

Relationship between interferon regulatory factor 4 genetic polymorphisms, measures of sun sensitivity and risk for non-Hodgkin lymphoma

Allison H. Gathany · Patricia Hartge · Scott Davis · James R. Cerhan ·
Richard K. Severson · Wendy Cozen · Nathaniel Rothman · Stephen J. Chanock ·
Sophia S. Wang

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Abstract

Objective Sun exposure and sensitivity, including pigmentation, are associated with risk for non-Hodgkin lymphoma (NHL). One variant in the immune regulatory factor 4 (*IRF4*) gene (rs12203592) is associated with pigmentation, and a different *IRF4* variant (rs12211228) is associated with NHL risk. We evaluated the

independent roles of these *IRF4* polymorphisms and sun sensitivity in mediating NHL risk and explored whether they are confounded or modified by each other.

Methods Genotyping of tag single nucleotide polymorphisms (SNPs) in the *IRF4* gene was conducted in 990 NHL cases and 828 controls from a multi-center US study. Measures of sun sensitivity and exposure were ascertained from computer-assisted personal interviews. We used logistic regression to compute odds ratios (OR) and 95% confidence intervals (CI) for NHL in relation to sun exposures, sun exposures in relation to *IRF4* genotypes, and NHL in relation to sun exposures. We further assessed the effects of sun exposures in relation to *IRF4* genotypes.

Results As previously reported, we found significant associations between *IRF4* rs12211228 and NHL and between hair and eye color and NHL. The *IRF4* rs12203592 polymorphism (CT/TT genotype) was statistically significantly associated with eye color and particularly with hair color (OR_{Light Blonde} = 0.24, 95% CI = 0.11–0.50, overall Chi square $p = 0.0002$). Analysis of joint effects between eye and hair color with the *IRF4* rs12203592 SNP did not reveal statistically significant p -interactions although NHL risk did decline with lighter hair color and presence of the variant *IRF4* rs12203592 allele, compared to those without a variant allele and with black/brown hair color.

Conclusions Our data do not statistically support a joint effect between *IRF4* and sun sensitivity in mediating risk for NHL. Further evaluation of joint effects in other and larger populations is warranted.

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A. H. Gathany · P. Hartge · N. Rothman · S. J. Chanock
Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, 6120 Executive Blvd., Rockville, MD 20852, USA

A. H. Gathany
Yale School of Public Health, New Haven, CT, USA

S. Davis
Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, USA

J. R. Cerhan
Mayo Clinic College of Medicine, Rochester, MN, USA

R. K. Severson
Karmanos Cancer Institute and Department of Family Medicine, Wayne State University, Detroit, MI, USA

W. Cozen
University of Southern California, Los Angeles, CA, USA

S. S. Wang (✉)
Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, 6120 Executive Blvd., EPS 7070, Rockville, MD 20852, USA
e-mail: wangso@mail.nih.gov

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Abbreviations

CAPI	Computer-assisted personal interview
CI	Confidence interval
CLL/SLL	Chronic lymphocytic leukemia/small lymphocytic lymphoma
DLBCL	Diffuse large B-cell lymphoma
HHHQ	Health habits and history questionnaire
HWE	Hardy–Weinberg equilibrium
ICD-O	International classification of diseases for oncology
MAF	Minor allele frequency
NA	Not applicable
NCI	National cancer institute
NHANES	National health and nutrition examination survey
NHL	Non-Hodgkin lymphoma
OR	Odds ratio
SEER	Surveillance, epidemiology, and end results
SNP	Single nucleotide polymorphism
WT	Wild-type

Introduction

Non-Hodgkin lymphomas (NHL) represent a heterogeneous group of cancers arising from lymphocytes for which the etiology remains largely unclear. While the major known risk factor for developing NHL is severe immunodeficiency [1], the increased NHL risk among those with a family history of hematopoietic disease [2–5] suggests an important role for genetic susceptibility in NHL etiology. Investigations of germline genetic variation in large epidemiologic case–control studies have identified potentially relevant loci that may play a role in modulating risk for NHL [6, 7].

A recent pooled analysis of three large population-based NHL case–control studies that included the present study found a significant association between a polymorphism in the *IRF4* gene, rs12211228 and NHL risk [8]. The *IRF4* gene (also known as *MUM1*) encodes a protein that is a member of the interferon regulatory factor family [9–12]. IRF4 is a B-cell proliferation and differentiation protein essential for class switch recognition and antibody maturation [13, 14] and is often found abnormally expressed in B cell lymphomas [15]. In addition to serving as a marker for lymphoid tumors such as NHL, IRF4 has also been reported to act as a potential marker for melanoma [16].

A recent large genome-wide association study demonstrated a convincing association between a different polymorphism of the *IRF4* gene, rs12203592, and pigmentation phenotypes, most notably hair color [17]. This *IRF4* SNP was also shown to be associated with skin color, eye color,

and a measure of skin tanning response to sunlight. This report was the first to suggest a link between a particular *IRF4* locus and human pigmentation, though the mechanism for the involvement of this immune regulatory gene in determining hair color and other pigmentation phenotypes remains unclear.

Interestingly, sun sensitivity and sun exposure have previously been linked with NHL. Hartge et al. [18] previously showed a gradient of decreasing NHL risk with increasingly light eye color, one pigmentation phenotype believed to act as a marker of increased sun sensitivity. This relationship between risk for NHL and sun sensitivity and exposure is further supported by recent work from the International Lymphoma Epidemiology Consortium (InterLymph)[19], where a pooled analysis of ten case–control studies of NHL showed a significant decrease in NHL risk with increasing recreational sun exposure.

