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## Genome-wide association study of follicular lymphoma identifies a risk locus at 6p21.32

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### Abstract

To identify susceptibility loci for non-Hodgkin lymphoma (NHL) subtypes, we conducted a three-stage genome-wide association study. We identified two variants associated with follicular lymphoma (FL) in 1,465 FL cases/6,958 controls at 6p21.32 (rs10484561, rs7755224,  $r^2=1.0$ ; combined  $p$ -values= $1.12 \times 10^{-29}$ ,  $2.00 \times 10^{-19}$ ), providing further support that MHC genetic variation influences FL susceptibility. Confirmatory evidence of a previously reported association was also found between chronic lymphocytic leukemia/small lymphocytic lymphoma and rs735665 (combined  $p$ -value= $4.24 \times 10^{-9}$ ).

Non-Hodgkin lymphoma (NHL) is a complex group of B- and T-cell neoplasms with >300,000 new cases diagnosed worldwide each year (<http://www-dep.iarc.fr/globocan/database.htm>). Family and epidemiological studies suggest an important genetic role in the etiology of lymphoma<sup>1</sup>, though the inherited genetic basis of the disease is largely unknown. Recently, we conducted a genome-wide association study (GWAS) of three common histological subtypes of NHL, follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and diffuse large B-cell lymphoma (DLBCL), using a pooled DNA genotyping strategy<sup>2</sup>. Due to experimental and technical noise associated with pooled DNA GWAS, we conducted a new individual genotyping-based study on a larger subset of NHL cases and control using a three-stage GWAS study design (Supplementary Table 1, Supplementary Fig. 1).

In Stage 1, we conducted a GWAS using a subset of samples (SF1 study) chosen from a larger population-based case-control study of NHL based in the San Francisco Bay Area<sup>3</sup>. After applying quality control metrics (Supplementary Methods), 213 FL, 211 CLL/SLL and 257 DLBCL cases and 750 controls were included in the final statistical analysis of Stage 1. The genome-wide results for FL, CLL/SLL and DLBCL are represented in Supplementary

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Fig. 2a-c, where overall, 18 SNPs showed unadjusted trend  $p$ -values below a  $10^{-5}$  threshold (Supplementary Table 2). The most notable findings were for SNPs associated with FL in the major histocompatibility complex (MHC) region on chromosome 6, concentrated around two independent peaks at 6p21.33 and 6p21.32 ( $r^2 < 0.01$ ; Figure 1). The strongest signal in 6p21.33 is located at the psoriasis susceptibility region 1 (*PSORS1*) (rs1265086, trend  $p$ -value =  $3.34 \times 10^{-6}$ , Supplementary Table 3), where we have previously detected a FL susceptibility locus<sup>2</sup>. The 6p21.32 association peak is located in a region encompassing the *HLA-DR* and *HLA-DQ* genes. Here, eight SNPs exhibited trend  $p$ -values  $> 10^{-4}$  (Supplementary Table 3).

In Stage 2, 40 SNPs with the lowest trend  $p$ -values for each NHL subtype (Supplementary Tables 4-6) were genotyped in two independent population-based case-control studies (SCALE4 for FL, Mayo-GEC5 for CLL/SLL) and in a separate sample of 118 DLBCL population-based cases and 651 controls (SF1B study) drawn from the same population as SF1 (Supplementary Table 1, Supplementary Fig. 1). Seven SNPs were associated with FL risk ( $p < 0.05$ ) in the SCALE study (Supplementary Table 7). The two SNPs with the lowest  $p$ -values, rs7755224 and rs10484561 (allelic  $p$ -values =  $6.30 \times 10^{-5}$  and  $1.20 \times 10^{-5}$ ) are located in the MHC Class II region at 6p21.32. They are in complete linkage disequilibrium (LD) ( $r^2 = 1.0$ ) and lie, respectively, 16kb and 29kb upstream of *HLA-DQB1*. Four additional SNPs were associated with FL in the MHC region at 6p21.33, including the two SNPs, rs6457327 and rs2517448 (allelic  $p$ -values =  $2.90 \times 10^{-2}$  and  $3.45 \times 10^{-2}$ ), previously reported in our pooled DNA GWAS<sup>2</sup>.

