

To Each Its Own: Linking the Biology and Epidemiology of NHL Subtypes

Jean L. Koff¹ · Dai Chihara² · Anh Phan¹ · Loretta J. Nastoupil² ·
Jessica N. Williams¹ · Christopher R. Flowers¹

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Abstract Non-Hodgkin lymphoma (NHL) constitutes a diverse group of more than 40 subtypes, each characterized by distinct biologic and clinical features. Until recently, pinpointing genetic and epidemiologic risk factors for individual subtypes has been limited by the relative rarity of each. However, several large pooled case-control studies have provided sufficient statistical power for detecting etiologic differences and commonalities between subtypes and thus yield new insight into their unique epidemiologic backgrounds. Here, we review the subtype-specific medical, lifestyle, and biologic components identified in these studies, which suggest that a complex interplay between host genetics, autoimmune

disorders, modifiable risk factors, and occupation contributes to lymphomagenesis.

Keywords Non-Hodgkin lymphoma · Autoimmune disorders · Epidemiology · Biology · NHL subtypes

Introduction

Non-Hodgkin lymphoma represents the most common hematologic malignancy in the world and comprises a heterogeneous group of more than 40 different subtypes [1]. In addition to harboring distinct biologic and clinical features, these subtypes also vary in terms of incidence by age, sex, ethnicity, and geographic distribution. While population-based cancer registry data has been helpful in characterizing the epidemiology of NHL as a whole [2–4], identifying risk factors for individual NHL subtypes has been difficult given the relatively low number of patients affected by each one.

In the last decade, several large epidemiological studies have identified numerous environmental, medical, lifestyle, and genetic risk factors for developing NHL via geospatial analyses, surveys, and examination of single nucleotide variants in genome-wide association studies (GWAS) and other genetic analyses [5–20]. These approaches have been applied to identify clinical, environmental, occupational, and genetic risk factors for specific NHL subtypes. Herein, we review the biologic processes and epidemiologic factors thought to contribute to lymphomagenesis and examine how these factors may interact in the development of specific NHL subtypes.

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✉ Christopher R. Flowers
crflowe@emory.edu

Jean L. Koff
jkoff@emory.edu

Dai Chihara
dchihara@mdanderson.org

Anh Phan
anh.thuy.phan@emory.edu

Loretta J. Nastoupil
lnastoupil@mdanderson.org

Jessica N. Williams
jnwill5@emory.edu

¹ Winship Cancer Institute, Emory University School of Medicine, 1365 Clifton Rd NE, Building B, Suite 4302, Atlanta, GA, USA

² Department of Lymphoma/Myeloma, MD Anderson Cancer Center, University of Texas, 1515 Holcombe Blvd, Unit 0429, Houston, TX, USA

Normal Lymphocyte Maturation: Setting the Stage for Lymphomagenesis

Since an understanding of physiologic B and T cell maturation lends insight into many of the mechanisms underlying lymphomagenesis, a brief review is provided here. During the process of differentiation, normal naïve lymphocytes undergo massive clonal expansion and mutagenesis. This requires major changes in gene expression, mediated in part by transcription factors, histone-modifying enzymes, and methylation changes in CpG dinucleotides. Some genetic instability is inherent to the physiologic processes responsible for producing antibody and T cell receptor diversity, as the involved enzymes introduce DNA double-strand breaks and point mutations to those genes. Lymphocytes are thus particularly predisposed to acquire chromosomal translocations and other oncogenic mutations when these processes are dysregulated, providing the groundwork for malignant transformation to lymphoma.

B cell development begins in the bone marrow, where progenitors progress through a series of steps resulting in the production of immunoglobulin (Ig) [21]. Most B cells undergo apoptosis in the bone marrow if they fail to produce surface IgM, or if their IgM binds self-antigen. Surviving mature B cells travel to secondary lymphoid tissues (e.g., lymph nodes and spleen) for exposure to antigen, migrate to the germinal center to proliferate, and undergo further Ig gene modification via somatic hypermutation and class switch recombination. Somatic hypermutation introduces point mutations, small deletions, and insertions into the variable region of the Ig gene to increase affinity for antigen. B cells with antibodies exhibiting high antigen affinity receive pro-survival signaling through their Ig receptors; however, most will die. Through class switch recombination, exons in the constant region of the Ig heavy chain are replaced by a recombination/deletion process, facilitating production of the secondary Ig isotypes IgG, IgA, and IgE [22]. Upon exiting the germinal center, B cells differentiate into either plasma cells or memory B cells.

