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Genetic Polymorphisms in DNA Repair Genes as Modulators of Hodgkin Disease Risk

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Abstract

BACKGROUND—Although the pathogenesis of Hodgkin disease (HD) remains unknown, the results of epidemiologic studies suggest that heritable factors are important in terms of susceptibility. Polymorphisms in DNA repair genes may contribute to individual susceptibility for development of different cancers. However, to the authors' knowledge, few studies to date have investigated the role of such polymorphisms as risk factors for development of HD.

METHODS—The authors evaluated the relation between polymorphisms in 3 nucleotide excision repair pathway genes (XPD [Lys751Gln], XPC [Lys939Gln], and XPG [Asp1104His]), the base excision repair XRCC1 (Arg399Gln), and double-strand break repair XRCC3 (Thr241Met) in a population of 200 HD cases and 220 matched controls. Variants were investigated independently and in combination; odd ratios (OR) were calculated.

RESULTS—A positive association was found for XRCC1 gene polymorphism Arg399Gln (OR, 1.77; 95% confidence interval [95% CI], 1.16–2.71) and risk of HD. The combined analysis demonstrated that XRCC1/XRCC3 and XRCC1/XPC polymorphisms were associated with a significant increase in HD risk. XRCC1 Arg/Arg and XRCC3 Thr/Met genotypes combined were associated with an OR of 2.38 (95% CI, 1.24–4.55). The XRCC1 Arg/Gln and XRCC3 Thr/Thr, Thr/Met, and Met/Met genotypes had ORs of 1.88 (95% CI, 1.02–4.10), 1.97 (95% CI, 1.05–3.73), and 4.13 (95% CI, 1.50–11.33), respectively. XRCC1 Gln/Gln and XRCC3 Thr/Thr variant led to a significant increase in risk, with ORs of 3.00 (95% CI, 1.15–7.80). Similarly, XRCC1 Arg/Gln together with XPC Lys/Lys was found to significantly increase the risk of HD (OR, 2.14; 95% CI, 1.09–4.23).

CONCLUSIONS—These data suggest that genetic polymorphisms in DNA repair genes may modify the risk of HD, especially when interactions between the pathways are considered.

Keywords

DNA repair; Hodgkin disease; susceptibility; genetic polymorphisms

The American Cancer Society estimated that 8220 new cases of Hodgkin disease (HD) would be diagnosed in the US in 2008, and that 1350 people would die of the disease.¹ Although the etiology of HD remains mostly unknown, it is likely that as with most cancers, both environmental and genetic factors are involved. DNA damage and subsequent repair are critical for maintaining genomic integrity and stability. In the general population, interindividual

variability in DNA repair capacity has been reported, and an association between reduced DNA repair and susceptibility to a variety of cancers, including breast, colon, and lung cancers²⁻⁶ and HD,⁷ has been documented.

Considerable progress has been made in identifying gene products that play a role in DNA repair pathways in mammalian cells,⁸ and it has been shown that defects in proteins involved in these pathways can have severe biologic effects.⁹ DNA repair proteins function as members of multiprotein complexes, making it likely that amino acid residues at protein-protein interfaces involved in the active sites will be important for protein function. DNA repair is genetically regulated,¹⁰ and 1 mechanism that may lead to the observed interindividual variations in repair capacity is the presence of single-nucleotide polymorphisms (SNPs) in DNA repair genes. Hundreds of SNPs in repair genes have been identified, and several epidemiologic studies have suggested wide population variability in DNA repair capacity phenotype as having a possible association with cancer risk.¹¹⁻¹³ Recent studies indicate that SNPs in DNA repair genes may modulate the DNA repair phenotype, particularly when these SNPs are located within coding or regulating regions, leading to alterations in protein expression and in functional properties of repair enzymes.¹⁴⁻¹⁶ Variants in the DNA repair genes were associated with risk of developing various solid tumors such as head and neck, bladder, and lung cancers.¹⁷⁻¹⁹ Several studies investigated the association between such SNPs and the development of hematologic malignancies, with conflicting results. Smedby et al. reported an association between XRCC3 variants, but not XRCC1 or ERCC2, and susceptibility to follicular lymphoma.²⁰ Similarly, Shen et al. observed that genetic polymorphisms in DNA repair genes, particularly ERCC5 and WRN, may play a role in the development of non-Hodgkin lymphoma and diffuse large B-cell lymphoma.²¹ Hayden et al., also reported an association between variants in XRCC5 and development of myeloma.²² Conversely, Deligezer et al. reported a lack of association between XRCC1 (Gln allele) and chronic myelogenous leukemia.²³ Similarly, Song et al. reported a lack of association between SNPs in XPD gene and risk of development of non-Hodgkin lymphoma.²⁴ To our knowledge, to date, only 1 study has investigated the role of DNA repair genetic polymorphisms in HD childhood cancer survivors²⁵; however, no data are available on the role of these polymorphisms in modulating HD risk in adults.

