Genetic susceptibility to lymphoma

Christine F. Skibola, John D. Curry, Alexandra Nieters

From the Division of Environmental Health Sciences, School of Public Health, 140 Warren Hall, University of California, Berkeley, CA 94720-7360, USA (CFS); Division of Immunology, Department of Molecular and Cell Biology, University of California, Berkeley, California 94720, USA (JDC); Division of Clinical Epidemiology, German Cancer Research Center, 69120 Heidelberg, Germany (AN).

Correspondence:
Christine Skibola, Ph.D., School of Public Health, 140 Earl Warren Hall University of California, Berkeley, Ca. 94720-7360, USA.
E-mail: chrisfs@berkeley.edu

ABSTRACT

Genetic susceptibility studies of lymphoma may serve to identify at risk populations and clarify important disease mechanisms. This review considered all studies published through October 2006 on the contribution of genetic polymorphisms in the risk of lymphoma. Numerous studies implicate the role of genetic variants that promote B-cell survival and growth with increased risk of lymphoma. Several reports including a large pooled study by InterLymph, an international consortium of non-Hodgkin lymphoma (NHL) case-control studies, found positive associations between variant alleles in *TNF* -308G>A and *IL10* -3575T>A genes and risk of diffuse large B-cell lymphoma. Four studies reported positive associations between a *GSTT1* deletion and risk of Hodgkin and non-Hodgkin lymphoma. Genetic studies of folate-metabolizing genes implicate folate in NHL risk, but further studies that include folate and alcohol intakes are needed. Links between NHL and genes involved in energy regulation and hormone production and metabolism may provide insights into novel mechanisms implicating neuro- and endocrine-immune cross-talk with lymphomagenesis. However, this links will need replication in larger populations. Numerous studies suggest that common genetic variants with low penetrance influence lymphoma risk, though replication studies will be needed to eliminate false positive associations.

Key words: lymphoma, genetic susceptibility, SNP, NHL, polymorphisms.

Non-Hodgkin's lymphoma (NHL) is a heterogeneous malignancy of B- and T-cells that involves their uncontrolled clonal expansion in the periphery. B-cell lymphomas make up the majority of cases and, of these, diffuse large B-cell lymphoma (DLCL) and follicular lymphoma (FL) are the two major subtypes.[1] In 2007, NHL will account for approximately 59,000 newly diagnosed cases and 19,000 deaths in the U.S., and over 300,000 cases and 172,000 deaths worldwide. New therapeutic regimens have begun to delay the number of deaths related to NHL, though causes for most cases remain undetermined. Familial aggregations for lymphoproliferative cancers have been documented for lymphomas and leukemias,[2-4] and several large-scale studies have reported associations between family history of hematopoietic malignancy and lymphoma risk.[5-7] However, twin studies do not support the role of highly penetrant genes in NHL risk. It is likely that more common genetic variants, each with apparently minor effects on tumor phenotype, may influence disease susceptibility with a greater population attributable risk. Their additive or multiplicative effects and interactions with environmental and infectious agents probably play a significant role in disease risk but have yet to be estimated due to the large populations required to measure them. To date, a number of case-control association studies have examined the role of genetic polymorphisms in the risk of lymphoma and several genetic variants have been identified as potential susceptibility loci. These studies may serve to identify at risk populations and to further clarify important disease mechanisms. In this review, we aim to summarize results of existing genetic association studies of lymphoma, discuss their potential biologic relevance and propose possible areas for future studies. Given the importance of understanding the underlying mechanisms involved in the pathogenesis of lymphoma, first we will briefly describe characteristics of genetic instability that occur as part of normal

B-cell development that may lead to pre-neoplastic changes relevant to lymphoma.

Normal B-cell development and genetic instability: potential underlying mechanisms of lymphomagenesis

B-cells differentiate from hematopoietic stem cells within the bone marrow and their maturation occurs in several stages involving genetic recombination and mutation to generate high affinity antibodies. Recombinase activating gene (RAG) proteins initiate DNA double-strand breaks allowing a fixed set of gene segments variable, diversity, joining (VDJ) to recombine to produce B-cell receptors specific for antigen. During this process, chromosomal translocations and mutations involving the immunoglobulin heavy (IgH) and light (IgL) chain genes and the T-cell receptor genes are common that can deregulate several oncogenes.[8] Further translocations and mutations can occur following antigenic dependent clonal expansion in the lymph nodes involving somatic hypermutation and class switching. These translocations and somatic mutations can disrupt B-cell homeostasis and lead to proliferation, blocked differentiation and immortalization of B-cells. Genetic factors that impair DNA repair can increase the likelihood of these pre-neoplastic lesions. Genomic lesions in B-cells that are not initially lethal could later be modulated by environmental (i.e., infectious agents), epigenetic (i.e., chromosomal hypo-or hypermethylation), disease (i.e., autoimmune disease), and genetic factors (i.e., genetic polymorphisms) that promote B-cell survival and proliferation, and may lead to the development and progression of lymphoma (Figure 1). Below we discuss how genetic polymorphisms may play a contributory role in this process.

Candidate gene association studies of lymphoma

The majority of candidate genes that have been investigated to date can be categorized into *functional groups* based on their potential biologic relevance. One group includes genes that influence DNA integrity and methylation. Polymorphisms in these genes could modulate the rate of chromosomal translocations, efficiency of DNA repair and DNA methylation status. Another major group involves genes that alter B-cell survival and growth including pro-inflammatory and regulatory cytokine genes, and genes involved in innate immunity, oxidative stress, energy regulation and hormone production. Another group are genes involved in xenobiotic metabolism. Risk alleles found in these pathways may provide clues to identify potential lymphomagens. On the basis of these studies, several gene variants have been associated with NHL and some have been replicated in more than one study suggesting their significance in lymphomagenesis. A summary of results from these studies is listed in Table 1 (*Supplementary online*) with particular emphasis on those that reported positive findings.

Genetic polymorphisms that modify DNA integrity and methylation patterns influence lymphoma risk
SNPs in genes involved in DNA double-strand break and repair

The high risk of lymphoproliferative disorders in individuals carrying germline mutations in the ataxia telangiectasia, mutated (*ATM*), and Nijmegen breakage syndrome (NBS1) genes that involve syndromes associated with aberrant DNA double-strand break repair (DSBR) underscores the relevance of this pathway in lymphomagenesis. Single nucleotide polymorphisms (SNPs) that hinder DNA repair mechanisms can increase the likelihood of pre-neoplastic lesions that may be relevant to lymphoma. For example, the *WRN* gene plays a crucial role in DNA DSBR and in other repair pathways. Mutations in this gene are associated with the autosomal recessive disorder, Werner syndrome, characterized by premature aging. More common genetic variants in *WRN* have been associated with NHL in two U.S. studies.[9,10] Specifically, the Arg and Ile alleles of two non-synonymous SNPs in the *WRN* gene (Cys1367Arg, Val114Ile) were underrepresented in NHL cases. Polymorphisms in five other non-homologous end joining /DNA DSBR genes (*LIG4, RAG1, BRCA1, BRCA2, XRCC3*) and in the DNA DSBR checkpoint gene, *TP53*, also have been associated with NHL or specific subtypes.[9-11] These studies highlight the relevance of genetic polymorphisms that may impede DNA DSBR, important during normal B-cell maturation in the bone marrow or as a result of humoral immune response to antigen in germinal centers, in the risk of lymphoma. Alkylating agents and other chemicals, oxidative stress, ionizing radiation and viruses provide other means to compromise genomic integrity. Mammalian cells have evolved numerous defense mechanisms to counter-balance these threats.[12] Mismatch repair recognizes and repairs misplaced nucleotides and, if defective, can lead to microsatellite instability and neoplastic transformation. Two small studies report positive associations with a SNP in the mismatch repair gene, *MSH2* (-6T>C), with NHL [13,14] suggesting the potential relevance of this mechanism. However, there is limited and sometimes contradictory evidence for the role of base excision repair and nucleotide excision repair pathways and lymphoma risk.[9-11]