Normal T cell development mirrors that of B cells: lymphocytes progress through a series of coordinated steps, undergoing positive and negative selection in the thymus until mature cells ultimately express a functional antigen receptor—the T cell receptor. While some T cell NHLs resemble normal lymphocytes at a distinct maturation stage (especially when gene expression profiling is considered), determining the cell of origin of many subtypes remains difficult. This is in sharp contrast to B cell lymphoma, in which each subtype corresponds with a normal cellular phenotype [23].

Genetic Lesions and Mechanisms of Lymphomagenesis

Balanced translocations leading to activated oncogenes are common events in many lymphoma subtypes. Frequently, the promoter of constitutively expressed Ig on chromosome 14 serves as a translocation partner in B cell lymphomas. For instance, in follicular lymphoma (FL), t(14,18) leads to overexpression of BCL2, an anti-apoptotic protein that promotes cell survival even in the harshly pro-death environment of the germinal center [24]. Similarly, constitutive expression of cyclin D1 in mantle cell lymphoma (MCL) results from t(11,14) and promotes proliferation [25].

The machinery involved in somatic hypermutation offers ample opportunity for gaining genetic lesions. In its ligation of DNA breaks induced by the enzyme activation-induced cytidine deaminase (AID), error-prone DNA polymerase generates point mutations. In fact, somatic hypermutation is known to target the coding regions of non-immunoglobulin genes such as *BCL6*, *PAX5*, and *c-MYC*, which may further explain why such genes are often involved in translocations.

AID-mediated DNA breaks also occur in class switch recombination, another process that may yield translocations if disrupted. Class switch recombination is implicated in the t(8,14) seen in sporadic Burkitt lymphoma, with translocation breakpoints involving the Ig heavy chain switch locus [26]. Additionally, defects in recombination are seen in activated B cell-like (ABC) diffuse large B cell lymphoma (DLBCL) but not in the germinal center B cell-like (GCB) subtype. This difference may thus contribute to the distinct mutations described in each subset (e.g., MYOM2, CD79 and MYD88 in ABC, and MLL2, BCL2, and CREBBP in GCB) [27].

The balanced translocations that often characterize B cell lymphoma subtypes are uncommon in T cell NHL. One notable exception is the anaplastic lymphoma kinase (ALK) translocation found in some anaplastic large cell lymphomas (ALCL). The *ALK* locus may be juxtaposed with a number of partners, each resulting in an oncogenic fusion protein. The most common of these, t(2,5), joins the promoter of nucleophosmin to the ALK catalytic domain, creating a constitutively active tyrosine kinase that contributes to malignant transformation and avoidance of apoptosis [28].

While balanced translocations may represent driving pathogenic events, unbalanced chromosomal gains and losses likely also cooperate to promote malignant transformation and cancer cell survival advantage. For instance, deletions and mutations of the p53 tumor suppressor gene have been reported in Burkitt lymphoma, FL, MCL, and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [29]. More recent studies also indicate that dysregulated epigenetic mechanisms contribute to lymphomagenesis [30].

Epidemiologic Studies by NHL Subtype

Identifying epidemiologic and genetic risk factors for developing specific NHL subtypes provides important correlates for the characterization of the particular molecular pathway abnormalities described in each. The International Lymphoma Epidemiology Consortium (InterLymph) was formed in 2001 to provide a comprehensive analysis of risk factors both particular to and shared by specific NHL subtypes. In a series of studies, InterLymph pooled cases and controls across studies and evaluated many exposures of interest, including medical and family history, lifestyle, and occupation factors, to provide well-powered comparisons of risk factors for specific NHL subtypes [31•, 32•, 33•, 34•, 35•, 36•, 37–40, 41•, 42]. InterLymph and others have also performed GWAS that have identified NHL subtype-specific single nucleotide variants (SNVs) associated with increased risk of developing lymphoma. We review recent key findings from these efforts by NHL subtype.

Diffuse Large B Cell Lymphoma

The most common NHL type, DLBCL comprises 25–30 % of NHL in Western countries [3, 4]. Although in many cases DLBCL is a curable disease, it is universally fatal if left untreated or treated improperly, and nearly 50 % of patients relapse [43, 44]. Gene expression profiling has provided some insight into this clinical heterogeneity, identifying two biologically distinct subtypes that appear to reflect unique cells of origin and harbor differing prognoses: the more favorable GCB and the more aggressive ABC DLBCL [45–47]. However, this subclassification represents only one step towards elucidating the complex underpinnings of lymphomagenesis and tumor behavior in DLBCL.

