IL-6 levels and genotype are associated with risk of young adult Hodgkin lymphoma


Identical twins of young adult Hodgkin lymphoma case subjects are much more likely to develop the disease compared with fraternal twins of case subjects, suggesting a genetic determinant. Interleukin 6 (IL-6) levels are increased in patients with Hodgkin lymphoma and are correlated with a poor prognosis. We hypothesized that a heritable abnormality in IL-6 regulation may predispose to young adult Hodgkin lymphoma. We obtained blood specimens from 88 young adult Hodgkin lymphoma case subjects and their twins as well as from 87 matched control subjects. IL-6 was measured from unstimulated peripheral blood mononuclear cell (PBMC) supernatant with enzyme-linked immunosorbent assays (ELISAs) and compared by using analysis of covariance. Unaffected identical twins of case subjects (surrogate case subjects) had a 87.8% higher IL-6 level compared with matched control subjects (mean difference, +483.7 pg/mL, P = .04). Analysis of the IL-6 174G>C promoter polymorphism genotypes showed that risk decreased with an increasing number of C alleles (P = .01). The CC (low secreting) genotype was associated with a decreased risk of young adult Hodgkin lymphoma relative to the GG (high secreting) genotype (odds ratio [OR] = .29; P = .03). Risk was decreased for both nodular sclerosis and other subtypes. Persons with genetically determined lower IL-6 levels may be less susceptible to young adult Hodgkin lymphoma. (Blood. 2004;103:3216-3221)

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Introduction

Hodgkin lymphoma is characterized clinically by symptoms resembling those of a chronic infectious disease and pathologically by a rare neoplastic giant cell (Hodgkin or Reed-Sternberg cell) surrounded by a mixed inflammatory and benign lymphocytic infiltrate that varies by histologic type. In developed countries, the age-specific incidence curve is bimodal, with a peak among young adults aged 15 to 34 years (young adult Hodgkin lymphoma), consisting mostly of the nodular sclerosis type, and a second peak among older adults (older than 50 years), consisting mainly of the mixed cellularity type. Risk factors (small sibship size, high socioeconomic status, and growing up in a single-family dwelling) strongly suggest that it results from delayed exposure to a common childhood virus. Epstein-Barr virus has been suggested as an etiologic agent on the basis of a higher frequency of past infectious mononucleosis in patients, higher Epstein-Barr virus (EBV) titers in prospective serologic studies, and demonstration of the Epstein-Barr viral genome in some Hodgkin lymphoma tumors. (Submitted more commonly in mixed cellularity tumors occurring in young children and the elderly than in nodular sclerosis tumors in young adults)

Genetic factors also contribute to susceptibility. A 3- to 7-fold higher risk of childhood and young adult Hodgkin lymphoma is reported in siblings of case subjects. We also reported that identical (monozygotic) twins of case subjects have a 100-fold higher risk of developing this lymphoma than that expected on the basis of population incidence, whereas no increased risk was observed among fraternal (dizygotic) twins of case subjects. We hypothesized that an inherited immune phenotype was responsible for the development of young adult Hodgkin lymphoma, based on several pieces of evidence: depression of cell-mediated immunity in patients, secretion of numerous cytokines by Hodgkin-Reed-Sternberg cells, the association with certain HLA types, and the presence of lipoid nephrosis in one monozygotic young adult Hodgkin lymphoma–concordant twin pair. Lipoid nephrosis is an autoimmune renal disease occasionally observed in patients with Hodgkin lymphoma and thought to be caused by a T-cell defect. Reports suggest that the cytokine interleukin-6 (IL-6) may play an especially important role in pathogenesis because patients with untreated Hodgkin lymphoma have higher serum IL-6 levels than control subjects, and IL-6 levels are correlated with prognosis. However, it is unclear whether this is a predisease abnormality related to a specific susceptibility or part of the general pathogenetic process.
Because Hodgkin lymphoma itself may affect immune function, patients do not offer a good opportunity to evaluate immune-related susceptibility factors, even when long in remission. However, to the extent that IL-6 levels are genetically controlled, the healthy monozygotic twin of a case subject can serve as a genetic surrogate with immune characteristics unaffected by the disease or its treatment. We examined levels of IL-6 from peripheral blood mononuclear cell (PBMC) supernatant in unaffected monozygotic twins of young adult Hodgkin lymphoma case subjects compared with those of matched control subjects (nonblood relatives within 5 years of age of the case subjects and their twins). A functional single nucleotide polymorphism (SNP) was identified in the promoter of the IL-6 gene at position −174 (−174G>C) that apparently regulates IL-6 protein levels such that the CC genotype is associated with lower IL-6 levels.24 We also compared genotypes of the −174G>C IL-6 promoter polymorphism in case subjects and their twins, to those of the same unrelated control subjects, to directly assess the genetic effect on the risk of young adult Hodgkin lymphoma.