Two SNPs with trend  $p$ -values  $< 0.05$  were positively associated with CLL/SLL risk in the Mayo-GEC study (rs735665 and rs484458, trend  $p$ -values =  $2.64 \times 10^{-3}$  and  $6.43 \times 10^{-3}$ ; Supplementary Table 7). Located in an intergenic region on 11q24.1, rs735665 was previously reported as a risk allele for CLL in a genome scan by Di Bernardo and colleagues<sup>6</sup>. Interestingly, two other SNPs, rs872071 and rs9378805, reported to be highly associated with CLL in that study were ranked among the top 100 CLL/SLL SNPs in our Stage 1 GWAS (trend  $p$ -values =  $7.17 \times 10^{-4}$  and  $1.75 \times 10^{-4}$  respectively).

None of the SNPs genotyped in Stage 2 for DLBCL showed evidence of association with disease risk ( $p$ -value  $< 0.05$ ). Failure to identify associated alleles may be due to the heterogeneity of DLBCL as evidenced from gene expression and immunophenotyping studies.

In Stage 3, the nine SNPs associated with FL and CLL/SLL risk were genotyped in 873 FL, 471 CLL/SLL, 916 DLBCL cases and 4,470 controls recruited from six case-control studies of European descent participating in the InterLymph Consortium (Supplementary Table 1, Supplementary Fig. 1). Again, rs10484561 was associated with increased FL risk across all studies, with trend  $p$ -values ranging from  $2.21 \times 10^{-2}$  to  $1.40 \times 10^{-10}$  (Table 1). The combined  $p$ -value reached  $1.12 \times 10^{-29}$  in the meta-analysis of samples from all three stages (combined odds ratio [OR] = 1.95, 95% confidence interval [CI] 1.72-2.22, Supplementary Table 8, Supplementary Fig. 3). No evidence was found of heterogeneity across studies (Cochran's  $Q$  statistic = 5.61, d.f. = 7,  $p$ -value = 0.5857;  $I^2$  heterogeneity index = 0%). Likewise, rs7755224 was associated with FL in the meta-analysis from all stages (combined  $p$ -value =  $2.00 \times 10^{-19}$ ,

OR=2.07, 95% CI 1.76-2.42, Supplementary Table 8, Supplementary Fig. 4) and no evidence was found of significant heterogeneity ( $Q=5.42$ , d.f.=3,  $p$ -value=0.1438;  $I^2=44.6\%$ ). While the association between rs6457327 and FL was replicated in Stage 2, and in three other independent sample sets<sup>2</sup>, this association was poorly replicated in the smaller studies from Stage 3, resulting in a weaker combined  $p$ -value ( $6.64 \times 10^{-6}$ ; OR=0.68, 95% CI 0.58-0.79, Supplementary Table 8) than previously reported<sup>2</sup> (see Supplementary Table 9 for additional information).

For CLL/SLL, rs735665 exhibited a trend  $p$ -value of  $3.58 \times 10^{-4}$  in Stage 3 and a combined  $p$ -value of  $4.24 \times 10^{-9}$  in the meta-analysis of all samples (OR=1.81, 95% CI 1.50-2.20; Supplementary Table 8). This finding confirms the previous association of rs735665 with CLL risk<sup>6</sup>, and further supports its role in CLL susceptibility.

To search for additional FL-associated variants that were not genotyped in the *HLA-DQB1* region in Stage 1, we imputed SNP genotypes in a 500kb region centered on rs10484561 (Figure 1). We identified four SNPs with imputed  $p$ -values  $< 10^{-3}$  that were in complete LD with rs10484561 ( $D'=1$ ,  $r^2=1$  in HapMap-CEU), although none showed stronger signals than rs10484561 or rs7755224 (Supplementary Table 10). These SNPs are located in a 100kb region of relatively high LD in chromosome 6p21.32 that covers *HLA-DQB1* and *HLA-DQA1*, and in close proximity to *HLA-DRB1*. Logistic regression analysis conditional on the associated SNPs in the region suggested that none were independent signals (Supplementary Table 11), and that a single locus or haplotype in LD with rs10484561/rs7755224 may harbor the causal variant(s). Analysis of SNP interactions and preliminary functional analyses did not provide further refinement of the signal (Supplementary Methods). However, one of the imputed SNPs, rs6457614, reported as a tag SNP for the *HLA-DQB1*\*0501 allele in European, African and Japanese populations<sup>7</sup>, suggested that the association signal may be driven by this protein variant. To verify our imputation, rs6457614 was genotyped in the SF1 study. We found 99% concordance between imputed and observed genotypes for rs6457614, which was in strong LD with rs10484561 ( $D'=0.99$ ,  $r^2=0.95$  in controls). Because *HLA-DRB1*\*0101 and *HLA-DQA1*\*0101 form the most frequent haplotype containing *HLA-DQB1*\*0501 in European American populations<sup>8</sup>, tag SNPs for these two MHC Class II alleles (rs4947332 and rs1794265, respectively)<sup>7</sup> also were genotyped in SF1. Genotyping results revealed that markers for an extended haplotype that includes *HLA-DRB1*\*0101-*HLA-DQA1*\*0101-*HLA-DQB1*\*0501-rs10484561 were associated with FL risk (OR=2.07, 95% CI=1.40-3.06,  $p$ -value= $2.32 \times 10^{-4}$ ).