In order to clarify the roles of these two *IRF4* polymorphisms and sun sensitivity in mediating NHL risk and to determine if their respective associations with NHL are confounded or modified by each other, we used a large US multi-center case–control study of NHL to evaluate the relationship between *IRF4* polymorphisms and markers of sun sensitivity and sun exposure and their roles in determining risk for non-Hodgkin lymphoma.

Materials and methods

Study population

The study population has been described previously in detail [3]. Briefly, we included 1,321 newly diagnosed non-Hodgkin lymphoma cases identified in four Surveillance, Epidemiology, and End Results (SEER) registries (Iowa; Detroit, MI; Los Angeles, CA; and Seattle, WA) between 1 July 1998 and 30 June 2000. Subjects were between the ages of 20 and 74 and had no evidence of HIV infection. A total of 1,057 population controls were identified by random digit dialing (under 65 years old) and from Medicare eligibility files (65 years and older). Overall participation rates were 76% in cases and 52% in controls; overall response rates were 59 and 44%, respectively. Written informed consent was obtained from each participant before interview. This study was approved by the institutional review boards at the NIH and at each participating SEER site (Iowa, Detroit, LA, and Seattle).

All study participants were asked to provide a venous blood or mouthwash buccal cell sample. We obtained blood samples from 1,172 (89%) cases (773 blood, 399 buccal) and 982 (93%) controls (668 blood, 314 buccal). Genotype frequencies were equivalent for individuals who provided blood compared with buccal cells.

Histopathology

Each SEER registry provided non-Hodgkin lymphoma pathology and subtype information derived from abstracted reports by the local diagnosing pathologist. All cases were histologically confirmed and coded according to the *International Classification of Diseases for Oncology, 2nd Edition* (ICD-O-2) [20] and updated to the World Health Organization classification/ICD-O-3 [21].

Questionnaire data

The study used a split-sample design to investigate multiple etiologic risk factors in detail without overburdening the participants. A core set of questions was given to all respondents, and the remainder of questions were given to participants in either Group A (all African-American participants and 50% of non-African-American participants) or Group B (50% of non-African-American participants). Prior to the in-person interview, participants were mailed a form for listing residential and job history and either a family and medical history questionnaire (Group A) or a diet and lifestyle questionnaire (Group B). During the home visit, a trained interviewer administered a computer-assisted personal interview (CAPI) that included core questions on demographics, height and weight, occupational history, pesticide exposure, hair color, and hair dye use. The Group A CAPI also included an extended medical history and use of illicit drugs, while the Group B CAPI included an abbreviated medical history, cell phone use, allergies, hobbies, eye color, skin complexion, and sun sensitivity/exposure.

Sun sensitivity and exposure. During the interview, we asked participants to estimate how many hours they spent in the sun during the summer in the middle of the day (10:00 AM–4:00 PM). We asked separately for weekdays and weekend days and separately for specific periods of their lives including teenage years, twenties, thirties, and the most recent decade. In the analysis, we estimated typical weekly exposure to strong sunlight as a weighted average of weekend and weekday values. We also asked about the use of sun lamps or tanning booths, the typical number of months per year they had a tan, pigmentation characteristics including eye color and skin complexion, and some common measures of skin response to sunlight, including sun rashes and typical reaction to first hour of sun with no tan and no sunburn.

DNA extraction and genotyping

Study participants who did not provide a biologic specimen, did not have sufficient material for DNA extraction or sufficient DNA for genotyping, or whose genotyped sex

was discordant from the questionnaire data were excluded from this analysis. As previously described [22], DNA was extracted from blood clots or buffy coats (BBI Biotech, Gaithersburg, MD) using Puregene Autopure DNA extraction kits (Gentra Systems, Minneapolis, MN). DNA was extracted from buccal cell samples by phenol–chloroform extraction methods [23].

We selected 15 tag single nucleotide polymorphisms (SNPs) in the *IRF4* gene as previously described [8]; these included the two *a priori* SNPs of interest—rs12211228 and rs12203592. Genotyping was conducted at the National Cancer Institute Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD) using a custom-designed GoldenGate assay (Illumina, www.illumina.com). Sequence data and assay conditions are provided at <http://snp500cancer.nci.nih.gov> [24]. SNP completion rates were >95% for the 15 *IRF4* SNPs. Forty replicate samples from two blood donors each and duplicate samples from 100 participants processed in an identical fashion were interspersed for all assays and blinded from the laboratory. The 15 *IRF4* SNPs were >95% concordant in the quality control samples. We excluded samples with a low completion rate (<90%; 11 cases, 6 controls). Hardy–Weinberg Equilibrium (HWE) was observed in the control group for all *IRF4* SNPs (assessed separately for non-Hispanic Caucasians and blacks).

The final analytic population consisted of 990 cases and 828 controls.

Statistical analysis

IRF4 and NHL. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) as an estimate of relative risk for non-Hodgkin lymphoma outcomes using dichotomous (overall NHL) and polytomous (NHL subtypes) unconditional logistic regression models with the homozygous wild-type genotype as the referent group. We conducted stratified analyses by age (<60 and ≥60 years), sex (male and female), and race (non-Hispanic Caucasians and blacks). Finding no significant differences in the risk estimates by each of these three strata, we pooled the results and adjusted for the study design variables: age (<50, 50–59, 60–69, 70+), sex, race/ethnicity (non-Hispanic Caucasian, black, other), and study site (Iowa, Los Angeles, Seattle, Detroit). We calculated the *p* for trend based on the three-level ordinal variable (0, 1, 2) of homozygote wild-type, heterozygote, and homozygote variant. In addition to the individual risk estimates for each genotype, we evaluated the dominant model with homozygote wild-type as the referent group for comparison with heterozygotes and homozygote variants combined.

