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Chemokine polymorphisms and lymphoma: a pooled analysis

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Abstract

Polymorphisms in chemokine genes have been associated with human immunodeficiency virus (HIV)-related non-Hodgkin lymphoma (NHL) but are understudied in non-HIV-related NHL. Associations of NHL and NHL subtypes with polymorphisms and haplotypes in *CCR5*, *CCR2*, *CCL5*, *CXCL12* and *CX3CR1* were explored in a pooled analysis of three case-control studies (San Francisco Bay Area, California; United Kingdom; total: cases N=1610, controls N=1992). Adjusted unconditional logistic regression was used to estimate relative risks among HIV-negative non-Hispanic Caucasians. The *CCR5M* $\Delta 32$ deletion reduced the risk of NHL (odds ratio=0.56, 95% confidence interval=0.38-0.83) in men but not women with similar effects observed for diffuse large-cell and follicular lymphoma (FL). NHL risk also was reduced in men with the *CCR2/CCR5* haplotype characterized by the *CCR5* $\Delta 32$ deletion. The *CCL5* -403A allele conferred reduced risks of FL and chronic lymphocytic leukemia/small lymphocytic lymphoma. Results should be interpreted conservatively. Continued investigation is warranted to confirm these findings.

Keywords

Lymphoma non-Hodgkin; Chemokines; Polymorphism, genetic; Case-Control

INTRODUCTION

Established risk factors for non-Hodgkin lymphoma (NHL) are related to severe immune suppression and include infection with human immunodeficiency virus-1 (HIV) and graft-versus-host disease.[1] In addition, variants in genes related to immune function, cell signaling, and steroidogenesis have been associated with NHL susceptibility and suggest etiologic differences by subtype.[2] More focused study of the association between chemokines and NHL has concentrated on AIDS-related lymphomas and was stimulated by

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

the discovery that the chemokine receptor CCR5 is a co-receptor for HIV; carriers of the *CCR5* $\Delta 32$ deletion are protected against HIV infection (homozygous variants) or have slower progression to AIDS (heterozygotes). Some of the first findings showed that risk for AIDS-related lymphoma was decreased in carriers of the deletion in *CCR5* $\Delta 32$ and increased in those with the for *CXCL12* (*SDF-1*) variant allele.[3, 4]

Chemokines first were identified about 20 years ago and initially were revealed to play a key role in leukocyte trafficking.[5, 6] Continued research has disclosed that chemokines are critical in lymphocyte development, angiogenesis, host response to infection and in inflammatory processes, especially antiviral and antitumor responses.[7-9] Additionally, T-helper 1 and 2 (Th1, Th2) cells that play a role in pro-inflammatory and anti-inflammatory immune responses can be distinguished by their chemokine production and chemokine receptor expression. For example, the receptors for chemokine ligand CCL5, CCR5 and CCR3, are differentially expressed by Th1/Th2 cells, with CCR5 predominantly expressed on Th1 cells and CCR3 predominantly expressed on Th2 cells. Chemokines expressed by B- and T-cell lymphomas have a role in tumor angiogenesis, progression, migration and metastasis.[10-14] Susceptibility, development and survival of other cancers including breast, prostate, melanoma, colon and hepatocellular cancer also have been associated with chemokine expression, levels and polymorphisms.[15-19]

To contribute new information on genetic associations between chemokines and non-AIDS-related NHL and NHL subtypes, we conducted a pooled analysis of genetic data from participants in three population-based case-control epidemiological studies of NHL in the San Francisco Bay Area, USA and in the UK. We explored associations between polymorphisms and haplotypes in chemokine genes *CCR5*, *CCR2*, *CCL5* (*RANTES*), *CXCL12* (*SDF-1*) and *CX3CR1* (fractalkine), and risk of all NHL, diffuse large B-cell, follicular and chronic lymphocytic leukemia/small lymphocytic lymphomas. Also, because data show that sex-related autoimmune diseases associated with increased NHL risk[20] may exhibit increased chemokine expression and levels,[21] and because chemokine expression differs by sex,[22-24] we explored whether chemokine gene variants associated with NHL and NHL subtypes differed by sex.

