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Host genetics in follicular lymphoma

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Abstract

The role of inherited (host) genetic susceptibility in the pathogenesis of follicular lymphoma (FL) is reviewed. First degree relatives of FL patients are at an increased risk of FL, suggesting a role for inherited factors. While there have been no linkage studies in FL families, candidate gene and genome-wide association studies have identified several risk loci which have been confirmed in independent studies. These include regions on 6p21.32-33 and TNF family members. Host genetics has also been hypothesized to influence treatment response, disease progression and overall survival. Early leads in FL prognosis include pathways that regulate immune function, antibody-dependent cellular cytotoxicity, chemotaxis, and one carbon metabolism, although few of these associations have been independently confirmed. While the use of host genetics to identify individuals at high risk of FL or to predict FL treatment response and prognosis appears to be very promising, it is not yet ready for the clinic.

Keywords

follicular lymphoma; genetics; single nucleotide polymorphisms; risk; prognosis

Introduction

Follicular lymphoma (FL) is one of the most commonly diagnosed subtypes of non-Hodgkin lymphoma (NHL) in western countries, with an annual incidence rate of 5.4 per 100,000 and an estimated 11,000 new cases diagnosed each year in the United States [1]. The median survival for FL is approximately 10 years, although there is substantial heterogeneity, with some patients progressing very slowly over many years and other patients progressing rapidly, particularly after transformation to aggressive lymphoma [2]. Environmental factors and somatic events are thought to be the predominant contributors to the development of FL, and in uniformly treated patients, clinical characteristics and the biology of the tumor clone are thought to be the predominant contributors to treatment response, disease progression, and overall survival [3, 4]. More recently, there has been a growing interest in the role of inherited (host) genetic susceptibility to the FL risk and prognosis.

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Evidence for an inherited component to follicular lymphoma risk

Overview

While there has been a long history of case reports of familial clustering of NHL, it was only until relatively recently that NHL was considered to have an important inherited genetic component outside of very rare hereditary cancer syndromes [3]. Chance, genetic factors, and shared environment all need to be considered when evaluating familial aggregation. Table 1 summarizes the major studies addressing familial risk for FL.

Familial Aggregation

The risk of NHL overall was elevated in first degree relatives of a proband with NHL in the Utah Population Database (Familial Relative Risk=1.68; 95% CI 1.04-2.48) [5] and in the Swedish Cancer Registry (Familial Index=1.5; 95% CI 1.1-2.2) [6]. Focusing on FL in the Swedish-Family Cancer Database, Altieri and colleagues [7] reported an elevated risk for FL in offspring with a parent or sibling with NHL (SIR=2.0; 95% CI 1.4-2.9), and this risk was even higher if the parent had FL (SIR=6.1; 95% CI 1.1-18.0). Risk of FL was also elevated if a parent had chronic lymphocytic leukemia (CLL) or T-cell lymphoma, although the estimates were based on very small numbers and were not statistically significant. In contrast, there was no elevation of FL risk if a parent had diffuse large B-cell lymphoma (DLBCL) or multiple myeloma. Similarly, in a more recent analysis of the Swedish databases, Goldin and colleagues [8] reported an increased risk of FL if there was a first degree relative with FL (RR=4.0; 95% CI 1.6-9.5) or CLL (RR=1.8; 95% CI 1.0-3.3), but not DLBCL (for which no cases were observed). Other analyses of the Swedish databases have found that first degree relatives of patients with Hodgkin lymphoma [9], CLL [7, 10], DLBCL [7, 8], multiple myeloma [7, 11], and lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia [12] are at a particularly high risk of developing the same malignancy as the index case, which supports at least a component of genetic susceptibility being unique to a given subtype of B-cell malignancy.

Case-control studies of family history

In a pooled analysis of 11 case-control studies (10,211 NHL cases and 11,905 controls) from the InterLymph consortium, NHL risk was elevated for individuals who reported first degree relatives with NHL (OR=1.5; 95% CI 1.2-1.9) [13]. FL risk was also specifically elevated for individuals who reported a first degree relative with NHL (OR=1.8; 95% CI 1.3-2.5), but was not elevated for individuals who reported a first degree relative with Hodgkin lymphoma, leukemia, or multiple myeloma. These estimates were generally similar to prior reports from studies not included in the pooled analysis [14, 15].