In the current study, we evaluated the role of SNPs in 5 DNA repair genes (XPC, XPD, XPG, XRCC1, and XRCC3) in HD development in adults. XPC, XPD, and XPG genes are in the nucleotide-excision repair (NER) pathway, which is mainly involved in repairing bulky DNA adducts and helix-distorting lesions. XRCC1 gene is in the base-excision repair (BER) pathway and is mainly involved in repair of oxidizing and alkylating DNA lesions. The XRCC3 gene is involved in double-strand break (DSB)/recombination repair pathway and restores DNA through recombination between the damaged strand and the homologous copy of the gene. The selected SNPs occur in different repair pathways; are coding polymorphisms that result in amino acid substitutions that are likely to affect the resulting protein structure and function; occur at a relatively high frequency, thus affecting a relatively large segment of the general population; and have been reported to be associated with different cancers.^{17-19,26}

MATERIALS AND METHODS

Study Subjects

The study population consisted of a cohort of 200 newly diagnosed, previously untreated adult patients with HD seen at The University of Texas M. D. Anderson Cancer Center between 1987 and 1992. Demographic information and the principal clinical characteristics (eg, age at diagnosis, sex, race/ethnicity, family history of cancer in first-degree and second-degree relatives, HD histologic subtypes, disease stage, and presence of B symptoms) were obtained from the interviewer-administered health risk questionnaires and medical records. Controls (n

= 220) were accrued through random-digit dialing and were frequency matched to cases with regard to age ($\pm$ years) sex, and race/ethnicity. Control participation rate using this method was 77%. Once eligible controls were identified, they were interviewed by telephone, and asked to either come to The University of Texas M. D. Anderson Cancer Center or to set up an off-site visit for venipuncture. The institutional review board of The University of Texas M. D. Anderson Cancer Center approved the study.

Genotyping Assay

SNPs in 5 DNA repair genes (XPC [rs#2228001], XPD [rs#28365048], XPG [rs#17655], XRCC1 [rs#25487], and XRCC3 [rs#861539]) were genotyped using Taq-Man-based methods. For each sample, 5 ng DNA was used per reaction with 2.5 μ L of 2X Universal Master Mix and 200 nM primers (Applied Biosystems, Foster City, Calif). All probes and primers were purchased from Applied Biosystems as “predesigned ready to order state” products. All reactions were performed in a 384-well plate sealed using an ABgene ALPS 300 heat sealer and clear heat-sealing film (ABgene, Rochester, NY). All genotypes were determined by endpoint reading on an ABI 7900HT Sequence Detection System (Applied Biosystems, Nærum, Denmark). Reactions were run for 49 cycles of 2 minutes at 50°C, 10 minutes at 95°C, 30 seconds at 92°C, and 1 minute at 60°C. Samples were coded for case-control status, and 5% of the samples were randomly selected and subjected to repeat analysis as quality control for verification of genotyping procedures. Two researchers independently reviewed all genotyping results.

Statistical Analysis

All statistical analyses were performed using the Stata statistical software package (version 8; StataCorp, College Station, Tex) and the open-source Java software Multifactor Dimensionality Reduction (MDR) (version 1.0.0rc1). Hardy-Weinberg equilibrium was tested using the observed genotype frequencies and chi-square test with 1 degree of freedom. The Pearson chi-square test was used to test for differences in distribution between the cases and controls with regard to sex, age, race, and smoking status. Logistic regression analysis was used to estimate the associations between each genotype and risk of HD by computing the odds ratios (ORs) and 95% confidence intervals (95% CIs) from both univariate and multivariate logistic regression analyses (adjusting for sex, age, race, and smoking status). To establish the genotype combinations more frequently associated with disease status, we used MDR analysis, a nonparametric approach that aims to identify combinations of multilocus genotypes and other factors associated with high or low risk of disease.^{27,28} We completed 10 MDR runs and calculated the mean cross-validation (CV) and mean testing accuracy (TA). The parsimonious interaction model that had the maximum mean TA and maximum mean CV consistency was identified and included in multivariable logistic regression analysis to estimate the association between HD risk and MDR-identified combinations. In addition, we calculated a cumulative genetic risk score (CGRS) by summing the value generated from the participants' genotype for each SNP; the higher the score, the greater the risk for disease. Multivariable logistic regression analysis was also used to estimate the association between the CGRS and disease risk.

