Published in final edited form as:

Leuk Res. 2013 September ; 37(9): 1120–1124. doi:10.1016/j.leukres.2013.05.003.

Polymorphisms in JAK/STAT Signaling Pathway Genes and Risk of Non-Hodgkin Lymphoma

Yingtai Chen, MD¹, Qing Lan, PhD², Tongzhang Zheng, ScD³, Nan Zhao, MD³, Theodore R. Holford, PhD³, Catherine Lerro, MPH³, Min Dai, PhD¹, Huang Huang, MD³, Jiaxin Liang, BA³, Shuangge Ma, PhD³, Brian Leaderer, PhD³, Peter Boyle, PhD⁴, Stephen Chanock, PhD², Nathaniel Rothman, MD², and Yawei Zhang, PhD³

¹Cancer Hospital/Institute, Chinese Academy of Medical Sciences, Beijing, China

²Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

³Yale University School of Public Health, New Haven, CT, USA

⁴International Prevention Research Institute, Lyon, France

Abstract

Impaired function of Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway genes leads to immunodeficiency and various hematopoietic disorders. We evaluated the association between genetic polymorphisms (SNPs) in 12 JAK/STAT pathway genes (*JAK3*, *STAT1*, *STAT2*, *STAT3*, *STAT4*, *STAT5a*, *STAT5b*, *STAT6*, *SCOS1*, *SCOS2*, *SCOS3*, and *SCOS4*) and NHL risk in a population-based case-control study of Connecticut women. We identified three SNPs in *STAT3* (rs12949918 and rs6503695) and *STAT4* (rs932169) associated with NHL risk after adjustment for multiple comparison. Our results suggest that genetic variation in JAK/STAT pathway genes may play a role in lymphomagenesis and warrants further investigation.

Key words

JAK/STAT signaling pathway; Non-Hodgkin Lymphoma; polymorphism; case-control study

© 2013 Elsevier Ltd. All rights reserved.

Address for correspondence and reprints: Yawei Zhang, MD, PhD, MPH, Department of Environmental Health Sciences, Yale University School of Public Health, 60 College Street, LEPH 440, New Haven, CT 06520, USA. Phone: 203-785-6210. yawei.zhang@yale.edu.

Authors' contributions: Y.C., Q.L., T.Z., T.H., B.L., P.B., M.D., N.R., and Y.Z. conceived and led the study; T.Z., T.H., B.L., and Y.Z. carried the population-based case-control study; Q.L., S.C., N.R. performed genotyping at NCI; Y.C., N.Z., H.H., J.L. S.M., and Y.Z. carried out the data analysis; Y.C., C.L., and Y.Z. drafted and revised the manuscript; and all authors reviewed and approved the manuscript.

Conflict of interest: The authors declare no competing financial interests.

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.

Introduction

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of lymphoproliferative malignancies. One of the few established risk factors for NHL is immunodeficiency resulting from immunosuppressive therapy, human immunodeficiency virus infection, and autoimmune diseases (1, 2). Several studies suggested that genetic variation in immune response and innate immune genes are associated with the risk of NHL (3–9).

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway plays a key role in the regulation of cellular responses to cytokines (i.e., IFN- α , IFN- β , IFN- γ , and the interleukins) (10). Activation of JAKs in response to different cytokine stimuli transduces the signal by phosphorylating the STAT proteins, which translocate to the nucleus to modify the expression of genes necessary for cell proliferation or differentiation (11). JAK3 knockout mice exhibited severe combined immunodeficiency (12, 13). Inactivation of *STAT* genes in mice results in various hematopoietic disorders (10).

In light of these essential functions of the role of JAK/STAT signaling pathway genes in immune system function, it is biologically plausible that alteration of these genes may be associated with lymphomagenesis. A recent European multi-center case-control study provided preliminary evidence that genetic variations in several genes involved in the JAK/STAT pathway were associated with the risk of lymphoma (14). To further examine the relationship between genetic polymorphisms in JAK/STAT pathway genes and NHL risk, we analyzed data from a population-based case-control study of Connecticut women.