**Patients, materials, and methods**

The study was approved by the Institutional Review Board of the Keck School of Medicine of the University of Southern California.

**Twins**

A total of 182 twin pairs in whom at least one member was diagnosed with young adult Hodgkin lymphoma (defined as Hodgkin lymphoma diagnosed before age 50) were identified from the rosters of the International Twin Study13,25 and California Twin Program.26 Of these, we were unable to locate either twin in 22 pairs, at least one twin was deceased in 37 pairs, the unaffected twin had an autoimmune disease or was taking steroids making 7 pairs ineligible; and the unaffected twin in 28 pairs refused participation. Specimens were obtained from both members of 61 monozygotic young adult Hodgkin lymphoma case subjects and their twins (55 unaffected and 6 affected) and from 27 dizygotic young adult Hodgkin lymphoma case subjects and their unaffected twins (88 total twin pairs), giving a participation rate of 76% (88 of 116). In the 6 pairs concordant for young adult Hodgkin lymphoma, the case subject was defined as the twin with the earlier diagnosis. Pathology reports and histopathologic slides were obtained for 95% (84 of 88) of the case subjects and for the 6 affected twins, and the Hodgkin lymphoma diagnosis was verified in all of them by a single hematopathologist (B.N.N.). The histologic distribution was nodular sclerosis (60 case subjects and 4 of the affected co-twins), mixed cellularity (14 case subjects and 1 affected co-twin), lymphocyte predominant (5 case subjects and 1 affected co-twin), and unclassifiable (5 case subjects). Slides and reports were unavailable for 4 case subjects. At the time of diagnosis, case subjects ranged in age from 15 to 45 years and at the time of participation from 22 to 59 years. The case subjects were diagnosed, on average, 16.7 years prior to participation so tumor tissue was not available for 4 case subjects. At the time of diagnosis, reports were unavailable for 4 case subjects, 1 unaffected co-twin, and 9 control subjects because either the quality of the DNA was too poor or the amount was insufficient.

**Control subjects**

Spouses within 5 years of the twins’ ages were used as control subjects. If there was no spouse (n = 12) or if both spouses refused (n = 3), twins were asked to choose a nonblood relative (ie, in-laws) or friend younger than 60 years. If the twins could not identify any eligible control subject (n = 13), a race/ethnicity-matched control subject was chosen from employees within our institution within 5 years of age of the twins. Blood samples were obtained from 87 control subjects, 68% spouses (n = 59), 17% nonblood relatives or friends (n = 15), and 15% hospital or university employees (n = 13).

**Other information**

Information on race, age, sex, date of diagnosis, zygosity, and history of infectious mononucleosis was collected from case subjects, their twins, and control subjects. Detailed analyses of the effect of infectious mononucleosis on risk of young adult Hodgkin lymphoma will be presented elsewhere.

**Laboratory analysis**

Each member of the twins–control subject triad had a blood specimen drawn on the same day and had it sent to us by overnight courier service. (When an institutional control was used, blood was drawn and held for 24 hours until the twins’ blood arrived so all the samples could be processed at the same time.) PBMCs were separated from the buffy coat by using Ficoll gradient. Cells (2 million/mL) were cultured in fetal calf serum media for 24 hours without added exogenous mitogens or other stimulant. The resulting supernatant from each culture was collected and split into 1-mL samples and frozen at −70°C. Viability of cells was tested by trypan blue exclusion; if more than 5% of cells were infusible, the culture was discarded. Levels of IL-6 were determined from PBMC supernatants by using an enzyme-linked immunosorbent assay (ELISA; Biosource, Camarillo, CA). Preliminary pilot studies showed no significant difference in ELISA results between supernatants from cells held for 24 hours before separation and culture and from cells processed immediately.