Several small studies have reported links between MHC Class II alleles and NHL<sup>9,10,11</sup>, with somewhat conflicting results that may be attributable to small sample size, the combined analysis of mixed NHL subtypes, and/or differences in ethnic groups being analyzed<sup>11</sup>. In a large pooled study within the InterLymph consortium, the variant allele for *TNF*-308G>A (rs1800629) and a *TNF/LTA* haplotype located in the MHC Class III region were positively associated with DLBCL risk, but no association was found for FL<sup>12</sup>. Further, MHC Class I and II alleles have been evaluated in the context of *TNF* extended haplotypes, which revealed independent positive associations for *TNF*-308A and *HLA-B*\*0801 alleles in risk of DLBCL<sup>13</sup>. These loci are not in LD with rs10484561 in our controls ( $r^2=0.014$  for rs10484561 and *TNF*-308A;  $r^2=0.007$  and 0.001 for rs10484561 and

HLA-B\*0801 tag SNPs [rs6457374, rs2844535]7), suggesting that our signal is not driven by these MHC Class III and I loci. Importantly, the association found here in the MHC Class II region also appears to be independent of the FL susceptibility locus at *PSORS12*, since the LD block at *HLA-DRB1-HLA-DQA1-HLA-DQB1* is located 1.43Mb downstream of the *PSORS1* locus (Figure 1), and the LD measurement between rs6457327 and rs10484561 ( $r^2 < 0.01$ ) in our controls and in HapMap-CEU indicates no correlation between these loci. Results from conditional logistic regression analysis adjusted for the additive effects of rs6457327 in the SF1 study provided additional evidence for an independent role of rs10484561 ( $p$ -value= $3.46 \times 10^{-5}$ ) in FL risk.

In conclusion, we have identified a new FL susceptibility locus at chromosome 6p21.32 with combined  $p$ -values of  $1.12 \times 10^{-29}$  and  $2.00 \times 10^{-19}$  for rs10484561 and rs7755224, respectively, providing evidence that genetic variation in the MHC Class II region is strongly associated with FL susceptibility. These loci appear to be part of an extended haplotype that includes *HLA-DRB1\*0101-HLA-DQA1\*0101-HLA-DQB1\*0501*. Of note, although rs10484561 showed a trend towards association in DLBCL in SF1 (trend  $p$ -value= $3.58 \times 10^{-2}$ ), we did not observe markedly significant associations between the MHC region with risk of CLL/SLL or DLBCL (Supplementary Fig. 5), which suggests that the influence of MHC genetic variation differs by NHL subtype.