Materials and Methods

A detailed description of the study population has been previously reported (3, 15–17). Briefly, a total of 601 incident cases and 717 population-based controls were enrolled and completed in-person interviews. All cases were histologically confirmed by two independent study pathologists and classified cases into NHL subtypes according to the World Health Organization classification system (18). We evaluated NHL overall and the three most common NHL subtypes: diffuse large B-cell lymphoma (DLBCL) (32.4%), follicular lymphoma (FL) (23.8%), and chronic lymphoid leukemia/small lymphocytic lymphoma (CLL/SLL) (11.3%). This study was approved by the Institutional Review Boards at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute (NCI).

DNA was extracted from blood samples (461 cases and 535 controls) using a phenol-chloroform extraction method (19). Genotyping was conducted at the NCI Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD) using an Illumina GoldenGate platform. DNA from 448 cases and 525 controls were submitted for genotyping. Duplicate samples from 100 study participants and 40 replicate samples from each of the two blood donors were interspersed throughout the plates used for genotype analysis for quality control purposes. A total of 97 SNPs from 12 JAK/STAT pathway genes were considered for this study. The completion rates for all SNPs were over 99% and the concordance rates for quality control samples were greater than 95% for all assays.

Hardy-Weinberg equilibrium (HWE) was assessed in non-Hispanic white controls for each SNP using a chi-square test. SNPs with a p-value >0.01 from the chi-square test were considered to be in HWE. The Minimum p (“minP”) tests for NHL overall and common subtypes were conducted to examine an association at the gene level. The minP test was based on permutation resampling and was conducted to assess the true statistical significance of the smallest p-trend within each gene region (20). This approach adjusts for the number of tag SNPs tested within each gene region as well as the underlying linkage disequilibrium pattern (20).

Unconditional logistic regression models were used to estimate the risk and calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for individual SNPs. Models were run for NHL overall, DLBCL, FL, and CLL/SLL, adjusted for age. To maximize statistical power, models for NHL subtypes were carried out using all controls as the reference group. We assigned the common homozygote as 0, the heterozygote as 1, and the homozygote variant as 2, and treated them continuously to perform trend analyses. Haplotype analyses were conducted for all genes in which more than one SNP was genotyped. Haplotype block structures were evaluated with HaploView using the four gamete rule (21). The individual haplotype frequencies were estimated through the expectation maximization algorithm under the assumption of the HWE. An unconditional logistic regression model was used to estimate the effect of individual haplotypes, with the most common haplotype as the reference. The false discovery rate (FDR) method (22) was applied to adjust for multiple comparisons. The FDR provides the expected ratio of erroneous rejections of the null hypothesis to the total number of rejected hypotheses. We set 0.20 as a significance level for FDR. All of our analyses were limited to non-Hispanic Caucasians. Statistical analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

The distribution of age, education level, and family history of cancer in first-degree relatives was similar for the cases and controls (Table 1). Of the 97 SNPs tested, seven SNPs were not in HWE and were excluded from the haplotype analyses (Table S1).

At the gene level, *STAT3* gene region was associated with NHL overall, DLBCL, and FL ($P=0.004$, 0.046 , and 0.01 respectively) (Table S1). *SOCS1* and *STAT5A* were associated with FL ($P=0.047$ and 0.008 respectively). CLL/SLL was found to be associated with *SOCS1*, *SOCS2*, and *SOCS4* ($P=0.028$, 0.036 , and 0.039 respectively). After adjustment for multiple comparisons, only the association between *STAT3* and NHL overall remained statistically significant.

As shown in Table 2, inverse associations were observed for *STAT3* rs12949918 (P -trend= 0.0020 , 0.0080 , and 0.011 for NHL overall, DLBCL, and FL respectively), rs6503695 (P -trend= 0.0020 , 0.035 , and 0.0030 for NHL overall, DLBCL, and FL respectively), and rs7217655 (P -trend= 0.017 and 0.017 for NHL overall and DLBCL respectively). *STAT3* rs12949918 CC genotype (referent=TT) was significantly associated with reduced risk of NHL overall (OR= 0.49 , 95%CI= 0.33 – 0.75 , $P=0.00098$), DLBCL (OR= 0.43 , 95%CI= 0.22 – 0.81 , $P=0.0094$), and FL (OR= 0.42 , 95%CI= 0.21 – 0.87 , $P=0.019$), but not CLL/SLL