Genetic Risk Factors for DLBCL

In the past decade, gene expression profiling and cell line studies have yielded significant insight into a number of molecular pathways that are dysregulated in DLBCL, including B cell receptor and NF- κ B signaling. GWAS have supplemented this work by identifying genetic variants associated with DLBCL. One study identified a novel susceptibility locus for DLBCL at 3q27 in the intergenic region between *BCL6* and *LPP* known to contain strong regulatory elements [48]. Dysregulation of both genes has been implicated in malignant transformation, and *BCL6* plays a particularly important role in germinal center formation during lymphocyte development [22]; thus, it is hypothesized that certain variants in the 3q27 locus may modulate the expression of one or both of these genes to contribute to lymphomagenesis.

Variants in several genes involved in augmenting the inflammatory milieu have been associated with increased

DLBCL risk, including cytokines such as IL-10 [19, 49] and activators of the complement system, such as *MASP2* [50]. SNVs in *CTLA4*, which codes for a negative regulator of T cell activation, were found more commonly in DLBCL patients in an Egyptian study [51]. Importantly, the prevalence of hepatitis C virus (HCV) infection was higher in patients harboring these SNVs. As HCV is suspected to contribute to NHL development through antigenic stimulation of B cells, it is possible that some *CTLA4* SNVs may cooperate with HCV infection to increase DLBCL risk above that conferred by either factor alone.

Interestingly, recent analyses suggest that the effect of certain SNVs may vary depending on ethnicity, highlighting possible interaction between genetic variants, environmental factors, and population genomics. For instance, while studies with predominantly Caucasian subjects identified the G308A SNV in *TNF* as a risk factor for DLBCL [12], the same variant was associated with decreased risk of DLBCL in Asian populations [52]. Another recent case-control study evaluated whether susceptibility to DLBCL increased in East Asian populations with the presence of SNVs previously identified as risk factors for the disease in European populations. Of the seven SNVs assessed (in *EXOC2*, *PVT1*, *HLA-B*, *NCOA1*, *CD86*, and *ARAP3*), only three were associated with increased DLBCL in those of East Asian ancestry [53•].

Several case-control studies indicate a possible link between SNVs in the methylenetetrahydrofolate reductase (*MTHFR*) gene and DLBCL, although these results have been controversial. A 2013 meta-analysis found that the C677T SNV in *MTHFR* was associated with increased DLBCL risk in East Asian populations, but not in populations of European heritage [54]. *MTHFR* functions as a key enzyme in folate metabolism and DNA synthesis, and reduced *MTHFR* activity may result in decreased methylation of deoxyuridine monophosphate. Thus, it is hypothesized that abnormal *MTHFR* function could lead to increased incorporation of uracil into DNA, thereby increasing the likelihood of DNA double-strand breaks and other aberrancies that could predispose to oncogenesis [55].

Epidemiological Risk Factors for DLBCL

Findings from the InterLymph NHL Subtypes Project confirmed several risk factors already reported for DLBCL and identified others never before described. The odds ratios and 95 % confidence intervals for epidemiological risk factors significantly associated with several NHL subtypes are shown in Table 1. Multivariate analyses of 4,667 cases and 22,639 controls revealed increased risk of DLBCL associated with B cell-activating autoimmune disease, HCV seropositivity, first-degree family history of NHL, and higher body mass index (BMI) as a young adult. Intriguingly, the study also suggested that DLBCL risk factors vary by gender and anatomical site of

Table 1 Odds ratios for all factors associated with significant increased risk of one or more B cell non-Hodgkin lymphoma subtypes