Genetic polymorphisms in one-carbon metabolism and risk of lymphoma

Epigenetic silencing of tumor suppressor and B-cell specific genes is an important mechanism in hematopoietic malignancies.[15,16] Genetic variants that influence methylation processes may promote lymphoma by mechanisms that involve hypo- or hypermethylation of proto-oncogenes or tumor suppressor genes, respectively, or through viral re-activation. Folate deficiency or genetic variation in folate metabolic pathways can influence DNA methylation patterns and also impede DNA synthesis and repair mechanisms. 5,10-methylenetetrahydrofolate reductase (*MTHFR*) is a key enzyme in the folate metabolic pathway
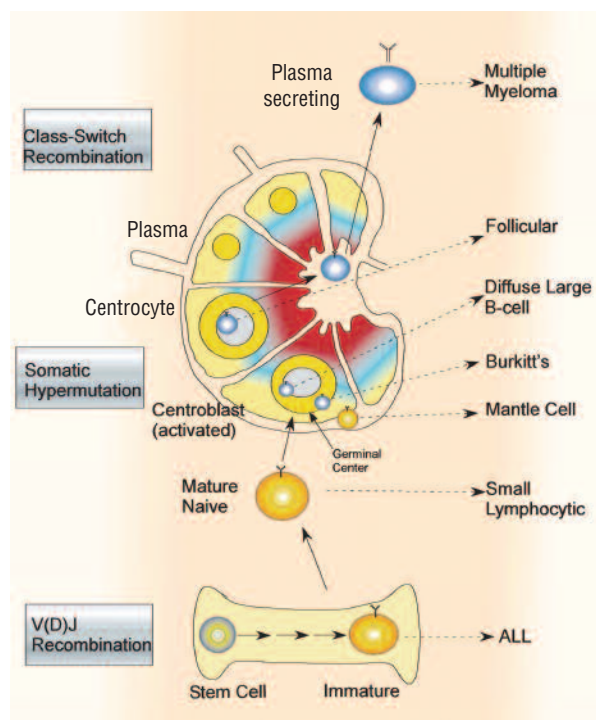
Figure 1. The normal life cycle of B-lymphocytes and the derivation of lymphoma subtypes. During normal B-cell development, hematopoietic stem cells first colonize the bone marrow and give rise to common lymphoid progenitor cells, some of which will differentiate to B-cell lineage. While in the bone marrow, V(D)J recombination machinery rearranges germline immunoglobulin (Ig) gene loci that lead to formation of chromosomal translocations. Mature naïve B-cells that express the B-cell receptor exit the bone marrow to lymph nodes and extra-lymphatic follicles. There, following antigenic stimulation, B-cells become activated undergoing a proliferative burst, generating the formation of germinal centers (GCs). In GCs, proliferating B-cells are subjected to somatic hypermutation directed at Ig genes. In vbb GCs, the most common aggressive lymphoma, diffuse large B-cell lymphoma (DLCL), can originate from activated B-cells, otherwise known as centroblasts, and the most common indolent lymphoma, follicular lymphoma (FL), can derive from centrocytes. FL can also transform to DLCL. Burkitt's lymphoma can derive from IgM-positive blasts of the early GC reaction. Some B-cells in GCs will further differentiate into memory cells while others will become plasma cells, which can give rise to multiple myeloma. Mantle zone lymphomas and some small lymphocytic lymphomas have unmutated V-region genes suggesting they originate from naïve peripheral B-cells. Class switch recombination permits B-cells to switch from membrane-bound to soluble B-cell receptors and also acts aberrantly to cause chromosomal translocations.

that catalyzes the production of 5-methyltetrahydrofolate, a major donor of one-carbon units for DNA synthesis and methylation processes (*Supplementary online Figure 1*). A 677C>T SNP in the *MTHFR* gene, associated with enzyme thermolability,[17] may hinder DNA methylation and shift the flux of one-carbon units toward purine and DNA synthesis and repair. Several NHL studies have examined polymorphisms involved in folate metabolism, although results have been inconsistent.[18-26]

Similar discrepancies also have been reported for polymorphisms in the thymidylate synthase (*TYMS*) and methionine synthase (*MTR*) genes. TYMS plays a critical role in maintaining balanced supplies of deoxynucleotides required for DNA synthesis (*Figure 1 supplementary online*). Impairments of this enzyme have been associated with

chromosome damage and fragile site induction.[27,28] A polymorphic 28-bp double (versus triple) repeat in the promoter region and a 6-bp deletion in the 3'UTR of the *TYMS* gene hinders *TYMS* gene expression and mRNA stability that may increase the rate of DNA double-strand breaks and chromosomal translocations. Positive associations with NHL have been reported for the 28-bp double repeat in an Asian study[29] and with the triple repeat in a British study,[19] but no associations were found in a U.S. study.[18] Furthermore, the 6-bp deletion has been positively[19] and inversely[18] associated with NHL. *MTR* catalyzes the re-methylation of homocysteine to methionine. The Gly allele of a SNP in the *MTR* gene (*MTR* 2756A>G, Asp919Gly), associated with lower homocysteine levels than the Asp allele, was inversely associated with lymphoma subtypes in Caucasians[24-26] and positively associated with NHL in another Caucasian study[18] and in an Asian population.[20,30]

Findings involving folate-metabolizing genes suggest a role for folate in lymphomagenesis that may involve DNA methylation and repair infidelity. The inconsistent findings in some studies may result from differences in folate status across populations since the influence of genetic variation on disease risk may be modified by folate status. Therefore, studies are needed that consider the complex interrelationship between genetics, folate intake, vitamin B_6 and B_{12}, and other factors that may affect vitamin B status such as alcohol.

SNPs that alter B-cell survival and growth influence lymphoma risk

Studies suggest that chronic inflammation may enhance lymphocyte neoplastic transformation by promoting proliferation and survival of mutated cells through activation of nuclear factor (NF)-κB and AP-1 response genes.[31] Obesity, autoimmune disease, infection, chemical exposures, and other inflammatory mediators that exacerbate oxidative stress can induce chronic inflammation. SNPs in genes involved in these processes may also play an important role in the pathogenesis of lymphoid neoplasms (*Figure 2 online*).

SNPs in pro-inflammatory cytokine genes influence risk of lymphoma

In perhaps the most noteworthy NHL risk alleles reported to date are SNPs in the tumor necrosis factor (TNF) and interleukin (*IL*)10 genes, reported by InterLymph, an international consortium of lymphoma epidemiological case-control studies.[32] Researchers found that the *TNF* –308AA genotype conferred 25% and 65% increased risks for NHL and DLCL respectively.[32] Similarly, polymorphisms in the *IL10* distal (-3575A>T) and proximal promoter (-1082A>G) regions, specifically the low IL-10 producer –3575A and –1082G alleles, were associated with modest increases in DLCL, but not FL risk. TNF-α, mainly produced by mast cells, macrophages and other immune cells, is a pro-inflammatory immunoregulatory cytokine and a key