With the exception of 2 control subjects, supernatants from all sets of case, twin, and control triads were tested at the same time, run on the same plate, and read together to minimize variability (the samples from these 2 control subjects and their matched twins were not included in the analysis). A positive and negative control plus 4 standards were run on each plate according to manufacturer’s instructions. If the standard curve deviated more than 10% from the average of all the standard curves (at any given concentration), the values from that plate were excluded.

DNA was isolated from PBMCs by using a 96-well robotic platform with silica membrane chemistry (BioRobot 3000; Qiagen, Valencia, CA) using a QIAamp 96 Blood BioRobot Kit (Qiagen). Genotyping of the single nucleotide polymorphism (−174G>C) in the IL-6 gene was performed by the Taqman assay,27 using primer sequences 5'-CAATGAGCACCTAAACGT-GCATTTGGCATCTTGAGT-3' (forward) and 5'-GGGCTGATGAAACCTTTATTAA-GATGATG-3' (reverse) and probe sequences 5'-TTTGAGATCGCAAGACG-3' (for allele G) and 5'-TTTGATCGGAAGACG-3' (for allele C).

The fluorescence signal was detected by using an ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City, CA). The alleles were then analyzed and determined by using the graphical view from ABI Sequence Detection software. Nine DNA samples with known genotypes confirmed by direct sequencing were used as positive controls with at least one water blank included on every plate as a negative control. Any samples with ambiguous allelic readings were repeated or sequenced. For the purpose of quality control of the genotyping, 20% of duplicate DNA samples were also included. Genotyping results were not available for 2 case subjects, 1 unaffected co-twin, and 9 control subjects because even the quality of the DNA was too poor or the amount was insufficient.

**Statistical analysis**

All analyses were performed with the Statistical Analysis System (SAS) version 8.1 software package (SAS Institute, Cary, NC). One pair who described themselves as monozygotic had different genotypes and was reclassified as dizygotic. IL-6 supernatant values from 39 pairs of unaffected monozygotic twins of case subjects (surrogate case subjects) and their matched controls were available. Data on IL-6 supernatant level were skewed so a natural log transformation was used to fulfill the model assumptions for the analysis of covariance (ANCOVA; GLM procedure in SAS). The geometric mean difference in IL-6 surrogate level between the unaffected monozygotic twins (surrogate case subjects) and their matched controls (from log-transformed values) was estimated in an ANCOVA model that included sex and age, modeled as a continuous variable.

The IL-6 −174G>C promoter polymorphism genotypes were classified as GG, GC, or CC, with GG as the reference group. Genotype frequencies in control subjects were examined for departure from Hardy-Weinberg equilibrium. Odds ratios (ORs) and 95% confidence intervals (CIs) were
used to estimate the effect of IL-6 genotype on young adult Hodgkin lymphoma risk between matched pairs (case and matched control subjects, or unaffected twins and matched control subjects), using multivariate conditional logistic regression (implemented through the PHREG procedure in SAS) according to standard methods.28,29 Because DNA could not be amplified for a few individuals, we included an indicator variable for missing values to maximize power.29,30 Numbers of C alleles (eg, 0, 1, and 2) were used as continuous variables to test for linear trend to assess the dose-response effect of the genotypes.

Additional analyses were performed stratifying on histologic type (nodular sclerosis and the remaining histologic types combined, other), because nodular sclerosis has a distinctive epidemiologic pattern and clinical presentation.31 Separate comparisons between the 6 affected twins of case subjects (ie, the second case in disease-concordant twin pairs) and control subjects were not analyzed statistically, but descriptive results are presented when possible. The relationship between genotype and phenotype (IL-6 level) among control subjects and unaffected twins was assessed by using similar ANCOVA analyses described earlier, adjusting for ELISA (IL-6 level) among control subjects and unaffected twins was assessed by using similar ANCOVA analyses described earlier, adjusting for ELISA plate, sex, and age; the latter modeled as a categorical variable. All hypothesis testing assumed a .05 significance level and 2-sided alternative hypothesis.