Twin Studies

In twin studies, if the concordance rate of a phenotype in monozygotic twins (who share all genes) is higher than the concordance rate for dizygotic twins (who share on average half of their genes), then there is strong evidence for a genetic component, assuming similar environmental exposures and access to health care. In a study of 44,788 pairs of twins from Scandinavia [16], there were no monozygotic twins who were concordant for NHL (81 pairs were discordant) and there were no dizygotic twins who were concordant for NHL (183 pairs were discordant), so the heritable risk could not be estimated. For leukemia, there was an excess of concordant monozygotic twins (2 concordant and 103 discordant pairs) compared to dizygotic twins (2 concordant and 198 discordant pairs), and the heritable risk was 0.21 (95% CI 0-0.54). Subtype data were not available for either the NHLs or leukemias, but given the strong evidence for an inherited component for CLL compared to myeloid leukemias [17], it is most probable that the heritability estimated in the twin study

was mainly due to CLL. These data suggest that there may not be a major genetic component for NHL as a group, although power was limited. An alternative explanation is that there is significant heterogeneity within NHL (some subtypes having a stronger genetic component relative to others) that is obscured by lumping all subtypes together.

Linkage Studies

Linkage studies use multi-case families or sib pairs to screen the genome to identify chromosomal regions that show excessive sharing of inherited alleles among affected individuals. The regions are then fine-mapped to identify causal variants. To date, there has not been a linkage study conducted in NHL overall or for FL specifically. However, studies conducted in high risk families with CLL [18], Hodgkin lymphoma [19], and Waldenstrom macroglobulinemia [20] have not detected genes with large effects. While these studies were in part hampered by relatively small sample size and disease heterogeneity [21], it also raises the hypothesis that multiple, low to moderate risk variants (~RRs=1.1 to 1.5) that are common in the population (>5%) may be more relevant than single, highly penetrant variants that are rare in the population, which is referred to as the common-disease, common-variant hypothesis [22].

Genetic association studies

With the advent of high throughput genotyping technologies and associated resources such as the HapMap [23], case-control studies (also commonly called association studies) of sequence variation in germline DNA have become the workhorse of genetic epidemiology. This study design compares allele or genotype frequencies in cases (patients) to unrelated controls (a group without the phenotype of interest). The most common type of genetic variation in the human genome is the single nucleotide polymorphism (SNP), which is a single base pair change in the DNA sequence. This change can occur in a coding region ("coding SNP") and can also lead to an amino acid change in the coded protein ("non-synonymous coding SNP"). Other variants, including rare variants (<5% frequency), insertions/deletions, block substitutions, inversions, and copy number variants, are less common and have not been studied as much to date [24].

The SNP association study is a very powerful strategy to identify low penetrance alleles relative to linkage studies, which are underpowered for this task. However, SNP association studies can also produce unreliable results due to small sample sizes (low power), uncontrolled multiple testing (leading to false positive results), selection bias in case or control ascertainment, and bias from population stratification (i.e., confounding by race or ethnicity) in poorly designed studies.

Host genetics of follicular lymphoma risk

Overview

Table 2 summarizes the major studies that have assessed host genetic susceptibility for FL risk. While virtually all of these studies were focused on risk of NHL overall, only those studies that specifically reported subtype results for FL and had at least 100 cases available for analysis are summarized. Significant findings were based on each author's interpretation of statistical significance, which for many studies was a (nominal) $p<0.05$, although other studies accounted for multiple testing, generally by using the false discovery rate [25]. Table 2 also separates results from single studies versus pooled analyses of multiple independent studies. The latter studies are more powerful, since they generally have a much larger sample size and specifically address replication across more than one independent study.

As shown in Table 2, earlier studies tended to assess a smaller number of genes (≤5), and SNP coverage was generally restricted to 1 or 2 SNPs within a gene. These SNPs were usually hypothesized to be "functional" because they either caused an amino acid change (which could lead to a biologically important protein structure change) led to an alteration in the function of the gene's promotor. As genotyping technologies evolved and costs decreased, more genes have been interrogated (often grouped into pathways or networks) and more SNPs within genes have been assessed. The HapMap initiative [23] allowed a more comprehensive assessment of genetic variation across a gene by using a "tagging" approach. This is most commonly done by using the HapMap to identify all common SNPs (>5% minor allele frequency) within a gene (exons and introns) as well as 5 kb upstream (to cover the location of most promotors) and 5 kb downstream, although the exact distance up and downstream of the gene is somewhat arbitrary and has varied across studies. Once defined, highly correlated (e.g., $r^2 \geq 0.8$) SNPs are grouped ("binned") together, and a subset of SNPs from each bin are selected for genotyping ("tagSNPs"). This approach, which takes advantage of linkage disequilibrium (LD) within the genome (correlation of SNPs), is a highly efficient approach to covering common genetic variation across a gene region.

The choice of candidate genes/pathways has been driven mainly by biologic knowledge of lymphoma, related diseases associated with lymphoma (e.g., autoimmune or infectious diseases), or findings from other cancers [26]. An alternative approach is the genome-wide association (GWA) study, which covers the entire genome and is agnostic to a particular gene or pathway – that is, it is hypothesis-free with respect to which SNPs are associated with disease.

