplotypes in *NFKBIA*, *PTGS2*, *CYP2C9*, and *UGT1A6* were not globally associated with HL risk overall. There was no significant heterogeneity in haplotype associations by age group, sex, tumor EBV status, histology, or regular aspirin use (data not shown).

Discussion

In this population-based case-control study, we found that a single SNP and haplotypes in *NFKB1*were significantly associated with risk of overall HL. In addition, selected SNPs in *NFKBIA*, and *CYP2C9* were suggestively associated with HL risk. There were no statistically significant interactions of genotype or haplotype with age group, sex, tumor EBV status, histology, or regular aspirin use, although this study had limited power to detect such interactions. Taken together, our results suggest that genetic variants in the NF-κB pathway and potentially in aspirin metabolism are involved in HL development. These etiologic pathways may affect HL risk independently of aspirin use, but biological interactions with aspirin may also exist, thereby suggesting mechanisms by which aspirin use may decrease HL risk. Larger studies, perhaps using pooled data, are needed to establish whether the association of polymorphic variation in *NFKB1*, *NFKBIA*, and *CYP2C9* with HL risk does or does not vary between regular and non-regular aspirin users, as well as whether the association with aspirin use varies by genotype.

Strong biochemical and genetic evidence has accumulated to establish the cancer-initiating and promoting properties of NF-κB, including inhibition of apoptosis, production of growth and angiogenesis factors, and direct stimulation of cell-cycle progression (19), including in hematopoietic cells (20). Activated NF-κB is detected in virtually all malignant HL cells (21), whereas NF-κB inhibition decreases proliferation and causes spontaneous apoptosis of HL cells (11,22). Because NF-κB signaling involves a cascade of interacting proteins, genetic variation in any of these proteins may affect NF-κB activity and, as a result, HL development. Genetic variation in *NFKB1*, which encodes a subunit of the most common NF-κB protein complex, was shown to be associated with risk of other malignancies (23–25), but has not previously been studied in relation to HL risk. Other studies found an association between *NFKB1* variation and risk of ulcerative colitis (26,27), a chronic inflammatory bowel disease

that is in turn associated with increased risk of HL (28–30), suggesting that these diseases may share NF-κB-mediated pathogenetic pathways.

In resting cells, NF-κB is sequestered in the cytoplasm by members of the IκB family (31), including NF-κBIα (also known as IκBα), which inhibits the DNA-binding activity of the NF-κB1 complex (32). A small study of eight familial HL cases found no mutations in the coding region or promoter of *NFKBIA*, and there was no difference in the frequency of four *NFKBIA* polymorphisms (including two SNPs in this study, rs696 and rs8904) between 51 HL cases and 50 controls (33). On the other hand, *NFKBIA* polymorphisms were associated with risk of multiple myeloma (34,35), as well as multiple sclerosis (36), sarcoidosis (37) and a subset of Crohn's disease (38)—chronic inflammatory diseases that may contribute to or share etiologic features with HL (39). Degradation of IκB, which allows NF-κB to translocate to the nucleus and activate transcription, occurs via phosphorylation by IκB kinases (IKKs) (40). IKKα in particular can also activate NF-κB by phosphorylating NF-κB2 directly, resulting in the induction of genes essential for B-cell development and formation of secondary lymphoid organs (41). Disease associations with *IKKA* polymorphisms have not been thoroughly examined, although a small Japanese case-control study found no association with risk of several autoimmune inflammatory conditions (42). Our findings that overall HL risk varied according to genetic variation in *NFKB1* indicate that the etiologic role of the NF-κB pathway in HL development may depend on genotype. Although we did not observe statistically significant associations with SNPs or haplotypes in *NFKBIA* or *IKKA*, it remains possible that these genes or others in the NF-κB pathway have an etiologic role not observed in our study.

When interpreting the results of our study, some limitations should be taken into account. First, due to sample size restrictions, our study had low statistical power for subgroup analyses and consideration of genotype models other than the additive. Therefore, we were likely unable to detect modest associations and, in particular, gene-environment interactions with HL risk. Given this limitation, it remains unclear whether the observed genetic associations are independent of aspirin use (i.e., do not vary between regular and non-regular aspirin users) or whether we lacked sufficient power to detect existing heterogeneity by aspirin use. Conversely, several of the observed nominal associations may be due to chance.

Second, we used a candidate-SNP approach that was not designed to include htSNPs capturing unique genetic variation across each gene, and we were thus unable to examine associations with haplotypes of all the selected genes. Because the selected SNPs had limited gene coverage and we included only a few genes in each biological pathway, our results do not rule out a true role of the studied genes and pathways in HL etiology. Likewise, we did not choose only functional SNPs, and some of the SNPs that we found to be associated with HL risk may be markers linked to the relevant functional genetic variants. According to current data from the HapMap CEU (Caucasian) sample, rs1585215 is in LD (r^2>0.5) with more than 70 other known SNPs in *NFKB1*, but all are intronic (17). Additional studies are needed to determine whether rs1585215 or a linked variant affects HL risk, and how the relevant SNP changes *NFKB1* function. Third, the lack of full study participation and provision of a DNA specimen, especially by controls, raises the possibility of selection bias, although it is somewhat unlikely that participation rates varied by the genotypes of interest in this study.