mediator of lymphocyte responses, natural killer cell activity and dendritic cell maturation. Elevated TNF-α expression augments anti-apoptotic behavior in B-cells through NF-κB activation that induces several anti-apoptotic factors including members of the Bcl2 family, cellular inhibitors of apoptosis, and cell cycle regulators[33] (*Figure 2 online*). The *TNF* –308A allele has been associated with higher constitutional and inducible expression of TNF-α,[34] and increased susceptibility for rheumatoid arthritis and Sjogren syndrome.[35] IL-10 is a potent immunoregulatory cytokine of T-cells produced by monocytes and lymphocytes that hinders the inflammatory response by inducing apoptosis in mast cells and macrophages, thus inhibiting TNF-α production.[39] Genetic factors that up-regulate TNF-α or down-regulate IL-10 may provide a pro-inflammatory milieu that favors lymphomagenesis. Recent studies exploring other *TNF* and *IL10* variants and haplotypes found further evidence for associations with NHL.[36-39] However, a number of studies reported conflicting results for another *TNF* variant (–857C>T).[39-42] The *TNF* gene is located on chromosome 6p21 in the human leukocyte antigen (HLA) class III region in close proximity to several other immunoregulatory factors. Inconsistent results in variant-disease associations located in this region may be the result of population differences in linkage disequilibrium between the studied variant and the *causal* variant elsewhere in the HLA region. Fine mapping of the HLA region will help to clarify this and should be a major objective in future genetic studies of NHL. IL-6 is a pro-inflammatory cytokine involved in regulation of immune defense mechanisms through initiation of acute phase responses. IL-6 serum levels have been positively associated with adiposity and type 2 diabetes, and elevated levels have been detected in HL patients. Studies by InterLymph found no association between an *IL6* promoter polymorphism (-174G>C) and NHL risk.[32] However, inverse associations have been reported between the -174C allele and risk of young adult HL,[43] young adult nodular lymphocyte predominant HL[44] and T-cell lymphoma,[37] but no associations have been found for multiple myeloma or CLL.[45,46] Inverse associations also have been reported between the *IL6* –174C allele and systemic-onset juvenile chronic arthritis[47] and Kaposi sarcoma in HIV-positive men.[48] An anti-inflammatory phenotype for the *IL6* –174C allele has been recently described involving elevated apolipoprotein (Apo)-C1 levels and reduced heat shock protein 60 autoantibodies and platelet factor 4 protein levels in serum of healthy adults.[49] Thus, the protective effects of the *IL6* –174C allele for HL suggest the relevance of inflammatory and pro-oxidative processes in HL that will require further investigation.

SNPs in the innate immunity genes, toll-like receptor 4 (TLR4) and caspase recruitment domain family, member 15 (CARD15/NOD2), influence lymphoma risk

NOD2 and TLR4 are pro-inflammatory mediators integral as a first line of defense against viral and bacterial infection, providing non-specific protection against numerous pathogens. NOD2 directs antimicrobial activity through a NF-κB-mediated pathway of inflammation and apoptosis.[50] A rare *CARD15* C insertion at nucleotide 1007 results in a premature stop codon that has been linked to autoimmune disorders such as Crohn's disease and psoriasis,[51] and to an excess risk of lymphoma.[52] Furthermore, studies by the InterLymph consortium found that this insertion was associated with an elevated, but imprecise, risk estimate for NHL (OR=2.3, 95% CI 0.12–135).[32] Yet another polymorphism in *CARD15* (Arg702Trp) was recently associated with an elevated risk of MALT lymphoma among *H. pylori* infected individuals.[53] Recent studies describe a *CARD15* C insertion phenotype associated with reduced intestinal expression of α- and β-defensins[54] that may compromise the intestinal antimicrobial barrier. The link between Crohn's disease and NHL and the association of NHL, and the *CARD15* variants, suggest that antigenic challenges to lymphoid tissue in the gastrointestinal tract can alter immune system responses and influence disease risk. Thus, further study of *CARD15* mutations and the role of defensins in NHL may be warranted.

The *TLR4* gene facilitates pro-inflammatory cytokine release by human cells in response to lipopolysaccharide, and mediates tolerance and B-cell activation. A *TLR4* polymorphism (Asp299Gly) in the extracellular domain weakens receptor signaling and reduces IL-12 and IFNγ levels. The *TLR4* 299Gly allele was inversely associated with risk of gastric MALT lymphoma[55] and DLCL,[52] and positively associated with MALT lymphoma and HL.[56] Nieters *et al*. also reported that a –16933T>A SNP in the *TLR2* gene, another important pattern recognition receptor involved in the resolution of inflammation, increased risk of FL. These studies suggest that SNPs in TLR signaling pathways may differentially affect risk of lymphoma subtypes, but will require replication in larger study populations. Furthermore, two studies reported that a functional variant (His165Arg) of an important innate immune response gene, the receptor for the FC portion of immunoglobulin G (*FCGR2A*), conferred an elevated NHL risk.[38,39] The Arg variant might favor lymphomagenesis based on impaired immunoglobulin G2-mediated phagocytosis[57] and promotion of antibody-based inflammation.[58]

Oxidative stress genes are implicated in NHL

Reactive oxygen species (ROS) are implicated in several inflammatory conditions and in cancer risk. Phagocytic macrophages and neutrophils are the initial inflammatory response against infectious agents and antigens. These cells undergo a respiratory burst, where the membrane-bound enzymes, NADPH-oxidase and nitric oxide synthase (NOS), produce superoxide anion radicals and nitric oxide radicals. The Leu/Leu genotype of a non-synonymous SNP in the nitric oxide synthase gene (*NOS2A* Ser608Leu), located in a functionally relevant domain, has been associated with gastric cancer[59] and a 2 to 3-fold increased risk

for NHL, DLCL and FL.[60] Bacterial infections such as *H. pylori* are characterized by extensive infiltration of neutrophils that release myeloperoxidase (MPO) which increases the oxidative potential of hydrogen peroxides in affected tissues. Heterozygosity for a *MPO* -463G>A SNP was over-represented among NHL cases, particularly for DLCL and MZL.[60] Conversion of the superoxide anion to hydrogen peroxide is spontaneous or catalyzed by superoxide dismutase (SOD). Expression of the mitochondrial antioxidant enzyme, manganese SOD (SOD2), is induced by the pro-inflammatory cytokines, IL-1 and TNF-α. The variant Ala allele of a non-synonymous SNP in *SOD2* (Val16Ala) that increases ROS scavenging[61] was associated with a marginal increased risk of B-cell lymphomas.[60] However, a pooled analysis of 1,593 NHL cases and 2,517 controls found no association of this variant with overall NHL risk, but homozygosity for the 16Ala allele was associated with decreased MZL risk.[62] In the same study, a variant in glutathione peroxidase 1 (*GPX1* Pro197Leu) conferred 25% and 33% increased risks of NHL and FL respectively.[62] Glutathione peroxidase is one of the most important antioxidant enzymes in humans that catalyzes the detoxification of hydrogen peroxide. These studies implicate pro-oxidant mechanisms that enhance free radical damage in increasing disease susceptibility. This may be particularly relevant in lymphocytes where chronic inflammation may increase the risk of neoplastic changes characteristic of the marginal-zone lymphomas.

SNPs in energy regulation genes are implicated in risk of NHL

An association between obesity and hemato-lymphopoietic cancers has been seen, with increased risks reported for NHL, leukemia and multiple myeloma.[63] Obesity is associated with impaired immune function and generalized inflammation characterized by increased circulation of pro-inflammatory mediators such as leptin, TNF-α, IL-6, C-reactive protein and reduced levels of the anti-inflammatory peptide, ghrelin. Links between NHL and polymorphisms in the leptin (*LEP*), leptin receptor (*LEPR*), neuropeptide Y (*NPY*) and ghrelin (*GHRL*) genes may provide new insights into mechanisms of lymphomagenesis involving neuro-immune cross-talk. NPY acts on the central nervous system as a strong appetite stimulator controlled by positive and negative feedback actions of ghrelin and leptin respectively to regulate energy balance. Obesity upsets this fine balance, resulting in leptin resistance, and elevated leptin and reduced ghrelin production. Leptin, NPY and ghrelin also exert major influences on humoral and cellular immune functions.[64,65] Notably, leptin promotes proinflammory cytokine release, anti-apoptotic behavior in lymphocytes and oxidative stress.[66] NPY suppresses innate immunity through natural killer cell activity inhibition, and increases adhesion, chemotaxis, phagocytosis and superoxide anion production in macrophages. Ghrelin stimulates growth hormone release and inhibits proliferation of inflammatory cytokines.