Candidate Genes and Pathways

Immunogenetics—Genes from the immune system have received the most attention in terms of the number of studies published, number of genes evaluated, and robustness of the results. Several genes are particularly noteworthy based on consistent findings in more than two independent studies. The *TNFRSF5* (*CD40*) SNP rs1883832, located in the Kozak region of the 5′UTR, was found to be positively associated with FL risk in 4 pooled studies (OR=1.6 for TT vs CC genotype, p-trend=0.001) [27]. Carriers of the TT genotype have lower CD40 translation efficiency, lower levels of circulating soluble CD40, and lower CD40 cell surface expression on dendritic cells, suggesting that the SNP (or one in strong LD) is functional, and could impact lymphomagenesis through dysregulation of the germinal center reaction [28].

SNPs in a second TNF family member, *TNFSF13B* (*BAFF*), have been correlated with FL risk. In one study, carriage of 3 risk alleles was associated both with FL risk (per high risk allele OR=1.43; p-trend=0.029) as well as serum BAFF levels in controls (p=0.02) [29]. In a report of 3 pooled studies [30], a different SNP from *TNFSF13B* was associated with FL risk (allelic OR=0.87, p=0.056), and this association was consistent within each study. BAFF is important in normal B-cell physiology, and altered expression is associated with autoimmune disease, other immune alterations, and B-cell malignancy [31].

In a pooled analysis of 3 studies [30], SNPs in *TNFSF7* (rs16994592 allelic OR=0.68, p-trend=0.0032), *FAS* (rs4934436 allelic OR=0.81, p-trend=0.0045) and *TANK* (rs1921310 allelic OR=0.82, p-trend=0.029) were all associated with FL risk, overall and in each study.

All of these results strongly suggest an important role for TNF family members, including CD40, BAFF, and FAS in FL risk, and suggest that downstream activation of the NF-κB pathway may be etiologically relevant. Interestingly, it has been clearly established that genetic variation in *TNF* and *LTA* is very unlikely to play a role in FL risk, but is clearly

associated DLBCL risk [32, 33]. A very limited evaluation of genes in the NF-κB pathway to date has not shown a consistent association with FL risk [30, 34].

Innate Immunity—SNPs from the innate immune genes *TLR10-TLR1-TLR6* were associated with FL risk in a pooled analysis of 3 studies, and the effect was consistent within the individual studies [35]; an association with *TLR6* was also reported in another study [36].

Cell Cycle/Apoptosis—In a pooled analysis of 3 studies [37], the SNP rs37899068 from *BCL2L11* (*BIM*) was strongly associated with FL risk (OR=1.65 for GG vs. AA genotype, p-trend=0.0004) [37], and SNPs in *CASP8* (rs6736233 allelic OR=1.42, p-trend=0.01; rs3769821 allelic OR=1.18, p-trend=0.02) and *CASP9* (rs4661636 allelic OR=0.83, p-trend=0.01) were also associated with FL risk [38]; all of these associations were also generally consistent within the individual studies.

Other Pathways—In an analysis of two pooled studies, A SNP in *ESR1* (rs3020314) was replicated, suggesting a role for estrogen in FL risk [39]. Multiple other pathways have been interrogated with many interesting leads (Table 2), particularly related to DNA repair, one carbon metabolism, and energy balance, although to date few genes have been evaluated across more than 2 studies and overall results have not been consistent. Pooling initiatives such as the InterLymph Consortium [32, 33] should help clarify the literature.

Genome-wide association studies—In contrast to candidate gene/pathway studies, GWA studies use a large number of SNPs (>100,000) spread across all chromosomes to identify genetic markers associated with case-control status. Most of these SNPs have been derived from the HapMap [23], and the ability to conduct these studies was made possible through the development of dense microchips that allow for simultaneous genotyping of large numbers of SNPs. Due to the large number of statistical tests involved, a stringent level of evidence (e.g., p values of $<5 \times 10^{-8}$) and replication across multiple independent studies is required to declare an association confirmed.

In NHL, there have been two GWA studies published to date. The first study by Skibola and colleagues [40] identified rs6457327 on 6p21.33 as a susceptibility locus for FL based on an evaluation of >500,000 SNPs in 189 FLs and 592 controls in the discovery phase and validation in another 456 cases and 2785 controls. In the combined dataset, this SNP had a MAF of 0.38 in the controls, and an allelic OR of 0.59 (95% CI 0.50-0.70) with a p-value of 4.7×10^{-11}. rs6457327 is not a functional SNP and is not in a gene, but it is 5kb downstream from the 3′ UTR of the *C6orf15* (*STG*) gene, which is near the psoriasis susceptibility region 1 (*PSORS1*). The actual causal variant associated with rs6457327 has yet to be identified.