MATERIALS AND METHODS

Study methodologies have been published for the two large population-based case-control studies of NHL conducted in six counties in the San Francisco Bay Area (NHL1 and NHL2) [2, 25] and for the UK study.[26] Within each study the eligibility criteria for cases and controls were identical with the exception of diagnosis with NHL. Eligible participants were those with incident NHL (all cases), able to complete an interview in English, residents of the study region at diagnosis/interview (1 of 6 San Francisco Bay Area counties for NHL1 and NHL2; 1 of 7 counties or 2 districts in the UK), alive, had no physician indicated contraindications to contact (NHL1 and NHL2 cases), or physician consent to contact (UK participants). Briefly, for the San Francisco Bay Area studies, incident cases 21 to 75 years old diagnosed from 1988 to 1994 (NHL1: N=1591, response rate=72%) and 21 to 85 years old diagnosed from 2001 to 2006 (NHL2: N=2055, response rate=70%) were identified by the Northern California Cancer Center registry using rapid case ascertainment methods. Eligible controls (NHL1: N=2515, response rate=78%; NHL2: N=2080, response rate=68%) were identified by random digit dial methods supplemented by random sampling of the Centers for Medicare & Medicaid Services lists for those aged 65 years or older and frequency-matched to cases by 5-year age-groups, sex and county of residence. In the UK study, patients aged 18-64 years diagnosed with incident lymphoma between 1998 and 2001 were identified from hospital hematology services in certain areas of the country (N=912, response rate=75%). For each case, one individually sex-, age- and ethnicity-matched

control was randomly selected from the same primary care practice list as the case (N=919, response rate=71%).

Pathology materials were reviewed to classify NHL histologic subtypes [27] using the Working Formulation (U.S. NHL1 study) and the World Health Organization (WHO) classification (U.S. NHL2 and U.K. studies). Participants provided informed consent for interview, biospecimen collection, access to pathology materials (for cases) and medical records (U.K. study). Study protocols were approved by the review committee for human research at the University of California, San Francisco and by the United Kingdom Multi-Regional Ethical Committee.

Genotyping

DNA was isolated from purified blood mononuclear cells using a Qiagen column method. For the NHL1 and UK studies, approximately 40ng of DNA was used for the initial polymerase chain reaction. PCR products were purified to remove unincorporated dNTP's and to digest unused primers. Genotypes were determined using three different single-base extension (SBE) reactions (Applied Biosystems, Foster City, CA) on an ABI Prism SNaPshot Multiplex Kit. Each SBE reaction contained 5μl SNaPshot Multiplex Ready Reaction Mix and 1.5pmol of each SBE primer. Reaction A (10μl) consisted of 3μl of purified PCR product and 1.5pmol of SBE primer (*CX₃CR₁* 249, *CX₃CR₁* 280, *CCR2* 64I, *CCR5* delta-32). Reaction B (10μl) combined 4μl purified PCR product with 1.5pmol of SBE primer (*CCR5* 59029, *CCR5* 59353, *CCL5* -403, *CXCL12* 3'A). Reaction C (10μl) contained 3μl of purified PCR product (*CCR5* 59653) and 1.5pmol of SBE primer (*CCR5* 59653). Restriction fragment length polymorphism assays were performed on the *CCR5* 59029 PCR product with BSP 1286 I (New England Biolabs, Beverly, MA) on 20 random samples post-SBE genotyping to insure consistent results. The SBE reaction was cycled 25 times (10sec at 96°C, 15sec at 50°C, 30sec at 60°C) and 0.05 units of shrimp alkaline phosphatase (USB Corporation, Cleveland, OH) were added to the SBE products to remove unincorporated ddNTP's. Gel electrophoresis was run on an ABI Prism® 377 DNA Sequencer with the 36E-1200 Control Module and data were analyzed using GeneScan® 3.1 software (Applied Biosystems, Foster City, CA).

For the NHL2 study genotyping for interim analyses[2] was performed using the Illumina GoldenGate assay on a BeadStation 500G Genotyping System (2 SNPs in *CX₃CR₁* and 1 SNP in *CCL5*) as previously described.[2] Genotype calls were made using the GenCall version 6.2.0.4 software package (Illumina, Inc., San Diego, CA).[2] Genotype data was accessed for 2 SNPs in *CX₃CR₁* that were genotyped as part of a genome-wide association study (GWAS) of NHL. In this GWAS, DNA from 757 NHL case and 811 control participants was genotyped using the Illumina Human CNV370-Duo BeadChip (Illumina, San Diego, CA), that includes >370,000 markers, providing 81% of the HapMap variation at $r^2 > 0.8$ in a Caucasian (HapMap-CEU) population. Genotype clustering was conducted with the Illumina Beadstudio software from data files created by the Illumina BeadArray reader. Samples and markers with call rates below 95% were excluded from further analysis.