(OR=0.36, 95%CI: 0.12–1.08, P=0.068). A similar pattern was observed for *STAT3* rs6503695 (OR_{CC}=0.49, 95%CI: 0.31–0.77, P=0.0024 for NHL overall; OR_{CC}=0.42, 95%CI: 0.20–0.89, P=0.024 for DLBCL; OR_{CC/CT}=0.50, 95%CI: 0.33–0.78, P=0.0022 for FL; and OR_{CC/CT}=0.55, 95%CI: 0.31–1.00, P=0.051 for CLL/SLL). *STAT3* rs7217655 TT genotype (referent=CC) showed a decreased risk of NHL overall (OR_{TT}=0.48, 95%CI: 0.30–0.77, P=0.0023), DLBCL (OR_{TT}=0.39, 95%CI: 0.18–0.83, P=0.014), and FL (OR_{TT}=0.39, 95%CI: 0.16–0.85, P=0.038). A significantly increased risk was observed for *STAT4* rs932169 for NHL overall (OR_{CG/CC}=1.60, 95%CI: 1.13–2.25, P=0.0074; P-trend=0.0059), but not for NHL subtypes. After adjustment for multiple comparisons, significant associations remained for *STAT3* (rs12949918 and rs6503695) and *STAT4* rs932169 for NHL overall.

STAT1 rs17749316 CG/GG genotypes (referent=CC) showed increased risks of NHL overall (OR_{CG/GG}=1.47, 95%CI: 1.03–2.11, P=0.034; P-trend=0.020) and FL (OR_{CG/GG}=1.87, 95%CI: 1.09–3.21, P=0.022; P-trend=0.0086). *STAT5a* rs16967637 showed a decreased risk of FL (OR_{AC/AA}=0.52, 95%CI: 0.34–0.82, P=0.0043; P-trend=0.0081). An association with *SOCS1* rs243317 CC genotype (referent=AA) was observed for NHL overall (OR=1.63, 95%CI: 1.03–2.57, P=0.037; P-trend=0.037), FL (OR=2.14, 95%CI: 1.06–4.35, P=0.035; P-trend=0.018), and CLL/SLL (OR=3.15, 95%CI: 1.34–7.38, P=0.0084; P-trend=0.018). However, none of these associations remained statistically significant after adjustment for multiple comparisons. The results for all other SNPs are presented in Table S2.

Haplotype analyses were consistent with the results of the individual SNP analyses and did not provide additional insight into these associations (data not shown).

Discussion

Our study found seven SNPs in *STAT3* (rs12949918, rs6503695, and rs7217655), *STAT1* (rs17749316), *STAT4* (rs932169), *STAT5a* (rs16967637), and *SOCS1* (rs243317) genes associated with the risk of either NHL overall or NHL subtypes. The strongest findings were two SNPs in *STAT3* (rs12949918 and rs6503695) genes inversely associated with the risk of NHL overall, DLBCL, and FL, and one SNP in *STAT4* (rs932169) gene positively associated with the risk of NHL overall.

Emerging evidence shows that *STAT3* plays a critical role in cancer development through its dual functions in tumor inflammation and immunity. *STAT3* promotes pro-oncogenic inflammatory pathways, including nuclear factor-kappaB (NF-kappaB) and interleukin-6 (IL-6)-GP130-JAK pathways, and by opposing *STAT1*- and NF-kappaB-mediated T helper 1 anti-tumor immune responses (23). Constitutive activation of *STAT3* has been detected in a variety of malignancies including the cancers of the breast, lung, head and neck, ovary, pancreas, and prostate, as well as melanoma, multiple myeloma, leukemia, and lymphoma (24). An inverse association with SNPs rs12949918 and rs6503695 observed in our study was consistent with the findings from a recently published European study (14). The exact underlying mechanisms responsible for our finding that *STAT3* polymorphisms conferred decreased risk of NHL remains unclear. In vitro studies have shown that the SNP rs4796793 could alter *STAT3* mRNA levels (25). Although this SNP was not genotyped in our study, it

was reported to be in strong LD with the SNP rs12949918 (26). Both rs12949918 and rs6503695 are located in the introns of the *STAT3* gene, suggesting that these SNPs may influence NHL risk by affecting gene transcriptional regulation and mRNA splicing.