In the second GWA study [41], a similar-sized discovery set (213 follicular cases and 750 controls) but a larger validation set (1252 follicular cases and 5261 controls) was used. In that study, a second susceptibility loci was identified for FL at 6p21.32 that was independent of rs6457327. The strongest SNP in this region was rs1048456, and it had a MAF of 0.13 and an allelic OR of 1.95 (95% CI 1.72-2.22) with a p-value of 1.1×10^{-29}. This SNP is in a 100kb region of high LD that includes MHC class II genes, and follow-up genotyping suggested that this locus is part of an extended haplotype that includes *HLA-DRB1*0101-HLA-DQA1*0101-HLA-DQB1*0501*.

These first two GWA studies, while underpowered in the discovery phase, were able to conclusively identify two independent susceptibility loci for FL. These studies should be viewed as only a first step, as a more fully powered discovery stage along with validation of a larger number of top hits is likely to identify many more susceptibility loci [42]. It will

ultimately be very interesting to see what percent of loci are unique versus shared across NHL subtypes.

Evidence for a host genetic component to FL prognosis

Familial aggregation and survival

There are few data on the role of familial aggregation in NHL prognosis. The most comprehensive data are from a study using population-based registries in Sweden and Denmark that identified 25,801 patients with NHL, of whom 206 had a first degree relative with any lymphoma [43]. In that study, mortality at 5 years (HR=0.91, 95% CI 0.74-1.12) and 10 years (HR=0.97, 95% CI 0.80-1.16) was not related to family history. Histologic subtype was available on 28% of the NHL cases, and of 4,359 patients with low grade lymphoma (mainly FL), 28 had a family history of lymphoma; family history in these patients was not associated with mortality at 5 years (HR=1.04, 95% CI 0.56-1.93) and 10 years (HR=1.14, 95% CI 0.66-1.98). In a separate analysis limited to the Swedish Family-Cancer Database, there was no difference in cause-specific or overall survival for patients with sporadic NHL compared to patients with a parent or offspring with NHL [44]. These limited results suggest that inherited factors may not play a major role in NHL or FL prognosis, although the low power of these studies limits any definitive conclusions.

Tumor microenvironment and prognosis

Biopsy samples of lymph nodes with FL contain both tumor cells and many non-neoplastic cells including T-cells, macrophages, and dendritic cells (termed the “tumor microenvironment”). As recently reviewed [4, 45], multiple characteristics of the tumor microenvironment have been linked with FL prognosis. While the most common somatic genetic defect in follicular lymphoma is the t(14;18) translocation, almost all most FL tumors have at least one additional karotypic abnormality (and an average of 6) [46]. However, the somatic changes that lead to a malignant phenotype alone cannot sustain FL growth, and *in vitro*, stromal cells and stimulation of the CD40 receptor in combination with cytokine cocktails are required for survival of tumor cells [47]. Gene-expression studies further support the importance of the host immunologic environment in FL [48-50], and one of the strongest predictors of FL survival is the gene expression signatures of nonmalignant tumor-infiltrating immune cells [49]. Integration of these observations leads to the hypothesis that FL is disease of functional B-cells in which intrinsic (specific molecular alterations) and extrinsic (immunologic and other regulatory networks) factors interact to promote neoplastic growth [45]. The immunologic and other regulatory networks have important host (germline) determinants. In other cancers, there is also growing evidence that host genetic background plays a role in cancer progression and metastasis [51]. Taken together, these data lead to the hypothesis that inherited, polymorphic genes influence FL prognosis.

Pharmacogenetics

The resistance to chemotherapy and toxicity to specific agents are thought to be largely determined by multiple enzymatic systems involved in the metabolism and function of these agents. Many of these enzyme systems are genetically polymorphic, leading to differential enzyme expression or function, and these changes have been linked to clinical response to therapy as well as toxicity [52].

Genetics of FL prognosis

Overview

Table 3 summarizes major studies that have assessed genetic susceptibility and FL prognosis. Significant findings were based on each author's interpretation of statistical significance, which for almost all studies was a (nominal) $p<0.05$. In contrast to studies assessing risk of FL, there are fewer studies assessing prognosis, and the number of genes and SNPs within genes has also been smaller. There have been no pooled analyses of studies, and no genome-wide studies of FL prognosis.

Immunogenetics

The first report in the literature on germline SNPs and FL prognosis were for genes encoding the cytokines TNF and LT-α [53]. Similar to risk studies, SNP in *TNF* and *LTA* were associated with DLBCL but not FL prognosis [53-55]. Cerhan and colleagues [55] conducted an evaluation of 44 candidate genes involved in immune and inflammation pathways with overall survival in 278 FL patients. SNPs in *IL8* (rs4073), *IL2* (rs2069762), *IL12B* (rs3212227), and *IL1RN* (rs454078) were the strongest and most robust predictors of survival using several model building strategies. A summary score of the number of deleterious genotypes from these four genes was strongly associated with survival after accounting for demographic and clinical variables (p=0.00006). Combining the SNPs and demographic and clinical variables further improved prediction ability over either one alone. In a time-dependent receiver-operator curve (ROC) analysis, the combined risk score had an area under the curve (AUC) of 0.76 at 60 months of follow-up (95% CI 0.70-0.82), which is nearing a level of meaningful clinical utility.