Statistical Analysis

Genotype analyses were restricted to HIV-negative non-Hispanic Caucasians (NHL1: cases N=262, controls N=516; NHL2: cases N=1124, controls N=1235; UK: cases N=224, controls N=241) All nine polymorphisms of interest were genotyped in the NHL1 study, three in the NHL2 study and four in the UK study (Table I). For each polymorphism, Hardy-Weinberg equilibrium (HWE) was tested among controls. Unconditional logistic regression adjusted for frequency-matched variables and study was used to estimate the risk of NHL, DLCL, FL and CLL/SLL associated with genotype. Participants with the most common

genotype or haplotype based on the frequency among controls were the referent group. Genotypes categorized as homozygous wild type (wt/wt), heterozygous (wt/var) and homozygous variant (var/var) were treated as ordinal variables in tests for linear trend. Haplotypes were explored in *CX3CR1* and in *CCR2* and *CCR5* based on results from earlier studies suggesting that haplotypes in these genes were associated with HIV progression.[28, 29] Haplotype blocks and measures of linkage disequilibrium (D' and r^2) were estimated using Haploview[30] and the four-gamete rule assuming a 1% probability for observing the fourth gamete. Haplotype analyses were conducted for all NHL and by common NHL subtypes DLCL, FL and CLL/SLL using haplo.stats in R v2.8.1 (www.r-project.org) that uses an estimation-maximization (EM) algorithm to infer unphased haplotype probabilities. Haplotype effects were estimated using a weighted adjusted logistic regression in a two-step EM algorithm.[31] SNPassoc in R was used to conduct analyses of haplotype-sex interactions and to obtain risk estimates from stratified models. Haplotypes with a frequency of <5% were designated as 'rare' and were pooled for haplotype analyses.

Statistical tests were two-sided and considered significant for p-values ≤ 0.05 . Interactions based on -2 log-likelihood results from nested models were considered significant for p-values ≤ 0.10 . Results for all NHL are presented stratified by sex whereas results for NHL subtypes are presented stratified by sex only when there was statistical interaction ($p \leq 0.10$) between the polymorphism/haplotype and sex. Data are not presented for cells with fewer than 5 observations.

RESULTS

In the pooled population, the median age of patients at diagnosis was 60 years (NHL1=60 years, NHL2=62 years, UK=55 years) and the median age of controls at interview was 59 years (NHL1=52 years, NHL2=64 years, UK=55 years). There were a greater proportion of men (927 cases, 1190 controls) than women (683 cases, 802 controls) with the predominance of men also observed by study (NHL1=66%, NHL2=58%, UK=52%) and within the NHL subtype subgroups.

Genotype frequencies among controls were in Hardy-Weinberg equilibrium (all $p > 0.24$). There was no evidence of heterogeneity in genotype odds ratios across studies (Breslow-Day test, all $p > 0.12$). Age-, sex- and study-adjusted analyses showed no association between chemokine gene polymorphisms and risk of all NHL (Table II). Results from analyses by DLCL, FL and CLL/SLL subtypes were consistent with results for all NHL with one exception: decreased risk of FL and of CLL/SLL was observed among carriers of the *CCL5* -403 (*RANTES*) variant allele (OR=0.78, $p_{\text{trend}}=0.02$; OR=0.64, $p_{\text{trend}}=0.004$; respectively). No other chemokine polymorphism was associated with risk of these common NHL subtypes.

Analyses to assess gene-sex interaction showed that the association between risk of NHL and the *CCR5* $\Delta 32$ (rs333) polymorphism was modified by sex ($p_{\text{interaction}}=0.01$, Table III). Decreased risk of NHL was observed in men (OR=0.56) but not in women (OR=1.2) who carried the *CCR5* $\Delta 32$ deletion (Table III). Similar *CCR5* $\Delta 32$ -sex interaction effects were observed for DLCL and FL ($p_{\text{interaction}}=0.05$, $p_{\text{interaction}}=0.10$, respectively; Table III). Men with the deletion were less likely to have been diagnosed with DLCL (OR=0.55, $p=0.03$) or FL (OR=0.59, $p=0.06$) compared with men without the deletion. Statistical interaction with sex also was evident for other *CCR5* polymorphisms, 59029 (rs1799987) and 59353 (rs1799988). However, these polymorphisms were analyzed in the NHL1 study only and no individual ORs for the associated genotypes differed from unity. Similarly, no individual OR differed from unity for the suggested *CX3CR1* 249-sex interaction observed in FL (Table III).

Analyses for *CCR2/CCR5* (all $D' > 0.96$) and for *CX3CR1* ($D' = 1.0$) haplotypes were conducted for all NHL and by DLCL and FL subtypes (Table IV). The *CCR2/CCR5* referent haplotype comprised the common alleles for the *CCR2* and *CCR5* polymorphisms. In these analyses there was an indication of haplotype-sex interaction ($p_{\text{interaction}}=0.045$, Table IV). Haplotype B, the only haplotype with the *CCR5* $\Delta 32$ deletion, was associated with reduced NHL risk among men (OR=0.57, $p=0.02$) but was increased somewhat among women (OR=1.6, $p=0.10$) compared with the referent (Table IV). No other *CCR2/CCR5* haplotypes were associated with risk of all NHL, DLCL or FL. The *CX3CR1 249/CX3CR1 280* referent haplotype comprised the common alleles for each polymorphism. No *CX3CR1* haplotypes were associated with risk of all NHL, DLCL, or FL and there was no evidence of statistical interaction by sex ($p_{\text{interaction}}=0.48$, Table IV).