These limitations are counterbalanced by the considerable strengths of our study. First, this is the largest genetic association study of HL to date, giving us greater power to detect associations. Second, we selected a range of target genes on several different but related biological pathways, enabling us to investigate a variety of avenues through which aspirin may influence HL development. Third, the population-based study design gave us the best possible estimate of the prevalence of regular aspirin use in the source population, represented by the controls. Fourth, 90% of our study population was non-Hispanic White based on self-report,

which has been shown to be accurate in classifying European genetic ancestry (43). Our secondary analysis restricted to Whites showed no difference in results, suggesting negligible bias due to population stratification (44).

In summary, by suggesting a genetic basis for the involvement of NF-κB in HL pathogenesis, our results highlight a biological pathway that is influenced by aspirin and affects HL development, and may explain the observed inverse association between regular aspirin use and HL risk. Additional biological processes influenced by aspirin, particularly those related to immune function, offer other promising avenues for research in HL etiology. Further large studies are needed to replicate our results, as well as enable more detailed investigation of interactions with aspirin use and disease subtype. If future findings support the hypothesis that regular aspirin use decreases HL risk, then these studies may offer a potential starting point for preventing HL and its adverse secondary health effects. A validated risk prediction model could aid in identifying subgroups that may benefit the most from regular aspirin use, particularly those at high risk of HL due to a strong family history, HIV infection or other immunodeficiency, and/or genetic susceptibility—perhaps, as our study suggests, including *NFKB1* genotype.

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Table 1

Characteristics of Hodgkin lymphoma cases and controls included in analysis

Characteristic	Cases (*N*=473)		Controls (*N*=373)	
	N	(%)	*N*	(%)
Age (years)				
15–39	287	(61%)	201	(54%)
40–54	111	(23%)	82	(22%)
55–79	75	(16%)	90	(24%)
Sex				
Male	242	(51%)	211	(57%)
Female	231	(49%)	162	(43%)
Race/ethnicity				
White	423	(89%)	336	(90%)
Black	13	(3%)	15	(4%)
Hispanic	20	(4%)	7	(2%)
Asian	4	(1%)	8	(2%)
Other/mixed/unknown	13	(3%)	7	(2%)
State				
Massachusetts	278	(59%)	215	(58%)
Connecticut	195	(41%)	158	(42%)
Education				
Less than high school	42	(9%)	19	(5%)
High school graduate	120	(26%)	90	(24%)
College	236	(51%)	183	(49%)
Advanced degree	68	(15%)	80	(22%)
Annual household income*				
<$60,000	121	(26%)	84	(23%)
$60,000–79,999	180	(39%)	161	(43%)
$80,000–99,999	98	(21%)	78	(21%)
≥$100,000	67	(14%)	50	(13%)
Percent below poverty level*				
<2%	96	(21%)	82	(22%)
2–<4%	139	(30%)	115	(31%)
4–<6%	83	(18%)	67	(18%)
≥6%	148	(32%)	109	(29%)
Aspirin use				
None	333	(73%)	224	(63%)
<2/week	70	(15%)	58	(16%)
≥2/week	54	(12%)	72	(20%)

*Based on participants' census tract of residence

Missing data are excluded.

Table 2

Distribution of aspirin-related genotypes among Hodgkin lymphoma cases and controls, and odds ratios (ORs) and 95% confidence intervals (CIs) for associations with risk of Hodgkin lymphoma

Gene	refSNP ID	Function	Genotype	Cases (*N*=473) *N*	(%)	Controls (*N*=373) *N*	(%)	OR*	(95% CI)
NFKB1 (nuclear factor kappa-B, subunit 1)									
	rs1585215	intron	AA	111	(25%)	151	(43%)	1.0	referent
			AG	250	(56%)	169	(48%)	**2.1**	**(1.5, 2.9)**
			GG	82	(19%)	33	(9%)	**3.5**	**(2.2, 5.7)**
								$P_{trend}=1.7\times10^{-8}$	
	rs1599961	intron	GG	170	(37%)	128	(35%)	1.0	referent
			GA	221	(48%)	175	(48%)	1.0	(0.7, 1.3)
			AA	66	(14%)	64	(17%)	0.8	(0.5, 1.2)
								$P_{trend}=0.29$	
	rs1609993	coding-synon	CC	388	(84%)	318	(86%)	1.0	referent
			CT	73	(16%)	52	(14%)	1.2	(0.8, 1.8)
			TT	3	(1%)	1	(0%)		
								$P=0.36$	
	rs3774936	intron	AA	204	(45%)	161	(44%)	1.0	referent
			AT	194	(43%)	168	(46%)	0.9	(0.7, 1.2)
			TT	56	(12%)	35	(10%)	1.2	(0.8, 2.0)
								$P_{trend}=0.76$	
	rs3774937	intron	TT	197	(44%)	157	(44%)	1.0	referent
			TC	197	(44%)	165	(46%)	0.9	(0.7, 1.3)
			CC	58	(13%)	35	(10%)	1.3	(0.8, 2.1)
								$P_{trend}=0.55$	
	rs3774938	intron	AA	165	(37%)	128	(37%)	1.0	referent
			AG	221	(49%)	169	(48%)	1.0	(0.8, 1.4)
			GG	65	(14%)	52	(15%)	1.0	(0.6, 1.5)
								$P_{trend}=0.96$	
NFKBIA (nuclear factor kappa-B inhibitor alpha)									
	rs696	intron	GG	156	(34%)	153	(42%)	1.0	referent
			GA	215	(46%)	158	(43%)	**1.3**	**(0.9, 1.8)**