STAT4 is one of seven proteins in the STAT family and is a critical mediator of proinflammatory immune responses (27). Activation of STAT4 promotes T helper 1 responses that produce IFN- γ , the receptor of which itself signals through STAT1 to increase anti-tumor responses through the activation of natural killer cells, macrophages and CD8⁺ T cell-mediated cytolytic activity (28, 29). *STAT4* polymorphisms have been linked to various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, inflammatory bowel diseases, primary Sjogren's syndrome, juvenile idiopathic arthritis, and primary antiphospholipid syndrome (30–32). Therefore, a link between genetic variation of *STAT4* and NHL is biologically plausible. An increased risk of NHL associated with *STAT4* rs932169 was observed in our study. However, this association was not shown in the European study (14).

STAT1 is required for the cellular response to many cytokines with antiviral activities or immunomodulatory functions (33–35). STAT1 deficiency leads to a rare immunodeficiency that affects the innate immune response against viruses and intracellular pathogens (36). Abnormal expression of STAT1 has been found in a variety of malignant cells derived from tumors such as breast cancer, head and neck cancer, melanoma, leukemia, and lymphoma (37, 38). STAT5 signaling has been shown to promote oncogenesis (39, 40). *SOCS1* interacts directly with the JAKs and inhibit their tyrosine-kinase activity (41) and has been reported as tumor suppressor (42). Both our study and recently published European study (14) found the polymorphisms in *STAT1*, *STAT5a* and *SOCS1* genes associated with the risk of NHL. However, we identified different SNPs and were not able to replicate previous reported findings.

This is the first population-based study in the US to investigate the association between genetic variations in JAK/STAT pathway genes and the risk of NHL. All cases were histologically confirmed. Several limitations should be considered when interpreting the findings. Blood samples used for genotyping were not available for all study subjects. However, no differences were found between those with and without genotyping data with respect to age, race, and case-control status. A small number of very aggressive cases may have died before the interview, and thus were underrepresented in this study. Moderate sample size limited our ability to investigate the association in rare NHL subtypes and potential gene-gene interactions.

Given our findings, it is likely that several genes in the JAK/STAT pathway, particularly *STAT3*, are associated with increased risk of NHL. Because of the essential role of JAK/STAT pathway in immune response, it is biologically plausible that variations in genes involved in JAK/STAT pathway are associated with the risk of NHL. Future studies with large sample size and complete genotyping coverage are warranted to confirm and further investigate associations between JAK/STAT genes and NHL. Additionally, future research should examine potential gene-gene and gene-environment interactions. In this way, investigators might elucidate the causal relationships between JAK/STAT pathway genes

and risk of NHL and its subtypes. In summary, our study provides evidence that genetic variations in JAK/STAT signaling pathway genes are associated with susceptibility to NHL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the NIH grants CA62006, CA165923, 1D43TW008323, 1D43TW007864, and HD70324, and the Intramural Research Program of the National Cancer Institute.