RESULTS

Characteristics of the Study Population

The distribution of demographic and clinical characteristics in cases and controls is presented in Table 1. By study design, there were no significant differences with regard to age, sex, or race between cases and controls. The mean ages $\pm$ standard deviation were 47.5 ± 13.4 years for the cases and 49.3 ± 15.2 years for the controls, and 34% of the cases and 33% of the controls were between the ages of 20 and 40 years. Approximately 54% of the cases were men,

compared with 56% of the controls. Approximately 51% of the cases were ever smokers, compared with 55% of the controls. Approximately 82% of the patients were white, compared with 89% of the controls. Among the cases, 80% had the nodular sclerosis subtype and 64% had stage I or II HD (grading determined according to the Ann Arbor staging system).

Frequency Distribution of Genotypes and Associations With HD Risk

All genotypes studied were in Hardy-Weinberg equilibrium. Table 2 summarizes the frequency of each SNP in the 5 DNA repair genes investigated in cases and controls and the associations of each SNP with HD risk. A significantly positive association was found between the XRCC1 Arg399Gln polymorphism and HD risk. The association was strongest for the heterozygote Arg/Gln genotype, which was significantly more frequent in the cases than the controls ($P = .04$). As a result, patients heterozygous for the XRCC1 Arg/Gln genotype had a 77% increase in risk (OR, 1.77; 95% CI, 1.16–2.71) after adjustment for age, sex, race, and smoking status. Patients homozygous for the Gln/Gln genotype demonstrated a 13% increase in risk; however, the number of homozygotes in each group was too small ($n = 10$ and 13 , respectively) to be reliably evaluated. The presence of any XRCC1 Gln (Arg/Gln or Gln/Gln) was associated with a 62% increase in risk (OR, 1.62; 95% CI, 1.08–2.43). Nonstatistically significant increased ORs were also observed for individuals who were heterozygous or homozygous for the XPG 1104 His allele (ORs, 1.17 and 1.55, respectively) and heterozygous for the XRCC3 214Met allele (OR, 1.29). Among the cases, no significant differences in genotype frequency were observed based on age at diagnosis, HD subtypes, the presence or absence of B symptoms, or family history of cancer (data not shown).

To determine whether individual polymorphisms in DNA repair genes might interact and modify the risk of developing HD, we used randomized MDR analysis that aims to identify combinations of multilocus genotypes. Our results demonstrated that the 2-locus interaction model involving XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms had the maximum CV of 10 and TA of 0.59 ($P < .001$). After adjustment for age, sex, race, and smoking status, XRCC1 and XRCC3 polymorphisms together were associated with a significant increase in HD risk. Specifically, the combination of the XRCC1 Arg399Arg and XRCC3 Thr241Met polymorphisms was associated with a 2-fold increase risk (OR, 2.38; 95% CI, 1.24–4.55). The XRCC1 Arg399Gln genotype and XRCC3 Thr241Thr, Thr241Met, and Met 241Met variants had ORs of 1.88 (95% CI, 1.02–3.54), 1.97 (95% CI, 1.05–3.73), and 4.13 (95% CI, 1.50–11.33), respectively (Table 3). The combinations of XRCC1 Gln399Gln with the XRCC3 Thr241Thr variant led to a significant increase in risk, with ORs of 3.00 (95% CI, 1.15–7.80). Similarly, XRCC1 Arg399Gln combined with the XPC Lys939Lys significantly increased HD risk (OR, 2.14; 95% CI, 1.09–4.23 [$P < .05$]).

Cumulative Genetic Risk Score and HD Risk

To calculate a cumulative genetic risk score, the participants' genotype for each SNP was assigned a value of 1 for a risk allele homozygote, 0 for a heterozygote, and -1 for a nonrisk allele homozygote. Then the CGRS was calculated by summing the values for each of the 5 SNPs in the cumulative genetic risk score panel. The effect of having >1 variant on modulating HD risk is shown in Table 4. By using no variant or 1 variant as the referent, we observed a 53%, 29%, and 98% increased HD risk associated with having 2, 3, or 4 combined variants, respectively (P for trend = .02). A combination of ≥ 4 variant genotypes in individuals was associated with an increased risk of HD compared with those with 0 to 2 variants (OR, 1.86; 95% CI, 1.15–3.02 [$P = .02$]).