Gene	refSNP ID	Function	Genotype	Cases (*N*=473) *N*	(%)	Controls (*N*=373) *N*	(%)	OR*	(95% CI)
			AA	92	(20%)	53	(15%)	**1.7**	**(1.1, 2.5)**
								P_{trend}=0.01	
	rs8904	intron	CC	162	(35%)	152	(42%)	1.0	referent
			CT	209	(45%)	158	(43%)	**1.2**	**(0.9, 1.6)**
			TT	92	(20%)	55	(15%)	**1.5**	**(1.0, 2.3)**
								P_{trend}=0.05	
	rs1050851	coding-synon	CC	296	(65%)	199	(55%)	1.0	referent
			CT	138	(30%)	143	(40%)	**0.7**	**(0.5, 0.9)**
			TT	21	(5%)	19	(5%)	**0.7**	**(0.4, 1.4)**
								P_{trend}=0.02	
	rs1957106	coding-synon	GG	233	(51%)	199	(55%)	1.0	referent
			GA	180	(40%)	144	(40%)	**1.0**	**(0.7, 1.4)**
			AA	40	(9%)	18	(5%)	**1.8**	**(1.0, 3.3)**
								P_{trend}=0.20	
IKKA/CHUK (inhibitor of nuclear factor kappa-B kinase alpha/conserved helix-loop-helix ubiquitous kinase)									
	rs2230804	coding-nonsynon	AA	118	(25%)	92	(26%)	1.0	referent
			AG	226	(49%)	171	(48%)	1.0	(0.7, 1.5)
			GG	119	(26%)	96	(27%)	1.0	(0.7, 1.4)
								P_{trend}=0.89	
PTGS2/COX2 (prostaglandin-endoperoxide synthase 2/cyclooxygenase-2)									
	rs5272	coding-nonsynon	AA	440	(97%)	358	(98%)	1.0	referent
			AG	14	(3%)	6	(2%)	1.6	(0.6, 4.4)
			GG	0	(0%)	0	(0%)		
								P=0.32	
	rs5277	coding-synon	GG	332	(72%)	282	(76%)	1.0	referent
			GC	116	(25%)	78	(21%)	1.2	(0.9, 1.7)
			CC	10	(2%)	9	(2%)	1.0	(0.4, 2.5)
								P_{trend}=0.44	
	rs20417		GG	279	(61%)	231	(65%)	1.0	referent
		5′ near gene	GC	151	(33%)	113	(32%)	1.2	(0.8, 1.6)

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Gene	refSNP ID	Function	Genotype	Cases (*N*=473) *N*	Cases (*N*=473) (%)	Controls (*N*=373) *N*	Controls (*N*=373) (%)	OR*	(95% CI)
			CC	24	(5%)	10	(3%)	2.1	(0.9, 4.6)
								P_{trend}=0.09	
	rs689466		AA	314	(69%)	249	(69%)	1.0	referent
		5′ near gene	AG	124	(27%)	99	(27%)	1.0	(0.7, 1.4)
			GG	19	(4%)	13	(4%)	1.2	(0.6, 2.4)
								P_{trend}=0.81	
CYP2C9 (cytochrome p450, family 2, subfamily C, polypeptide 9)									
	rs1057910	coding-nonsynon	AA	395	(85%)	324	(87%)	1.0	referent
			AC	70	(15%)	46	(12%)	1.3	(0.9, 1.9)
			CC	0	(0%)	1	(0%)		
								P=0.22	
	rs1799853	coding-nonsynon	CC	344	(73%)	293	(79%)	1.0	referent
			CT	126	(27%)	70	(19%)	**1.4**	**(1.0, 2.0)**
			TT	0	(0%)	7	(2%)		
								***P* =0.04**	
UGT1A6 (UDP glucuronosyltransferase 1 family, polypeptide A6)									
	rs1105879	coding-nonsynon	TT	185	(40%)	151	(42%)	1.0	referent
			TG	227	(49%)	163	(46%)	1.1	(0.8, 1.5)
			GG	52	(11%)	43	(12%)	1.0	(0.6, 1.6)
								P_{trend}=0.67	
	rs2070959	coding-nonsynon	AA	202	(44%)	170	(46%)	1.0	referent
			AG	212	(46%)	160	(43%)	1.1	(0.8, 1.5)
			GG	44	(10%)	38	(10%)	1.0	(0.6, 1.7)
								P_{trend}=0.63	
LTC4S (leukotriene C4 synthase)									
	rs730012		AA	247	(55%)	205	(57%)	1.0	referent
		5′ near gene	AC	178	(40%)	132	(37%)	1.2	(0.9, 1.6)
			CC	25	(6%)	24	(7%)	0.8	(0.4, 1.5)
								P_{trend}=0.85	

Missing data are excluded.