FCGR3A and FCGR2A

The affinity to the Fcγ receptor and triggering of ADCC by rituximab appears to be influenced by a functional SNP in *FCGR3A* (rs396991) such that carrying a variant F allele is associated with a decreased affinity for IgG [56]. In a study of previously untreated FL patients, Cartron and colleagues [57] found that carriers of the VV genotype had a better overall response to single-agent rituximab, and a trend towards better PFS at 3 years (56% for VV patients versus 35% for VF/FF patients, p=0.2). Significantly better PFS for *FCGR3A* SNP was observed by Weng and Levy [58] in recurrent FL and Ghielmini et al [59] in newly diagnosed FL. Weng and Levy [58] also found an independent SNP in *FCGR2A* (rs1801274) that predicted treatment response and EFS to single agent rituximab; this SNP was later found to be in LD with the *FCGR3A* SNP rs396991 [60]. Interestingly, the *FCGR3A* SNP rs396991 does not appear to predict response or prognosis in FL patients treated with CHOP [61, 62] or R-CHOP [63].

DNA repair and One Carbon Metabolism

DNA repair and one-carbon metabolism genes play critical roles in DNA synthesis and sensitivity to damage. Wang *et al.* [64] evaluated the association of 34 SNPs from 19 genes in five DNA repair pathways and 30 SNPs from 18 one-carbon metabolism genes using a population-based sample of 192 FL cases. None of the DNA repair genes were associated with OS, while for one-carbon metabolism, SNPs in *MTHFR* (rs1801131), *FTHFD* (rs1127717), and *GGH* (rs719235) were associated with OS. A summary SNP risk score from these 3 genes and clinical and demographic variables was strongly associated with OS ($p=1.9 \times 10^{-6}$) and in a time-dependent ROC analysis, the combined SNP plus clinical risk score had an AUC of 0.72 at 60 months of follow-up.

GSTs

GSTs are a multigene family of enzymes that detoxify electrophilic compounds through conjugation with reduced glutathione. Hohaus *et al.* reported that having a deletion in *GSTM1* or *GSTT1*, particularly in both genes, was associated with poorer disease-free survival in FL (HR=1.8, 95% CI 1.0-3.4) after adjusting for the FLIPI [65]. This could not be confirmed for OS in a second study [66].

Summary

Preliminary leads from the literature include pathways that regulate the balance between Th1 and Th2 phenotype for T lymphocytes (e.g., *IL2* and *IL12B*); antibody-dependent cellular cytotoxicity (*FCGRA3*); regulation of the inflammatory pathway via interleukin 1 (*IL1RN*); chemotaxis for neutrophils and monocytes (*IL8*); and one-carbon metabolism (*MTHFR, FTHFD, GGH*), but these need further validation. Besides candidate gene and pathway approaches, a more agnostic approach using genome-wide scans could be considered, but must be tempered with the need for large sample sizes and replication studies in order to account for the high type I and type II error rates with this approach. Ultimately, it is expected that clinical, treatment, host genetic, tumor biomarkers, and their interactions will greatly improve our ability to predict FL prognosis.

Clinical Relevance

Given an estimated lifetime risk of NHL of 1 in 48 (2.1%) in the United States [1] and a RR of 1.5 for the risk of NHL in first degree family members [13], then the absolute lifetime risk of NHL is 3.2% in first degree relatives of an NHL patient. For FL, the estimated lifetime risk is 1 in 278 (0.36%) [1], and using a RR of 4.0 for the risk of FL in first degree family members [8], then the absolute lifetime risk of FL is 1.4% among first degree relatives of FL patients. The clinical significance of the absolute increased risk to relatives of patients with FL is not trivial, although the relatively low incidence of FL, the modest familial risk, and the lack of a screening test/clinical intervention all argue against clinical surveillance of families of FL patients at this time. Results of candidate gene studies of risk are too preliminary to move to the clinic, and even replicated loci are too few that they are not useful in identifying individuals at high risk of FL.

Similarly, evaluation of SNPs in genes to predict response to therapy and prognosis are not ready for clinical use. Using germline SNP markers is attractive, since they can be obtained from multiple types of biologic specimens (peripheral blood, buccal cells) and are relatively easily and reliably measured (i.e., genotyped). Early results suggest SNP markers add important additional prediction beyond clinical factors, and the interaction of SNPs with treatments (pharmacogenetics) remains to be fully explored in FL. Individually, the SNP markers are only modestly associated with prognosis (HRs 1.5-2.0), but combining multiple markers appears to strengthen prediction ability, consistent with a polygenic model of disease pathogenesis. Ultimately, the clinical validity (by assessing sensitivity, specificity, and positive and negative predictive values) will need to be established for genetic markers, along with demonstrated clinical utility to improve the management of FL patients.