DISCUSSION

DNA damage induced by endogenous and exogenous carcinogens can lead to mutations, genomic instability, and malignant transformation.²⁹ Normal function of DNA repair enzymes is essential for the damage to be effectively removed from the DNA.³⁰ During the last decade, studies have identified several variant alleles that may modulate DNA repair capacity. Elevated levels of DNA adducts, increased sensitivity to ionizing radiation, and chromosomal instability in lymphocytes of healthy subjects³¹⁻³³ have all been associated with variant alleles in DNA repair genes, especially XRCC1 and XRCC3.³⁴ Numerous studies have reported the association between genetic polymorphisms in DNA repair genes and the different cancers,^{17-19,26} including non-Hodgkin lymphoma.³⁵⁻³⁷ However, to our knowledge to date, only 1 study investigated the role of such polymorphisms in survivors of childhood HD.²⁵ In the current study, we examined the role of polymorphisms in 5 DNA repair genes involved in the NER, BER, and DSB repair pathways in modulating the risk of adult HD. Our results suggest that variations in DNA repair genes, particularly in combination, may modulate HD risk.

In the current study, individuals having the variant XRCC1 399Gln allele had an increased risk of developing HD. XRCC1 is an important player in the BER pathway, in which it is a multidomain protein that complexes with 3 other DNA repair enzymes in the pathway, namely, DNA ligase III, DNA polymerase β , and poly(adenosine diphosphate ribose) polymerase.^{38,39} There is evidence that XRCC1 can bind directly to both gapped and nicked DNA, as well as to gapped DNA complexes with DNA polymerase β , indicating that XRCC1 might be independently involved in DNA damage recognition.⁴⁰ Some studies have suggested that the XRCC1 codon 399Gln allele may lead to diminished DNA repair proficiency compared with the Arg allele.⁴¹⁻⁴³ The XRCC1 Arg399Gln has been associated with decreased DNA repair capacity⁴⁴ and subsequent accumulation of unrepaired DNA damage⁴⁵ and increased cancer risk.⁴⁶⁻⁴⁸ Furthermore, with regard to the biologic significance, an association between the XRCC1 399Gln allele and p53 mutations⁴⁹ has been suggested, with loss of the transcriptional activity of p53 and involvement in pathogenesis of Hodgkin lymphoma⁵⁰ and defective regulation of Reed-Sternberg cells.^{51,52}

A few studies have addressed the effect of interaction between the BER and DSB pathway gene variants on modulating susceptibility to cancer, with conflicting results.^{18,53-55}

In the current study, we used MDR analysis to identify possible specific interactions among the SNPs in the 5 DNA repair genes. We found that the XRCC3 (Thr/Met) in the presence of the XRCC1 (Arg/Gln) led to an increased risk of disease (OR, 1.97; 95% CI, 1.05–3.73); such risk was further increased when the XRCC3 (Met/ Met) was present together with XRCC1 (Arg/Gln) (OR, 4.13; 95% CI, 1.50–11.33). The presence of the XRCC3 (Thr/Met) together with the XRCC1 (Gln/Gln) also led to a significant 3-fold increase in risk. These results suggest that the XRCC1 variant either independently or in combination with the XRCC3 variants increases the risk of HD. XRCC3 is involved in homologous recombination repair and is required for repair of double-strand breaks, thus may be an important contributor to genomic stability.

Similarly, interaction between XRCC1 Gln allele and XPC 939Lys was observed. XPC is 1 of the NER pathway genes that have been associated with increased risk of head and neck cancer, esophageal cancer, and melanoma.^{17,56,57} Our results suggest the presence of a possible coordination between the 2 repair systems that may contribute to individual susceptibility to HD. These findings are similar and in accordance with other studies that examined such combined effects on modulating susceptibility to lung cancer.^{58,59}

It is unlikely that single-locus effects can explain the risk of developing cancer, because complex diseases most likely result from genetic variants in multiple genes in different

pathways. The cumulative genetic risk score is used to calculate the risk by summing the number of adverse alleles across the SNPs for the genes studied.^{60,61} In the current study, we observed an increase in HD risk depending on the number of variant alleles involved, in which having ≥ 4 variants was associated with a statistically significant increased risk of HD. The cumulative genetic risk score, however, does not reflect an interaction among SNPs per se, but the risk association with the accumulation of risk alleles. These results are based on a limited number of SNPs and need to be replicated in larger studies that test a panel of SNPs in the different DNA repair pathways.