DISCUSSION

Our results showed that HIV-negative non-Hispanic Caucasian men who carry the *CCR5* $\Delta 32$ deletion were less likely to have been diagnosed with all NHL, DLCL or FL compared with men without the deletion. Further, the *CCR2/CCR5* haplotype characterized by the *CCR5* $\Delta 32$ deletion was the only *CCR2/CCR5* haplotype associated with reduced risk of NHL among men. In addition, the *CCL5 -403 (RANTES)* variant allele was associated with a reduced risk of FL and of CLL/SLL with no evidence of a sex-specific effect. No associations were observed for other chemokine polymorphisms or among women only. Although patterns of association showed some consistency, a number of statistical tests were conducted and sparse data in some sex-stratified analyses resulted in low power to test hypotheses. Therefore, results from these analyses should be interpreted conservatively and require further confirmation in other large studies.

Chemokines play an important role in B-cell development and maturation,[32] and their expression on B- and T-cells varies between normal and neoplastic cells and by type of lymphoproliferative disorder.[10, 11, 14] Several variants in chemokine genes have been associated with increased risk of AIDS-related NHL although we found no published reports that evaluated chemokine gene polymorphisms and susceptibility to NHL, DLCL, FL or CLL/SLL in a population-based study among HIV-negative participants. Investigated in susceptibility studies of other cancers, genetic variability in *CCR2*, *CCR5* and *CXCL12* has been associated with hepatocellular carcinoma,[15] cervical,[33] pancreatic[34] and prostate cancers,[16] whereas increased expression of chemokines including *CXCL12 (SDF-1)* and *CCL5 (RANTES)* has contributed to tumor angiogenesis, metastasis, progression and survival in breast, prostate and colon cancers.(reviewed in[35, 36])

The decreased NHL risk with the *CCR5* $\Delta 32$ deletion and no association with the *CCR2-64I* variant allele among men in our pooled population is consistent with results for AIDS-related B-cell NHL.[4] Our finding of a *CCR5* $\Delta 32$ deletion effect on risk of DLCL or FL in HIV-negative non-Hispanic Caucasian men has not been reported previously. Furthermore, only the *CCR2/CCR5* haplotype that included the *CCR5* $\Delta 32$ deletion was associated with decreased NHL risk in men and not in women. The *CCR5* $\Delta 32$ deletion typically results in retention of CCR5 in the endoplasmic reticulum with complete or diminished CCR5 expression on the cell membrane.[37] Diminished CCR5 receptor expression (predominantly expressed on pro-inflammatory Th1 cells) may reduce binding of CCL5 to CCR5 (a Th1 dampening effect). Consequently, binding of CCL5 to another of its potential receptors, *i.e.* CCR3 (largely expressed on Th2 cells), may increase, thereby favoring a Th2 anti-inflammatory response. Interestingly, exposures that favor a Th2 response pathway, *e.g.* atopy and allergies, have been associated with decreased NHL risk.[38]

The reduced risk of FL and CLL/SLL associated with the *-403 G>A* variant located in the promoter region of *CCL5* has not been reported previously. However, in recent studies of other cancers, the *CCL5 -403A* allele was associated with a decreased risk for gastric cancer in women,[17] an increased risk for prostate cancer in men[39] and an increased risk of pancreatic cancer especially among those with a history of pancreatitis.[34] The *-403 A* allele results in up-regulation of *CCL5*, and also has been associated with increased risk of atopy.[40-42] these data suggest that *CCL5* up-regulation may increase the Th2 response, possibly through increased binding sites for CCR3. Thus, NHL susceptibility may be altered through a pathway/mechanism that is similar to that for atopy. In contrast, studies of other cancers have assessed *CCL5* expression [43-46] and have found that increased expression was related to cancer progression, cell survival and metastasis. Further, *CCL5* increases transcription of angiogenic factors, especially matrix metalloprotease-9,[47] which in turn releases VEGF from endothelial cell membranes, thus contributing to tumor angiogenesis. The apparent disparate genetic effects on susceptibility, tumor progression and metastasis may be partly explained by the differential effects of the *CCL5 -403A* polymorphism in other cancers, the redundancy in chemokines such that most chemokines bind to multiple receptors that are expressed on a variety of cell types and tissues, and the reported pleiotropic effects of *CCL5*. [48] Additional research is needed to clarify the role of *CCL5* in biologic pathways and mechanisms that may influence cancer development and progression.