* Adjusted for 5-year age group, sex, state, and race/ethnicity

P-values are not Bonferroni-adjusted.

Table 3

Distribution of aspirin-related genotypes among Hodgkin lymphoma cases and controls by age group, and odds ratios (ORs) and 95% confidence intervals (CIs) for associations with risk of Hodgkin lymphoma by age group

			Ages 15–49 years						Ages 50–79 years						
			Cases (*N*=379)		Controls (*N*=262)				Cases (*N*=94)		Controls (*N*=111)				
Gene	**refSNP ID**	**Genotype**	***N***	**(%)**	***N***	**(%)**	**OR***	**(95% CI)**	***N***	**(%)**	***N***	**(%)**	**OR**	**(95% CI)**	$P_{heterogeneity}$
NFKB1 (nuclear factor kappa-B, subunit 1)															
	rs1585215	AA	94	(27%)	101	(41%)	1.0	referent	17	(19%)	50	(46%)	1.0	referent	
		AG	195	(55%)	120	(49%)	1.8	(1.2, 2.6)	55	(60%)	49	(45%)	3.7	(1.8, 7.6)	
		GG	63	(18%)	23	(9%)	3.0	(1.7, 5.3)	19	(21%)	10	(9%)	5.4	(2.0, 14.5)	0.25
							$P_{trend}=2.8\times10^{-5}$						$P_{trend}=1.7\times10^{-4}$		
	rs1599961	GG	141	(39%)	87	(34%)	1.0	referent	29	(31%)	41	(37%)	1.0	referent	
		GA	173	(48%)	122	(47%)	0.9	(0.6, 1.3)	48	(51%)	53	(48%)	1.3	(0.6, 3.2)	
		AA	49	(13%)	48	(19%)	0.6	(0.4, 1.0)	17	(18%)	16	(15%)	1.3	(0.7, 2.5)	0.26
							$P_{trend}=0.09$						$P_{trend}=0.44$		
	rs1609993	CC	305	(82%)	227	(87%)	1.0	referent	83	(88%)	91	(82%)	1.0	referent	
		CT	63	(17%)	32	(12%)	1.5	(0.9, 2.3)	10	(11%)	20	(18%)	0.6	(0.3, 1.4)	0.06
		TT	2	(1%)	1	(0%)			1	(1%)	0	(0%)			
							$P=0.10$						$P=0.26$		
	rs3774936	AA	168	(47%)	109	(43%)	1.0	referent	36	(39%)	52	(48%)	1.0	referent	
		AT	152	(42%)	120	(47%)	0.8	(0.6, 1.2)	42	(45%)	48	(44%)	1.2	(0.7, 2.3)	
		TT	41	(11%)	26	(10%)	1.0	(0.6, 1.7)	15	(16%)	9	(8%)	2.1	(0.8, 5.5)	0.31
							$P_{trend}=0.59$						$P_{trend}=0.16$		
	rs3774937	TT	162	(45%)	107	(43%)	1.0	referent	35	(39%)	50	(46%)	1.0	referent	
		TC	157	(43%)	117	(47%)	0.9	(0.6, 1.2)	40	(44%)	48	(44%)	1.2	(0.6, 2.2)	
		CC	43	(12%)	25	(10%)	1.1	(0.6, 2.0)	15	(17%)	10	(9%)	1.8	(0.7, 4.8)	0.58
							$P_{trend}=0.96$						$P_{trend}=0.24$		
	rs3774938	AA	139	(39%)	88	(36%)	1.0	referent	26	(29%)	40	(37%)	1.0	referent	
		AG	173	(48%)	117	(48%)	1.0	(0.7, 1.4)	48	(53%)	52	(49%)	1.5	(0.8, 2.9)	
		GG	48	(13%)	37	(15%)	0.8	(0.5, 1.4)	17	(19%)	15	(14%)	1.6	(0.6, 3.9)	0.38
							$P_{trend}=0.53$						$P_{trend}=0.25$		
NFKBIA (nuclear factor kappa-B inhibitor alpha)															

