NIH Public Access
Author Manuscript
Leuk Res. Author manuscript; available in PMC 2012 July 1.

Published in final edited form as:
Leuk Res. 2011 July ; 35(7): 968–970. doi:10.1016/j.leukres.2010.12.012.

Polymorphisms in integrin genes and lymphoma risk

Min Shen[1], **Tongzhang Zheng**[2], **Qing Lan**[1], **Yawei Zhang**[2], **H. Dean Hosgood III**[1], **Shelia H. Zahm**[1], **Theodore R. Holford**[2], **Brian Leaderer**[2], **Meredith Yeager**[1], **Jeff Yuenger**[1], **Stephen Chanock**[1], and **Nathaniel Rothman**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

[2]Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, CT, USA

Abstract

Immune deficiency is one of the best characterized and strongest known risk factors for non-Hodgkin lymphoma (NHL). We studied the association between single nucleotide polymorphisms (SNPs) in integrin genes that are important components in human innate immunity and the risk of NHL in a population-based case–control study of women in Connecticut, USA. A total of 373 tag SNPs in 33 gene regions were included in the analysis of 448 cases and 525 controls. The *ADAM19* rs11466782 SNP was associated with an increased risk of lymphoma (OR, 1.73; 95 % CI, 1.28–2.35; $P_{additive} = 0.0004$), and the *ICAM3* rs2304240 (OR, 0.67; 95 % CI, 0.52–0.86; $P_{additive} = 0.002$) and the *PTGDR* rs708486 SNPs (OR, 0.75; 95 % CI, 0.63–0.90; $P_{additive} = 0.002$) were associated with reduced risk of lymphoma. Two gene regions (*ADAM19* (P=0.009) and *ICAM3* (P=0.009)) displayed global associations with lymphoma risk at the P<0.01 level. While our results suggest that genetic polymorphisms in integrin genes may play a role in the genesis of lymphoma in women, they should be viewed as exploratory until they are replicated in additional populations.

Keywords

lymphoma; integrin; innate immunity; single nucleotide polymorphism

Introduction

Immune deficiency is one of the best characterized and strongest known risk factors for non-Hodgkin lymphoma (NHL) (Grulich *et al*, 2007). Certain autoimmune diseases and

Corresponding Author: H. Dean Hosgood, PhD, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, MSC 7240 6120 Executive Blvd., Bethesda, MD, 20892-7240, USA, Tel: 301-594-4649, Fax: 301-402-1819, hosgoodd@mail.nih.gov.

Authors' Contributions

All authors had full access to all of the study data and have contributed to, seen, and approved the final version of the manuscript; TZ, NR, QL, SZ, and SC designed this study, managed data collection, and participated in data processing; MS participated in data processing, conducted most of the analyses, and was primarily responsible for writing the paper; HDH was also involved with data processing and the analysis incorporated suggestions by YZ, TH, BL, JY, MY, NR, and QL.

Conflict of Interest

No authors have any or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

infections (EBV, HIV), along with weakened immunity have been found to increase lymphoma susceptibility.

Innate immunity is the first barrier of the human body to clear non-specific antigens and interacts with the adaptive immune system during physiological and chronic inflammation (Kabelitz & Medzhitov, 2007). Integrins are important components in innate immunity because they mediate attachment between cells or between a cell and the extracellular matrix. They also play a role in cell communication and transduce cell-cell and cell-matrix information, allowing rapid and flexible responses to changes in the environment (Hynes, 2002).

To test the hypothesis that genetic variation in genes coding integrins may play a role in lymphoma carcinogenesis, we evaluated genetic polymorphisms in 33 integrin genes in a population-based case-control study among women in Connecticut.

Materials and Methods

Details of this population-based case control study are described elsewhere (Morton *et al*, 2003). Briefly, incident female NHL cases were identified using the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource. Eligible cases included female adults of Connecticut diagnosed with incident NHL (ICD-O: M-9590-9642, 9690-9701, 9740-9750). A population-based control group was enrolled in Connecticut and the controls were frequency matched to cases by age within 5-year groups. From 1995 to 2001, 601 NHL eligible cases (72% of all eligible cases) and 717 qualified controls participated in this study. There were 145 diffuse large B-cell lymphomas (DLBCL), 105 follicular lymphomas (FL), 52 small cell lymphocytic lymphomas/chronic lymphocytic leukemias (SLL/CLL), 29 marginal zone lymphomas (MZBL), and 32 T-cell lymphomas. Blood samples were available from 461 cases and 535 controls.