Differential sex-effects of NHL risk associated with *CCR5* polymorphisms have not been published for other NHL studies. The overall frequency of the *CCR5 Δ32* deletion in our pooled control population was consistent with that observed in other populations of European Caucasians [49] although no comparable data have been published for sex-specific *CCR5 Δ32* genotype frequencies. Some supportive evidence for potential gene-sex effects of *CCR5* SNPs with disease susceptibility has been provided by a study of gastric cancer [17] and studies of other chronic diseases, diabetes[50] and Lofgren syndrome.[51] *In vitro* data showing that estrogens alter chemokine expression also may partly explain our sex-specific results. However, the most compelling data have come from a study among transsexuals where *in vivo*, estrogens plus anti-androgens in male-to-female transsexuals increased the expression of several chemokine receptors including Th1-predominant *CCR5* whereas testosterone in female-to-male transsexuals resulted in a switch to a Th2 pathway as exhibited by a diminished Th1/Th2 cytokine expression ratio.[22] In contrast, sex-related chemokine effects from the few studies of other chronic diseases have not shown a consistent sex-pattern of risk.[17, 50, 51] Also, despite restricting our analyses to non-Hispanic white participants, it is possible that underlying population stratification may have influenced our results, even in a relatively homogeneous population. Therefore, although intriguing, our results should be interpreted cautiously and warrant continued research to confirm and clarify potential sex-related effects on immune function.

Our pooled results provide new data on risk of NHL and NHL subtypes to suggest that functional genetic polymorphisms in the chemokine *CCL5* and its receptor *CCR5* alter NHL susceptibility mainly in men. There was some suggestion that the polymorphism effects may differ by NHL subtype with inverse associations for *CCL5* observed mainly in FL and CLL/SLL, whereas inverse associations with *CCR5* were observed for DLCL and FL. Given the key role of chemokines in cell trafficking, in inflammatory processes and in the development and prognosis of AIDS-related NHL and other cancers, it is plausible that polymorphisms in these chemokines influence susceptibility for non-AIDS-related lymphoma. However, our results should be interpreted conservatively as a number of statistical tests were conducted and there were a small number of exposed in some analyses. Larger pooled studies with increased power to test potential effects by sex and by NHL subtype are needed to confirm our findings.

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Table I

Chemokine and chemokine receptor polymorphisms genotyped in three pooled population-based case-control studies, San Francisco Bay Area, US (NHL1, NHL2) and UK

Chemokine SNP	Characteristics	NHL1 (Cases N=262, Controls N=516)	NHL2 (Cases N=1124, Controls N=1235)	UK (Cases N=224, Controls N=241)
<i>CX3CR1</i>				
280 (rs3732378)	G>A substitution in nonsynonymous coding region on Chr3 results in a T/M amino acid change	X	X	X
249 (rs3732379)	C>T substitution in nonsynonymous coding region on Chr3 results in a V/I amino acid change	X	X	X
<i>RANTES/CCL5 -403</i> (rs2107538)	C>T substitution in 5' TR region on Chr17	X	X	
<i>CCR2 64I</i> (rs1799864)	G>A substitution in nonsynonymous coding region on Chr3 results in a V/I amino acid change	X		X
<i>CCR5</i>				
$\Delta 32$ (rs333)	Complex insertion-deletion on Chr3	X		X
59353 (rs1799988)	C>T substitution in 5' UTR region on Chr3	X		
59653 (rs1800024)	C>T substitution in intronic region on Chr3	X		
59029 (rs1799987)	A>G substitution in intronic region on Chr3	X		
<i>CXCL12/SDF-1</i> (rs1801157)	C>T substitution in 3' UTR region on Chr10	X		

Table II

Pooled odds ratios (OR) and 95% confidence intervals (CI) for risk of non-Hodgkin lymphoma (NHL), diffuse large-cell (DLCL), follicular (FL) and chronic lymphocytic leukemia/small lymphocytic lymphomas (CLL/SLL) associated with polymorphisms in chemokine and chemokine receptor genes in HIV-negative non-Hispanic Caucasian participants, UK and San Francisco Bay Area