			Ages 15–49 years						Ages 50–79 years						
			Cases (*N*=379)		Controls (*N*=262)				Cases (*N*=94)		Controls (*N*=111)				
Gene	**refSNP ID**	**Genotype**	***N***	**(%)**	***N***	**(%)**	**OR***	**(95% CI)**	***N***	**(%)**	***N***	**(%)**	**OR**	**(95% CI)**	$P_{heterogeneity}$
	rs696	GG	112	(30%)	105	(41%)	**1.0**	**referent**	44	(47%)	48	(44%)	1.0	referent	
		GA	181	(49%)	110	(43%)	**1.6**	**(1.1, 2.3)**	34	(37%)	48	(44%)	0.8	(0.4, 1.5)	
		AA	77	(21%)	39	(15%)	**2.0**	**(1.2, 3.2)**	15	(16%)	14	(13%)	1.1	(0.4, 2.6)	0.11
								P_{trend}=0.002						P_{trend}=0.83	
	rs8904	CC	117	(32%)	103	(41%)	**1.0**	**referent**	45	(48%)	49	(44%)	1.0	referent	
		CT	176	(48%)	109	(43%)	**1.4**	**(1.0, 2.1)**	33	(35%)	49	(44%)	0.8	(0.4, 1.4)	
		TT	77	(21%)	42	(17%)	**1.7**	**(1.1, 2.7)**	15	(16%)	13	(12%)	1.1	(0.5, 2.8)	0.17
								P_{trend}=0.02						P_{trend}=0.88	
	rs1050851	CC	235	(65%)	144	(57%)	1.0	referent	61	(67%)	55	(50%)	1.0	referent	
		CT	111	(30%)	97	(38%)	0.7	(0.5, 1.0)	27	(30%)	46	(42%)	0.5	(0.3, 1.0)	
		TT	18	(5%)	11	(4%)	1.0	(0.4, 2.1)	3	(3%)	8	(7%)	0.3	(0.1, 1.4)	0.35
								P_{trend}=0.13						P_{trend}=0.03	
	rs1957106	GG	180	(50%)	135	(54%)	**1.0**	**referent**	53	(59%)	64	(58%)	1.0	referent	
		GA	147	(40%)	104	(41%)	**1.0**	**(0.7, 1.5)**	33	(37%)	40	(36%)	0.9	(0.5, 1.7)	
		AA	36	(10%)	12	(5%)	**2.3**	**(1.1, 4.6)**	4	(4%)	6	(5%)	0.8	(0.2, 3.0)	0.30
								P_{trend}=0.08						P_{trend}=0.67	
IKKA/CHUK (inhibitor of nuclear factor kappa-B kinase alpha/conserved helix-loop-helix ubiquitous kinase)															
	rs2230804	AA	96	(26%)	60	(24%)	1.0	referent	22	(24%)	32	(29%)	1.0	referent	
		AG	184	(50%)	127	(51%)	0.9	(0.6, 1.4)	42	(45%)	44	(40%)	1.3	(0.6, 2.6)	
		GG	90	(24%)	62	(25%)	0.9	(0.6, 1.5)	29	(31%)	34	(31%)	1.1	(0.5, 2.4)	0.66
								P_{trend}=0.72						P_{trend}=0.77	
PTGS2/COX2 (prostaglandin-endoperoxide synthase 2/cyclooxygenase-2)															
	rs5272	AA	352	(97%)	249	(98%)	1.0	referent	88	(98%)	109	(99%)	1.0	referent	
		AG	12	(3%)	5	(2%)	1.6	(0.6, 4.7)	2	(2%)	1	(1%)	1.1	(0.1, 18.5)	0.93
		GG	0	(0%)	0	(0%)			0	(0%)	0	(0%)			
								P=0.37						*P*=0.96	
	rs5277	GG	267	(73%)	192	(74%)	1.0	referent	65	(71%)	90	(81%)	1.0	referent	
		GC	96	(26%)	59	(23%)	1.1	(0.8, 1.6)	20	(22%)	19	(17%)	1.6	(0.8, 3.3)	

			Ages 15–49 years						Ages 50–79 years						
			Cases (*N*=379)		Controls (*N*=262)				Cases (*N*=94)		Controls (*N*=111)				
Gene	**refSNP ID**	**Genotype**	***N***	**(%)**	***N***	**(%)**	**OR***	**(95% CI)**	***N***	**(%)**	***N***	**(%)**	**OR**	**(95% CI)**	$P_{heterogeneity}$
		CC	4	(1%)	7	(3%)	0.4	(0.1, 1.4)	6	(7%)	2	(2%)	4.0	(0.6, 22.2)	0.07
								P_{trend}=0.80						P_{trend}=0.05	
	rs20417	GG	224	(62%)	157	(64%)	1.0	referent	55	(59%)	74	(69%)	1.0	referent	
		GC	118	(33%)	83	(34%)	1.0	(0.7, 1.5)	33	(35%)	30	(28%)	1.6	(0.9, 3.0)	
		CC	19	(5%)	7	(3%)	2.0	(0.8, 4.9)	5	(5%)	3	(3%)	2.5	(0.5, 12.5)	0.54
								P_{trend}=0.31						P_{trend}=0.08	
	rs689466	AA	246	(67%)	174	(69%)	1.0	referent	68	(75%)	75	(70%)	1.0	referent	
		AG	103	(28%)	71	(28%)	1.1	(0.8, 1.6)	21	(23%)	28	(26%)	0.7	(0.4, 1.5)	
		GG	17	(5%)	9	(4%)	1.4	(0.6, 3.2)	2	(2%)	4	(4%)	0.6	(0.1, 3.3)	0.49
								P_{trend}=0.43						P_{trend}=0.29	
CYP2C9 (cytochrome p450, family 2, subfamily C, polypeptide 9)															
	rs1057910	AA	319	(86%)	231	(89%)	1.0	referent	76	(82%)	93	(84%)	1.0	referent	
		AC	53	(14%)	28	(11%)	1.4	(0.8, 2.2)	17	(18%)	18	(16%)	1.2	(0.6, 2.5)	0.70
		CC	0	(0%)	1	(0%)			0	(0%)	0	(0%)			
								P=0.22						P=0.67	
	rs1799853	CC	271	(72%)	211	(81%)	**1.0**	**referent**	73	(78%)	82	(75%)	1.0	referent	
		CT	105	(28%)	43	(17%)	**1.7**	**(1.1, 2.5)**	21	(22%)	27	(25%)	0.9	(0.4, 1.7)	0.08
		TT	0	(0%)	6	(2%)			0	(0%)	1	(1%)			
								***P*=0.01**						P=0.67	
UGT1A6 (UDP glucuronosyltransferase 1 family, polypeptide A6)															
	rs1105879	TT	149	(40%)	101	(41%)	1.0	referent	36	(39%)	50	(46%)	1.0	referent	
		TG	183	(49%)	114	(46%)	1.1	(0.8, 1.6)	44	(47%)	49	(45%)	1.2	(0.7, 2.3)	
		GG	39	(11%)	33	(13%)	0.8	(0.5, 1.4)	13	(14%)	10	(9%)	1.7	(0.6, 4.6)	0.33
								P_{trend}=0.72						P_{trend}=0.26	
	rs2070959	AA	165	(45%)	115	(44%)	1.0	referent	37	(40%)	55	(50%)	1.0	referent	
		AG	169	(46%)	115	(44%)	1.0	(0.7, 1.5)	43	(46%)	45	(41%)	1.4	(0.8, 2.7)	
		GG	31	(8%)	29	(11%)	0.8	(0.4, 1.3)	13	(14%)	9	(8%)	2.1	(0.8, 5.7)	0.16
								P_{trend}=0.57						P_{trend}=0.11	