In a U.S. study, Skibola *et al.* found that the G allele for a SNP in the promoter region of the *LEP* gene (19A>G) gave up to a 2-fold increased risk of NHL, particularly FL.[67] Further, gene-gene interaction was reported between LEP –2548G>A and *LEPR* Gln223Arg polymorphisms. Similar associations were observed in a U.K. study that found a 50% reduced FL risk associated with the *LEP* –19AA genotype and a 90% increased risk of FL among women associated with the *LEPR* 223ArgArg genotype.[68] In the U.S. study population, four closely linked *NPY* variants were associated with up to a two-fold increased risk for NHL and FL.[69] Of these, an *NPY* 1128T>C functional SNP may be particularly relevant as it has been associated with elevated NPY levels, enhanced angiogenesis, and lymphocyte proliferation.[70] Furthermore, two variants in the *GHRL* gene (-4427G>A and 5179A>G) gave 20-70% reduced risks for NHL, especially for DLCL, though no associations were found in the functionally relevant Leu72Met SNP[69] percent that has been associated with reduced BMI and abdominal visceral fat. These studies further implicate obesity in the pathogenesis of NHL that may involve its adverse action on immune system functions.

SNPs in genes involved in sex hormone production and metabolism influence lymphoma risk

Other less obvious but noteworthy loci linked to lymphoma are SNPs in genes that influence sex hormone production and metabolism. Prolactin and estrogens, important in female reproduction, also function as immune modulators that affect apoptosis, activation and proliferation of immune cells, and promote B-cell proliferation and survival. Elevated prolactin levels have been associated with progression of hematological diseases such as AML and NHL.[71,72] Two studies investigating SNPs in the *CYP17A1* gene that encodes a key enzyme involved in estrogen and testosterone synthesis[73,74] reported that the homozygous variant for a *CYP17A1* 34T>C SNP conferred a 40% increase in NHL risk, particularly for DLCL, where risks for the –34CC genotype were ~2-fold. The *CYP17* –34CC genotype has been previously associated with elevated serum dehydroepiandrosterone sulphate and estradiol levels.[75] Skibola *et al.* also found that SNPs in the catechol-O-methyltransferase (*COMT*) gene, involved in estrogen metabolism, and in the prolactin (*PRL*) gene, that influences lymphocyte prolactin levels, were associated with lymphoma risk.[73] These results highlight a potential role of sex hormones in lymphoid tissue proliferation and ultimate neoplastic transformation.

Limited evidence for detoxification genes in risk of lymphoma

Glutathione S-transferases (*GSTM1, GSTT1, GSTP1*) are involved in the detoxification of a wide range of carcinogens, including benzene, organochlorine compounds, organophosphate pesticides, tobacco smoke, chemotherapeutic agents and reactive oxygen species. Deletion polymorphisms in *GSTM1* (*GSTM1*0*) and *GSTT1* (*GSTT1*0*)
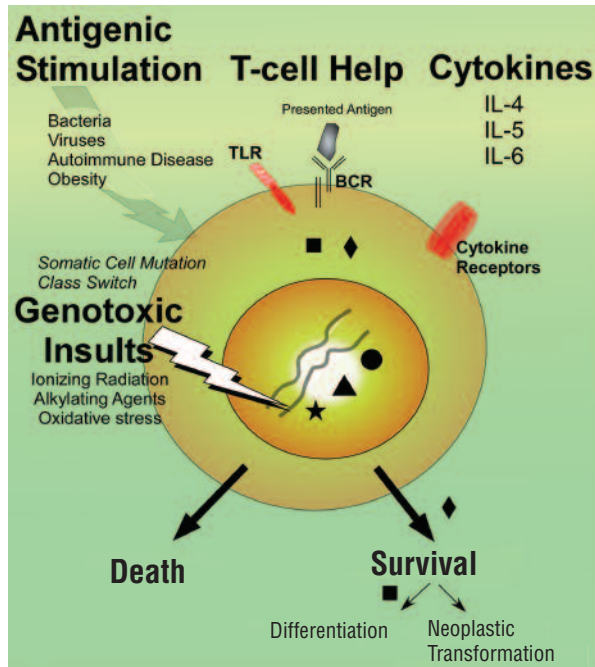
Figure 2. Environmental and genetic influences on fate of a naive mature B-cell encountering antigen. In early and late stages of B-cell development, genetic polymorphisms and environmental exposures influence the fate of a B-cell and its chances of undergoing neoplastic transformation. Genetic polymorphisms that influence DNA repair (G) such as *XRCC3* and *TYMS* can increase the likelihood of chromosomal translocations and mutations that occur during normal B-cell maturation and as a result of genotoxic environmental exposures or endogenous genotoxic processes including class switch recombination and somatic cell hypermutation. Polymorphisms that impair DNA methylation (P) such as in the *MTHFR* and *MTR* genes may promote lymphoma by mechanisms involving hypo- or hypermethylation of proto-oncogenes or tumor suppressor genes. SNPs in genes that deliver positive signals for B-cell growth and survival (R), such as in *TNF*, *LEP* and *CYP17A1*, or that block differentiation (L), such as in *BCL-6*, can enhance immortalization of B-cells. Oxidative stress genes such as *SOD2* and *NOS2A* (*) may influence whether cells are protected from the harmful effects of reactive oxygen species. Chronic antigenic stimulation of B-cells, through infection or pro-inflammatory conditions such as autoimmune disease or obesity, can activate B-cells and enhance their proliferation and survival. For lymphoma, this may be particularly relevant to growth, survival and ultimate transformation of B-cells that already carry pre-neoplastic lesions. SNPs can heighten these inflammatory responses (i.e., in pro-inflammatory cytokines, oxidative stress genes). The consistent associations found between B-cell NHL with genetic variants in pro-inflammatory factors such as *TNF* and leptin and the association of viral, bacterial, and other exogenous agents leading to persistent inflammation, suggest this to be a relevant mechanism underlying lymphomagenesis.

result in loss of enzymatic activity. Evidence of higher risk of NHL and HL in *GSTT1* null homozygotes was reported in several studies.[76-79] Proposed mechanisms could include impaired neutralization of reactive oxygen species or reduced deactivation of carcinogenic intermediates of polycyclic aromatic hydrocarbons. No associations were found between *GSTM1* and *GSTP1* polymorphisms and NHL risk.[76,80,81] Homozygous variants of a paraoxonase-1 (*PON1*) Gln192Arg SNP that determines efficiency of hydrolysis and detoxification of specific organophosphates[82] was associated with a 2.5-fold elevated NHL risk.[76] The 192Arg allele also has been implicated in

organophosphate toxicity in sheep farmers that dip animals in the pesticide diazinon.[83] Another study found no effect of the Gln192Arg variant, but an increased risk of FL and T-NHL associated with a non-synonymous *PON1* Leu55Met variant.[84] Single reports also suggest some relevance of genetic variants in phase I cytochrome P450 enzymes (*CYP1B1, CYP2E1*) and epoxide hydrolase 1 (*EPHX1*) in the etiology of lymphomas.[80,84] These enzymes metabolize benzene, ethanol, halogenated solvents and xenobiotic epoxide substrates, respectively. N-acetyltransferase enzymes, *NAT1* and *NAT2*, catalyze the metabolization of aromatic and heterocyclic amines via N- or O-acetylation. One large study found a 60% increased risk associated with the *NAT1*10/10 genotype and a 20% increased risk in intermediate and rapid *NAT2* acetylators compared to slow acetylators.[85] Interestingly, among intermediate/rapid acetylators, NHL risk was specifically elevated among current smokers compared with non-smokers (OR=2.44, 95%CI=1.15-5.20)[85] highlighting the importance of combined gene-environment analysis. Other smaller studies found only limited evidence for a role of *NAT1* and *NAT2* variants in lymphomagenesis.[75,81,86]

Despite their crucial role in activation of potential carcinogens and detoxification of putative environmental lymphomagens, with the exception of *GSTT1*0, there are few genetic data on the contribution of xenobiotic metabolizing genes in the pathogenesis of lymphomas even in occupationally exposed populations.