		All NHL		DLCL		FL		CLL/SLL	
Chemokine polymorphism	Genotype	Controls (N=1992) n (%)	OR (95%CI)*	(N=534) n (%)	OR (95%CI)*	(N=453) n (%)	OR (95%CI)*	(N=314) n (%)	OR (95%CI)*
<i>CX₃CR₁ 249^{†§}</i>									
	VV	766 (52)	1.0	236 (53)	1.0	204 (51)	1.0	126 (52)	1.0
	VI	592 (40)	0.98 0.83 – 1.2	175 (40)	0.94 0.75 – 1.2	165 (41)	1.0 0.82 – 1.3	93 (38)	0.99 0.73 – 1.3
	II	121 (8)	0.93 0.69 – 1.2	31 (7)	0.84 0.55 – 1.3	30 (8)	0.91 0.59 – 1.4	23 (10)	1.2 0.72 – 2.0
	VI/II	713 (48)	0.97 0.83 – 1.1	206 (47)	0.93 0.75 – 1.2	195 (49)	1.0 0.81 – 1.3	116 (48)	1.0 0.77 – 1.4
p for trend									
<i>CX₃CR₁ 280[§]</i>									
	TT	1352 (68)	0.64	380 (72)	1.0	306 (68)	1.0	209 (67)	1.0
	TM	572 (29)	0.94 0.81 – 1.1	134 (25)	0.82 0.66 – 1.03	128 (29)	0.96 0.76 – 1.2	90 (29)	1.1 0.84 – 1.4
	MM	53 (3)	1.3 0.89 – 1.9	17 (3)	1.2 0.66 – 2.1	14 (3)	1.1 0.62 – 2.1	13 (4)	1.7 0.87 – 3.3
	TM/MM	625 (32)	0.98 0.84 – 1.1	151 (28)	0.85 0.69 – 1.05	142 (32)	0.98 0.78 – 1.2	103 (33)	1.2 0.88 – 1.5
p for trend									
<i>CCR5 Δ32^{†‡}</i>									
	+/+	563 (76)	0.87	380 (80)	1.0	158 (80)	0.96	25 (83)	1.0
	+/-	171 (23)	0.76 0.57 – 1.03	37 (18)	0.75 0.50 – 1.1	37 (19)	0.81 0.54 – 1.2	5 (17)	0.68 0.25 – 1.8
	-/-	11 (1)	1.2 0.48 – 3.1	4 (2)	-	3 (2)	-	0	-
	+/-,-/-	182 (24)	0.79 0.59 – 1.05	41 (20)	0.79 0.53 – 1.2	40 (20)	0.82 0.56 – 1.2	5 (17)	0.63 0.24 – 1.7
p for trend									
<i>CCR2 64T[‡]</i>									
	VV	610 (82)	0.19	391 (82)	1.0	156 (80)	0.39	24 (80)	1.0
	VI	131 (18)	1.0 0.76 – 1.4	81 (17)	0.76 0.48 – 1.2	38 (19)	1.2 0.82 – 1.9	6 (20)	1.0 0.41 – 2.7
	II	3 (0.4)	-	3 (1)	-	2 (1)	-	0	-
	VI/II	134 (18)	1.1 0.78 – 1.4	84 (18)	0.75 0.47 – 1.2	40 (20)	1.3 0.85 – 1.9	6 (20)	1.0 0.40 – 2.6

		All NHL		DLCL		FL		CLL/SLL	
Chemokine polymorphism		Controls (N=1992)		(N=534) n (%)		(N=453) n (%)		(N=314) n (%)	
Genotype		n (%)	OR (95%CI)*	n (%)	OR (95%CI)*	n (%)	OR (95%CI)*	n (%)	OR (95%CI)*
p for trend									
<i>CCL5 -403'</i>									
GG		1199 (69)	0.63	984 (72)	1.0	278 (69)	0.20	240 (78)	0.98
GA		476 (27)	0.88 0.75 - 1.04	337 (25)	1.0	108 (27)	1.0 0.78 - 1.3	59 (19)	0.64 0.47 - 0.87
AA		59 (3)	0.85 0.56 - 1.3	41 (3)	1.2 0.71 - 2.2	4 (1)	-	8 (3)	0.63 0.30 - 1.4
GA/AA		535 (31)	0.88 0.75 - 1.03	378 (28)	1.0	125 (31)	1.0 0.81 - 1.3	67 (22)	0.64 0.47 - 0.85
p for trend									
<i>CXCL12 3' A**</i>									
GG		336 (66)	0.11	164 (64)	1.0	52 (63)	0.64	21 (72)	0.004
GA		161 (32)	1.1 0.79 - 1.5	85 (33)	1.0	28 (34)	1.1 0.67 - 1.8	7 (24)	0.68 0.28 - 1.6
AA		14 (3)	0.84 0.31 - 2.3	6 (2)	-	3 (4)	-	1 (3)	-
GA/AA		175 (34)	1.1 0.78 - 1.5	91 (36)	1.1 0.69 - 1.8	35 (35)	1.01 0.64 - 1.6	8 (28)	0.71 0.31 - 1.7
p for trend									
<i>CCR5 59353^{†**}</i>									
TT		105 (20)	0.77	52 (20)	1.0	19 (23)	0.58	8 (27)	0.54
TC		254 (50)	1.1 0.71 - 1.6	134 (52)	1.0	41 (50)	0.89 0.49 - 1.6	14 (47)	0.75 0.30 - 1.8
CC		153 (30)	0.89 0.57 - 1.4	70 (27)	0.77 0.39 - 1.5	22 (27)	1.1 0.56 - 2.2	8 (27)	0.69 0.25 - 1.9
CT/CC		407 (79)	1.0 0.68 - 1.5	204 (80)	0.84 0.48 - 1.5	63 (77)	1.3 0.73 - 2.3	22 (73)	0.73 0.31 - 1.7
p for trend									
<i>CCR5 59029^{†**}</i>									
GG		103 (20)	0.56	51 (21)	1.0	19 (24)	0.44	8 (29)	0.49
GA		251 (50)	1.0 0.68 - 1.5	126 (51)	1.0	40 (50)	0.86 0.47 - 1.6	12 (43)	0.64 0.25 - 1.6
AA		153 (30)	0.88 0.56 - 1.4	69 (28)	0.72 0.36 - 1.4	21 (26)	1.2 0.60 - 2.3	8 (29)	0.68 0.24 - 1.9
GA/AA		404 (80)	0.96 0.65 - 1.4	195 (79)	0.81 0.46 - 1.4	61 (76)	1.3 0.73 - 2.4	20 (71)	0.66 0.27 - 1.5
p for trend									
<i>CCR5 59653^{**}</i>									
CC		409 (80)	0.54	209 (81)	1.0	72 (87)	0.32	26 (84)	0.48
CT		100 (19)	0.93 0.63 - 1.4	46 (18)	1.0	11 (13)	0.64 0.32 - 1.3	5 (16)	0.78 0.29 - 2.1
TT		3 (1)	-	3 (1)	-	0	-	0	-
CT/TT		103 (20)	0.96 0.65 - 1.4	49 (19)	0.62 0.32 - 1.2	11 (13)	1.04 0.52 - 2.1	5 (16)	0.76 0.28 - 2.0