			Ages 15–49 years						Ages 50–79 years						
			Cases (*N*=379)		Controls (*N*=262)				Cases (*N*=94)		Controls (*N*=111)				
Gene	**refSNP ID**	**Genotype**	***N***	**(%)**	***N***	**(%)**	**OR***	**(95% CI)**	***N***	**(%)**	***N***	**(%)**	**OR**	**(95% CI)**	$P_{heterogeneity}$
LTC4S (leukotriene C4 synthase)															
	rs730012	AA	201	(56%)	147	(58%)	1.0	referent	46	(51%)	58	(54%)	1.0	referent	
		AC	135	(38%)	90	(36%)	1.1	(0.8, 1.5)	43	(47%)	42	(39%)	1.4	(0.8, 2.6)	
		CC	23	(6%)	16	(6%)	1.0	(0.5, 2.0)	2	(2%)	8	(7%)	0.3	(0.1, 1.8)	0.24
							P_{trend}=0.82						P_{trend}=0.90		

Missing data are excluded.

*Adjusted for 5-year age group, sex, state, and race/ethnicity

P-values are not Bonferroni-adjusted.

Table 4

Distribution of aspirin-related genotypes among Hodgkin lymphoma (HL) cases by tumor Epstein-Barr virus (EBV) status, and odds ratios (ORs) and 95% confidence intervals (CIs) for associations with risk of HL by EBV status, compared with all controls

			EBV-negative HL (*N*=290 cases)				EBV-positive HL (*N*=92 cases)				
Gene	**refSNP ID**	**Genotype**	***N***	**(%)**	**OR***	**(95% CI)**	***N***	**(%)**	**OR***	**(95% CI)**	$P_{heterogeneity}$
NFKB1(nuclear factor kappa-B, subunit 1)											
	rs1585215	AA	69	(26%)	1.0	referent	19	(22%)	1.0	referent	
		AG	153	(57%)	2.0	(1.4, 3.0)	53	(61%)	2.6	(1.4, 4.7)	
		GG	48	(18%)	3.2	(1.9, 5.6)	15	(17%)	3.3	(1.4, 7.4)	0.77
					$P_{trend}=3.0\times10^{-6}$				$P_{trend}=8.1\times10^{-4}$		
	rs1599961	GG	104	(37%)	1.0	referent	35	(39%)	1.0	referent	
		GA	136	(49%)	1.0	(0.7, 1.4)	42	(47%)	0.9	(0.5, 1.5)	
		AA	40	(14%)	0.8	(0.5, 1.2)	12	(13%)	0.6	(0.3, 1.3)	0.55
					$P_{trend}=0.31$				$P_{trend}=0.25$		
	rs1609993	CC	240	(84%)	1.0	referent	71	(79%)	1.0	referent	
		CT	43	(15%)	1.1	(0.7, 1.8)	18	(20%)	1.7	(0.9, 3.1)	0.19
		TT	2	(1%)			1	(1%)			
					P=0.55				P=0.09		
	rs3774936	AA	125	(45%)	1.0	referent	40	(45%)	1.0	referent	
		AT	118	(43%)	0.9	(0.6, 1.2)	39	(44%)	0.9	(0.6, 1.6)	
		TT	33	(12%)	1.2	(0.7, 2.0)	10	(11%)	1.0	(0.4, 2.3)	0.68
					$P_{trend}=0.97$				$P_{trend}=0.93$		
	rs3774937	TT	120	(44%)	1.0	referent	40	(45%)	1.0	referent	
		TC	121	(44%)	0.9	(0.7, 1.3)	39	(44%)	1.0	(0.6, 1.6)	
		CC	34	(12%)	1.2	(0.7, 2.1)	10	(11%)	1.0	(0.4, 2.3)	0.63
					$P_{trend}=0.72$				$P_{trend}=0.93$		
	rs3774938	AA	101	(36%)	1.0	referent	33	(38%)	1.0	referent	
		AG	136	(49%)	1.1	(0.7, 1.5)	42	(49%)	1.0	(0.6, 1.7)	
		GG	40	(14%)	1.0	(0.6, 1.6)	11	(13%)	0.8	(0.3, 1.7)	0.40
					$P_{trend}=0.93$				$P_{trend}=0.55$		
NFKBIA (nuclear factor kappa-B inhibitor alpha)											
	rs696	GG	94	(33%)	1.0	referent	32	(36%)	1.0	referent	
		GA	131	(46%)	1.3	(0.9, 1.9)	39	(44%)	1.2	(0.7, 2.1)	