Additional studies needed to explore the HLA region

The HLA region located on chromosome 6 (6p21.3) has now been mapped and approximately 220 genes have been defined. Many of these genes encode proteins involved in immune and inflammatory responses such as *TNF, LTA*, heat shock protein 70 and *PRL*.[87] Few studies have explored the association of HLA genes with lymphoid malignancies; existing reports are mainly for HL. Two consecutive markers, D6S265 and D6S510, located in the HLA class I region have been identified as susceptibility loci for EBV-positive HL.[88] Furthermore, some studies have identified HL-associated HLA class II susceptibility alleles.[89,90] What has emerged from these studies is that HLA-*DPB1*0301 appears to give susceptibility and *DPB1*0201 resistance to HL. Also, HLA class II *DRB1*1501 and *DQB1*0602 alleles, or linked loci, may increase risk of sporadic and familial HL.[89,91] Thus far, few studies have explored the association of HLA polymorphisms with NHL risk and results have been inconclusive.[92,93] Fine map genotyping in the HLA region may help to clarify the significance of variability in this region for HL and other lymphoma subtypes.

Genome screens

Few genome screens for lymphoma have been performed to date. Recently, a genome-wide linkage search of 115 families segregating CLL with or without additional B-cell lymphoproliferative disorders found evidence for a major susceptibility locus on the pericentric

region of chromosome11 (chr11p11).[94] Linkage was suggested for four other chromosomal regions (5q22-23, 6p22, 10q25, and 14q32). Furthermore, a genome screen on 44 high-risk families for HL identified strong linkage on chromosome 4 (near marker D4S394) and suggestive linkage on chromosomes 2 and 11.[95] Larger studies involving dense mapping in these regions and more exploratory studies involving whole genome scans for NHL will help to describe disease mechanisms and identify relevant pathways. To this end, plans for collaborative genome scan studies involving InterLymph consortium investigators are currently underway.

Conclusions

Case-control association studies provide further support for a genetic component to lymphoma. These studies suggest that disease mechanisms involving faulty DNA repair and genetic and environmental factors that deliver positive signals for B-cell survival and proliferation play important roles in lymphomagenesis (Figure 2). However, some genetic associations presented in this review may be false positive associations due to population stratification, improper control selection, genotyping error or other underlying causes. To date, most association studies have been limited by population size, restricting the potential investigation of gene-gene and gene-environment interactions. Larger collaborative studies using dense mapping to refine candidate regions, and exploratory studies involving whole genome scans followed by replication and multi-center pooled analyses will help to eliminate false positive findings, further clarify disease mechanisms and identify relevant pathways. InterLymph's successful identification of two susceptibility alleles in *TNF* and IL10 highlight the importance of consortia to validate biomarkers, particularly related to NHL subtypes. A thorough exposure assessment using biomarkers and the WHO-defined classification of lymphoma subtypes will also be needed to assess gene-environment interactions. Functional studies such as animal knockout or knockdown models and cellular models will help verify actual disease-predisposing variants to establish that the identified *causal variant* alters function and that the sequence change contributes to the illness phenotype. To summarize, these studies will broaden our current understanding of important mechanistic pathways involved in lymphomagenesis and provide clues about environmental agents and lifestyle exposures that contribute to disease risk that may be translated to NHL screening, prevention or treatment regimens.

Authors' Contributions

CFS and AN wrote the manuscript; JDC contributed to the table designs and legends.

References

1. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting--Airlie House, Virginia, November, 1997. Hematol J 2000; 1:53-66.
2. Segel GB, Lichtman MA. Familial (inherited) leukemia, lymphoma, and myeloma: an overview. Blood Cells Mol Dis 2004;32:246-61.
3. Linet MS, Pottern LM. Familial aggregation of hematopoietic malignancies and risk of non-Hodgkin's lymphoma. Cancer Res 1992 Oct 1;52 Suppl 19:5468s-73s.
4. Houlston RS, Catovsky D, Yuille MR. Genetic susceptibility to chronic lymphocytic leukemia. Leukemia 2002;16:1008-14.
5. Goldin LR, Pfeiffer RM, Li X, Hemminki K. Familial risk of lymphoproliferative tumors in families of patients with chronic lymphocytic leukemia: results from the Swedish Family-Cancer Database. Blood 2004;104:1850-4.
6. Chang ET, Smedby KE, Hjalgrim H, Porwit-MacDonald A, Roos G, Glimelius B, et al. Family history of hematopoietic malignancy and risk of lymphoma. J Natl Cancer Inst 2005;97:1466-74.
7. Altieri A, Bermejo JL, Hemminki K. Familial risk for non-Hodgkin lymphoma and other lymphoproliferative malignancies by histopathologic subtype: the Swedish Family-Cancer Database. Blood 2005;106:668-72.
8. Willis TG, Dyer MJ. The role of immunoglobulin translocations in the pathogenesis of B-cell malignancies. Blood 2000;96:808-22.
9. Shen M, Zheng T, Lan Q, Zhang Y, Zahm SH, Wang SS, et al. Polymorphisms in DNA repair genes and risk of non-Hodgkin lymphoma among women in Connecticut. Hum Genet 2006;119:659-68.
10. Hill DA, Wang SS, Cerhan JR, Davis S, Cozen W, Severson RK, et al. Risk of non-Hodgkin lymphoma (NHL) in relation to germline variation in DNA repair and related genes. Blood 2006;.
11. Smedby KE, Lindgren CM, Hjalgrim H, Humphreys K, Schollkopf C, Chang ET, et al. Variation in DNA repair genes ERCC2, XRCC1, and XRCC3 and risk of follicular lymphoma. Cancer Epidemiol Biomarkers Prev 2006;15:258-65.
12. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:1513-30.
13. Mino C, Fiallo BF, Morillo SA, Acosta A, Gimenez P, Ocampo L, et al. Analysis of the polymorphism [gIVS12-6T > C] in the hMSH2 gene in lymphoma and leukemia. Leuk Lymphoma 2003;44:505-8.
14. Hishida A, Matsuo K, Hamajima N, Ito H, Ogura M, Kagami Y, et al. Polymorphism in the hMSH2 gene (gIVS 12-6T-->C) and risk of non-Hodgkin lymphoma in a Japanese population. Cancer Genet Cytogenet 2003;147:71-4.
15. Ushmorov A, Leithauser F, Sakk O, Weinhausel A, Popov SW, Moller P, et al. Epigenetic processes play a major role in B-cell-specific gene silencing in classical Hodgkin lymphoma. Blood 2006;107:2493-500.
16. Galm O, Herman JG, Baylin SB. The fundamental role of epigenetics in hematopoietic malignancies. Blood Rev 2006;20:1-13.
17. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995; 10:111-3.
18. Skibola CF, Forrest MS, Coppede F, Agana L, Hubbard A, Smith MT, et al. Polymorphisms and haplotypes in folate-metabolizing genes and risk of non-Hodgkin lymphoma. Blood 2004;104:2155-62.
19. Lightfoot TJ, Skibola CF, Willett EV, Skibola DR, Allan JM, Coppede F, et al. Risk of non-Hodgkin lymphoma associated with polymorphisms in folate-metabolizing genes. Cancer

Epidemiol Biomarkers Prev 2005; 14:2999-3003.