**Results**

Demographic characteristics of young adult Hodgkin lymphoma case subjects, unaffected twins, affected twins, and control subjects are shown in Table 1. Young adult Hodgkin lymphoma case subjects, their twins, and control subjects were predominantly white, reflecting both the demographic composition of the twins in the registry (95% white) and the more than 3-fold higher risk of young adult Hodgkin lymphoma among whites compared with other racial/ethnic groups. Case subjects and unaffected twins were slightly more likely to be female; thus, control subjects (consisting mainly of spouses) were slightly more likely to be male. The age distribution was similar for the case subjects and control subjects.

Monozygotic unaffected twins (surrogate case subjects) had IL-6 levels that were 87.5% higher than those of matched control subjects (mean difference = 483.7 pg/mL; P = .04) (Table 2). There was no appreciable change in the IL-6 difference when values were adjusted for sex; adjustment for age changed the result only very slightly, indicating that these 2 variables had little effect on IL-6 level.

Because IL-6 phenotype differed between the unaffected twins (genetic surrogates) and the control subjects, we assessed the −174G>C IL-6 genotype, a functional polymorphism in the IL-6 promoter,24 on all subjects with available DNA (251 subjects total). Genotype frequencies among control subjects were in Hardy-Weinberg equilibrium, with the GC genotype being the most common (50%), followed by GG (32%) and CC (18%). Genotypes did not differ by age (P = .80) or sex (P = .91) in control subjects.

There was a strong association between genotype and young adult Hodgkin lymphoma risk (Table 3). The CC genotype of the IL-6 promoter polymorphism was associated with a statistically significant 71% decreased risk relative to the GG genotype, (OR for CC versus GG genotype = 0.29, 95% CI = 0.10-0.87). Carriers of the GC allele had a risk that was intermediate between CC and GG (OR for GC versus GG genotype = 0.50, 95% CI = 0.22-1.13), consistent with a log additive model of inheritance. The linear trend for decreasing young adult Hodgkin lymphoma risk with increasing numbers of C alleles was statistically significant (P = .01). Similar trends were seen when monozygotic and dizygotic case subjects and control subjects were analyzed separately.

The effect of the C allele on risk was greater among case subjects longer in remission (> 16.7 years since diagnosis), compared with

<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics of the subjects studied</th>
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<tr>
<td><strong>Control subjects, n = 87 (%)</strong></td>
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<td><strong>Case subjects, n = 88 (%)</strong></td>
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<tr>
<td><strong>Unaffected twins, n = 82 (%)</strong></td>
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<tr>
<td><strong>Affected twins, n = 6 (%)</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td><strong>Age at participation, y</strong></td>
</tr>
<tr>
<td>At least 30 or younger</td>
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<tr>
<td>31-40</td>
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<tr>
<td>41-50</td>
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<tr>
<td>51-60</td>
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<tr>
<td><strong>Race</strong></td>
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<tr>
<td>White</td>
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<tr>
<td>African-American</td>
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<td>Asian</td>
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<tr>
<td><strong>Zygosity</strong></td>
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<tr>
<td>Monozygotic</td>
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<td>Dizygotic</td>
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</table>

*Case subjects diagnosed with young adult Hodgkin lymphoma (aged 15-49 years at diagnosis). —indicates not applicable.

<table>
<thead>
<tr>
<th>Table 2. Mean and percentage of difference in IL-6 supernatant levels (pg/mL) between monozygotic (MZ) unaffected twins of case subjects (surrogate case subjects) and matched control subjects (n = 39 pairs)</th>
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<tbody>
<tr>
<td><strong>MZ unaffected twins vs control subjects</strong></td>
</tr>
<tr>
<td>Unadjusted</td>
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<tr>
<td>Adjusted for sex</td>
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<tr>
<td>Adjusted for sex and age‡</td>
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*Geometric mean difference from log-transformed IL-6 levels. 
‡Value obtained by using ANCOVA (SAS GLM procedure). 
‡Age is modeled as a continuous variable.
casestudents more recently diagnosed (< 16.7 years since diagnosis), but differences were based on small numbers and did not reach statistical significance.