Sun sensitivity and NHL. In order to assess the association between the ordinal pigmentation and sun exposure

variables and NHL, we calculated the OR and 95% CI using dichotomous and polytomous unconditional logistic regression models for NHL overall and NHL subtypes, respectively. We also calculated the p for trend value for linear trend in regression based on the categorical variables (0, 1, 2, etc.) for each level of exposure (e.g., for eye color: dark brown (0), light brown [1], hazel (2), blue (3), green/blue-green (4)). For eye and hair color, skin complexion, reaction to first sun of the season, and hours in the mid-day sun in the last 10 years, the category corresponding to the lowest level of sun sensitivity or exposure was used as the referent category. All analyses were conducted both crude and adjusted for the study design variables age, race/ethnicity, sex, and study site. We note that we also included adjustment for education as a surrogate for SES; though education was slightly associated with sunlight exposure, additional adjustment for education did not appreciably alter the risk estimates for NHL (<10%) and we therefore retained the most parsimonious model in our final model which excluded education. Secondary analyses restricted to subjects with genotype data and non-Hispanic Caucasian subjects with genotype data were also performed to assess consistency across population subgroups (adjusted for age, sex, and study site).

IRF4 and sun sensitivity. Among controls, we used logistic regression adjusted for age, sex, and study site to model the association between pigmentation or sun exposure and *IRF4* genotypes. For each exposure category, the OR and 95% CI were calculated for the heterozygotes and homozygous variants using the wild-type homozygotes as the referent group. We also calculated the p for trend across the genotypes in each exposure category to assess likelihood of that exposure category with each additional minor allele. We also conducted this analysis restricted to non-Hispanic Caucasians in the control group due to known variation in eye color, hair color, and other phenotypic features across race groups.

Joint effects of IRF4 and sun sensitivity. For each sun sensitivity exposure, we calculated the OR and 95% CI for NHL using a common referent group and also stratified by *IRF4* genotype under the dominant model, combining heterozygotes and homozygous variants. We calculated the p -value for interaction for each exposure and *IRF4* SNP for NHL risk based on the scored variable for each risk factor and for the genotype. In these calculations, we scored the genotype using a two-level categorization to assess risk for the presence of a variant allele. Statistical significance for interaction was evaluated with the Wald test in models that included a product term for the scored risk factor and the scored genotype. The category corresponding to the lowest level of sun sensitivity or sun exposure was used as the referent group for each exposure. Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows selected characteristics of the NCI-SEER study population. Briefly, the majority of cases and controls were non-Hispanic Caucasians, cases were slightly younger than controls, and there were slightly more men than women in both cases and controls. Cases and controls were distributed roughly evenly into interview groups A and B. The most common NHL subtypes were diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma.

IRF4 and NHL. Fifteen SNPs in the *IRF4* gene were evaluated for associations with non-Hodgkin lymphoma (Supplementary Table 1). We observed a significant decrease in risk for NHL with the *IRF4* SNP rs12211228 (OR_{CG} = 0.81, 95% CI = 0.65–1.00; OR_{CC} = 0.76, 95% CI = 0.35–1.65; p -trend = 0.04; Table 2). Results were consistent when restricted to non-Hispanic Caucasian subjects. We observed no statistically significant association between the *IRF4* SNP rs12203592 and NHL (Table 2). Further, no other *IRF4* SNPs showed a statistically significant association with overall NHL (Supplementary Table 1).

Sun sensitivity and NHL. Lighter eye and hair color were both statistically significantly associated with decreased NHL risk (Table 3). The associations were more pronounced for eye color than hair color, and both associations were consistent in analyses restricted to participants with *IRF4* genotype data and/or subjects self-reported as non-Hispanic Caucasians. Hours in the mid-day sun in the last 10 years was also associated with decreased NHL risk. Other markers of coloring and sun exposure and sensitivity including skin complexion and reaction to first sun of the season were not associated with NHL risk.

IRF4 and sun sensitivity. Table 4 shows associations between the two *a priori* *IRF4* SNPs of interest (rs12203592 and rs12211228) and measures of sun sensitivity and sun exposure among non-Hispanic Caucasian population controls. Presence of the variant allele in the *IRF4* SNP rs12203592 was associated with eye color and hair color. The association between hair color and the *IRF4* rs12203592 SNP was most pronounced with increasingly light hair color. Compared to dark brown eyes, the magnitude of association was equivalent for all other eye colors which were strongly associated with the *IRF4* rs12203592 variant allele. Curiously, the association between *IRF4* rs12203592 with hair color and eye color appear to be in opposite directions; this is consistent with the original GWAS results from Han et al. [17] though was not further explored.

