HHS Public Access

Author manuscript

*Leukemia*. Author manuscript; available in PMC 2016 April 27.

Published in final edited form as:

*Leukemia*. 2010 May ; 24(5): 1055–1058. doi:10.1038/leu.2010.17.

# Human leukocyte antigen (*HLA*) *A1-B8-DR3* (8.1) haplotype, tumor necrosis factor (*TNF*) G-308A, and risk of non-Hodgkin lymphoma

**AM Abdou**[1], **X Gao**[1], **W Cozen**[2], **JR Cerhan**[3], **N Rothman**[4], **MP Martin**[1], **S Davis**[5], **M Schenk**[6], **SJ Chanock**[7], **P Hartge**[4], **M Carrington**[1], and **SS Wang**[4,8]

[1]Basic Research Program, SAIC-Frederick Inc. Laboratory of Genomic Diversity, NCI-Frederick, Frederick, MD, USA

[2]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA

[3]Mayo Clinic, College of Medicine, Rochester, MN, USA

[4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, MD, USA

[5]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, USA

[6]Department of Family Medicine and Public Health Sciences, Wayne State University and the Karmanos Cancer Institute, Detroit, MI, USA

[7]Core Genotyping Facility, Advanced Technology Center, National Cancer Institute, NIH, DHHS, Gaithersburg, MD, USA

[8]Division of Etiology, Department of Population Sciences, Beckman Research Institute and the City of Hope, Duarte, CA, USA

Large-scale consortial efforts now provide convincing evidence that the pro-inflammatory cytokine tumor necrosis factor (*TNF*) promoter polymorphism (*TNF* G-308A), which is thought to increase *TNF*-α protein expression resulting in inflammation, is associated with increased risk of non-Hodgkin lymphoma (NHL) and specifically with the NHL subtype, diffuse large B-cell lymphoma (DLBCL) among Caucasians.[1] The largest effort to date from the International Lymphoma Epidemiology Consortium (InterLymph) comprising 7999 incidence NHL cases and 8452 controls report that *TNF*-308A carriers have a 1.25-fold (per allele) increased risk for DLBCL and a 1.35-fold increased risk for marginal zone lymphoma.[2]

A limitation to the published association studies, however, is the inability to delineate the association between *TNF* and NHL from human leukocyte antigen (*HLA*) alleles that are known to be in linkage disequilibrium. *TNF* is located on chromosome 6p21.3 among the Class III genes of the major histocompatibility complex, 250 kb centromeric to the *HLA-B*

**Conflict of interest**

The authors declare no conflict of interest.

Supplementary Information accompanies the paper on the Leukemia website (http://www.nature.com/leu)

locus and 850 kb telomeric to the Class II *HLA-DR* locus. It is well documented that Caucasian populations carry the 8.1 ancestral haplotype (AH) that includes the *TNF*-308A allele (*HLA-A1-B8-TNF-308A-DR3-DQ2*).[3] Notably, the 8.1 AH is implicated in the risk of numerous autoimmune conditions, including those associated with NHL (for example, systemic lupus erythematosus and Sjogren's syndrome).[3–5] It remains unknown, however, whether the association reported for *TNF*-308A is due to or independent from *HLA* alleles and/or haplotypes.

Here, we present data from 555 controls and 610 cases from a US population-based case–control study of NHL where *HLA* Class I and Class II alleles were evaluated in the context of *TNF* with regard to their role in risk for NHL and NHL subtypes.

As has been previously described,[6] the multi-center National Cancer Institute—Surveillance, Epidemiology and End Results (NCI-SEER) NHL case–control study population comprised 1321 newly diagnosed NHL cases identified in four Surveillance, Epidemiology, and End Results registries (Iowa; Detroit, MI; Los Angeles, CA; Seattle, WA) aged 20–74 years between July 1998 and June 2000 without evidence of HIV infection; 1057 population controls were identified by random digit dialing (<65 years) and from Medicare eligibility files (≥65 years). Written informed consent was obtained from each participant before interview. All study participants were also asked to provide a venous blood or mouthwash buccal cell sample. The present analysis was conducted on subset of non-Hispanic Caucasian cases and controls who provided blood (Supplementary Table 1); DNA were extracted using Puregene Autopure DNA extraction kits (Gentra Systems, Minneapolis, MN, USA). Duplicate samples from 100 participants processed in an identical manner were interspersed for all assays and blinded from the laboratory. Agreement for QC duplicates was ≥99%.