DNA was extracted from blood samples using phenol-chloroform extraction and genotyped by a GoldenGate Illumina assay. Genes in the same gene region were also genotyped. Gene region was defined as a chromosome region with multiple genes within a range of 200,000 bases upstream or downstream. A total of 973 subjects (448 cases and 525 controls) were successfully genotyped. The assay was initially designed to examine 386 single nucleotide polymorphisms (SNPs) in 33 gene regions (43 genes). However, 13 SNPs were excluded due to assay failure. A final total of 373 tag SNPs in 33 gene regions were included in the analysis (Supplementary Table 1). Approximately 99.7% of assays had a completion rate of ≥95 % for all samples and 99.5% of assays reached ≥95% concordance among quality control samples.

The genotype data were analyzed by comparing the homozygotes and the heterozygotes of the variant with the homozygote of the common allele in an unconditional logistic regression, adjusted for age and race. An additive model was applied by treating the genotypes as values of 0, 1, and 2 in one model in order to test for a linear trend. A gene region-based test, permutation-based resampling method (10,000 permutations), was applied to assess the true statistical significance of the smallest p-trend within each gene region. This method automatically adjusts for the number of tag SNPs tested within that gene region, as well as the underlying linkage disequilibrium pattern. Haplotype analysis was carried out for all gene regions and all contiguous locus subsets in a gene region were examined to identify sub-haplotypes with the strongest omnibus association with lymphoma risk. Given the possibility of false positive results due to multiple comparisons, we evaluated the robustness of our results using the False Discovery Rate (FDR). All data were analyzed with the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Statistical Analysis Software, version 9.13 (SAS Institute Inc, 1996) if not specified otherwise.

Results

Selected demographic characteristics of cases and controls were similar with respect to age, race, education, and family history of cancer (Table 1).

The genotype frequencies for cases and controls, and the effect of these SNPs and gene regions on lymphoma risk are provided in Supplementary Table 2. Among the 373 tag SNPs in 33 gene regions, three SNPs were statistically significant at the level of 0.005 in the additive model (Table 2). *ADAM19* rs11466782 was associated with increased risk of lymphoma (OR, 1.73; 95 % CI, 1.28–2.35; $P_{additive} = 0.0004$), and *ICAM3* rs2304240 (OR, 0.67; 95 % CI, 0.52–0.86; $P_{additive} = 0.002$) and *PTGDR* rs708486 (OR, 0.75; 95 % CI, 0.63–0.90; $P_{additive} = 0.002$) were associated with reduced risk of lymphoma. The association of *ADAM19* rs11466782 with NHL risk was also significant for several NHL subtypes, especially for FL (OR_{trend}, 2.20; 95 % CI, 1.37–3.52; P, 0.001).

Two gene regions (*ADAM19* (P=0.009) and *ICAM3* (P=0.009)) displayed global association with lymphoma risk at the P<0.01 level. The smallest FDR value (0.16) was obtained for *ADAM19* rs11466782. Haplotype analyses did not provide additional information beyond results from individual SNP analyses.

Discussion

We found that several SNPs in genes involved in integrins were associated with lymphoma risk in women. This is the first report that a polymorphism in *ADAM19* is associated with the risk of lymphoma.

The protein coded by *ADAM19* is a cell surface glycoprotein with several functional domains and works as an endopeptidase/metalloprotease that cleaves extracellular matrix proteins and sheds growth factors and cytokines. It plays essential roles in embryo implantation, cardiovascular morphogenesis, neurogenesis, and other developmental processes (Qi *et al*, 2009). ADAM19 is upregulated in human brain tumors and is also over-expressed by many human cancerous cell lines including cancers of the colon, ovary, lung, and brain (Qi *et al*, 2009). Abnormally high expression of this gene is also linked to inflammation and fibrosis of the lung and kidney. ADAM19 may participate in the pathology of cancers through several mechanisms by promoting cell growth and invasion (Mochizuki & Okada, 2007). The *ADAM19* rs11466782 is in Intron 14 (ivs14 -152 T>C), close to exon 15, which is a conserved cysteine-rich domain that regulates the protein's metalloprotease activity.

ICAM3 is a transmembrane glycoprotein and expressed by all leucocytes. It functions not only as an adhesion molecule, but also as a potent signalling molecule for immune response. The *ICAM3* was found to be overexpressed in lymphoid neoplasms (Beltran & Boissier, 2009; Cordell *et al*, 1994). The polymorphism *ICAM3* rs2304240 is located at one end of a conserved intercellular adhesion molecule domain and close to the other important conserved immunoglobulin domain.