Summary

Our understanding of the role of host genetics in FL etiology and prognosis is still rudimentary. However, there are many encouraging leads. In terms of understanding etiology, novel loci are rapidly being identified, with the hope that these results can be used to identify new causal and risk modifying pathways for FL development, and perhaps new approaches to risk stratification. Host genetics may also help with prognostication. To date, the only prognostic factors used clinically to manage FL patients are clinical factors that are

part of the Follicular Lymphoma Prognostic Index (FLIPI) [67]. These represent disease burden but not disease pathogenesis, and therefore, they have limited value in understanding lymphomagenesis and disease progression. Host genetics that underlie immunologic and treatment response, toxicity, and general host response may help to improve prognostic models, individualize cancer treatment (increase efficacy and decrease toxicity), and identify novel treatment targets or approaches.

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PRACTICE POINTS

- Follicular lymphoma (FL) aggregates in families, and first degree relatives of FL patients have an approximately 4-fold increased risk of FL
- The absolute risk of FL is only increased from a baseline risk of 0.36% for sporadic FL to 1.4% in individuals with a first degree relative with FL, and thus active clinical surveillance of FL patient's family members is not warranted
- A family history of CLL is also associated with an increased risk of FL, but a family history of DLBCL or multiple myeloma do not appear to increase the risk of FL
- A family history of NHL does not appear to be an important prognostic factor in FL
- The use of single nucleotide polymorphisms (SNPs) to identify individuals at high risk of FL or to predict treatment response and prognosis in FL patients is a promising approach that is not yet ready for the clinic

RESEARCH AGENDA

- Accelerate the identification and replication of SNPs associated with both FL risk and prognosis
- Understand the similarities and differences in the host genetics of risk and prognosis among the major NHL subtypes
- Conduct studies to identify gene-environment interactions for FL risk and gene-treatment interactions for FL prognosis.
- Increase our knowledge of FL genetics in racial and ethnic groups not of European descent
- Evaluate other types of genetic variation, including copy number variants and rare variants, with FL risk and prognosis

Table 1

Risk of follicular lymphoma by type of hematologic malignancy in relatives

Reference (first author, year)	Study Population	Diagnosis in relative(s)	Observed	Expected	Risk (95%CI)
Cohort studies					
Altieri,2005 [7]	Swedish Family-Cancer Database	NHL in a parent or sibling	29	--	2.0 (1.4-2.9)
		FL in a parent	3	--	6.1 (1.1-18.0)
		CLL in a parent	7	--	1.7 (0.6-3.4)
		DLBCL in a parent	0	--	--
		TCL in a parent	2	--	8.7 (0.8-32.1)
		MM in a parent	8	--	1.2 (0.5-2.4)
Goldin, 2009 [8]	Swedish databases	FL in a 1st degree relative	--	--	4.0 (1.6-9.5)
Case-control studies					
Pottern,1991 [14]	Iowa and Minnesota, USA	Lymphoma in a parent	4/190	10/1197	2.2 (0.6-7.9)
		Lymphoma in a sibling	2/178	6/1153	2.4 (0.3-13.3)
Chang, 2005 [15]	Sweden	NHL in a parent or sibling	10/221	26/1203	2.0 (0.9-4.2)
		CLL in a parent or sibling	2/229	5/1224	1.7 (0.3-8.9)
		MM in a parent or sibling	9/222	12/1217	3.6 (1.5-8.7)
Wang, 2007 [13]	Pooled analysis of 11 case-control studies	NHL in a 1st degree relative	55/1703	140/10776	1.8 (1.3-2.5)
		HL in a 1st degree relative	14/1703	55/10776	1.2 (0.7-2.3)
		LK in a 1st degree relative	54/1703	277/10776	1.1 (0.8-1.5)
		MM in 1st degree relative	10/1703	38/10776	1.2 (0.6-2.4)

Abbreviations: NHL (non-Hodgkin lymphoma), FL (follicular lymphoma), CLL (chronic lymphocytic leukemia), DLBCL (diffuse large B-cell lymphoma), TCL (T-cell lymphoma), MM (multiple myeloma), HL (Hodgkin lymphoma), LK (leukemia)