NHL pathology and subtype information were derived from abstracted reports by the local diagnosing pathologist. All cases were histologically confirmed and have been coded according to the International Classification of Diseases for Oncology (ICD), 2nd Edition and updated to the WHO/ICD-O-3. In addition to NHL overall, we evaluated the histologic subtypes DLBCL, follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and T-cell lymphomas (includes mycosis fungoides/sezary syndrome, peripheral T-cell lymphomas, and T/NK-cell lymphomas not otherwise specified).

Four-digit *HLA* Class I (A, B, C) and Class II genotyping (DR) was conducted at the NCI Laboratory for Genomic Diversity (Frederick, MD, USA) (AMA) according to sequence-specific oligonucleotide probe hybridization and sequence-based typing protocols developed by the 13th International Histocompatibility Workshop.[7] *HLA* alleles were defined as presence or absence of the specific allele ('+' if the individual had either one or two copies of the allele, and '−' if the individual had no copies of the allele). *TNF* genotyping was conducted at the National Cancer Institute Core Genotyping Facility (Gaithersburg, MD, USA) using the Taqman (Foster City, CA, USA) platform. *TNF G-308A* was defined by genotype (GG (referent), GA and AA).[6] Haplotypes for *HLA-A-B-DR* were determined using 'FastHap', which determines haplotypes by expectation maximization (http://

home.ncifcrf.gov/ccr/lgd/bioinformatics/index_n.asp). For *HLA* and *TNF*, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the magnitude and statistical significance of associations. All risk estimates are presented for non-Hispanic Caucasians and adjusted for the study design variables: sex, age (<45, 45–64, 65+ years) and study center (Detroit, Iowa, Los Angeles, Seattle). We also conducted analyses among all cases and controls (665 controls and 715 cases) adjusted for race and results were consistent. All logistic regression models were unconditional and conducted using SAS 9.1.3 (SAS Institute, Cary, NC, USA). All tests of statistical significance are two-sided.

We found the *HLA-A*01-B*08-DR*03* haplotype associated with elevated risk of DLBCL (Table 1). The association appeared driven by the individual alleles that are part of the ancestral 8.1 haplotype, notably *HLA-B*0801* ($OR_{DLBCL}$ = 1.63, 95% CI = 1.08–2.45). *HLA-B*0801* was also associated with elevated risks of marginal zone, follicular and T-cell lymphomas though not statistically significant. Similar associations were observed for *HLA-DRB1*0301*.

The association between *TNF*-308A and NHL/DLBCL has been previously reported in this population;[7] among the case and control subset comprising the present analysis, the association between *TNF*-308A and DLBCL remained statistically significant ($OR_{AG/AA}$ = 1.78, 95% CI = 1.22–2.59, referent = GG) (Table 1).

Risks for DLBCL among individuals with the *HLA-A*01-B*08-DR*03-TNF* haplotype (OR = 1.65, 95% CI = 1.00–2.72) were not more pronounced than that observed for *TNF* (Table 1).

We further evaluated the association between *TNF* and DLBCL in the context of each *HLA* allele constituting the *A*01-B*08-DR*03* haplotype. We observed statistically significantly elevated DLBCL risk among those with the *TNF*-308A variant allele with or without the *HLA-B*0801* allele ($OR_{HLA\text{-}B^*0801+}$ = 1.78, 95% CI = 1.15–2.76; $OR_{HLA\text{-}B^*0801-}$ = 1.95, 95% CI = 1.11–3.42) or *HLA-A*01-B*08-DR*03* haplotype ($OR_{HLA\text{-}A^*01-B^*08\text{-}DR^*03+}$ = 1.80, 95% CI = 1.08–3.00; $OR_{HLA\text{-}A^*01\text{-}B^*08\text{-}DR^*03-}$ = 1.63, 95% CI = 1.00–2.68) (Table 2). Similar risk associations for DLBCL were observed for those with the *TNF* G-308A variant allele, with or without the *HLA-A*01* or *HLA-DR*03* alleles.

Interestingly, for NHL risk overall, we observed a statistically significant elevated risk among those with the *HLA-B*08* allele, regardless of *TNF* G-308A status ($OR_{TNF\ GG}$ = 2.97, 95% CI = 1.06–8.32; $OR_{TNF\ GA/AA}$ = 1.43, 95% CI = 1.05–1.94) (Table 2). Though the numbers of individuals who carried *HLA-B*08* without *TNF* G-308A were small ($n$ = 15 for NHL; $n$ = 5 in controls), we note that there was no significant association between *TNF*-308A and NHL in the absence of *HLA-B*08* ($n$ = 58 in NHL; $n$ = 47 in controls). These results suggest a potential role for *HLA-B*08* as an independent susceptibility allele for overall NHL risk.