To our knowledge, the current study is the first to report HD risk and the modulating effect of SNPs in DNA repair genes individually and in combination. Given the multiple pathways involved in repairing DNA damage, genetic variants in the different repair pathways should therefore be further evaluated to better understand cancer susceptibility in these patients. In the current study, we demonstrated that SNPs in the XRCC1, XRCC3, and XPC genes in combination are associated with development of HD. Our sample size provided limited power for gene-gene interaction assessments; therefore, we cannot exclude the possibility that some of these findings may be due to chance, and thus should be interpreted with caution. HD is highly curable because of remarkable treatment advances; however, HD survivors report a higher rate of subsequent malignancies than do survivors of other cancers. DNA repair variants may play a potentially important role in an individual's susceptibility to developing late complications. Therefore, larger studies are warranted to investigate the role of additional DNA repair genes with regard to both HD risk and outcome.

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Table 1

Demographic Characteristics of the HD Cases and Controls

	No. of Cases. (%)	No. of Controls (%)	<i>P</i>
Total	200 (100)	220 (100)	
Age, y			.78
Mean	47.5 ± 13.4	49.3 ± 15.2	
20–40	68 (34)	72 (33)	
>40	132 (66)	148 (67)	
Sex			.62
Women	93 (46)	97 (44)	
Men	107 (54)	123 (56)	
Race			.53
White	163 (82)	195 (89)	
Others	37 (18)	25 (11)	
Smoking status *			.45
Never	95 (51)	120 (55)	
Ever	92 (49)	100 (45)	
Family history of cancer			.35
No	119 (60)	97 (44)	
Yes	81 (40)	123 (56)	
Histologic subtype			
Nodular sclerosis	159 (80)		
Others	41 (20)		
Stage			
I	25 (12)		
II	103 (52)		
III	45 (22)		
IV	27 (14)		

HD indicates Hodgkin disease.

* Smoking status was unknown in 13 of the HD patients, and B-symptom status was unknown in 2 patients.

Table 2

Distribution Frequency of the DNA Genotypes Among Cases and Controls

	No. of Cases (%) [*]	No. of Controls (%) [*]	<i>P</i> [†]	Adjusted [‡] OR (95% CI)
Subjects analyzed	200 (100)	220 (100)		
XPC codon 939			.35	
Lys/Lys	75 (38)	79 (36)		
Lys/Gln	94 (47)	97 (44)		0.95 (0.61–1.46)
Gln/Gln	29 (15)	44 (20)		0.67 (0.37–1.19)
Any Gln	123 (62)	141 (64)		0.87 (0.59–1.32)
XPD codon 751			.35	
Lys/Lys	99 (51)	107 (49)		
Lys/Gln	81 (41)	83 (38)		1.05 (0.69–1.59)
Gln/Gln	16 (8)	27 (12)		0.64 (0.32–1.28)
Any Gln	97 (49)	110 (51)		0.95 (0.64–1.41)
XPG codon 1104			.40	
Asp/Asp	104 (53)	127 (58)		
Asp/His	78 (39)	80 (37)		1.17 (0.77–1.77)
His/His	16 (8)	12 (5)		1.55 (0.68–3.50)
Any His	94 (47)	92 (42)		1.22 (0.82–1.81)
XRCC1 codon 399			.04	
Arg/Arg	73 (37)	102 (47)		
Arg/Gln	106 (53)	89 (41)		1.77 (1.16–2.71)
Gln/Gln	20 (10)	28 (13)		1.13 (0.58–2.17)
Any Gln	126 (63)	117 (53)		1.62 (1.08–2.43)
XRCC3 codon 241			.62	
Thr/Thr	82 (44)	104 (48)		
Thr/Met	87 (47)	90 (42)		1.29 (0.84–1.97)
Met/Met	18 (10)	22 (10)		1.08 (0.53–2.20)
Any Met	105 (56)	112 (52)		1.25 (0.83–1.87)

OR indicates odds ratio; 95% CI, 95% confidence interval.

^{*} Because of missing data, 198 cases and 220 controls for XPC, 196 cases and 217 controls for XPD, 198 cases and 219 controls for XPG, 199 cases and 219 controls for XRCC1, and 187 cases and 216 controls for XRCC3 were analyzed in the logistic regression models.