Exposure category	Overall NHL OR (95 % CI)	DLBCL	BL	LPL/AWM	FL	CLL/SLL	MZL	MCL
Autoimmune disease								
Any B cell-activating disease	1.96 (1.60–2.40)	2.45 (1.91–3.16)	1.22 (0.29–5.04)	2.61 (1.34–5.08)	1.27 (0.90–1.79)	1.07 (0.70–1.64)	5.46 (3.81–7.83)	1.03 (0.41–2.54)
Sjögren’s syndrome	7.52 (3.68–15.4)	8.77 (3.94–19.5)	–	12.1 (3.16–46.6)	3.32 (1.19–8.80)	0.55 (0.07–4.43)	38.1 (16.9–85.6)	–
Systemic lupus erythematosus	2.83 (1.82–4.41)	2.49 (1.42–4.37)	–	8.41 (2.81–25.2)	1.81 (0.91–3.59)	2.19 (0.92–5.25)	6.54 (3.10–13.8)	2.97 (0.68–13.1)
Any T cell-activating disease	1.07 (0.95–1.21)	1.08 (1.09–1.28)	0.57 (0.25–1.32)	1.00 (0.59–1.71)	0.90 (0.72–1.11)	1.04 (0.83–1.30)	1.08 (0.75–1.56)	1.01 (0.64–1.59)
Celiac disease	1.77 (1.05–2.99)	2.09 (1.04–4.18)	–	1.28 (0.17–9.64)	1.27 (0.53–3.01)	0.60 (0.14–2.61)	–	1.15 (0.15–8.71)
Systemic sclerosis/scleroderma	1.03 (0.41–2.58)	0.71 (0.16–3.24)	20.2 (2.44–166)	–	1.08 (0.23–5.00)	–	2.69 (0.50–14.7)	–
HCV positive	1.81 (1.369–2.37)	2.33 (1.71–3.19)	3.05 (0.90–10.3)	2.70 (1.11–6.56)	0.57 (0.30–1.10)	2.08 (1.23–3.49)	3.04 (1.65–5.60)	–
Cigarette smoking								
Duration ≥ 20 years	1.06 (0.99–1.14)	1.02 (0.92–1.12)	0.77 (0.51–1.17)	1.50 (1.10–2.04)	1.19 (1.06–1.33)	0.84 (0.74–0.96)	1.27 (1.03–1.57)	1.24 (0.96–1.61)
Family history of hematologic malignancy								
Any	1.72 (1.54–1.93)	1.57 (1.34–1.83)	0.51 (0.41–1.62)	1.65 (1.03–2.65)	1.48 (1.25–1.75)	2.17 (1.77–2.65)	1.73 (1.33–2.25)	1.99 (1.39–2.84)
HL	1.65 (1.18–2.29)	2.08 (1.38–3.15)	–	2.16 (0.50–9.36)	1.48 (0.90–2.40)	1.26 (0.60–2.64)	2.74 (1.36–5.51)	1.51 (0.46–5.03)
NHL	1.79 (1.51–2.13)	1.84 (1.46–2.33)	0.75 (0.23–2.43)	1.20 (0.52–2.76)	1.99 (1.55–2.54)	1.92 (1.42–2.61)	1.65 (1.10–2.46)	1.95 (1.14–3.34)
Leukemia	1.51 (1.29–1.77)	1.16 (0.92–1.47)	0.88 (0.35–2.20)	2.19 (1.21–3.96)	0.97 (0.74–1.28)	2.41 (1.85–3.14)	1.66 (1.15–2.38)	1.98 (1.21–3.24)
Multiple myeloma	1.77 (1.15–2.72)	1.35 (0.71–2.57)	–	–	1.93 (1.06–3.51)	1.99 (0.92–4.33)	0.55 (0.13–2.37)	3.10 (1.05–9.10)
Occupational history								
Painter	1.22 (0.99–1.51)	1.02 (0.76–1.37)	2.28 (0.97–5.33)	0.66 (0.16–2.72)	1.31 (0.93–1.84)	1.05 (0.66–1.67)	1.68 (0.97–5.33)	1.39 (0.67–2.91)
General farm worker	1.28 (1.10–1.50)	1.09 (0.87–1.37)	1.49 (0.59–3.78)	1.26 (0.64–2.47)	1.18 (0.88–1.57)	1.46 (1.15–1.85)	1.21 (0.75–1.95)	1.21 (0.67–2.19)

Abbreviations: OR odds ratio, CI confidence interval, HL Hodgkin lymphoma, NHL non-Hodgkin lymphoma, DLBCL diffuse large B cell lymphoma, BL Burkitt lymphoma, LPL/AWM lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia, FL follicular lymphoma, CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma, MZL marginal zone lymphoma, MCL mantle cell lymphoma

disease. For females, work as a field crop/vegetable farmer, seamstress/embroiderer, or hairdresser was associated with increased risk, while for males, risk increased with work as a driver or operator of material handling equipment. Smoking was found to be associated with central nervous system, testicular, and cutaneous DLBCL, inflammatory bowel disease with gastrointestinal DLBCL, and farming and hair dye use with mediastinal DLBCL. Other studies using geospatial analyses have identified environmental exposures associated with the risk of DLBCL [56•]. Emerging studies are beginning to integrate data from environmental exposures, epidemiological surveys, and genetic measures to examine the interactions between host genetics and environment in the development of NHL [57•], but additional comprehensive analyses are needed to identify target populations for prevention measures.