References

- Alexander DD, Mink PJ, Adami HO, Chang ET, Cole P, Mandel JS, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. *Int J Cancer*. 2007; 120(Suppl 12):1–39. [PubMed: 17405121]
- Schulz TF. Cancer and viral infections in immunocompromised individuals. *Int J Cancer*. 2009 Oct 15; 125(8):1755–1763. [PubMed: 19588503]
- Lan Q, Zheng T, Rothman N, Zhang Y, Wang SS, Shen M, et al. Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma. *Blood*. 2006 May 15; 107(10):4101–4108. [PubMed: 16449530]
- Bassig BA, Zheng T, Zhang Y, Berndt SI, Holford TR, Hosgood HD 3rd, et al. Polymorphisms in complement system genes and risk of non-Hodgkin lymphoma. *Environ Mol Mutagen*. 2012 Mar; 53(2):145–151. [PubMed: 22170086]
- Hu W, Bassig BA, Xu J, Zheng T, Zhang Y, Berndt SI, et al. Polymorphisms in pattern-recognition genes in the innate immunity system and risk of non-Hodgkin lymphoma. *Environ Mol Mutagen*. 2013 Jan; 54(1):72–77. [PubMed: 23055202]
- Shen M, Zheng T, Lan Q, Zhang Y, Hosgood HD 3rd, Zahm SH, et al. Polymorphisms in integrin genes and lymphoma risk. *Leuk Res*. 2011 Jul; 35(7):968–970. [PubMed: 21239057]
- Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. *Lancet Oncol*. 2006 Jan; 7(1):27–38. [PubMed: 16389181]
- Wang SS, Cozen W, Cerhan JR, Colt JS, Morton LM, Engels EA, et al. Immune mechanisms in non-Hodgkin lymphoma: joint effects of the TNF G308A and IL10 T3575A polymorphisms with non-Hodgkin lymphoma risk factors. *Cancer Res*. 2007 May 15; 67(10):5042–5054. [PubMed: 17510437]
- Purdue MP, Lan Q, Krickler A, Grulich AE, Vajdic CM, Turner J, et al. Polymorphisms in immune function genes and risk of non-Hodgkin lymphoma: findings from the New South Wales non-Hodgkin Lymphoma Study. *Carcinogenesis*. 2007 Mar; 28(3):704–712. [PubMed: 17056605]
- Ward AC, Touw I, Yoshimura A. The Jak-Stat pathway in normal and perturbed hematopoiesis. *Blood*. 2000 Jan 1; 95(1):19–29. [PubMed: 10607680]
- Darnell JE Jr, Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science*. 1994 Jun 3; 264(5164):1415–1421. [PubMed: 8197455]
- Nosaka T, van Deursen JM, Tripp RA, Thierfelder WE, Witthuhn BA, McMickle AP, et al. Defective lymphoid development in mice lacking Jak3. *Science*. 1995 Nov 3; 270(5237):800–802. [PubMed: 7481769]
- Park SY, Saijo K, Takahashi T, Osawa M, Arase H, Hirayama N, et al. Developmental defects of lymphoid cells in Jak3 kinase-deficient mice. *Immunity*. 1995 Dec; 3(6):771–782. [PubMed: 8777722]