The *IRF4* rs12211228 SNP that was associated with NHL was not statistically significantly associated with any of the measures of sun sensitivity or sun exposure in this study (Table 4). All results were consistent in analyses

Table 1 Characteristics of NCI-SEER case–control study participants

Characteristic	Controls n (%)	NHL cases n (%)
SEER registry		
Detroit	139 (17)	197 (20)
Iowa	246 (30)	301 (30)
Los Angeles	199 (24)	234 (24)
Seattle	244 (29)	258 (26)
Sex		
Male	443 (54)	536 (54)
Female	385 (47)	454 (46)
Age (years)		
<50	203 (25)	277 (28)
50–59	177 (21)	235 (24)
60–69	285 (34)	311 (31)
70+	163 (20)	167 (17)
Race/Ethnicity		
White, non-Hispanic	646 (78)	828 (84)
Black	112 (14)	64 (6)
Asian/other/unknown	70 (8)	98 (10)
Education		
<12 years	77 (9)	98 (10)
12–15 years	485 (59)	611 (62)
16+ years	266 (32)	280 (28)
NHL histology		
DLBCL	–	294 (30)
Follicular lymphoma	–	246 (25)
Marginal zone lymphoma	–	82 (8)
CLL/SLL	–	101 (10)
Mantle cell lymphoma	–	40 (4)
Lymphoplasmacytic lymphoma	–	24 (2)
Burkitt lymphoma	–	11 (1)
Mycosis fungoides/Sézary syndrome	–	18 (2)
Peripheral T-cell lymphoma	–	41 (4)
NHL, not otherwise specified	–	133 (13)
DNA source		
Blood	598 (72)	688 (69)
Buccal	230 (28)	302 (31)
Interview group		
Group A*	461 (56)	547 (55)
Group B**	367 (44)	443 (45)
Total participants	828	990

CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma, *DLBCL* diffuse large B-cell lymphoma, *NCI* National Cancer Institute, *NHL* non-Hodgkin lymphoma, *SEER* surveillance, epidemiology, and end results

* Group A: extended medical history, use of illicit drugs, family medical history in addition to core questions

** Group B: abbreviated medical history, allergies, hobbies, sun exposure (including eye color and skin complexion), phone use, food frequency questionnaire in addition to core questions

expanded beyond non-Hispanic Caucasians and adjusted for race/ethnicity.

The remaining *IRF4* SNPs evaluated were not found to be statistically significantly associated with measures of sun sensitivity (data not shown).

Joint effects of IRF4 and sun sensitivity in NHL risk. Table 5 shows the joint effects between eye and hair color and NHL risk for the two *a priori* *IRF4* SNP genotypes. We observed no statistically significant *p*-interactions for either the *IRF4* rs12203592 or rs12211228 SNP with hair color or eye color. However, the risk estimates for NHL among individuals with lighter eye and hair color appeared more pronounced in those with either variant *IRF4* allele than in those with the corresponding common homozygote genotype. This is also observed in stratified analysis (Supplementary Table 2) whereby associations with NHL for eye and hair color appear more pronounced among those with a variant *IRF4* SNP. No joint effects with hair or eye color were observed for the remaining thirteen *IRF4* SNPs evaluated (data not shown).

Discussion

The independent associations observed in our data are consistent with those previously published for sun sensitivity and NHL [19], for *IRF4* rs12203592 and hair color [17], and for *IRF4* rs12211228 and NHL [8], to which our data contributed. Of note, the *IRF4* rs12203592 SNP associated with hair color was not associated with NHL, and the *IRF4* rs12211228 SNP associated with NHL was not associated with hair color. The two *IRF4* SNPs are neither correlated nor in linkage disequilibrium with one another ($r^2=0.001$, $D'=0.04$), and accordingly we found no statistically significant *p*-interactions between *IRF4* SNPs, measures of sun sensitivity such as hair color, and NHL risk. We do note that although associations between hair color and NHL risk were observed among those with and without variant *IRF4* rs12203592 or rs12211228 alleles, the risk estimates were slightly more pronounced among those with either variant *IRF4* genotype. We, therefore, cannot discount a possible interrelationship between the *IRF4* SNPs with sun sensitivity and NHL risk given our relatively small sample size to evaluate joint effects. We believe that further evaluation, such as in consortial settings where adequate sample sizes are available to assess joint effects, are needed to determine whether these two pathways both function through immune mediation or separately with one through immune mediation and one through pigmentation.

The major strengths of this study include the use of population-based selection for both cases and controls and

Table 2 Association between selected *IRF4* SNPs and overall risk for non-Hodgkin lymphoma

<i>IRF4</i> SNP	Genotype	All subjects			Non-Hispanic Caucasian subjects			All subjects in interview Group B [†]		
		Controls <i>n</i> (%)	All NHL <i>n</i> (%)	OR (95% CI)*	Controls <i>n</i> (%)	All NHL <i>n</i> (%)	OR (95% CI)**	Controls <i>n</i> (%)	All NHL <i>n</i> (%)	OR (95% CI)*
rs12203592	CC	605 (73)	730 (74)	1.00 (Ref.)	444 (69)	588 (71)	1.00 (Ref.)	252 (70)	307 (71)	1.00 (Ref.)
	CT	202 (24)	239 (24)	0.92 (0.74, 1.15)	182 (28)	219 (27)	0.90 (0.72, 1.14)	98 (27)	115 (27)	0.95 (0.69, 1.31)
	TT	18 (2)	19 (2)	0.81 (0.42, 1.57)	17 (3)	19 (2)	0.85 (0.43, 1.67)	8 (2)	9 (2)	0.96 (0.36, 2.57)
	CT or TT	220 (27)	258 (26)	0.91 (0.74, 1.13)	199 (31)	238 (29)	0.90 (0.72, 1.13)	106 (30)	124 (29)	0.95 (0.69, 1.30)
	<i>p</i> -trend			0.3764			0.3588			0.7572
rs12211228	GG	576 (70)	724 (73)	1.00 (Ref.)	436 (68)	588 (71)	1.00 (Ref.)	258 (72)	305 (71)	1.00 (Ref.)
	CG	236 (29)	253 (26)	0.81 (0.65, 1.00)	196 (30)	227 (27)	0.85 (0.68, 1.07)	96 (27)	122 (28)	1.06 (0.77, 1.46)
	CC	14 (2)	13 (1)	0.76 (0.35, 1.65)	12 (2)	13 (2)	0.88 (0.40, 1.98)	6 (2)	5 (1)	0.81 (0.24, 2.75)
	CG or CC	250 (30)	266 (27)	0.80 (0.65, 0.99)	208 (32)	240 (29)	0.85 (0.68, 1.07)	102 (28)	127 (29)	1.05 (0.76, 1.43)
	<i>p</i> -trend			0.0432			0.1923			0.8636

CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma, *CI* confidence interval, *DLBCL* diffuse large B-cell lymphoma, *OR* odds ratio, *NHL* non-Hodgkin lymphoma, *SNP* single nucleotide polymorphism

* Adjusted for age, race/ethnicity, sex, study site

** Adjusted for age, sex, study site

[†] Group B participants have data on eye color, skin complexion, sun exposures, and diet

Table 3 Association between pigmentation and sun exposures and overall risk for non-Hodgkin lymphoma

Exposure	All subjects				All subjects with genotype data				Non-Hispanic Caucasians w/genotype data					
	Controls		All NHL		Controls		All NHL		Controls		All NHL		OR (95% CI)*	
	n (%)	n (%)	OR (95% CI)*	n (%)	n (%)	n (%)	n (%)	OR (95% CI)*	n (%)	n (%)	n (%)	OR (95% CI)*	n (%)	
Eye color														
Dark brown	93 (20)	158 (29)	1.00	(Ref.)	73 (20)	121 (28)	1.00	(Ref.)	55 (17)	96 (24)	1.00	(Ref.)		
Light brown	41 (9)	50 (9)	0.76	(0.47, 1.25)	32 (9)	34 (8)	0.65	(0.37, 1.16)	23 (7)	30 (8)	0.75	(0.39, 1.45)		
Hazel	84 (18)	96 (17)	0.64	(0.43, 0.96)	71 (20)	73 (17)	0.61	(0.39, 0.95)	69 (21)	69 (17)	0.57	(0.35, 0.92)		
Blue	180 (39)	188 (34)	0.60	(0.42, 0.84)	140 (39)	155 (36)	0.66	(0.45, 0.98)	138 (42)	153 (39)	0.65	(0.43, 0.97)		
Green/Blue-green	64 (14)	59 (11)	0.49	(0.31, 0.78)	45 (12)	49 (11)	0.61	(0.36, 1.02)	43 (13)	47 (12)	0.59	(0.34, 1.01)		
<i>p</i> -trend				0.0005				0.0378					0.0295	
Hair color														
Black/dark brown	462 (44)	572 (43)	1.00	(Ref.)	354 (43)	401 (41)	1.00	(Ref.)	198 (31)	273 (33)	1.00	(Ref.)		
Medium brown	223 (21)	317 (24)	1.00	(0.80, 1.25)	177 (21)	261 (26)	1.13	(0.87, 1.46)	162 (25)	239 (29)	1.07	(0.82, 1.41)		
Light Brown/dark blonde	239 (23)	285 (22)	0.81	(0.65, 1.02)	189 (23)	214 (22)	0.84	(0.65, 1.09)	182 (28)	206 (25)	0.81	(0.61, 1.06)		
Light blonde	93 (9)	86 (7)	0.62	(0.45, 0.87)	75 (9)	66 (7)	0.65	(0.45, 0.94)	73 (11)	64 (8)	0.63	(0.43, 0.93)		
Red	39 (4)	58 (4)	1.02	(0.66, 1.57)	33 (4)	47 (5)	1.05	(0.65, 1.71)	31 (5)	46 (6)	1.05	(0.64, 1.73)		
<i>p</i> -trend				0.0294				0.0870					0.0640	
Skin complexion														
Dark	20 (4)	30 (5)	1.00	(Ref.)	18 (5)	28 (6)	1.00	(Ref.)	15 (5)	23 (6)	1.00	(Ref.)		
Medium	252 (55)	306 (56)	0.77	(0.42, 1.41)	198 (55)	232 (54)	0.74	(0.40, 1.40)	174 (53)	204 (52)	0.77	(0.38, 1.53)		
Light	189 (41)	215 (39)	0.69	(0.37, 1.29)	145 (40)	172 (40)	0.72	(0.38, 1.39)	139 (42)	168 (43)	0.74	(0.37, 1.51)		
<i>p</i> -trend				0.2387				0.4904					0.5588	
Reaction to first sun of season														
No change	19 (4)	22 (4)	1.00	(Ref.)	17 (5)	18 (4)	1.00	(Ref.)	14 (4)	16 (4)	1.00	(Ref.)		
Tan w/o burn	75 (16)	88 (16)	1.03	(0.51, 2.06)	64 (18)	71 (17)	1.10	(0.52, 2.33)	54 (17)	59 (15)	1.03	(0.45, 2.33)		
Mild burn to tan	200 (44)	245 (45)	1.04	(0.54, 2.00)	152 (42)	182 (42)	1.16	(0.57, 2.37)	137 (42)	168 (43)	1.14	(0.53, 2.44)		
Burn w/o blisters	131 (29)	143 (26)	0.90	(0.46, 1.77)	100 (28)	118 (27)	1.10	(0.53, 2.29)	96 (30)	112 (28)	1.01	(0.46, 2.20)		
Blistering burn	34 (7)	51 (9)	1.32	(0.61, 2.84)	25 (7)	41 (10)	1.64	(0.71, 3.81)	24 (7)	39 (10)	1.52	(0.62, 3.71)		
<i>p</i> -trend				0.8448				0.3468					0.4966	
Hours in mid-day sun (last 10 years)														
<7 h/week	159 (35)	216 (39)	1.00	(Ref.)	120 (34)	162 (38)	1.00	(Ref.)	114 (35)	147 (37)	1.00	(Ref.)		
<14 h/week	126 (27)	145 (26)	0.84	(0.61, 1.15)	103 (29)	115 (27)	0.82	(0.57, 1.17)	93 (29)	107 (27)	0.89	(0.61, 1.29)		
<28 h/week	123 (27)	131 (24)	0.73	(0.53, 1.02)	93 (26)	105 (24)	0.80	(0.55, 1.16)	84 (26)	94 (24)	0.83	(0.56, 1.23)		
28+ h/week	51 (11)	59 (11)	0.73	(0.46, 1.15)	42 (12)	50 (12)	0.77	(0.47, 1.27)	35 (11)	47 (12)	0.92	(0.54, 1.58)		
<i>p</i> -trend				0.0579				0.1982					0.4924	