20. Matsuo K, Hamajima N, Suzuki R, Ogura M, Kagami Y, Taji H, et al. Methylenetetrahydrofolate reductase gene (MTHFR) polymorphisms and reduced risk of malignant lymphoma. Am J Hematol 2004; 77: 351-7.

21. Gemmati D, Ongaro A, Scapoli GL, Della PM, Tognazzo S, Serino ML, et al. Common gene polymorphisms in the metabolic folate and methylation pathway and the risk of acute lymphoblastic leukemia and non-Hodgkin's lymphoma in adults. Cancer Epidemiol Biomarkers Prev 2004;13:787-94.

22. Toffoli G, Rossi D, Gaidano G, Cecchin E, Boiocchi M, Carbone A. Methylenetetrahydrofolate reductase genotype in diffuse large B-cell lymphomas with and without hypermethylation of the DNA repair gene O6-methylguanine DNA methyltransferase. Int J Biol Markers 2003;18:218-21.

23. Rudd MF, Sellick GS, Allinson R, Matutes E, Catovsky D, Houlston RS. MTHFR polymorphisms and risk of chronic lymphocytic leukemia. Cancer Epidemiol Biomarkers Prev 200;13:2268-70.

24. Lincz LF, Scorgie FE, Kerridge I, Potts R, Spencer A, Enno A. Methionine synthase genetic polymorphism MS A2756G alters susceptibility to follicular but not diffuse large B-cell non-Hodgkin's lymphoma or multiple myeloma. Br J Haematol 2003; 120:1051-4.

25. Linnebank M, Schmidt S, Kolsch H, Linnebank A, Heun R, Schmidt-Wolf IG, et al. The methionine synthase polymorphism D919G alters susceptibility to primary central nervous system lymphoma. Br J Cancer 2004;90:1969-71.

26. Niclot S, Pruvot Q, Besson C, Savoy D, Macintyre E, Salles G, et al. Implication of the folate-methionine metabolism pathways in susceptibility to follicular lymphomas. Blood 2006;108:278-85.

27. Hori T, Ayusawa D, Shimizu K, Koyama H, Seno T. Assignment of human gene encoding thymidylate synthase to chromosome 18 using interspecific cell hybrids between thymidylate synthase-negative mouse mutant cells and human diploid fibroblasts. Somat Cell Mol Genet 1985;11:277-83.

28. Hori T, Ayusawa D, Shimizu K, Koyama H, Seno T. Chromosome breakage induced by thymidylate stress in thymidylate synthase-negative mutants of mouse FM3A cells. Cancer Res 1984;44:703-9.

29. Hishida A, Matsuo K, Hamajima N, Ito H, Ogura M, Kagami Y, et al. Associations between polymorphisms in the thymidylate synthase and serine hydroxymethyltransferase genes and susceptibility to malignant lymphoma. Haematologica 2003; 88:159-66.

30. Matsuo K, Suzuki R, Hamajima N, Ogura M, Kagami Y, Taji H, et al. Association between polymorphisms of folate- and methionine-metabolizing enzymes and susceptibility to malignant lymphoma. Blood 2001;97:3205-9.

31. Karin M, Cao Y, Greten FR, Li ZW. NF-kB in cancer: from innocent bystander to major culprit. Nat Rev Cancer 2002;2:301-10.

32-. 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;7:27-38.

33. Karin M, Greten FR. NF-kB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 2005;5:749-59.

34. Allen RD. Polymorphism of the human TNF-alpha promoter--random variation or functional diversity? Mol Immunol 1999;36:1017-27.

35. Bayley JP, Ottenhoff TH, Verweij CL. Is there a future for TNF promoter polymorphisms? Genes Immun 2004;5:315-29.

36. Spink CF, Keen LJ, Mensah FK, Law GR, Bidwell JL, Morgan GJ. Association between non-Hodgkin lymphoma and haplotypes in the TNF region. Br J Haematol 2006; 133:293-300.

37. 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; 107:4101-8.

38. Wang SS, Cerhan JR, Hartge P, Davis S, Cozen W, Severson RK, et al. Common genetic variants in proinflammatory and other immunoregulatory genes and risk for non-Hodgkin lymphoma. Cancer Res 2006; 66:9771-80.

39. Purdue MP, Lan Q, Kricker 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; 28:704-12.

40. Hellmig S, Fischbach W, Goebeler-Kolve ME, Folsch UR, Hampe J, Schreiber S. A functional promotor polymorphism of TNF-alpha is associated with primary gastric B-Cell lymphoma. Am J Gastroenterol 2005;100:2644-9.

41. Wu MS, Chen LT, Shun CT, Huang SP, Chiu HM, Wang HP, et al. Promoter polymorphisms of tumor necrosis factor-alpha are associated with risk of gastric mucosa-associated lymphoid tissue lymphoma. Int J Cancer 2004;110:695-700.

42. Tsukasaki K, Miller CW, Kubota T, Takeuchi S, Fujimoto T, Ikeda S, et al. Tumor necrosis factor alpha polymorphism associated with increased susceptibility to development of adult T-cell leukemia/lymphoma in human T-lymphotropic virus type 1 carriers. Cancer Res 2001;61:3770-4.

43. Cozen W, Gill PS, Ingles SA, Masood R, Martinez-Maza O, Cockburn MG, et al. IL-6 levels and genotype are associated with risk of young adult Hodgkin lymphoma. Blood 2004;103:3216-21.

44. Cordano P, Lake A, Shield L, Taylor GM, Alexander FE, Taylor PR, et al. Effect of IL-6 promoter polymorphism on incidence and outcome in Hodgkin's lymphoma. Br J Haematol 2005;128:493-5.

45. Zheng C, Huang DR, Bergenbrant S, Sundblad A, Osterborg A, Bjorkholm M, et al. Interleukin 6, tumour necrosis factor alpha, interleukin 1b and interleukin 1 receptor antagonist promoter or coding gene polymorphisms in multiple myeloma. Br J Haematol 2000;10:39-45.

46. Hulkkonen J, Vilpo J, Vilpo L, Koski T, Hurme M. Interleukin-1b, interleukin-1 receptor antagonist and interleukin-6 plasma levels and cytokine gene polymorphisms in chronic lymphocytic leukemia: correlation with prognostic parameters. Haematologica 2000;85:600-6.

47. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369-76.

48. Foster CB, Lehrnbecher T, Samuels S, Stein S, Mol F, Metcalf JA, et al. An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in men infected with human immunodeficiency virus. Blood 2000; 96: 2562-7.

49. Hegedus CM, Skibola CF, Bracci PM, Holly EA, Smith MT. Screening the human serum proteome for genotype-phenotype associations: An analysis of the IL6-174G>C polymorphism. Proteomics 2007; 7:548-57.

50. Chamaillard M, Philpott D, Girardin SE, Zouali H, Lesage S, Chareyre F, et al. Gene-environment interaction modulated by allelic heterogeneity in inflammatory diseases. Proc Natl Acad Sci USA 2003;100:3455-60.