## Supplementary Material

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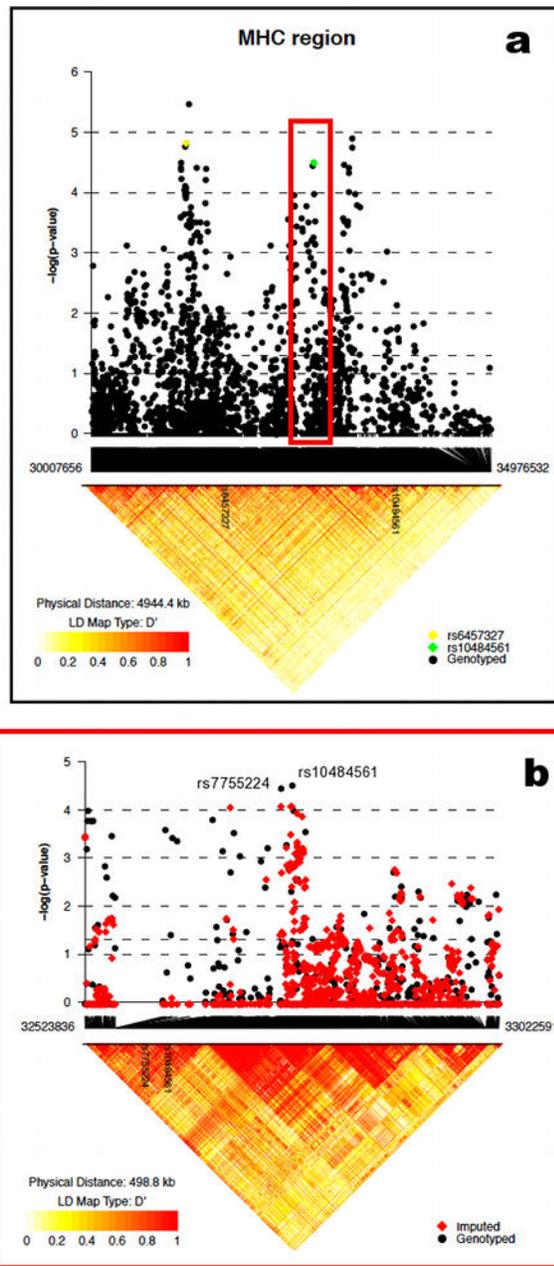
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**Figure 1. LD and association results for the FL-associated regions in the major histocompatibility complex (MHC)**

In the main panel, trend p-values (as  $-\log_{10}$ ) are shown for SNPs genotyped in the MHC region between positions 30,000Mb and 35,000Mb, where two independent FL-associated peaks were found. The first peak, represented by rs6457327 (in yellow), is located at 6p21.33 in the MHC Class I region. The second independent peak, represented by rs10484561 (in green), is located at 6p21.32 in the MHC Class II region. The secondary panel shows the SNPs genotyped (in black) and imputed (in red) in Stage 1 in a 500kb region centered on rs10484561 at 6p21.32. Imputations were based on data from HapMap

Phase II release #22 in CEU population. Figure constructed using the `snp.plotter` R package (<http://cbdb.nimh.nih.gov/~kristin/snp.plotter.html>).

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**Table 1**

Summary statistics for association between rs10484561 and FL in all three stages.

Stage	Dataset	Population	# FL cases	# controls	MAF (cases/controls)	Variant allele OR (95% CI)	Allelic OR (95% CI)	Trend <i>p</i> -value	Genotypic <i>p</i> -value
1	SF1	SF Bay Area NHL2 study - USA	213	750	0.21/0.13	2.06 (1.49-2.85)	1.81 (1.36-2.39)	3.21E-005	5.88E-005
	SCALE	Denmark/Sweden	379	791	0.18/0.11	1.67 (1.26-2.20)	1.71 (1.34-2.19)	1.83E-005	2.91E-005
3	NCI-SEER	USA	153	482	0.20/0.13	1.61 (1.05-2.46)	1.73 (1.21-2.45)	5.94E-003	1.53E-003
	NSW	New South Wales and Australian Capital Territory, Australia	141	369	0.18/0.10	2.08 (1.32-3.27)	1.93 (1.30-2.85)	1.06E-003	3.50E-003
	Yale	USA	98	460	0.18/0.12	1.83 (1.12-2.99)	1.61 (1.05-2.41)	2.21E-002	7.06E-002
	BC	British Columbia, Canada	174	610	0.21/0.10	2.29 (1.57-3.33)	2.30 (1.66-3.17)	5.02E-007	1.12E-006
	EpiLymph	Czech Republic, France, Germany, Ireland, Italy, and Spain	195	1864	0.25/0.12	2.50 (1.83-3.41)	2.43 (1.89-3.12)	1.40E-010	1.12E-009
SF2	SF Bay Area-NHL1 study USA	112	685	0.20/0.14	1.72 (1.11-2.64)	1.64 (1.13-2.35)	9.24E-003	3.36E-003	
			<b># total FL cases</b>	<b># total controls</b>		<b>Combined OR<sup>c</sup></b>	<b>Combined OR<sup>c</sup></b>	<b>Combined <i>p</i>-value<sup>d</sup></b>	
			1465	6011		1.95 (1.72-2.22)	1.12E-029		

OR = odds ratio, CI= confidence interval, FL=follicular lymphoma

<sup>c</sup> Combined OR calculated using a fixed effect, inverse variance meta-analysis

<sup>d</sup> Combined *p*-value calculated using a weighted *z* score-based meta-analysis