The risk of being a surrogate case subject (unaffected monozygotic twin of a case subject) was lower among carriers of the C genotype (OR for CC versus GG = 0.29, P = .06), as the linear trend was not statistically significant (P = .58). However, the genotype distribution of C alleles was lower among control subjects, but differences were based on small numbers and did not reach statistical significance. For age, there was a statistically significant inverse correlation with young adult Hodgkin lymphoma risk (that is, risk of being a case subject or the twin of a case subject).

Discussion

Our results suggest that genetically determined lower IL-6 levels confer protection against young adult Hodgkin lymphoma. We found that unaffected monozygotic twins of case subjects had statistically significantly higher IL-6 supernatant levels compared with control subjects, consistent with the hypothesis that an inherited tendency to produce more IL-6 may confer susceptibility, whereas lower levels may be associated with protection. The C allele of the −174G>C promoter polymorphism, associated with lower IL-6 levels, was strongly and statistically significantly inversely correlated with young adult Hodgkin lymphoma risk (that is, risk of being a case subject or the twin of a case subject).

IL-6 is involved in a variety of health consequences, and empirical evidence indicates that it is related specifically to the pathogenesis of Hodgkin lymphoma. The majority of Hodgkin and Reed-Sternberg cells express IL-6 transcripts, and Hodgkin lymphoma cell lines produce IL-6 in supernatant culture. Patients with untreated Hodgkin lymphoma have high levels of IL-6, and these levels are correlated with presence of “B” symptoms (fever, night sweats), stage, and prognosis. This evidence suggests a strong link between IL-6 and pathogenesis but not necessarily etiology. Our results suggest that the association may be causal, based on both the IL-6 genotype association and the phenotype difference in unaffected identical twins of case subjects (surrogate case subjects) compared with control subjects.

Although IL-6 levels are higher in the elderly and are modified by sex hormones, we did not observe statistically significant associations between IL-6 levels or IL-6 genotype and either age or sex within this group of subjects. High IL-6 levels are associated with several other conditions, such as obesity and cardiovascular disease, but none of the case subjects or unaffected twins in this study had these conditions, and they are not linked to young adult Hodgkin lymphoma generally, so they do not provide a likely explanation for the findings.

Misclassification of zygosity could have affected the phenotype results, biasing findings toward the null hypothesis. However, self-reported zygosity has been validated both by others and in this cohort of twins. IL-6 genotypes of all twins in this set were reclassified; only one pair reporting monozygosity had unlike genotypes, and that pair was reclassified as dizygotic.

Table 4. Mean IL-6 PBMC supernatant levels (pg/mL) in unaffected monozygotic and dizygotic twins and control subjects by −174G>C genotype (n = 115)

<table>
<thead>
<tr>
<th>Mean* IL-6 PBMC supernatant level (pg/mL) by genotype</th>
<th>GG</th>
<th>GC</th>
<th>CC</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for ELISA plate</td>
<td>967.9</td>
<td>467.0</td>
<td>356.5</td>
<td>.06</td>
</tr>
<tr>
<td>Adjusted for sex and ELISA plate</td>
<td>997.6</td>
<td>789.8</td>
<td>402.5</td>
<td>.06</td>
</tr>
<tr>
<td>Adjusted for age and ELISA plate</td>
<td>1023.5</td>
<td>885.8</td>
<td>447.8</td>
<td>.10</td>
</tr>
<tr>
<td>Adjusted for age, sex, and ELISA plate</td>
<td>1011.9</td>
<td>906.3</td>
<td>455.9</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Geometric mean from log-transformed IL-6 levels.
†P was obtained by using ANOVA (SAS GLM procedure) for overall difference in IL-6 PBMC supernatant levels by genotype.
‡Age is modeled as an 8-level categorical variable (< 25, 25-29, 30-34, 40-44, 45-49, 50-54, and 55+ years).
If the IL-6 –174G>C genotype polymorphism affects disease risk through regulation of IL-6 level, we expect a strong genotype-phenotype correlation. There have been a total of 7 studies\textsuperscript{24,42-47} examining the association between IL-6 –174G>C genotype and IL-6 production, but only 2\textsuperscript{24,47} were specifically designed to address the genotype-phenotype relationship by using appropriate subjects and adjusting for confounders such as body weight, sex, and age. In these 2 studies\textsuperscript{24,47} investigators found that individuals homozygous for the CC genotype had significantly lower IL-6 levels compared with persons with GG and GC genotypes. Although our study was not designed to test this association, we found similar results, although the trends were only marginally significant because of low power. Further studies will be necessary to clarify the relationship between the IL-6 –174G>C polymorphism and IL-6 production.