14. Butterbach K, Beckmann L, de Sanjose S, Benavente Y, Becker N, Foretova L, et al. Association of JAK-STAT pathway related genes with lymphoma risk: results of a European case-control study (EpiLymph). *Br J Haematol*. 2011 May; 153(3):318–333. [PubMed: 21418178]
15. Zhang Y, Holford TR, Leaderer B, Boyle P, Zahm SH, Flynn S, et al. Hair-coloring product use and risk of non-Hodgkin's lymphoma: a population-based case-control study in Connecticut. *American journal of epidemiology*. 2004 Jan 15; 159(2):148–154. [PubMed: 14718216]
16. Zhang Y, Lan Q, Rothman N, Zhu Y, Zahm SH, Wang SS, et al. A putative exonic splicing polymorphism in the BCL6 gene and the risk of non-Hodgkin lymphoma. *Journal of the National Cancer Institute*. 2005 Nov 2; 97(21):1616–1618. [PubMed: 16264183]
17. Lan Q, Zheng T, Chanock S, Zhang Y, Shen M, Wang SS, et al. Genetic variants in caspase genes and susceptibility to non-Hodgkin lymphoma. *Carcinogenesis*. 2007 Apr; 28(4):823–827. [PubMed: 17071630]
18. Jaffe, E.; Harris, N.; Stein, H.; Vardiman, J., editors. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. IARC Press; Lyon: 2001.
19. Garcia-Closas M, Egan KM, Abruzzo J, Newcomb PA, Titus-Ernstoff L, Franklin T, et al. Collection of genomic DNA from adults in epidemiological studies by buccal cytobrush and mouthwash. *Cancer Epidemiol Biomarkers Prev*. 2001; 10(6):687–696. [PubMed: 11401920]
20. Chen BE, Sakoda LC, Hsing AW, Rosenberg PS. Resampling-based multiple hypothesis testing procedures for genetic case-control association studies. *Genet Epidemiol*. 2006 Sep; 30(6):495–507. [PubMed: 16755536]
21. Wang N, Akey JM, Zhang K, Chakraborty R, Jin L. Distribution of recombination crossovers and the origin of haplotype blocks: the interplay of population history, recombination, and mutation. *Am J Hum Genet*. 2002; 71(5):1227–1234. Epub 2002 Oct 12. [PubMed: 12384857]
22. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Statist Soc B*. 1995; 57(1):289–300.
23. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer*. 2009 Nov; 9(11):798–809. [PubMed: 19851315]
24. Yu H, Jove R. The STATs of cancer--new molecular targets come of age. *Nat Rev Cancer*. 2004 Feb; 4(2):97–105. [PubMed: 14964307]
25. Ito N, Eto M, Nakamura E, Takahashi A, Tsukamoto T, Toma H, et al. STAT3 polymorphism predicts interferon- α response in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2007 Jul 1; 25(19):2785–2791. [PubMed: 17602083]
26. Jiang B, Zhu ZZ, Liu F, Yang LJ, Zhang WY, Yuan HH, et al. STAT3 gene polymorphisms and susceptibility to non-small cell lung cancer. *Genet Mol Res*. 2011; 10(3):1856–1865. [PubMed: 21948749]
27. Kaplan MH. STAT4: a critical regulator of inflammation in vivo. *Immunol Res*. 2005; 31(3):231–242. [PubMed: 15888914]
28. Chang HC, Han L, Goswami R, Nguyen ET, Pelloso D, Robertson MJ, et al. Impaired development of human Th1 cells in patients with deficient expression of STAT4. *Blood*. 2009 Jun 4; 113(23):5887–5890. [PubMed: 19359411]
29. Takeda K, Akira S. STAT family of transcription factors in cytokine-mediated biological responses. *Cytokine Growth Factor Rev*. 2000 Sep; 11(3):199–207. [PubMed: 10817963]
30. Liang YL, Wu H, Shen X, Li PQ, Yang XQ, Liang L, et al. Association of STAT4 rs7574865 polymorphism with autoimmune diseases: a meta-analysis. *Mol Biol Rep*. 2012 Sep; 39(9):8873–8882. [PubMed: 22714917]
31. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Hu Z, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet*. 2009 Nov; 41(11):1234–1237. [PubMed: 19838193]
32. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PTK, KIAA1542 and other loci. *Nat Genet*. 2008 Feb; 40(2):204–210. [PubMed: 18204446]
33. Jankowski M, Kopinski P, Goc A. Interleukin-27: biological properties and clinical application. *Arch Immunol Ther Exp (Warsz)*. 2010 Dec; 58(6):417–425. [PubMed: 20872282]

34. Strengell M, Matikainen S, Siren J, Lehtonen A, Foster D, Julkunen I, et al. IL-21 in synergy with IL-15 or IL-18 enhances IFN-gamma production in human NK and T cells. *J Immunol*. 2003 Jun 1; 170(11):5464–5469. [PubMed: 12759422]
35. Zhang C, Zhang J, Niu J, Tian Z. Interleukin-15 improves cytotoxicity of natural killer cells via up-regulating NKG2D and cytotoxic effector molecule expression as well as STAT1 and ERK1/2 phosphorylation. *Cytokine*. 2008 Apr; 42(1):128–136. [PubMed: 18280748]
36. Vairo D, Tassone L, Tabellini G, Tamassia N, Gasperini S, Bazzoni F, et al. Severe impairment of IFN-gamma and IFN-alpha responses in cells of a patient with a novel STAT1 splicing mutation. *Blood*. 2011 Aug 18; 118(7):1806–1817. [PubMed: 21772053]
37. Bowman T, Garcia R, Turkson J, Jove R. STATs in oncogenesis. *Oncogene*. 2000 May 15; 19(21):2474–2488. [PubMed: 10851046]
38. Buettner R, Mora LB, Jove R. Activated STAT signaling in human tumors provides novel molecular targets for therapeutic intervention. *Clin Cancer Res*. 2002 Apr; 8(4):945–954. [PubMed: 11948098]
39. Lin TS, Mahajan S, Frank DA. STAT signaling in the pathogenesis and treatment of leukemias. *Oncogene*. 2000 May 15; 19(21):2496–2504. [PubMed: 10851048]
40. Schwaller J, Parganas E, Wang D, Cain D, Aster JC, Williams IR, et al. Stat5 is essential for the myelo- and lymphoproliferative disease induced by TEL/JAK2. *Mol Cell*. 2000 Sep; 6(3):693–704. [PubMed: 11030348]
41. Yasukawa H, Misawa H, Sakamoto H, Masuhara M, Sasaki A, Wakioka T, et al. The JAK-binding protein JAB inhibits Janus tyrosine kinase activity through binding in the activation loop. *EMBO J*. 1999 Mar 1; 18(5):1309–1320. [PubMed: 10064597]
42. Weniger MA, Melzner I, Menz CK, Wegener S, Bucur AJ, Dorsch K, et al. Mutations of the tumor suppressor gene SOCS-1 in classical Hodgkin lymphoma are frequent and associated with nuclear phospho-STAT5 accumulation. *Oncogene*. 2006 Apr 27; 25(18):2679–2684. [PubMed: 16532038]