Chemokine polymorphism	Genotype	Controls (N=1992)		All NHL		DLCL		FL		CLL/SLL	
		n (%)	(N=1610) n (%)	OR (95%CI) *	(N=534) n (%)	OR (95%CI) *	(N=453) n (%)	OR (95%CI) *	(N=314) n (%)	OR (95%CI) *	
p for trend				0.99		0.15		0.51		0.56	

* Adjusted for age and study. ORs and 95% CIs are not presented when there were <5 exposed case or control participants

[†] Interaction of sex and genotype assuming dominant inheritance in age- and study-adjusted unconditional logistic regression models observed with: CCR5 Δ32 (all NHL: p=0.01, DLCL: p=0.05, FL: p=0.10); CCR5 59353 (all NHL: p=0.02); CCR5 59029 (all NHL: p=0.04); CX3CR1 249 (FL: p=0.08). See Table III for detail.

[§] San Francisco Bay Area NHL1 and NHL2, UK

[‡] San Francisco Bay Area NHL1 and UK

[¶] San Francisco Bay Area NHL2 and UK

^{**} San Francisco Bay Area NHL1

Pooled odds ratios (OR) and 95% confidence intervals (CI) for risk of all NHL, diffuse large cell (DLCL) and follicular (FL) lymphoma associated with polymorphisms in chemokine and chemokine receptor genes by sex in HIV-negative non-Hispanic Caucasians, UK and San Francisco Bay Area

Table III

Chemokine polymorphism	Genotype	Men			Women			χ^2 p-value for interaction [†]
		NHL Cases (N=927) n (%)	Controls (N=1190) n (%)	OR (95%CI) [*]	NHL Cases (N=683) n (%)	Controls (N=802) n (%)	OR (95%CI) [*]	
<i>CCR5</i> $\Delta 32$ [§] ALL NHL	+/+	213 (82)	352 (73)	1.0	167 (70)	211 (81)	1.0	0.01
	+/-	44 (17)	123 (25)	0.55 0.37-0.82	43 (20)	48 (18)	1.2 0.73-1.8	
	-/-	4 (2)	8 (2)	-	4 (2)	3 (1)	-	
	+/-, -/-	48 (18)	131 (27)	0.56 0.38-0.83	47 (22)	51 (19)	1.2 0.76-1.8	
	+/+	92 (81)	352 (73)	0.008 1.0	71 (78)	211(81)	0.38 1.0	
p for trend DLCL								0.05
p-value FL	+/-, -/-	21(19)	131 (27)	0.55 0.32 - 0.95	20 (22)	51 (19)	1.2 0.69 - 2.3	0.10
				0.03			0.47	
	+/+	81 (81)	352 (73)	1.0	77 (79)	211(81)	1.0	
p-value <i>CX3CR1</i> 249 [‡] FL	+/-, -/-	19 (19)	131 (27)	0.59 0.34 - 1.03	21 (21)	51 (19)	1.1 0.64 - 2.0	0.08
				0.06			0.65	
	VV	98 (48)	481 (55)	1.0	106 (54)	285 (50)	1.0	
p-value <i>CCR5</i> 59353 ^{**} All NHL	VI/II	106 (52)	426 (47)	1.2 0.90 - 1.7	89 (46)	287 (50)	0.82 0.60 - 1.1	0.02
				0.21			0.25	
	TT	32 (22)	73 (20)	1.0	20 (18)	32 (22)	1.0	
	TC	82 (56)	179 (49)	0.96 0.58 - 1.6	52 (47)	75 (51)	1.1 0.58 - 2.2	
	CC	32 (22)	112 (31)	0.59 0.32 - 1.1	38 (35)	41 (28)	1.5 0.73 - 3.0	
p for trend <i>CCR5</i> 59029 ^{**} All NHL	CT/CC	114 (78)	291 (80)	0.82 0.50 - 1.3	90 (82)	116 (78)	1.2 0.67 - 2.3	0.04
				0.06			0.24	
	GG	31 (22)	71 (20)	1.0	20 (19)	32 (22)	1.0	
	GA	77 (55)	177 (49)	0.90 0.54 - 1.5	49 (46)	74 (50)	1.1 0.55 - 2.1	