Genetic and Epidemiological Risk Factors for Follicular Lymphoma

Follicular lymphoma (FL) is an indolent lymphoma that accounts for about 15–20 % of NHL in the Western world [43, 58–60]. It is more common in Caucasians than in Black or Asian Americans but, unlike other NHL subtypes, has similar incidence rates in men and women, with the median age of diagnosis in the sixth decade of life [58, 61]. Interestingly, although FL is defined by t(14,18), which results in overexpression of the anti-apoptotic protein BCL2, this translocation has been identified in ostensibly normal B cells of healthy individuals, implying that the translocation alone is not sufficient to induce lymphomagenesis [62].

Multiple GWAS of FL have revealed susceptibility variants in human leukocyte antigen (HLA) class I and II regions, highlighting an important role of such variants in FL pathogenesis [63–67]. In 2014, InterLymph published a large-scale two-stage GWAS involving 4523 FL cases and 13,344 controls that identified susceptibility SNVs in the HLA region, and in 5 non-HLA loci [68]. These included regions near genes coding for BCL2, suggesting a role for SNVs in predisposing towards acquisition of the characteristic (14,18) translocation, and CXCR5, a receptor expressed on mature B cells, some T cells, and dendritic cells involved in B cell migration and activation. FL-associated SNVs near CXCR5 have been previously reported [69]. The authors proposed a dynamic function for CXCR5 in altering the immune milieu of the tumor microenvironment as a possible mechanism for influencing FL initiation and progression.

Epigenetic variants have also been identified by recent GWAS in FL. A 2014 study found that a specific G>T SNV in the stem-loop sequence of microRNA-618 was associated with increased risk of FL, with in vitro data suggesting that the variant results in decreased microRNA-618 expression [70]. Although the downstream effects of such a change remain incompletely characterized, targetome profiling of

microRNA-618 lends hypothesis-generating insight into candidate genes for which post-translational dysregulation could contribute to follicular lymphomagenesis.

In its case-control study of 3530 FL cases and 22,639 controls, InterLymph identified family history of NHL, higher body mass index as a young adult, and work as a spray painter as risk factors. Interestingly, cigarette smoking and Sjögren's syndrome were found to be associated with increased FL risk only in females.

Genetic and Epidemiological Risk Factors for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) represent two manifestations of the same disease and harbor identical pathologic and immunophenotypic features. The distinction between the two relies on clinical presentation: in CLL, malignant cells appear primarily in the peripheral blood and bone marrow, while SLL presents predominantly in the lymph nodes [71]. Although CLL/SLL is relatively common in Western countries, it is quite rare in Asia [2–4]. However, recent studies show that the CLL/SLL incidence is increasing in Asian populations and that incidence is increased in people of Asian descent living in the USA compared to those who live in Asia, suggesting that components of the Western lifestyle may contribute to development of this disease [72, 73].

In the largest GWAS meta-analysis in CLL to date, nine novel risk loci for CLL were identified in addition to 13 previously described [74]. The proximity of some of these variants to genes involved in apoptosis, such as *CASP10/CASP8*, may provide a clue to their biological relevance, although more work is needed to elucidate this link. Variants in *IRF8*, which codes for a transcription factor integral to myeloid and B cell development, have also been recently associated with increased risk of CLL [75].

InterLymph confirmed previously identified risk factors for CLL/SLL such as HCV infection, family history of hematologic malignancy, work or residence on a farm, and increased height in a multivariate analysis of 2440 cases and 15,186 controls. In addition, occupation as a hairdresser was identified as a novel risk factor.

Genetic and Epidemiological Risk Factors for Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is a common indolent subtype that accounts for 5–10 % of NHL and comprises three distinct diseases: extranodal MZL of mucosa-associated lymphoid tissue (MALT), splenic MZL, and nodal MZL [58]. Several inflammatory diseases are known to be strongly associated with extranodal MZL of specific anatomic sites, including *Helicobacter pylori* infection in gastric MALT lymphoma,

Chlamydia psittaci infection in ocular adnexal MALT lymphoma, *Borrelia burgdorferi* infection with cutaneous MALT lymphoma, Sjögren's syndrome with salivary gland MALT lymphoma, and Hashimoto thyroiditis with thyroid MALT lymphoma. In fact, antibiotic eradication of *H. pylori* alone results in lymphoma regression in about half of gastric MALT lymphoma patients [76, 77].