51. Yamada R, Ymamoto K. Recent findings on genes associated with inflammatory disease. Mutat Res 2005;573:136-51.

52. Forrest MS, Skibola CF, Lightfoot TJ, Bracci PM, Willett EV, Smith MT, et al. Polymorphisms in innate immunity genes and risk of non-Hodgkin lymphoma. Br J Haematol 2006; 134:180-3.

53. Rosenstiel P, Hellmig S, Hampe J, Ott S, Till A, Fischbach W, et al. Influence of polymorphisms in the NOD1/CARD4 and NOD2/CARD15 genes on the clinical outcome of Helicobacter pylori infection. Cell Microbiol 2006; 8: 1188-98.

54. Wehkamp J, Schmid M, Fellermann K, Stange EF. Defensin deficiency, intestinal microbes, and the clinical phenotypes of Crohn's disease. J Leukoc Biol 2005;77:460-5.

55. Hellmig S, Fischbach W, Goebeler-Kolve ME, Folsch UR, Hampe J, Schreiber S. Association study of a

functional Toll-like receptor 4 polymorphism with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma 2005;46:869-72.

56. Nieters A, Beckmann L, Deeg E, Becker N. Gene polymorphisms in Toll-like receptors, interleukin-10, and interleukin-10 receptor alpha and lymphoma risk. Genes Immun 2006; 7:615-24.

57. Salmon JE, Millard S, Schachter LA, Arnett FC, Ginzler EM, Gourley MF, et al. Fcg RIIA alleles are heritable risk factors for lupus nephritis in African Americans. J Clin Invest 1996;97:1348-54.

58. Hogarth PM. Fc receptors are major mediators of antibody based inflammation in autoimmunity. Curr Opin Immunol 2002;14:798-802.

59. Shen J, Wang RT, Wang LW, Xu YC, Wang XR. A novel genetic polymorphism of inducible nitric oxide synthase is associated with an increased risk of gastric cancer. World J Gastroenterol 2004;10:3278-83.

60. Wang SS, Davis S, Cerhan JR, Hartge P, Severson RK, Cozen W, et al. Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma. Carcinogenesis 2006; 27:1828-34.

61. Hiroi S, Harada H, Nishi H, Satoh M, Nagai R, Kimura A. Polymorphisms in the SOD2 and HLA-DRB1 genes are associated with nonfamilial idiopathic dilated cardiomyopathy in Japanese. Biochem Biophys Res Commun 1999;261:332-9.

62. Lightfoot T, Skibola CF, Adamson P, Forest M, Smith A, Morgan G, et al. Polymorphisms in the oxidative stress genes, superoxide dismutase, glutathione peroxidase and catalase and risk of non-Hodgin lymphoma. Haematologica 2006;91:1222-7.

63. Skibola CF. Obesity, diet and risk of non-Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prev 2007; 16:392-5.

64. Bedoui S, Kawamura N, Straub RH, Pabst R, Yamamura T, von Horsten S. Relevance of neuropeptide Y for the neuroimmune crosstalk. J Neuroimmunol 2003;134:1-11.

65. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, et al. Ghrelin inhibits leptin- and activation-induced pro-inflammatory cytokine expression by human monocytes and T cells. J Clin Invest 2004;114:57-66.

66. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911-9.

67. Skibola CF, Holly EA, Forrest MS, Hubbard A, Bracci PM, Skibola DR, et al. Body mass index, leptin and leptin receptor polymorphisms, and non-hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2004; 13:779-86.

68. Willett EV, Skibola CF, Adamson P, Skibola DR, Morgan GJ, Smith MT, et al. Non-Hodgkin's lymphoma, obesity and energy homeostasis polymorphisms. Br J Cancer 2005; 93:811-6.

69. Skibola DR, Smith MT, Bracci PM, Hubbard AE, Agana L, Chi S, et al. Polymorphisms in ghrelin and neuropeptide Y genes are associated with non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2005;14:1251-6.

70. Ding B. Distribution of the NPY 1128C allele frequency in different populations. J Neural Transm 2003; 110:1199-204.

71. Gado K, Rimanoczi E, Hasitz A, Gigler G, Toth BE, Nagy GM, et al. Elevated levels of serum prolactin in patients with advanced multiple myeloma. Neuroimmunomodulation 2001; 9:231-6.

72. Hooghe R, Merchav S, Gaidano G, Naessens F, Matera L. A role for growth hormone and prolactin in leukaemia and lymphoma? Cell Mol Life Sci 1998;54:1095-101.

73. Skibola CF, Bracci PM, Paynter RA, Forrest MS, Agana L, Woodage T, et al. Polymorphisms and haplotypes in the cytochrome P450 17A1, prolactin, and catechol-O-methyltransferase genes and non-Hodgkin lymphoma risk. Cancer Epidemiol Biomarkers Prev 2005; 14:2391-401.

74. Skibola CF, Lightfoot T, Agana L, Smith A, Rollinson S, Kao A, et al. Polymorphisms in cytochrome P450 17A1 and risk of non-Hodgkin lymphoma. Br J Haematol 2005; 129: 618-21.

75. Sharp L, Cardy AH, Cotton SC, Little J. CYP17 gene polymorphisms: prevalence and associations with hormone levels and related factors. a HuGE review. Am J Epidemiol 2004;160:729-40.

76. Kerridge I, Lincz L, Scorgie F, Hickey D, Granter N, Spencer A. Association between xenobiotic gene polymorphisms and non-Hodgkin's lymphoma risk. Br J Haematol 2002; 118:477-81.

77. Rollinson S, Levene AP, Mensah FK, Roddam PL, Allan JM, Diss TC, et al. Gastric marginal zone lymphoma is associated with polymorphisms in genes involved in inflammatory response and antioxidative capacity. Blood 2003;102:1007-11.

78. Hohaus S, Massini G, D'Alo' F, Guidi F, Putzulu R, Scardocci A, et al. Association between glutathione S-transferase genotypes and Hodgkin's lymphoma risk and prognosis. Clin Cancer Res 2003; 9:3435-40.

79. Wu MS, Shun CT, Huang SP, Cheng AL, Chen LT, Lin JT. Effect of interleukin-1b and glutathione S-transferase genotypes on the development of gastric mucosa-associated lymphoid tissue lymphoma. Haematologica 2004;89:1015-7.

80. Sarmanova J, Benesova K, Gut I, Nedelcheva-Kristensen V, Tynkova L, Soucek P. Genetic polymorphisms of biotransformation enzymes in patients with Hodgkin's and non-Hodgkin's lymphomas. Hum Mol Genet 2001;10:1265-73.

81. Chiu BC, Kolar C, Gapstur SM, Lawson T, Anderson JR, Weisenburger DD. Association of NAT and GST polymorphisms with non-Hodgkin's lymphoma: a population-based case-control study. Br J Haematol 2005;128:610-5.

82. Costa LG, Cole TB, Jarvik GP, Furlong CE. Functional genomic of the paraoxonase (PON1) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. Annu Rev Med 2003; 54:371-92.

83. Mackness B, Durrington P, Povey A, Thomson S, Dippnall M, Mackness M, et al. Paraoxonase and susceptibility to organophosphorus poisoning in farmers dipping sheep. Pharmacogenetics 2003;13:81-8.

84. Khalsa SB, Ralph MR, Block GD. Chloride conductance contributes to period determination of a neuronal circadian pacemaker. Brain Res 1990;520:166-9.

85. Morton LM, Schenk M, Hein DW, Davis S, Zahm SH, Cozen W, et al. Genetic variation in N-acetyltransferase 1 (NAT1) and 2 (NAT2) and risk of non-Hodgkin lymphoma. Pharmacogenet Genomics 2006; 16: 537-45.