Taken together, our results show an association between the *TNF*-308A variant allele with DLBCL in both the presence and the absence of the *HLA-A* 01-B*08-DR*03* alleles and haplotype. Our results suggest that the associations between *TNF*-308A and DLBCL, now consistently reported and demonstrated in large-scale consortial efforts,[1,2] do not appear to

be confounded by the association with the *HLA-A*01-B* 08-DR*03* or any of its constituents, which are known to be in LD with *TNF*-308A ($D' = 0.7$ in our population), though these associations could still be enhanced by it. We note that of the individuals carrying the *HLA-A*01-B*08-DR*03* haplotype, 99% had a variant *TNF*-308A allele (GA or AA genotype). Notably, 15% of the population had a variant *TNF*-308A allele in the absence of the *HLA-A*01-B*08-DR*03* haplotype, which allowed us to evaluate whether the reported increased DLBCL risk with *TNF*-308A would also be observed independent of the *HLA-A*01-B*08-DR*03* haplotype and alleles. Whether the *TNF*-308A is the causal DLBCL SNP remains to be confirmed, but our data suggest that the biologic role of the *TNF* gene and, specifically, the immune mechanisms of inflammation through NF-kB, which is activated by TNF-α, are worth further investigation in understanding DLBCL etiology.

We note that the association between *HLA-B*08* and DLBCL was more pronounced than that for the *HLA-A*01-B*08-DR*03* haplotype. This appears consistent with the literature that has demonstrated that the AH 8.1 haplotype is largely carried by most individuals who have *HLA-B8*, and which is known for its unique cleft motif.[3] The AH 8.1 is associated with numerous autoimmune conditions that are also NHL risk factors (for example, Sjogren's syndrome and systemic lupus erythematosis)[8] and thought to result from higher TNF-α expression and supported by studies showing elevated TNF-α expression among healthy individuals with AH 8.1.[3] It has been hypothesized that *TNF* may influence the *HLA* alleles within AH 8.1 by influencing the inflammatory reactions and response to infections.[3] Larger studies will be required to determine whether DLBCL risks observed for individuals with both the AH 8.1 (or *HLA-B*08* allele) and *TNF*-308A allele differ from those with only *TNF*-308A.

Finally, our results also suggest a possible role that *HLA* may have in NHL etiology. In particular, the association between *HLA-B*08* allele was significantly associated with elevated NHL risk overall regardless of *TNF* G-308A status.

We believe our results shed important light on the role of *TNF* and *HLA* in NHL etiology but recognize that to definitively delineate potential effects of *HLA* from *TNF*-308A will require replication of our results in an independent study and further evaluation in non-Caucasian populations where linkage disequilibrium patterns differ. For example, another AH (58.1) that includes *HLA-A33*, *-B58*, *TNF*-308A, and *-DR3* is found among Asian populations and we cannot exclude the potential influence of *HLA-A*33* and *-B*58* because of the rarity of these alleles in our Caucasian population.

Study strengths include the population-based design and four-digit *HLA* genotyping for *HLA* Class I A, B, and C alleles and for *HLA* Class II DR alleles. As we did not include *HLA-DQ* alleles or other non-*HLA* alleles in the major histocompatibility complex region, we cannot discount their possible involvement in NHL etiology and affect on the reported *TNF*-308A association. We also had limited power to detect modest independent associations and potential interactions between these loci. We also cannot rule out the contributions of other potentially important immune genes in the major histocompatibility complex class III loci.

In summary, our results suggest that individuals with a variant *TNF* G-308A allele have increased DLBCL risk even in the absence of *HLA-A**01-B**08-DR**03* alleles and haplotype, providing further evidence of the importance of *TNF* in DLBCL etiology. Our results also indicate that *HLA-B**08* is associated with NHL risk regardless of *TNF* G-308A status, implicating a potential role for *HLA* in NHL etiology. Further investigation of these results in relation to lymphoma prognosis may also be warranted.[9,10]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank Peter Hui of the Information Management Services Inc. for programming support. We also gratefully acknowledge the contributions of the staff and scientists at the SEER centers of Iowa, Los Angeles, Detroit and Seattle for the conduct of the study's field effort. We especially acknowledge the contributions of study site principle investigators Richard Severson (Detroit) and Leslie Bernstein (Los Angeles), without whom the study would not have been possible. The NCI-SEER study was supported by the Intramural Research Program of the NIH (NCI), and by Public Health Service (PHS) contracts N01-PC-65064, N01-PC-67008, N01-PC-67009, N01-PC-67010 and N02-PC-71105.