A GWAS of 1281 MZL cases and 7127 controls of European ancestry identified independent loci in the HLA region significantly associated with MZL risk [78]. The authors proposed that these independent associations in the HLA region and their localization around known B cell genes associated with autoimmunity raise the possibility of shared genetic effects spanning B cell NHL and autoimmune diseases.

InterLymph represents the first large epidemiological study of MZL subtypes, evaluating 1052 MZL cases (extranodal 633, nodal 157, splenic 140, MZL-not otherwise specified 120) and 13,766 controls. It is worth noting that 60 % of cases examined were extranodal MZL, so results from analyses of nodal and splenic subtypes were based on a relatively small number of cases. B cell-activating autoimmune disorders were associated with all MZL subtypes, highlighting the contribution of chronic immune stimulation to this disease. Family history of hematologic malignancy was associated with increased risk for nodal and extranodal MZL, while novel associations were found between asthma and permanent hair dye use with splenic MZL and occupation as a metal worker with nodal MZL. Unsurprisingly, Sjögren's syndrome was highly associated with salivary gland MALT lymphoma, and peptic ulcers with gastric MALT lymphoma.

Epidemiological Risk Factors for Burkitt Lymphoma

Burkitt lymphoma is a highly aggressive lymphoma characterized by dysregulation of MYC and constituting 1–5 % of all NHL in adults [4, 79]. It is categorized into three histologically indistinguishable subtypes: endemic, which is clearly associated with Epstein-Barr virus infection; immunodeficiency-associated, seen in immunosuppressed patients as a result of human immunodeficiency virus infection or solid organ transplant; and sporadic, which previously had no clear risk factors. InterLymph evaluated 295 cases and 21,818 controls to examine risk factors for sporadic Burkitt lymphoma, with age-stratified analyses to account for the two age peaks seen in disease incidence (during childhood and in the seventh decade of life). In patients younger than 50 years old, eczema, highest quartile of height, and work as a charworker or cleaner were associated with increased risk. In patients older than 50, only HCV was identified as a risk factor, emphasizing the age-specific nature of risk factors for this disease.

Epidemiological Risk Factors for Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphoma (LPL) is a rare, indolent type of NHL with cells spanning the spectrum of plasmacytic differentiation from small lymphocytes to true plasma cells, which often produce paraproteins such as IgM or IgG. Waldenström's macroglobulinemia represents a subset of LPL characterized by bone marrow involvement and monoclonal IgM gammopathy [58]. InterLymph analyzed 374 cases of LPL (of which only three were Waldenström's macroglobulinemia) along with 23,096 controls and confirmed a strong association with chronic immune stimulation (specifically, autoimmune diseases such as Sjögren's syndrome and systemic lupus erythematosus), HCV infection, and family history of hematologic malignancy. The study also identified novel associations with cigarette smoking and occupation as a medical doctor.

Epidemiological Risk Factors for Mantle Cell Lymphoma

MCL is an aggressive disease with poor prognosis that remains essentially incurable with conventional chemotherapy. The vast majority of cases are characterized by t(11,14), which results in constitutive expression of cyclin D1. MCL is a rare disease constituting only 2–10 % of all NHL cases [58], which accounts for the paucity of known risk factors other than a 2:1 male predominance in this subtype. A recent study noted that MCLs had a mutational profile distinct from other B cell NHLs [80]. In its multivariate analyses of 557 MCL cases and 13,766 controls, InterLymph identified family history of hematologic malignancy and residence on a farm as risk factors for the disease [36••].

Peripheral T Cell Lymphoma

Peripheral T cell lymphoma (PTCL) accounts for 5–10 % of NHL and comprises a heterogeneous group of lymphomas derived from mature T and natural killer cells, with more than 20 distinct entities defined by characteristic morphologic, molecular, and clinical features, including site of disease [3, 58]. The most common subtypes are PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). Unfortunately, most PTCL are characterized by poor response to treatment, with the notable exception of ALCL carrying an *ALK* translocation.