CI confidence interval, IU international unit, NHL non-Hodgkin lymphoma, OR odds ratio

* Adjusted for age, race/ethnicity, sex, and study site

** Adjusted for age, sex, and study site

Table 4 Association between pigmentation and sun exposures and selected *IRF4* SNPs among non-Hispanic Caucasian controls

<i>IRF4</i>	CC		CT		TT		CT/TT		Chi square	
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI)*	<i>n</i> (%)	OR (95% CI)*	<i>n</i> (%)	OR (95% CI)*	<i>p</i>	<i>p</i>
Eye color										
Dark brown	49 (89)	6 (11)	1.00 (Ref.)	0 (0)	–	6 (11)	1.00 (Ref.)	0.0569		
Light brown	16 (70)	6 (26)	4.46 (1.05, 19.00)	1 (4)	–	7 (30)	5.17 (1.25, 21.35)			
Hazel	41 (60)	26 (38)	4.71 (1.69, 13.14)	1 (1)	–	27 (40)	4.85 (1.75, 13.47)			
Blue	89 (65)	43 (32)	4.47 (1.73, 11.57)	4 (3)	–	47 (35)	4.81 (1.87, 12.36)			
Green/blue-green	29 (67)	13 (30)	4.68 (1.29, 17.05)	1 (2)	–	14 (33)	4.92 (1.36, 17.83)			
Hair color										
Black/dark brown	112 (57)	77 (39)	1.00 (Ref.)	8 (4)	1.00 (Ref.)	85 (43)	1.00 (Ref.)	0.0002		
Medium brown	107 (66)	50 (31)	0.63 (0.40, 1.00)	4 (2)	0.53 (0.15, 1.86)	54 (34)	0.62 (0.40, 0.97)			
Light brown/dark blonde	141 (78)	37 (20)	0.35 (0.22, 0.57)	3 (2)	0.27 (0.07, 1.08)	40 (22)	0.35 (0.22, 0.55)			
Light blonde	62 (85)	10 (14)	0.24 (0.11, 0.50)	1 (1)	0.19 (0.02, 1.57)	11 (15)	0.23 (0.11, 0.47)			
Red	22 (71)	8 (26)	0.55 (0.22, 1.35)	1 (3)	0.54 (0.06, 4.83)	9 (29)	0.55 (0.23, 1.30)			
Skin complexion										
Dark	14 (93)	1 (7)	1.00 (Ref.)	0 (0)	–	1 (7)	1.00 (Ref.)	0.2223		
Medium	122 (70)	49 (28)	5.47 (0.66, 45.23)	3 (2)	–	52 (30)	5.76 (0.70, 47.28)			
Light	88 (65)	44 (32)	7.25 (0.88, 60.03)	4 (3)	–	48 (35)	7.86 (0.95, 64.70)			
Reaction to First Sun of Season										
No change	11 (79)	2 (14)	1.00 (Ref.)	1 (7)	1.00 (Ref.)	3 (21)	1.00 (Ref.)	0.0644		
Tan w/o burn	35 (65)	18 (33)	2.38 (0.38, 14.70)	1 (2)	0.36 (0.01, 9.85)	19 (35)	1.69 (0.34, 8.27)			
Mild burn to tan	101 (74)	34 (25)	1.45 (0.28, 7.60)	1 (1)	–	35 (26)	0.93 (0.22, 3.91)			
Burn w/o blisters	65 (69)	26 (28)	2.36 (0.43, 13.06)	3 (3)	0.32 (0.02, 4.85)	29 (31)	1.58 (0.37, 6.81)			
Blistering burn	10 (42)	13 (54)	8.09 (1.04, 62.71)	1 (4)	1.25 (0.05, 28.98)	14 (58)	5.31 (0.88, 31.89)			
Hours in mid-day sun (last 10 years)										
<7 h/week	82 (72)	30 (26)	1.00 (Ref.)	2 (2)	1.00 (Ref.)	32 (28)	1.00 (Ref.)	0.6797		
<14 h/week	57 (63)	31 (34)	1.60 (0.84, 3.02)	3 (3)	2.70 (0.41, 17.94)	34 (37)	1.66 (0.90, 3.09)			
<28 h/week	61 (73)	21 (25)	0.88 (0.43, 1.79)	1 (1)	1.09 (0.09, 12.85)	22 (27)	0.89 (0.44, 1.78)			
28+ h/week	22 (63)	12 (34)	1.62 (0.61, 4.30)	1 (3)	0.98 (0.05, 19.91)	13 (37)	1.55 (0.61, 3.99)			
<i>IRF4</i>										
	GG	CG	CC	CG/CC						
(rs12211228)	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI)*	<i>n</i> (%)	OR (95% CI)*	<i>n</i> (%)	OR (95% CI)*	<i>p</i>		
Eye color										
Dark brown	44 (80)	10 (18)	1.00 (Ref.)	1 (2)	1.00 (Ref.)	11 (20)	1.00 (Ref.)	0.7095		
Light brown	15 (65)	8 (35)	2.13 (0.64, 7.04)	0 (0)	–	8 (35)	1.82 (0.56, 5.88)			
Hazel	51 (74)	17 (25)	1.46 (0.58, 3.70)	1 (1)	0.40 (0.02, 7.52)	18 (26)	1.34 (0.55, 3.29)			