## References

1. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006; 7:27–38. [PubMed: 16389181]
2. Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, de Sanjose S, Hughes AM, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. Am J Epidemiology. 2010; 171:267–276.
3. Candore G, Lio D, Colonna RG, Caruso C. Pathogenesis of autoimmune diseases associated with 8. 1 ancestral haplotype: effect of multiple gene interactions. Autoimmun Rev. 2002; 1:29–35. [PubMed: 12849055]
4. Newton JL, Harney SM, Timms AE, Sims AM, Rockett K, Darke C, et al. Dissection of class III major histocompatibility complex haplotypes associated with rheumatoid arthritis. Arthritis Rheum. 2004; 50:2122–2129. [PubMed: 15248209]
5. Schotte H, Willeke P, Tidow N, Domschke W, Assmann G, Gaubitz M, et al. Extended haplotype analysis reveals an association of TNF polymorphisms with susceptibility to systemic lupus erythematosus beyond HLA-DR3. Scand J Rheumatol. 2005; 34:114–121. [PubMed: 16095006]
6. Wang SS, Cerhan JR, Hartge P, Davis S, Cozen W, Severson RK, et al. Common genetic variants in proinflammatory and other immunoregulatory genes and risk for non-Hodgkin lymphoma. Cancer Res. 2006; 66:9771–9780. [PubMed: 17018637]
7. Tilanus, MG.; Hansen, JA.; Hurley, CK. IHWG Technical Manual: Genomic Analysis of the Human MHC. IHWG; Seattle, WA: 2002.
8. Shiina T, Hosomichi K, Inoko H, Kulski JK. The HLA genomic loci map: expression, interaction, diversity and disease. J Hum Genet. 2009; 54:15–39. [PubMed: 19158813]
9. Juszczynski P, Kalinka E, Bienvenu J, Woszczek G, Borowiec M, Robak T, et al. Human leukocyte antigens class II and tumor necrosis factor genetic polymorphisms are independent predictors of non-Hodgkin lymphoma outcome. Blood. 2002; 100:3037–3040. [PubMed: 12351419]
10. Nowak J, Kalinka-Warzocha E, Juszczynski P, Bilinski P, Mika-Witkowska R, Zajko M, et al. Association of human leukocyte antigen ancestral haplotype 8. 1 with adverse outcome of non-Hodgkin's lymphoma. Genes Chromosomes Cancer. 2007; 46:500–507. [PubMed: 17311253]

**Table 1**

Main associations between *HLA-A*0101*, *HLA-B*0801*, *HLA-DR*0301* and *TNF* with all NHL and NHL subtypes (DLBCL, follicular, marginal zone, SLL/CLL and T-cell lymphomas) among non-Hispanic Caucasians, adjusted for age, sex and study center.