Genetic Risk Factors for PTCL

Given the difficulty in defining a genetic basis for most T cell lymphomas, recent efforts have employed gene expression profiling in an attempt to identify phenotypic differences among these tumors. For example, gene expression profiling studies demonstrate that hepatosplenic T cell lymphomas may be completely segregated from other T cell NHL, emphasizing

the distinct clinicopathological characteristics of this subtype. Supervised analysis has also allowed for a distinction between $\alpha\beta$ and $\gamma\delta$ T cell lymphomas [81]. Interestingly, although *TP53* mutations are uncommon in T cell NHL, whole-genome sequencing has revealed recurrent rearrangements of p53-related genes in PTCL such as a truncated p63 protein that inhibits p53 in a dominant negative fashion, indicating another mechanism for silencing p53 tumor suppression [82]. In AITL, gene expression profiling studies revealed mutations in a RHOA GTPase [83] as well as upregulation of genes related to vascular endothelial growth factor A [84], which may play roles in AITL pathogenesis. Gene expression profiling also helped characterize PTCL-NOS, a heterogeneous group of tumors. PTCL-NOS subgroups may be distinguished based on the level of expression of NF- κ B pathway genes, and by correlation with the profiles of either CD4+ T cells or CD8+ T cells [85, 86].

Epidemiological Risk Factors for PTCL

To determine epidemiological risk factors for PTCL, InterLymph analyzed 584 cases (PTCL-NOS 234, AITL 81, ALCL 164, others 57) and 15,912 controls. Several factors were associated with higher risk of one or more PTCL subtypes, including family history of hematologic malignancies, history of psoriasis, smoking history, and occupation as an electrical

fitter or in the textile industry (Table 2). As expected, celiac disease was strongly associated with enteropathy-associated T cell lymphoma, but also with PTCL-NOS and ALCL.

Epidemiological Risk Factors for Mycosis Fungoides/Sézary Syndrome

Mycosis fungoides (MF) is the most common type of cutaneous T cell lymphoma (CTCL), representing nearly half of all CTCL cases [58]. It commonly follows an indolent clinical course but may progress to Sézary syndrome (SS), a rarer form of CTCL characterized by erythroderma, generalized lymphadenopathy, and peripheral blood involvement. The age-adjusted incidence of MF/SS is estimated at 0.5 per 100,000 in the Western world, with the rate of MF about 1.5 times higher among African-Americans compared to Whites [87].

InterLymph evaluated 324 cases (MF 271, SS 13, MF/SS 40) and 17,217 controls to identify several risk factors, including smoking history ≥ 40 years, adult body mass index >30 kg/m² [2], history of eczema, personal or family history of multiple myeloma, and occupation as a crop or vegetable farmer, painter, woodworker, or general carpenter. Notably, the association between eczema and MF/SS risk increased for those diagnosed with eczema within 10 years of their diagnosis of MF/SS, indicating that MF may have initially been

Table 2 Odds ratios for all factors associated with significant increased risk of peripheral T cell lymphoma and/or mycosis fungoides/Sézary syndrome

Exposure category	PTCL OR (95 % CI)	MF/SS
Autoimmune disease		
Psoriasis	2.41 (1.15–5.04)	–
Systemic lupus erythematosus	3.90 (1.24–12.3)	5.03 (1.17–21.6)
Any T cell-activating disease	1.95 (1.37–2.77)	1.66 (1.00–2.75)
Celiac disease	14.8 (7.27–30.2)	–
Systemic sclerosis/scleroderma	–	8.87 (1.11–71.3)
Eczema		
Any diagnosis	–	2.38 (1.73–3.29)
Diagnosis within 10 years of NHL	–	4.87 (2.15–11.02)
Cigarette smoking		
Duration ≥ 20 years	1.75 (1.33–2.30)	1.22 (0.84–1.77)
Duration ≥ 40 years	–	1.55 (1.04–2.31)
BMI 35–50 kg/m ²	–	1.57 (1.03–2.40)
Family history of hematologic malignancy		
Any	1.86 (1.26–2.74)	1.16 (0.68–1.98)
Leukemia	1.84 (1.09–3.13)	1.06 (0.49–2.29)
Multiple myeloma	2.86 (0.98–8.37)	6.11 (2.36–15.8)
Occupational history		
Painter	1.45 (0.73–2.88)	3.42 (1.81–6.47)
General farm worker	0.79 (0.40–1.56)	2.07 (1.06–4.07)
General carpenter	–	4.07 (1.54–10.8)

Abbreviations: OR odds ratio, CI confidence interval, PTCL peripheral T cell lymphoma, MF/SS mycosis fungoides/Sézary syndrome, BMI body mass index

misdiagnosed as eczema in some cases. It is also worth noting that since both multiple myeloma and MF carry higher incidence in African-Americans, their apparent association may be confounded by this shared racial predisposition.