Gene	refSNP ID	Genotype	EBV-negative HL (*N*=290 cases) *N*	(%)	OR*	(95% CI)	EBV-positive HL (*N*=92 cases) *N*	(%)	OR*	(95% CI)	$P_{heterogeneity}$
		AA	58	(20%)	1.7	(1.1, 2.7)	18	(20%)	1.6	(0.8, 3.2)	0.99
					P_{trend}=0.02				P_{trend}=0.16		
	rs8904	CC	97	(34%)	1.0	referent	33	(37%)	1.0	referent	
		CT	128	(45%)	1.2	(0.9, 1.7)	39	(43%)	1.2	(0.7, 2.0)	
		TT	59	(21%)	1.5	(1.0, 2.5)	18	(20%)	1.5	(0.8, 3.0)	0.96
					P_{trend}=0.06				P_{trend}=0.23		
	rs1050851	CC	186	(66%)	1.0	referent	58	(66%)	1.0	referent	
		CT	81	(29%)	0.6	(0.4, 0.9)	27	(31%)	0.7	(0.4, 1.2)	
		TT	15	(5%)	0.9	(0.4, 1.8)	3	(3%)	0.6	(0.2, 2.3)	0.63
					P_{trend}=0.03				P_{trend}=0.14		
	rs1957106	GG	141	(51%)	1.0	referent	42	(49%)	**1.0**	**referent**	
		GA	113	(41%)	1.0	(0.7, 1.4)	34	(40%)	**1.2**	**(0.7, 2.1)**	
		AA	24	(9%)	1.7	(0.8, 3.2)	10	(12%)	**2.7**	**(1.1, 6.7)**	0.34
					P_{trend}=0.31				**P_{trend}=0.06**		
IKKA/CHUK (inhibitor of nuclear factor kappa-B kinase alpha/conserved helix-loop-helix ubiquitous kinase)											
	rs2230804	AA	70	(25%)	1.0	referent	24	(27%)	1.0	referent	
		AG	139	(49%)	1.0	(0.7, 1.6)	42	(47%)	1.0	(0.6, 1.8)	
		GG	76	(27%)	1.0	(0.7, 1.6)	23	(26%)	0.9	(0.5, 1.8)	0.84
					P_{trend}=0.86				P_{trend}=0.79		
PTGS2/COX2 (prostaglandin-endoperoxide synthase 2/cyclooxygenase-2)											
	rs5272	AA	269	(97%)	1.0	referent	84	(95%)	1.0	referent	
		AG	9	(3%)	1.8	(0.6, 5.3)	4	(5%)	2.1	(0.5, 8.0)	0.66
		GG	0	(0%)			0	(0%)			
					P=0.29				*P*=0.29		
	rs5277	GG	212	(75%)	1.0	referent	62	(70%)	1.0	referent	
		GC	70	(25%)	1.1	(0.8, 1.7)	22	(25%)	1.2	(0.7, 2.2)	
		CC	2	(1%)	0.3	(0.1, 1.3)	4	(5%)	2.0	(0.6, 7.0)	0.12
					P_{trend}=0.74				P_{trend}=0.25		
	rs20417	GG	170	(61%)	**1.0**	**referent**	49	(56%)	1.0	referent	
		GC	93	(33%)	**1.2**	**(0.9, 1.7)**	35	(40%)	1.5	(0.9, 2.6)	