Table 4 continued

IRF4	GG		CG		CC		CG/CC		Chi square	
	n (%)	n (%)	n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	p	OR (95% CI)*	p	
(rs12211228)										
Blue	96 (70)	38 (28)	1.64	(0.73, 3.69)	4 (3)	1.68	(0.18, 15.72)	42 (30)	1.65	(0.76, 3.58)
Green/blue-green	29 (69)	13 (31)	1.83	(0.64, 5.27)	0 (0)	–	–	13 (31)	1.54	(0.55, 4.31)
Hair color										
Black/dark brown	137 (69)	55 (28)	1.00	(Ref.)	6 (3)	1.00	(Ref.)	61 (31)	1.00	(Ref.)
Medium brown	102 (63)	58 (36)	1.38	(0.87, 2.18)	2 (1)	0.48	(0.09, 2.46)	60 (37)	1.29	(0.82, 2.02)
Light brown/dark blonde	124 (69)	54 (30)	1.15	(0.73, 1.82)	3 (2)	0.62	(0.15, 2.56)	57 (31)	1.10	(0.70, 1.72)
Light blonde	50 (68)	23 (32)	1.12	(0.62, 2.05)	0 (0)	–	–	23 (32)	1.03	(0.57, 1.87)
Red	23 (77)	6 (20)	0.59	(0.22, 1.59)	1 (3)	1.01	(0.11, 9.48)	7 (23)	0.63	(0.25, 1.61)
Skin complexion										
Dark	14 (93)	1 (7)	1.00	(Ref.)	0 (0)	–	–	1 (7)	1.00	(Ref.)
Medium	124 (71)	46 (26)	5.39	(0.67, 43.48)	4 (2)	–	–	50 (29)	5.74	(0.71, 46.25)
Light	97 (73)	39 (28)	4.19	(0.48, 36.91)	2 (1)	–	–	41 (30)	4.86	(0.56, 42.31)
Reaction to first sun of season										
No change	12 (86)	2 (14)	1.00	(Ref.)	0 (0)	–	–	2 (14)	1.00	(Ref.)
Tan w/o burn	41 (76)	12 (22)	1.48	(0.23, 9.73)	1 (2)	–	–	13 (24)	1.48	(0.23, 9.73)
Mild burn to tan	102 (74)	33 (24)	1.83	(0.36, 9.31)	2 (1)	–	–	35 (26)	1.96	(0.39, 9.90)
Burn w/o blisters	64 (67)	30 (32)	2.67	(0.52, 13.79)	1 (1)	–	–	31 (33)	2.72	(0.53, 14.05)
Blistering burn	15 (63)	9 (38)	4.61	(0.57, 37.05)	0 (0)	–	–	9 (38)	4.61	(0.57, 37.05)
Hours in mid-day sun (last 10 years)										
<7 h/week	78 (68)	34 (30)	1.00	(Ref.)	2 (2)	1.00	(Ref.)	36 (32)	1.00	(Ref.)
<14 h/week	71 (77)	19 (21)	0.63	(0.33, 1.22)	2 (2)	1.28	(0.17, 9.67)	21 (23)	0.66	(0.35, 1.26)
<28h/week	59 (70)	24 (29)	1.16	(0.58, 2.29)	1 (1)	0.57	(0.04, 7.83)	25 (30)	1.11	(0.57, 2.18)
28+ h/week	25 (71)	9 (26)	0.99	(0.37, 2.68)	1 (3)	1.11	(0.05, 25.05)	10 (29)	1.00	(0.38, 2.63)

Confidence interval *CI*, international unit *IU*, odds ratio *OR*, single nucleotide polymorphism *SNP*

* Adjusted for age, sex, study site

Table 5 Joint effects of eye color and hair color (excluding red hair) and overall non-Hodgkin lymphoma risk with *IRF4* genotype, among non-Hispanic Caucasians