[†] Two-sided chi-square test for the difference in the genotype or allele distributions between the cases and the controls was performed.

[‡] Adjusted for age, sex, race, and smoking status.

Table 3

Interaction Between Genotypes and Modulation of HD Risk

Combinations Between Polymorphisms					
XRCC3 Codon 241	XRCC1 Codon 399	No. of Cases (%)	No. of Controls (%)	Adjusted OR (95% CI)	P*
Thr/Thr	Arg/Arg	20 (11)	53 (27)	Referent	
Thr/Met		40 (22)	34 (17)	2.38 (1.24–4.55)	.01
Met/Met		1 (1)	4 (2)	0.16 (0.02–1.30)	.09
Any Met		41 (22)	38 (19)	1.81 (0.97–3.36)	.07
Thr/Thr	Arg/Gln	45 (24)	40 (20)	1.88 (1.02–3.54)	.05
Thr/Met		47 (25)	42 (21)	1.97 (1.05–3.73)	.04
Met/Met		12 (6)	7 (4)	4.13 (1.50–11.33)	.01
Any Met		59 (32)	49 (25)	2.30 (1.25–4.20)	.01
Thr/Thr	Gln/Gln	13 (7)	9 (5)	3.00 (1.15–7.80)	.03
Thr/Met		5 (3)	8 (4)	0.48 (0.15–1.59)	.23
Met/Met		3 (2)	2 (1)	1.28 (0.20–8.15)	.79
Any Met		8 (4)	10 (5)	0.61 (0.22–1.70)	.34
Thr/Thr	Any Gln	58 (31)	49 (25)	2.08 (1.14–3.79)	.02
Any Met		67 (36)	59 (30)	1.81 (1.02–3.23)	.05
XPC Codon 939	XRCC1 Codon 399				
Lys/Lys	Arg/Arg	27 (14)	42 (19)	Referent	
Lys/Gln		35 (18)	38 (17)	1.51 (0.82–2.80)	.19
Gln/Gln		11 (6)	22 (10)	0.74 (0.31–1.76)	.50
Any Gln		46 (23)	60 (27)	1.19 (0.64–2.21)	.57
Lys/Lys	Arg/Gln	40 (20)	26 (12)	2.14 (1.09–4.23)	.03
Lys/Gln		50 (25)	49 (22)	1.37 (0.71–2.64)	.35
Gln/Gln		16 (8)	13 (6)	1.83 (0.76–4.36)	.18
Any Gln		66 (33)	62 (28)	1.78 (0.96–3.280)	.12
Lys/Lys	Gln/Gln	9 (5)	10 (5)	1.33 (0.48–4.69)	.58
Lys/Gln		9 (5)	10 (5)	1.33 (0.48–3.68)	.58
Gln/Gln		2 (1)	8 (4)	0.37 (0.07–1.87)	.23
Any Gln		11 (6)	18 (8)	1.38 (0.52–2.89)	.17
Lys/Lys	Any Gln	49 (25)	36 (16)	2.19 (1.10–4.37)	.03

Combinations Between Polymorphisms					
XRCC3 Codon 241	XRCC1 Codon 399	No. of Cases (%)	No. of Controls (%)	Adjusted OR (95% CI)	P*
Any Gln		77 (39)	80 (37)	1.46 (0.46–2.32)	.91

HD indicates Hodgkin disease; OR, odds ratio; 95% CI, 95% confidence interval.

* Cases and controls were analyzed with adjustment for age, sex, race, and smoking status in logistic regression models.

Table 4**Cumulative Genetic Score and Hodgkin Disease Risk**

No. of Variants	No. of Cases (%) [*]	No. of Controls (%) [*]	Adjusted OR (95% CI)	<i>p</i> [†]
0–1	23 (13)	35 (16)	Referent	
2	46 (25)	63 (30)	1.53 (0.68–2.40)	.68
3	52 (29)	67 (31)	1.29 (0.70–2.37)	.96
4+	61 (34)	48 (23)	1.98 (1.05–3.80)	.02
0–2	69 (38)	98 (46)	Referent	
3	52 (29)	67 (31)	1.21 (0.46–3.23)	.26
4+	61 (34)	48 (23)	1.86 (1.15–3.02)	.02

OR indicates odds ratio; 95% CI, 95% confidence interval.

^{*} Complete data with all variants were available for 182 cases and 213 controls.

[†] Adjusted for age, sex, race, and smoking status.