Table 1

Distributions of demographic characteristics of the study population

Demographic characteristics	Cases (n=432)		Controls (n=494)	
	N	%	N	%
Age (years)				
<50	86	19.9%	93	18.8%
50–70	210	48.6%	212	42.9%
>70	136	31.5%	189	38.3%
Education				
<12 years	53	12.3%	55	11.1%
12 years-College	327	75.7%	368	74.5%
Graduate or higher	52	12.0%	71	14.4%
Family history of cancer in first degree relatives				
No	88	20.4%	122	24.7%
NHL	9	2.1%	2	0.4%
Other cancer	335	77.5%	370	74.9%

Table 2

Associations between selected JAK/STAT pathway gene SNPs and risk of NHL overall and its common subtypes including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

SNPs*	NHL overall				DLBCL			FL			CLL/SLL		
	Controls	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value
SOCST1 rs243317													
AA	225	176			70			36			17		
AC	215	195	1.17(0.89–1.55)	0.26	49	0.74(0.49–1.12)	0.16	51	1.53(0.95–2.44)	0.078	22	1.35(0.70–2.61)	0.38
CC	41	52	1.63(1.03–2.57)	0.037	17	1.39(0.74–2.61)	0.31	14	2.14(1.06–4.35)	0.035	10	3.15(1.34–7.38)	0.0084
AC or CC	256	247	1.25(0.96–1.62)	0.10	66	0.84(0.58–1.24)	0.39	65	1.63(1.04–2.55)	0.034	32	1.64(0.88–3.04)	0.12
Trend	481	423	1.24(1.01–1.51)	0.037	136	1.00(0.75–1.34)	1.00	101	1.48(1.07–2.05)	0.018	49	1.69(1.10–2.61)	0.018
STAT1 rs17749316													
CC	417	344			114			78			40		
CG	63	74	1.40(0.97–2.03)	0.069	21	1.21(0.71–2.07)	0.49	20	0.69(0.96–2.96)	0.069	8	1.34(0.60–2.99)	0.48
GG	2	6	3.62(0.72–18.17)	0.12	2	4.42(0.61–32.08)	0.14	3	7.26(1.17–45.24)	0.034	1	4.79(0.42–54.26)	0.21
CG or GG	65	80	1.47(1.03–2.11)	0.034	23	1.30(0.77–2.18)	0.33	23	1.87(1.09–3.21)	0.022	9	1.45(0.67–3.14)	0.34
Trend	482	424	1.48(1.06–2.07)	0.020	137	1.35(0.84–2.19)	0.22	101	1.91(1.18–3.10)	0.0086	49	1.52(0.76–3.05)	0.24
STAT3 rs12949918													
TT	152	162			56			45			19		
CT	240	213	0.84(0.63–1.12)	0.24	66	0.74(0.49–1.12)	0.15	45	0.67(0.42–1.06)	0.085	26	0.88(0.47–1.65)	0.69
CC	89	47	0.49(0.33–0.75)	0.00098	14	0.43(0.22–0.81)	0.0094	11	0.42(0.21–0.87)	0.019	4	0.36(0.12–1.08)	0.068
CT or CC	329	260	0.75(0.57–0.98)	0.038	80	0.65(0.44–0.97)	0.035	56	0.60(0.39–0.93)	0.022	30	0.73(0.40–1.35)	0.32
Trend	481	422	0.73(0.60–0.89)	0.0020	136	0.68(0.51–0.90)	0.0080	101	0.66(0.47–0.91)	0.011	49	0.68(0.44–1.06)	0.092
STAT3 rs6503695													
TT	194	206			64			58			27		
CT	223	185	0.78(0.59–1.03)	0.085	64	0.85(0.57–1.26)	0.42	35	0.53(0.33–0.85)	0.0077	19	0.62(0.33–1.15)	0.13
CC	64	33	0.49(0.31–0.77)	0.0024	9	0.42(0.20–0.89)	0.024	8	0.41(0.19–0.92)	0.030	3	0.33(0.10–1.14)	0.081
CT or CC	287	218	0.72(0.55–0.93)	0.014	73	0.75(0.51–1.11)	0.15	43	0.50(0.33–0.78)	0.0022	22	0.55(0.31–1.00)	0.051
Trend	481	424	0.73(0.60–0.89)	0.0020	137	0.73(0.54–0.98)	0.035	101	0.59(0.42–0.84)	0.0030	49	0.60(0.37–0.96)	0.033
STAT3 rs7217655													
CC	198	192			68			47			20		