Gene	refSNP ID	Genotype	EBV-negative HL (*N*=290 cases) *N*	(%)	OR*	(95% CI)	EBV-positive HL (*N*=92 cases) *N*	(%)	OR*	(95% CI)	$P_{heterogeneity}$
		CC	16	(6%)	**2.5**	**(1.0, 5.8)**	3	(3%)	1.3	(0.3, 5.4)	0.53
						P_{trend}=0.05				P_{trend}=0.13	
	rs689466	AA	185	(67%)	1.0	referent	71	(79%)	1.0	referent	
		AG	81	(29%)	1.1	(0.7, 1.5)	14	(16%)	0.5	(0.3, 0.9)	
		GG	12	(4%)	1.2	(0.5, 2.7)	5	(6%)	1.2	(0.4, 3.7)	0.08
						P_{trend}=0.61				P_{trend}=0.20	
CYP2C9 (cytochrome p450, family 2, subfamily C, polypeptide 9)											
	rs1057910	AA	240	(84%)	1.0	referent	73	(83%)	1.0	referent	
		AC	46	(16%)	1.4	(0.9, 2.2)	15	(17%)	1.5	(0.8, 3.0)	0.71
		CC	0	(0%)			0	(0%)			
						P=0.15				*P*=0.19	
	rs1799853	CC	209	(73%)	1.0	referent	65	(71%)	1.0	referent	
		CT	79	(27%)	1.5	(1.0, 2.2)	26	(29%)	1.5	(0.9, 2.6)	0.74
		TT	0	(0%)			0	(0%)			
						P=0.03				*P*=0.15	
UGT1A6 (UDP glucuronosyltransferase 1 family, polypeptide A6)											
	rs1105879	TT	109	(38%)	1.0	referent	39	(43%)	1.0	referent	
		TG	142	(50%)	1.2	(0.8, 1.6)	42	(46%)	1.0	(0.6, 1.7)	
		GG	34	(12%)	1.1	(0.7, 1.9)	10	(11%)	0.9	(0.4, 2.0)	0.49
						P_{trend}=0.49				P_{trend}=0.88	
	rs2070959	AA	123	(44%)	1.0	referent	41	(45%)	1.0	referent	
		AG	129	(46%)	1.1	(0.8, 1.5)	42	(46%)	1.1	(0.7, 1.9)	
		GG	30	(11%)	1.1	(0.7, 2.0)	8	(9%)	0.9	(0.4, 2.1)	0.78
						P_{trend}=0.58				P_{trend}=0.94	
LTC4S (leukotriene C4 synthase)											
	rs730012	AA	139	(50%)	1.0	referent	49	(57%)	1.0	referent	
		AC	119	(43%)	1.4	(1.0, 1.9)	33	(38%)	1.0	(0.6, 1.7)	
		CC	20	(7%)	1.2	(0.6, 2.3)	4	(5%)	0.7	(0.2, 2.2)	0.39
						P_{trend}=0.14				P_{trend}=0.66	

Missing data are excluded.

* Adjusted for 5-year age group, sex, state, and race/ethnicity

P-values are not Bonferroni-adjusted.

Table 5

Estimated haplotype frequencies in Hodgkin lymphoma cases and controls, and odds ratios (ORs), 95% confidence intervals (CIs), and global *P*-values for associations with risk of Hodgkin lymphoma

		Cases (*N*=473)		Controls (*N*=373)				
Gene	**Haplotype**	***N* (alleles)**	**(%)**	***N* (alleles)**	**(%)**	**OR***	**(95% CI)**	**P_{global}**
NFKB1 (nuclear factor kappa-B, subunit 1)								
	A-G-C-A-T-A	396	(42%)	377	(51%)	1.0	referent	
	G-A-C-T-C-G	318	(34%)	240	(32%)	1.4	(1.1, 1.9)	
	A-G-T-A-T-A	65	(7%)	52	(7%)	1.3	(0.8, 2.0)	
	G-G-C-A-T-A	95	(10%)	6	(1%)	73.6	(18.7, 290.2)	
	A-A-C-A-T-G	41	(4%)	60	(8%)	0.8	(0.5, 1.3)	
	other	29	(3%)	10	(1%)	---	---	**6.0×10^{-21}**
NFKBIA (nuclear factor kappa-B inhibitor alpha)								
	G-C-C-G	328	(35%)	265	(36%)	1.0	referent	
	A-T-C-A	199	(21%)	128	(17%)	1.1	(0.8, 1.5)	
	G-C-T-G	137	(15%)	146	(20%)	0.7	(0.5, 1.0)	
	A-T-C-G	154	(16%)	107	(14%)	1.0	(0.7, 1.4)	
	G-C-C-A	58	(6%)	46	(6%)	0.8	(0.5, 1.4)	
	other	64	(7%)	48	(6%)	---	---	0.13
PTGS2/COX2 (prostaglandin-endoperoxide synthase 2/cyclooxygenase-2)								
	A-G-G-A	433	(46%)	382	(51%)	1.0	referent	
	A-G-C-A	194	(21%)	136	(18%)	1.2	(0.9, 1.6)	
	A-G-G-G	164	(17%)	126	(17%)	1.1	(0.8, 1.4)	
	A-C-G-A	134	(14%)	94	(13%)	1.1	(0.8, 1.5)	
	other	18	(2%)	8	(1%)	---	---	0.69
CYP2C9 (cytochrome p450, family 2, subfamily C, polypeptide 9)								
	A-C	752	(79%)	621	(84%)	1.0	referent	
	A-T	123	(13%)	75	(10%)	1.4	(1.0, 2.0)	
	C-A	68	(7%)	45	(6%)	1.2	(0.8, 2.0)	
	other	3	(0%)	2	(0%)	---	---	0.09
UGT1A6 (UDP glucuronosyltransferase 1 family, polypeptide A6)								
	T-A	607	(65%)	487	(65%)	1.0	referent	
	G-G	310	(33%)	239	(32%)	1.0	(0.8, 1.3)	

Gene	Haplotype	Cases (*N*=473) *N* (alleles)	(%)	Controls (*N*=373) *N* (alleles)	(%)	OR*	(95% CI)	P_{global}
	other	23	(2%)	20	(3%)	---	---	0.78

*Adjusted for 5-year age group, sex, state, and race/ethnicity

SNPs are ordered in the same sequence as in Table 2.

P-values are not Bonferroni-adjusted.