In summary, we found that genetic polymorphisms in a number of integrin genes were associated with lymphoma risk in women. This suggests that integrins, especially *ADAM19*, may play a role in the pathogenesis of lymphoma. While we attempted to account for possible spurious findings due to multiple comparisons by evaluating False Discovery Rates

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

of the minP results, it is still possible that our analyses may have led to false positive or false negative findings; therefore, these results need to be replicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under contract N01-CO-12400. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. Support for this study was also provided by the NIH grant CA62006 (T.Z).

References

1. Beltran S, Boissier J. Are schistosomes socially and genetically monogamous? Parasitol Res. 2009; 104:481–483. [PubMed: 18946680]
2. Cordell JL, Pulford K, Turley H, Jones M, Micklem K, Doussis IA, Tyler X, Mayne K, Gatter KC, Mason DY. Cellular distribution of human leucocyte adhesion molecule ICAM-3. J Clin Pathol. 1994; 47:143–147. [PubMed: 8132828]
3. Grulich AE, Vajdic CM, Cozen W. Altered immunity as a risk factor for non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2007; 16:405–408. [PubMed: 17337643]
4. Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002; 110:673–687. [PubMed: 12297042]
5. Kabelitz D, Medzhitov R. Innate immunity--cross-talk with adaptive immunity through pattern recognition receptors and cytokines. Curr Opin Immunol. 2007; 19:1–3. [PubMed: 17157490]
6. Mochizuki S, Okada Y. ADAMs in cancer cell proliferation and progression. Cancer Sci. 2007; 98:621–628. [PubMed: 17355265]
7. Morton LM, Holford TR, Leaderer B, Zhang Y, Zahm SH, Boyle P, Flynn S, Tallini G, Owens PH, Zhang B, Zheng T. Alcohol use and risk of non-Hodgkin's lymphoma among Connecticut women (United States). Cancer Causes Control. 2003; 14:687–694. [PubMed: 14575367]
8. Qi B, Newcomer RG, Sang QX. ADAM19/adamalysin 19 structure, function, and role as a putative target in tumors and inflammatory diseases. Curr Pharm Des. 2009; 15:2336–2348. [PubMed: 19601835]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Characteristics of cases and controls.

Characteristic	Cases (%)(n=448)	Controls (%)(n=525)	p [a]
Age (years)			
<50	89 (20%)	99 (19%)	0.17
50–69	218 (49%)	231 (44%)	
70+	141 (31%)	195 (37%)	
Race			
Caucasian	432 (96%)	494 (94%)	0.09
Other	16 (4%)	31 (6%)	
Education			
<12 years	58 (13)	63 (12)	0.46
12 years–Some college	337 (75)	386 (74)	
College graduate or higher	53 (12)	76 (14)	
Family history [b]			
No	93 (21%)	129 (25%)	0.16
Any cancer	355 (79%)	396 (75%)	

[a] Pearson χ^2 test;

[b] Family history of cancer in first degree relatives.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 2

Logistic regression analysis of selected SNPs on the risk of NHL among women in Connecticut, adjusted for age and race.

	Controls	%	Cases	%	OR	95% CI	P
ADAM19 rs11466782 (IVS14-152 A>G)							
AA	445	85	341	76	1		
AG	77	15	101	23	1.76	1.26–2.45	**0.0009**
GG	3	1	6	1	2.65	0.66–10.71	0.17
AG/GG	80	15	107	24	1.79	1.29–2.48	**0.0004**
Trend					1.73	1.28–2.35	**0.0004**
ICAM3 rs2304240 (Ex2-35 G>A)							
GG	349	66	335	75	1		
AG	154	29	107	24	0.73	0.55–0.98	**0.04**
AA	22	4	6	1	0.29	0.11–0.72	**0.01**
AG/AA	176	34	113	25	0.68	0.51–0.90	**0.01**
Trend					0.67	0.52–0.86	**0.002**
PTGDR rs708486 (IVS1-478 A>G)							
AA	163	31	168	38	1		
AG	252	48	215	48	0.80	0.60–1.06	0.12
GG	109	21	65	15	0.55	0.38–0.81	**0.002**
AG/GG	361	69	280	63	0.72	0.55–0.95	**0.02**
Trend					0.75	0.63–0.90	**0.002**