TABLE 2

Genetic factors associated with follicular lymphoma risk

Reference (first author, year)	Study Population	N, FL	N, Controls	Gene or Pathway	# Genes	# SNPs	Summary of significant associations with FL
Single Study Reports - Candidate Gene/Pathway							
Fitzgibbon, 1999 [54]	UK	121	88	*TNF, LTA*	2	2	No significant findings
Skibola, 2004 [68]	SF-1	131	805	Obesity	2	1	*LEP* (rs2167270)
Skibola, 2004 [69]	SF-1	122	731	One carbon	5	10	*MTHFR* (rs1801133)
Chiu, 2005 [70]	Nebraska	112	535	Metabolism	5	5	No significant findings
Lightfoot, 2005 [71]	UK	207	755	One carbon	5	8	No significant findings
Skibola, 2005 [72]	SF-1	112	684	Hormone	3	17	*PRL* (rs1341239); *COMT* (rs737865)
Skibola, 2005 [73]	SF-1	112	684	*GHRL, NPY*	2	8	*NPY* (rs16147, rs16139, rs11557492, rs5574)
Skibola, 2005 [74]	UK	214	762	*CYP17A1*	1	2	No significant main effects
Willett, 2005 [75]	UK	210	754	Obesity	3	4	*LEP* (rs2167270, rs7799039)
Zhang, 2005 [76]	Yale	106	535	*BCL6*	1	1	*BCL6* (rs1056932)
de Roos, 2006 [77]	NCI-SEER	272	982	Metabolism	11	15	*PON1* (rs854560)
Forrest, 2006 [78]	SF-1	322	1441	Immune	6	7	*CARD15* (rs2066847/rs5743293)
Hill, 2006 [79]	NCI-SEER	280	982	DNA repair	19	34	*RAG1* (rs2227973)
Lan, 2006 [80]	Yale	119	597	Th1/Th2	20	39	*IL10* (rs1800890); *IFNGR1* (rs3799488)
Morton, 2006 [81]	NCI-SEER	216	922	NAT1/NAT2	2	10	*NAT1*10/*10; NAT2* (intermed/rapid)
Niclot, 2006 [82]	France	172	206	One carbon	4	5	*MTR* (rs1805087); *TYMS* (repeat)
Shen, 2006 [83]	Yale	119	597	DNA repair	18	32	*WRN* (rs1346044); *XRCC3* (rs861539); *XRCC1* (rs1799782)
Smedby, 2006 [84]	Sweden	430	605	DNA repair	3	19	*XRCC3* (rs3212024, rs3212038, rs3212090)
Spink, 2006 [85]	UK	211	478	*TNF*	1	10	*TNF* haplotypes
Wang, 2006 [86]	NCI-SEER	280	982	Immune	36	57	*IL15RA* (rs2296135), *FCGR2A* (rs1801274), *IL10RA* (rs9610)
Wang, 2006[87]	NCI-SEER	265	982	Cell Cycle	7	12	No significant findings
Wang, 2006 [88]	NCI-SEER	280	982	Ox Stress	10	13	*NOS2A* (rs2297518); *PPARG* (rs3856806)
Cerhan, 2007 [36]	Mayo	113	484	Immune	1253	9412	*CREB1; FGG; MAP3K5; LSP1; ITGB3* (rs5918); *TLR6* (rs5743815); *SELPLG* (rs7300972)
Lech-Maranda, 2007 [89]	France	100	112	*IL10*	1	3	No significant findings
Lee, 2007 [90]	Australia	211	506	One carbon	10	14	*TYMS* (rs699517)
Lim, 2007 [91]	NCI-SEER	271	949	One carbon	18	30	No significant findings
Novik, 2007 [92]	Vancouver	140	531	*H2AFX*	1	3	*H2AFX* (rs2509049)