86. Lemos MC, Cabrita FJ, Silva HA, Vivan M, Placido F, Regateiro FJ. Genetic polymorphism of CYP2D6, GSTM1 and NAT2 and susceptibility to haematological neoplasias. Carcinogenesis 1999;20: 1225-9.

87. Complete sequence and gene map of a human major histocompatibility complex. The MHC sequencing consortium. Nature 1999; 401:921-3.

88. Diepstra A, Niens M, Vellenga E, van Imhoff GW, Nolte IM, Schaapveld M, et al. Association with HLA class I in Epstein-Barr-virus-positive and with HLA class III in Epstein-Barr-virus-negative Hodgkin's lymphoma. Lancet 2005; 365:2216-24.

89. Klitz W, Aldrich CL, Fildes N, Horning SJ, Begovich AB. Localization of predisposition to Hodgkin disease in the HLA class II region. Am J Hum Genet 1994; 54: 497-505.

90. Alexander FE, Jarrett RF, Cartwright RA, Armstrong AA, Gokhale DA, Kane E, et al. Epstein-Barr Virus and HLA-DPB1-*0301 in young adult Hodgkin's disease: evidence for inherited susceptibility to Epstein-Barr virus in cases that are EBV(+ve). Cancer Epidemiol Biomarkers Prev 2001;10:705-9.

91. Harty LC, Lin AY, Goldstein AM, Jaffe ES, Carrington M, Tucker MA, et al. HLA-DR, HLA-DQ, and TAP genes in familial Hodgkin disease. Blood 2002;99:690-3.

92. Nathalang O, Tatsumi N, Hino M, Prayoonwiwat W, Yamane T, Suwanasophon C, et al. HLA class II polymorphism in Thai patients with non-Hodgkin's lymphoma. Eur J Immunogenet 1999;26:389-92.

93. Al Tonbary Y, Abdel-Razek N, Zaghloul H, Metwaly S, El Deek B, El Shawaf R. HLA class II polymorphism in Egyptian children with lymphomas. Hematology 2004; 9:

139-45.

94. Sellick GS, Webb EL, Allinson R, Matutes E, Dyer MJ, Jonsson V, et al. A high-density SNP genome-wide linkage scan for chronic lymphocytic leukemia-susceptibility loci. Am J Hum Genet 2005;77:420-9.

95. Goldin LR, McMaster ML, Ter Minassian M, Saddlemire S, Harmsen B, Lalonde G, et al. A genome screen of families at high risk for Hodgkin lymphoma: evidence for a susceptibility gene on chromosome 4. J Med Genet 2005; 42:595-601.

96. Steffen J, Varon R, Mosor M, Maneva G, Maurer M, Stumm M, et al. Increased cancer risk of heterozygotes with NBS1 germline mutations in Poland. Int J Cancer 2004; 111:67-71.

97. Hishida A, Matsuo K, Tajima K, Ogura M, Kagami Y, Taji H, et al. Polymorphisms of p53 Arg72Pro, p73 G4C14-to-A4T14 at exon 2 and p21 Ser31Arg and the risk of non-Hodgkin's lymphoma in Japanese. Leuk Lymphoma 2004; 45:957-64.

98. Chouchane L, Ahmed SB, Baccouche S, Remadi S. Polymorphism in the tumor necrosis factor-alpha promotor region and in the heat shock protein 70 genes associated with malignant tumors. Cancer 1997;80:1489-96.

99. Demeter J, Porzsolt F, Ramisch S, Schmid M, Messer G. Polymorphism of the tumour necrosis factor-a and lymphotoxin-alpha genes in hairy cell leukaemia. Br J Haematol 1997;97:132-4.

100. Bel Hadj Jrad B, Chatti A, Laatiri A, Ahmed SB, Romdhane A, Ajimi S, et al. Tumor necrosis factor promoter gene polymorphism associated with increased susceptibility to non-Hodgkin's lymphomas. Eur J Haematol 2007; 78: 117-22.

101. Fitzgibbon J, Grenzelias D, Matthews J, Lister TA, Gupta RK. Tumour necrosis factor polymorphisms and susceptibility to follicular lymphoma. Br J Haematol 1999; 107:388-91.

102. Matsuo K, Hamajima N, Suzuki R, Nakamura S, Seto M, Morishima Y, et al. No substantial difference in genotype frequencies of interleukin and myeloperoxidase polymorphisms between malignant lymphoma patients and non-cancer controls. Haematologica 2001; 86: 602-8.

103. Vasku JA, Vasku A, Goldbergova M, Vasku V. Heterozygote AG variant of -596 A/G IL-6 gene polymorphism is a marker for cutaneous T-cell lymphoma (CTCL). Clin Immunol 2004;113:256-60.

104. Breen EC, Boscardin WJ, Detels R, Jacobson LP, Smith MW, O'Brien SJ, et al. Non-Hodgkin's B cell lymphoma in persons with acquired immunodeficiency syndrome is associated with increased serum levels of IL10, or the IL10 promoter -592 C/C genotype. Clin Immunol 2003;109:119-29.

105. Cunningham LM, Chapman C, Dunstan R, Bell MC, Joske DJ. Polymorphisms in the interleukin 10 gene promoter are associated with susceptibility to aggressive non-Hodgkin's lymphoma. Leuk Lymphoma 2003;44:251-5.

106. Lech-Maranda E, Baseggio L, Bienvenu J, Charlot C, Berger F, Rigal D, et al. Interleukin-10 gene promoter polymorphisms influence the clinical outcome of diffuse large B-cell lymphoma. Blood 2004; 103: 3529-34.

107. Dean M, Jacobson LP, McFarlane G, Margolick JB, Jenkins FJ, Howard OM, et al. Reduced risk of AIDS lymphoma in individuals heterozygous for the CCR5-d32 mutation. Cancer Res 1999;59:3561-4.

108. Rabkin CS, Yang Q, Goedert JJ, Nguyen G, Mitsuya H, Sei S. Chemokine and chemokine receptor gene variants and risk of non-Hodgkin's lymphoma in human immunodeficiency virus-1-infected individuals. Blood 1999;93:1838-42.

109. De Roos AJ, Gold LS, Wang S, Hartge P, Cerhan JR, Cozen W, et al. Metabolic gene variants and risk of non-Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prev 2006; 15:1647-53.

110. Wang SS, Cozen W, Severson RK, Hartge P, Cerhan JR, Davis S, et al. Cyclin D1 splice variant and risk for non-Hodgkin lymphoma. Hum Genet 2006;120:297-300.

111. Lossos IS, Jones CD, Zehnder JL, Levy R. A polymorphism in the BCL-6 gene is associated with follicle center lymphoma. Leuk Lymphoma 2001;42:1343-50.

112. 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. J Natl Cancer Inst 2005;97:1616-8.

113. Lan Q, Zheng T, Chanock S, Zhang Y, Shen M, Wang SS, et al. Genetic variants in caspase genes and susceptibility to non-Hodgkin's lymphoma. Carcinogenesis 2007; 28: 823-7.

114. Piras G, Monne M, Uras A, Palmas A, Murineddu M, Arru L, et al. Genetic analysis of the 2q33 region containing CD28-CTLA4-ICOS genes: association with non-Hodgkin's lymphoma. Br J Haematol 2005;129:784-90.

115. Cheng TY, Lin JT, Chen LT, Shun CT, Wang HP, Lin MT, et al. Association of T-cell regulatory gene polymorphisms with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. J Clin Oncol 2006;24:3483-9.

116. Zhu Y, Leaderer D, Guss C, Brown HN, Zhang Y, Boyle P, et al. Ala394Thr polymorphism in the clock gene NPAS2: A circadian modifier for the risk of non-Hodgkin's lymphoma. Int J Cancer 2007;120:432-5.