| *Allele or haplotype*[*] | *Control* n *(%)* | *NHL* n *(%)* | *OR (95%CI)* | *DLBCL* n *(%)* | *OR (95%CI)* | *Follicular* n *(%)* | *OR (95%CI)* | *Marginal Zone* n *(%)* | *OR (95%CI)* | *CLL/SLL* n *(%)* | *OR (95%CI)* | *T cell* n *(%)* | *OR (95%CI)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *HLA-A*01-B*08-DR*03* | | | | | | | | | | | | | |
| − | 438 (87) | 455 (84) | 1.0 (ref) | 123 (81) | 1.0 (ref) | 128 (86) | 1.0 (ref) | 36 (80) | 1.0 (ref) | 71 (87) | 1.0 (ref) | 28 (82) | 1.0 (ref) |
| + | 67 (13) | 88 (16) | 1.21 (0.89–1.78) | 29 (19) | 1.59 (0.98–2.59) | 21 (14) | 1.05 (0.61–1.80) | 9 (20) | 1.65 (0.75–3.61) | 11 (13) | 0.97 (0.48–1.94) | 6 (18) | 1.28 (0.49–3.28) |
| *HLA-A*0101* | | | | | | | | | | | | | |
| − | 373 (70) | 389 (67) | 1.0 (ref) | 107 (65) | 1.0 (ref) | 108 (67) | 1.0 (ref) | 30 (64) | 1.0 (ref) | 58 (71) | 1.0 (ref) | 25 (69) | 1.0 (ref) |
| + | 162 (30) | 188 (33) | 1.12 (0.88–1.45) | 58 (35) | 1.28 (0.88–1.86) | 54 (33) | 1.19 (0.81–1.74) | 17 (36) | 1.35 (0.72–2.54) | 24 (29) | 0.96 (0.57–1.61) | 11 (31) | 1.07 (0.51–2.29) |
| *HLA-B*0801* | | | | | | | | | | | | | |
| − | 435 (81) | 432 (70) | 1.0 (ref) | 120 (73) | 1.0 (ref) | 121 (74) | 1.0 (ref) | 34 (72) | 1.0 (ref) | 64 (78) | 1.0 (ref) | 28 (74) | 1.0 (ref) |
| + | 102 (19) | 148 (25) | **1.45 (1.09–1.94)** | 45 (27) | **1.63 (1.08–2.45)** | 42 (26) | 1.42 (0.93–2.17) | 13 (28) | 1.69 (0.85–3.33) | 18 (22) | 1.18 (0.67–2.09) | 10 (26) | 1.50 (0.69–3.26) |
| *HLA-DR*0301* | | | | | | | | | | | | | |
| − | 415 (80) | 405 (74) | 1.0 (ref) | 110 (72) | 1.0 (ref) | 113 (75) | 1.0 (ref) | 28 (62) | 1.0 (ref) | 65 (79) | 1.0 (ref) | 24 (67) | 1.0 (ref) |
| + | 105 (20) | 145 (26) | **1.41 (1.06–1.88)** | 43 (28) | **1.55 (1.02–2.36)** | 38 (25) | 1.30 (0.83–2.00) | 17 (38) | **2.47 (1.29–4.71)** | 17 (21) | 1.04 (0.58–1.86) | 12 (33) | 1.91 (0.90–4.04) |
| *TNF G-308A* | | | | | | | | | | | | | |
| GG | 383 (73) | 375 (67) | 1.0 (ref) | 98 (61) | 1.0 (ref) | 107 (69) | 1.0 (ref) | 29 (63) | 1.0 (ref) | 64 (80) | 1.0 (ref) | 22 (58) | 1.0 (ref) |
| GA | 130 (25) | 170 (30) | **1.33 (1.02–1.75)** | 56 (35) | **1.72 (1.17–2.54)** | 44 (28) | 1.19 (0.79–1.79) | 16 (35) | 1.61 (0.84–3.09) | 16 (20) | 0.70 (0.39–1.27) | 14 (37) | 1.77 (0.86–3.66) |
| AA | 12 (2) | 16 (3) | 1.45 (0.67–3.14) | 7 (4) | 2.37 (0.90–6.27) | 4 (3) | 1.17 (0.36–3.79) | 1 (2) | 1.23 (0.15–9.78) | — | — | 2 (5) | 2.95 (0.57–15.3) |
| GA/AA | 142 (27) | 186 (33) | **1.34 (1.03–1.75)** | 63 (39) | **1.78 (1.22–2.59)** | 48 (31) | 1.19 (0.80–1.77) | 17 (37) | 1.58 (0.83–3.00) | 16 (20) | 0.65 (0.36–1.18) | 16 (42) | 1.87 (0.93–3.75) |
| *HLA-A*01-B*08-DR*03-TNF-A* | | | | | | | | | | | | | |
| − | 425 (87) | 441 (84) | 1.0 (ref) | 120 (81) | 1.0 (ref) | 121 (85) | 1.0 (ref) | 36 (82) | 1.0 (ref) | 69 (87) | 1.0 (ref) | 28 (82) | 1.0 (ref) |
| + | 62 (13) | 82 (18) | 1.27 (0.89–1.82) | 28 (19) | **1.65 (1.00–2.72)** | 21 (15) | 1.17 (0.68–2.01) | 8 (18) | 1.57 (0.69–3.56) | 19 (13) | 0.96 (0.46–1.98) | 6 (18) | 1.33 (0.52–3.45) |

Abbreviations: CI, confidence intervals; DLBCL, diffuse large B-cell lymphoma; HLA, human leukocyte antigen; NHL, non-Hodgkin lymphoma; OR, odds ratios; TNF, tumor necrosis factor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

[*] Numbers are not equivalent for each allele because of their differential genotyping completion rates. Results with $P<0.05$ are indicated in bold font.