<i>IRF4</i> SNP	Exposure	Genotype	Controls <i>n</i> (%)	All NHL <i>n</i> (%)	OR (95% CI)*	<i>p</i> -value	<i>p</i> -interaction	
rs12203592	Eye color						0.5475	
		Dark brown	CC	49 (15)	79 (20)	1.00 (Ref.)		
			CT/TT	6 (2)	17 (4)	1.66 (0.60, 4.55)		0.3259
	Light brown	CC	16 (5)	20 (5)	0.80 (0.37, 1.71)	0.5589		
		CT/TT	7 (2)	10 (3)	0.83 (0.29, 2.37)	0.7312		
	Hazel	CC	41 (13)	49 (12)	0.74 (0.43, 1.29)	0.2944		
		CT/TT	27 (8)	20 (5)	0.44 (0.22, 0.88)	0.0204		
	Blue	CC	89 (27)	99 (25)	0.69 (0.44, 1.11)	0.1241		
		CT/TT	47 (14)	54 (14)	0.71 (0.41, 1.22)	0.2118		
	Green/blue-green	CC	29 (9)	30 (8)	0.58 (0.31, 1.11)	0.0991		
		CT/TT	14 (4)	16 (4)	0.67 (0.30, 1.52)	0.3356		
		Hair color						0.6251
	Black/dark brown	CC	112 (18)	160 (21)	1.00 (Ref.)			
		CT/TT	85 (14)	112 (14)	0.92 (0.63, 1.34)	0.6706		
	Medium brown	CC	107 (17)	166 (21)	1.09 (0.77, 1.54)	0.6402		
		CT/TT	54 (9)	72 (9)	0.94 (0.61, 1.45)	0.7721		
	Light brown/dark blonde	CC	141 (23)	174 (22)	0.85 (0.61, 1.18)	0.3330		
		CT/TT	40 (7)	32 (4)	0.55 (0.32, 0.94)	0.0282		
Light blonde	CC	62 (10)	58 (7)	0.65 (0.42, 1.01)	0.0546			
	CT/TT	11 (2)	6 (1)	0.36 (0.13, 1.00)	0.0496			
rs12211228	Eye color						0.5878	
		Dark brown	GG	44 (13)	67 (17)	1.00 (Ref.)		
		CG/CC	11 (3)	29 (7)	1.69 (0.76, 3.77)	0.2011		
	Light brown	GG	15 (5)	23 (6)	1.04 (0.48, 2.25)	0.9121		
		CG/GG	8 (2)	7 (2)	0.54 (0.18, 1.63)	0.2710		
	Hazel	GG	51 (16)	49 (12)	0.62 (0.36, 1.09)	0.0946		
		CG/GG	18 (6)	20 (5)	0.73 (0.34, 1.55)	0.4098		
	Blue	GG	96 (29)	105 (27)	0.73 (0.45, 1.18)	0.1951		
		CG/GG	42 (13)	48 (12)	0.76 (0.43, 1.35)	0.3501		
	Green/blue-green	GG	29 (9)	34 (9)	0.71 (0.38, 1.35)	0.3008		
		CG/GG	13 (4)	13 (3)	0.64 (0.27, 1.52)	0.3096		
		Hair color						0.3200
	Black/dark brown	GG	137 (22)	187 (24)	1.00 (Ref.)			
		CG/GG	61 (10)	86 (11)	1.03 (0.69, 1.54)	0.8772		
	Medium Brown	GG	102 (17)	176 (23)	1.27 (0.91, 1.78)	0.1550		
		CG/GG	60 (10)	63 (8)	0.76 (0.50, 1.16)	0.2007		
	Light brown/dark blonde	GG	124 (20)	146 (19)	0.85 (0.61, 1.18)	0.3219		
		CG/GG	57 (9)	60 (8)	0.76 (0.49, 1.17)	0.2066		
Light blonde	GG	50 (8)	46 (6)	0.65 (0.41, 1.04)	0.0727			
	CG/GG	23 (4)	18 (2)	0.58 (0.30, 1.13)	0.1094			

CI Confidence interval, NHL non-Hodgkin lymphoma, OR odds ratio, SNP single nucleotide polymorphism

* Adjusted for age, sex, and study center

the ascertainment of data on a range of measures designed to assess sun sensitivity and sun exposure in study subjects. Also, our study population reflects all three previously reported independent associations at the basis of this

analysis, making it ideal for investigating potential joint effects. Study limitations include lower sample sizes available for some primary and secondary analyses resulting from the split-sample design, which allowed for

the collection of sun exposure and sun sensitivity data in only half of the participant pool. This decreased the study's power to detect significant interactions. Additionally, the relatively low participation and response rates for the study increase the potential for selection bias in the sample.

We acknowledge that our data may not have detected a joint effect because none existed, because of limited sample size and power to detect a joint effect, or because of our imperfect measures for both genotype and sun exposures, which may have biased our results toward the null. The *IRF4* SNPs associated with NHL and hair color were originally identified as part of a tagging algorithm and thus are considered markers of susceptibility. The SNPs evaluated are thus surrogates and likely in linkage disequilibrium with the causal SNP. In addition, the specific mechanism by which sun sensitivity and sun exposure affects NHL risk is unknown and the pigmentation phenotypes such as hair color are considered surrogates for this measure. We, therefore, cannot exclude the possibility that our null observations for joint effects between *IRF4* and sun sensitivity are due to our having a poor surrogate marker for the causal factor(s). Finally, we also cannot exclude the possibility that joint effects may exist for specific NHL subtypes which we were unable to evaluate due to small numbers in our study.

In summary, our data support that genetic polymorphisms in the immune regulatory gene *IRF4* are linked to both risk for non-Hodgkin lymphoma and to hair color and other phenotypic measures of sun sensitivity and exposure. Further evaluation of joint effects in independent and larger populations is needed. If joint effects are shown, further investigations to identify the mechanisms by which sun sensitivity or exposure and *IRF4* genes function to modulate risk for NHL are warranted.

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