Discussion

Recent pooled case-control studies examining genome-wide associations and epidemiological risk factors provide an enhanced understanding of subtype-specific risk factors that include genetics, medical history, family history, lifestyle factors, and occupations. These results suggest a complex interplay between host genetics, autoimmune disorders, modifiable risk factors, and occupation that contributes to lymphomagenesis in ways not fully understood (Fig. 1). It is important to note that despite their broad scope, several important factors were not assessed in these studies, including diet and infection other than HCV. Additionally, as in many studies, the populations analyzed were largely of Caucasian ancestry, and thus, it is unclear whether the risk factors identified are generalizable to non-Caucasian populations. In general, NHL risk factors among racial and ethnic minorities remain incompletely described [59, 87–93], and future analyses are needed to evaluate these factors and others not captured by the InterLymph study.

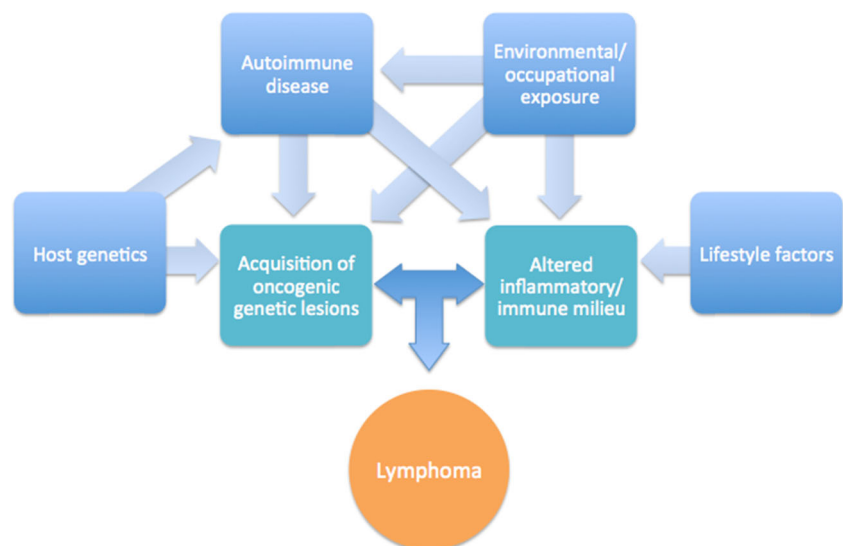
Identifying the interactions between epidemiologic components and genetic factors such as SNVs will help create a comprehensive model capable of predicting the probability of developing NHL subtypes, and could yield valuable insights regarding the biologic underpinnings of lymphomagenesis, which would provide targets for further molecular study and therapy. Recent work by Wang et al. utilized data from InterLymph to examine the relationship between history of autoimmune disease and five SNVs in common susceptibility

immune-response gene loci found to confer increased risk of NHL (i.e., in *IL10*, *TNF α* , and HLA class genes), with the goal of determining whether these factors contributed to NHL risk independently or through a joint pathway [57]. This group found that NHL risk across major subtypes increased in individuals with B cell-mediated autoimmune conditions who harbored *TNF* G308A variants. This effect was especially pronounced in MZL, where risk increased from threefold with the GG genotype to eightfold with the AG or AA genotype. There was little evidence for interaction between autoimmune disease and four other SNVs. However, the apparent synergy between B cell-mediated autoimmunity and *TNF* G308A in augmenting NHL risk may imply a shared biologic pathway that promotes a chronic inflammatory state through increased expression of *TNF- α* and resultant NF- κ B activation [94–96]. Indeed, a distinct pattern of immune response, termed T-helper 17 and characterized by inflammation, B cell activation, and production of certain inflammatory cytokines (including *TNF- α*), has been recognized as a central player in driving autoimmunity [97–99]. Given the proposed interaction between *TNF* G308A and autoimmune disease to increase NHL risk, it is possible that the T-helper 17 response may contribute to the pathogenesis of both autoimmune disease and NHL. Future studies investigating the link between autoimmune disorders and B cell NHL could complement such work by evaluating the B cell repertoire and specific mutations common between lymphoma subtypes and specific autoimmune diseases.

Conclusion

The unique glimpse into NHL subtype-specific epidemiology afforded by large case-control studies represents an important

Fig. 1 Proposed interactions between etiologic factors contributing to development of non-Hodgkin lymphoma subtypes



step towards understanding the complex network of factors underlying lymphomagenesis. Further work is needed to incorporate such epidemiologic studies with population genetics and lymphoma biology to build models for risk prediction and identify novel preventive and therapeutic targets.

Compliance with Ethics Guidelines

Conflict of interest The author(s) declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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