**Table 2**

Risk estimates for NHL, DLBCL, marginal zone and T-cell lymphoma among non-Hispanic Caucasians with the *TNF G-308A* variant allele delineated by the presence or absence of the *HLA-A*01-B*08-DR*03* haplotype, adjusted for age, sex and study center

| *Allele or haplotype*[a] | *TNF G-308A* | *Control* n *(%)* | *NHL* n *(%)* | *OR (95%CI)* | *DLBCL* n *(%)* | *OR (95%CI)* | *Marginal Zone* n *(%)* | *OR (95%CI)* |
|---|---|---|---|---|---|---|---|---|
| *HLA-A*01* | | | | | | | | |
| − | GG | 305 (59) | 303 (55) | 1.0 (ref) | 81 (51) | 1.0 (ref) | 25 (54) | 1.0 (ref) |
| − | GA/AA | 57 (11) | 74 (13) | 1.32 (0.90–1.94) | 23 (14) | 1.57 (0.91–2.72) | 5 (11) | 1.02 (0.37–2.82) |
| + | GG | 75 (14) | 68 (12) | 0.93 (0.64–1.35) | 17 (11) | 0.90 (0.50–1.62) | 4 (9) | 0.66 (0.22–1.98) |
| + | GA/AA | 83 (16) | 111 (20) | 1.35 (0.97–1.88) | 39 (24) | **1.83 (1.15–2.89)** | 12 (26) | 1.84 (0.88–3.86) |
| *HLA-B*08* | | | | | | | | |
| − | GG | 376 (72) | 358 (64) | 1.0 (ref) | 94 (59) | 1.0 (ref) | 29 (63) | 1.0 (ref) |
| − | GA/AA | 47 (9) | 58 (10) | 1.30 (0.86–1.97) | 22 (14) | **1.95 (1.11–3.42)** | 5 (11) | 1.25 (0.45–3.45) |
| + | GG | 5 (1) | 15 (3) | **2.97 (1.06–8.32)** | 3 (2) | 2.55 (0.59–11.0) | 0 (0) | — |
| + | GA/AA | 94 (18) | 128 (23) | **1.43 (1.05–1.94)** | 41 (26) | **1.78 (1.15–2.76)** | 12 (26) | 1.72 (0.84–3.55) |
| *HLA-DR*03* | | | | | | | | |
| − | GG | 341 (68) | 325 (61) | 1.0 (ref) | 85 (57) | 1.0 (ref) | 23 (52) | 1.0 (ref) |
| − | GA/AA | 60 (12) | 67 (13) | 1.17 (0.80–1.71) | 23 (15) | 1.57 (0.91–2.70) | 5 (11) | 1.15 (0.42–3.17) |
| + | GG | 24 (5) | 27 (5) | 1.17 (0.66–2.08) | 7 (5) | 1.08 (0.44–2.63) | 4 (9) | 2.52 (0.79–8.02) |
| + | GA/AA | 78 (15) | 111 (21) | **1.50 (1.07–2.08)** | 34 (23) | **1.80 (1.12–2.89)** | 12 (27) | **2.35 (1.11–4.98)** |
| *HLA-A*01-B*08-DR*03* | | | | | | | | |
| − | GG | 355 (72) | 345 (66) | 1.0 (ref) | 91 (61) | 1.0 (ref) | 27 (61) | 1.0 (ref) |
| − | GA/AA | 71 (14) | 95 (18) | 1.37 (0.97–1.94) | 29 (20) | **1.63 (1.00–2.68)** | 9 (20) | 1.60 (0.71–3.57) |
| + | GG | 1 (<1) | 1 (<1) | 0.87 (0.05–14.5) | 0 (0) | — | 0 (0) | — |
| + | GA/AA | 63 (13) | 83 (16) | 1.35 (0.94–1.94) | 28 (19) | **1.80 (1.08–3.00)** | 8 (18) | 1.70 (0.73–3.96) |

Abbreviations: CI, confidence intervals; DLBCL, diffuse large B-cell lymphoma; HLA, human leukocyte antigen; NHL, non-Hodgkin lymphoma; OR, odds ratios; TNF, tumor necrosis factor.

[a]Numbers are not equivalent for each allele because of their differential genotyping completion rates. Results with $P<0.05$ are indicated in bold font.