Chenokine polymorphism	Genotype	Men		Women		OR (95%CI) *	χ^2 p-value for interaction†
		NHL Cases (N=927) n (%)	Controls (N=1190) n (%)	NHL Cases (N=683) n (%)	Controls (N=802) n (%)		
	AA	32 (23)	111 (31)	37 (35)	42 (28)	1.4 0.69 – 2.9	
	GA/AA	109 (78)	288 (80)	86 (81)	116 (78)	1.2 0.64 – 2.2	
p for trend				0.08		0.30	

* Results are presented by sex only for those polymorphisms that showed gene × sex statistical interaction (p<0.10) in age-and study-adjusted unconditional logistic regression models. ORs and 95% CIs are not presented when there were <5 exposed case or control participants

† Interaction of sex and genotype assuming dominant inheritance

§ San Francisco Bay Area NHL1 and UK

‡ San Francisco Bay Area NHL1, NHL2 and UK

** San Francisco Bay Area NHL1 study only

Results* for risk of non-Hodgkin lymphoma (NHL) by sex in HIV-negative non-Hispanic white participants for *CCR2* V64I, *CCR5* 59029, *CCR5* 59353, *CCR5* 59653 and *CCR5* Δ32 and for *CX3CR1* V249I and *CX3CR1* T280M haplotypes, San Francisco Bay Area

Table IV

All NHL									
Haplotype	<i>CCR2</i> <i>V64I</i>	<i>CCR5</i> <i>59029</i>	<i>CCR5</i> <i>59353</i>	<i>CCR5</i> <i>59653</i>	<i>CCR5</i> <i>Δ32</i>	Freq. Ctrl / Ca	Men & Women OR 95% CI	Men OR 95% CI	Women OR 95% CI
Referent	V	G	T	C	+	0.45/0.47	1.0	1.0	1.0
A	V	A	C	C	+	0.31/0.32	0.94 0.73 – 1.2	0.85 0.61 – 1.2	1.1 0.75 – 1.7
B	V	A	C	C	-	0.13/0.11	0.85 0.60 – 1.2	0.57 0.35 – 0.92	1.6 0.91 – 2.8
C	I	A	C	T	+	0.10/0.09	0.95 0.65 – 1.4	0.78 0.48 – 1.3	1.3 0.69 – 2.5
Rare	*	*	*	*	*	0.007/0.014	1.7 0.54 – 5.1	2.4 0.60 – 9.4	0.81 0.13 – 5.0
Global p-value							0.58	0.08	0.74
Haplotype × Sex P _{interaction}							0.045		
				<i>CX3CR1</i> <i>V249I</i>	<i>CX3CR1</i> <i>T280M</i>				
Referent				V	T	0.72 / 0.72	1.0		
A				I	M	0.17/ 0.17	0.92 0.63 – 1.3		
B				I	T	0.11/ 0.11	1.5 0.95 – 2.3		
Rare				V	M	0.001 / 0	-		
Global p-value						0.75			
Haplotype × Sex P _{interaction}							0.48		

* Results are adjusted for age and sex (age alone in sex-stratified analyses) and were computed using SNPassoc and haplo.stats in R assuming an additive inheritance mode. The most frequent haplotype was used as the referent group. Rare haplotypes (frequencies <0.05) were pooled for analyses and designated as 'Rare'. Global p-values for *CCR2/CCR5* haplotype by subtypes diffuse large-cell lymphoma (DLCL) =0.70, p for interaction=0.18; for follicular lymphoma (FL) =0.53, p for interaction=0.38. Global p-value for *CX3CR1* haplotype by subtypes DLCL= 0.69, p for interaction=0.67; for FL 0.92, p for interaction=0.35.