SNPs*	NHL overall				DLBCL				FL				CLL/SLL			
	Controls	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value	Cases	OR(95%CI)	P-value
CT	213	197	0.97(0.73–1.28)	0.81	60	0.81(0.54–1.21)	0.31	45	0.93(0.59–1.46)	0.75	25	1.19(0.64–2.22)	0.58			
TT	67	31	0.48(0.30–0.77)	0.0023	9	0.39(0.18–0.83)	0.014	6	0.39(0.16–0.85)	0.038	4	0.60(0.20–1.82)	0.37			
CT or TT	280	228	0.85(0.65–1.11)	0.23	69	0.71(0.48–1.04)	0.082	51	0.80(0.51–1.24)	0.31	29	1.05(0.57–1.91)	0.88			
Trend	478	420	0.78(0.64–0.96)	0.017	137	0.70(0.52–0.94)	0.017	98	0.74(0.53–1.03)	0.078	49	0.90(0.58–1.40)	0.64			
<i>STAT4 rs932169</i>																
GG	409	331			107			79			38					
CG	70	89	1.57(1.11–2.22)	0.011	28	1.52(0.93–2.48)	0.094	21	1.53(0.88–2.65)	0.13	10	1.56(0.74–3.27)	0.24			
CC	1	3	3.53(0.36–34.30)	0.28	1	4.31(0.27–70.05)	0.30	1	3.99(0.25–65.0)	0.33	1	9.79(0.59–163)	0.11			
CG or CC	71	92	1.60(1.13–2.25)	0.0074	29	1.56(0.96–2.53)	0.073	22	1.57(0.92–2.71)	0.10	11	1.69(0.82–3.46)	0.15			
Trend	480	423	1.59(1.14–2.22)	0.0059	136	1.57(0.98–2.50)	0.059	101	1.58(0.94–2.65)	0.081	49	1.77(0.91–3.46)	0.094			
<i>STAT5A rs16967637</i>																
CC	222	219			61			63			27					
AC	215	168	0.79(0.60–1.04)	0.091	64	1.08(0.72–1.60)	0.72	32	0.53(0.33–0.84)	0.0076	20	0.76(0.41–1.40)	0.38			
AA	45	35	0.80(0.50–1.30)	0.37	11	0.88(0.43–1.82)	0.74	6	0.50(0.20–1.23)	0.13	2	0.36(0.08–1.57)	0.17			
AC or AA	260	203	0.79(0.61–1.03)	0.080	75	1.04(0.71–1.53)	0.83	38	0.52(0.34–0.82)	0.0043	22	0.69(0.38–1.25)	0.22			
Trend	482	422	0.85(0.69–1.04)	0.12	136	0.99(0.74–1.34)	0.97	101	0.36(0.42–0.88)	0.0081	49	0.69(0.42–1.12)	0.13			

* Hardy weinberg equilibrium p-value: rs243317 (p=0.30), rs17749316 (p=0.82), rs12949918 (p=0.74), rs6503695 (p=0.99), rs7217655 (p=0.43), rs932169 (p=0.76), and rs16967637 (p=0.49).