The CC polymorphism has been linked with a decreased risk of juvenile rheumatoid arthritis,\textsuperscript{24} type 1 juvenile diabetes mellitus,\textsuperscript{48} and Kaposi sarcoma (among men infected with HIV).\textsuperscript{49} Proposed mechanisms of these associations include decreased inflammation associated with lower IL-6 levels,\textsuperscript{24} increased insulin sensitivity,\textsuperscript{48} and more activated (less suppressed) cell-mediated immunity.\textsuperscript{49}

However, the mechanism by which the CC polymorphism and/or lower IL-6 levels would protect against young adult Hodgkin lymphoma is unclear. IL-6 is a potent B-cell stimulatory cytokine\textsuperscript{50} and, therefore, has the potential to contribute to the genesis and/or growth of Hodgkin-Reed-Sternberg cells (the neoplastic cells of Hodgkin lymphoma) in several ways. It has been determined that Hodgkin-Reed-Sternberg cells originate from germinal center cells in lymph nodes.\textsuperscript{51} Germinal center cells that fail to produce antibody binding them to the local dendritic cells are destined for apoptosis.\textsuperscript{52} It has been proposed that Hodgkin-Reed-Sternberg cells develop from a subset of these cells that escape apoptosis, either by down-regulation of natural killer and cytotoxic T lymphocytes,\textsuperscript{53} or by up-regulation of bcl-2 or other antiapoptotic proteins.\textsuperscript{54} IL-6 is associated with antiapoptotic activity and can up-regulate bcl-2.\textsuperscript{55} and bcl-2 expression has been reported to occur more often in nodular sclerosis tumors (more common in young adults) than in those of other histologic subtypes.\textsuperscript{54}

Hodgkin-Reed-Sternberg cells themselves secrete IL-6 and express IL-6 receptor\textsuperscript{56} and thus function simultaneously as a source of IL-6 and as target cells. Hodgkin-Reed-Sternberg cells are known to secrete other cytokines besides IL-6,\textsuperscript{32,33} including tumor necrosis factor α (TNF-α) and IL-1β, cytokines that up-regulate IL-6 secretion.\textsuperscript{37} Thus, IL-6 may function in an autocrine loop to enhance Hodgkin-Reed-Sternberg cell growth and to promote cell survival. EBV can also up-regulate IL-6 secretion\textsuperscript{56}; however, because most tumors in young adults are negative for EBV DNA,\textsuperscript{57} this is probably not an important mechanism for this subset of Hodgkin lymphoma.

Nodular sclerosis is the most common histology found in young adult Hodgkin lymphoma and is considered by some to be a separate disease on the basis of distinct epidemiology,\textsuperscript{3} lower prevalence of EBV,\textsuperscript{57} and association with polymorphisms of the antigen processing genes (TAP 1 and 2)\textsuperscript{16,58} and specific HLA types.\textsuperscript{16,58} In our study, we found that both nodular sclerosis and the other subtypes showed the same general pattern of decreasing risk with increasing number of C alleles, although the trend was slightly stronger for the nodular sclerosis subset.

Although protein secretion appears to be primarily regulated by the promoter in the multiple response element (in which the –174 polymorphism is located),\textsuperscript{37} other polymorphisms have been described downstream from the promoter and may play a role in IL-6 regulation.\textsuperscript{42} Other cytokines described earlier such as IL-1β, TNF-α, or IL-10 can bind to the IL-6 promoter and increase or decrease expression, and there are functional polymorphisms associated with these that could influence overall IL-6 expression and secretion.\textsuperscript{37} We plan to evaluate the relationship of the other IL-6 polymorphisms, and those of other pertinent cytokines, to young adult Hodgkin lymphoma risk in future studies.

In summary, we provide evidence that a genotype associated with altered IL-6 function may contribute to the etiology of young adult Hodgkin lymphoma.

Acknowledgments

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