Reference (first author, year)	Study Population	N, FL	N, Controls	Gene or Pathway	# Genes	# SNPs	Summary of significant associations with FL
Purdue, 2007 [93]	Australia	209	518	*VDR*	1	3	No significant findings
Purdue, 2007 [94]	Australia	205	498	Immune	23	36	*TNF* (1799724), *TGFB1* (rs1982073)
Cerhan, 2008 [34]	Mayo	113	475	Immune	11	54	*LTA* (rs2239704); *TNF* (rs361525); *NFKB1* (rs4648022)
Cerhan, 2009 [95]	Mayo	113	475	Complement	31	167	*C2* (rs7746553); *C7* (rs13157656); *C9* (rs187875, rs261752)
Hoffman, 2009[96]	Yale	135	527	*CRY2*	1	5	*CRY2* (rs11038689, rs7123390, rs1401417)
Novak, 2009 [29]	Mayo	113	475	*TNFSF13B*	1	9	*TNSF13B* (rs1224141, rs12583006, rs12428930)
Schuetz, 2009[97]	Vancouver	216	793	DNA repair	4	19	No significant findings
Wang, 2010 [98]	NCI-SEER	168	520	HLA	4	178	*HLA-DRB1*0101; HLA-DRB1*13*
Pooled Reports - Candidate Gene/Pathways							
Lightfoot, 2006[99]	2 studies	381	1446	Ox Stress	3	5	*GPX1* (rs1050450)
Rothman, 2006 [32]	8 studies	894	3564	Immune	9	12	No significant findings
Skibola, 2008 [28]	3 studies	394	2481	Immune	2	9	*TNFRSF5* (rs1883832)
Skibola, 2008 [39]	2 studies	278	1534	Multiple	146	768	*ESR1* (3020314)
Lan, 2009 [38]	3 studies	540	1808	Caspase	12	79	*CASP8* (rs6736233, rs3769821); *CASP9* (rs4661636)
Morton, 2009 [37]	3 studies	540	1808	Apotosis	20	203	*BCL2L11* (rs3789068)
Purdue, 2009 [35]	3 studies	540	1808	Immune	5	36	*TLR10-TLR1-TLR6* (rs10008492)
Wang, 2009 [30]	3 studies	540	1808	TNF, NFkB	58	500	*TNFSF7* (rs16994592); *TNFSF13B* (rs2582869); *TANK* (rs1921310); *RAS* (rs4934436); *C22ORF18* (rs6002551)
Skibola, 2010 [33]	8 studies	715	3323	Immune	4	5	No significant findings
Nieters, 2010 [27]	4 studies	503	3600	Immune	1	1	*TNFRSF5* (rs1883832)
Pooled Reports – Genome-Wide Association Studies							
Skibola, 2009 [40]	3-stage	645	3377	Illumina 550v.3	--	~500, 000	6p21.33 (rs6457327)
Conde, 2010 [41]	3-stage	1465	6011	Illumina CNV370	--	312,768	6p21.32 (rs10484561, rs7755224)

TABLE 3

Genetic factors associated with follicular lymphoma prognosis

Reference (first author, year)	Study population	FL Cases	Gene or Pathway	# Genes	# SNPs	Summary of Findings
Warzocha, 1998 [53]	French cohort	96	*TNF-LTA*	2	2	*TNF* (1800629)-*LTA* (rs909253) haplotype not associated with PFS or OS
Fitzgibbon, 1999 [54]	UK cohort enrolled 1971-98	121	*TNF-LTA*	2	2	*TNF* (1800629)-*LTA* (rs909253) haplotype not associated with PFS or OS
Cartron, 2002 [57]	French clinical trial of patients treated rituximab as frontline therapy	49	*FCGR3A*	1	1	*FCGR3A* (rs396991) associated with objective response to rituximab; suggestive trend with PFS (p=0.2)
Weng & Levy, 2003 [58]	California cohort treated with rituximab as 2nd-line therapy, enrolled 1993-2003	89	*FCGR3A & FCGR2A*	2	2	*FCGR3A* (rs396991) and *FCGR2A* (rs1801274) independently associated with response to ritumixab and EFS
Weng, 2004 [61]	FL patients treated with only chemotherapy	158	*FCGR3A & FCGR2A*	2	2	No association with EFS
Ghielmini, 2005 [59]	SAKK trial 35/98 of single agent rituximab, enrolled 1998-2002	185*	*FCGR3A*	1	1	*FCGR3A* (rs396991) associated with EFS
Hohaus, 2007 [65]	Italian cohort enrolled 1990-2005	89	GSTs	3	3	*GSTM1* and *GSTT1* associated with EFS, but not OS. *GSTP1* not associated with EFS or OS
Carlotti, 2007 [63]	Italian cohort of patients treated with CHOP and rituximab	94	*FCGR3A & FCGR2A*	2	2	No associations with response, EFS, or OS
Cerhan, 2007 [55]	US Population-based sample enrolled 1998-2000	278	Immune	44	73	*IL8* (rs4073), *IL2* (rs2069762), *IL12B* (rs3212227), and *IL1RN* (rs454078) associated with OS
Pennell, 2008 [62]	Canadian cohort of 69 low grade patients enrolled 1990-95	69†	*FCGR3A*	1	1	No association with EFS or OS
Wang, 2009 [64]	US Population-based sample enrolled 1998-2000	192	DNA repair & one carbonmetabolism	36	66	No DNA repair genes associated with OS; *MTHFR* (rs1801131), *FTHFD* (rs1127717) and *GGH* (rs719235) associated with OS
Wrench, 2009 [100]	UK cohort enrolled 1971-98	226	*TP53* & *MDM2*	2	2	No association with PFS or OS
Han, 2010 [66]	Connecticut population-based sample enrolled 1996-2000	117	Xenobiotic	11	21	*GSTT1* null associated with OS

*Number with SNP data less than 185.

†Low grade cases from the Working Formulation (a majority expected to be FL)

Abbreviations: FL, follicular lymphoma; PFS, progression-free survival; OS, overall survival