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Interaction Involving Amino Acids in HLA Proteins and Smoking in Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a complex autoimmune disease involving gene-environment interactions. Different subtypes of RA, based on the presence of specific antibodies, differ in each etiology. Interacting effects have been found in HLA-DRB1 shared epitope alleles with smoking, in relation to the increased risk of one subgroup of RA.

Aims: To identify interactions involving imputed amino acids in HLA proteins and smoking regarding risk of developing serologically defined subgroups of rheumatoid arthritis.

Methods: Two materials respectively including 3000 and 4337 individuals aged 18-70 recruited during 1996-2009 from the EIRA study, a population-based case-control study were used for this investigation. Serum antibodies against cyclic citrullinated peptide (CCP) were examined to decide subtypes of RA. We used 8961 genetic markers in HLA that were imputed from a reference panel based on individuals of European decent. Lifestyle variables including smoking were obtained from questionnaires. We used logistic regression to estimate odds ratios regarding risk of developing different subgroups of RA. We used attributable proportion to estimate interaction between genetic markers and smoking with consideration taken to genetic models.

Results: 48 amino acid positions in HLA-DRB1, DQA1, DQB1 regions were associated with interacting effects with smoking in ACPA-positive RA. Results are similar in two materials, and 22 remained after controlling for shared epitope

alleles in DRB1. No SNPs or interacting effect were found significant in ACPA-negative RA after correction for multiple testing.
Conclusion: The study found interacting effects in HLA proteins independent of shared epitope alleles with smoking, in relation to the risk of development of ACPA-positive RA.

Keywords: Amino Acid Substitution / genetics Smoking HLA
Arthritis, Rheumatoid / genetics Gene-environment Interaction
Polymorphism, Single Nucleotide Models, Statistical

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List of abbreviations

ACCP	Antibodies to cyclic citrullinated peptide
ACPA	Anti-citrullinated peptide antigens
ACR	American College of Rheumatology
AP	Attributable proportion
APC	Antigen-presenting cell
CI	Confidence interval
EIRA	Epidemiological Investigation of Rheumatoid Arthritis
GWAS	Genome-wide association study
HLA	Human leukocyte antigen molecule
LD	Linkage disequilibrium
MAF	Minor allele frequency
MHC	Major histocompatibility complex
MS	Multiple sclerosis
OR	Odds ratio
PCR	Polymerase chain reaction
RA	Rheumatoid arthritis
RERI	Relative excess risk due to interaction
RF	Rheumatoid factor
RR	Relative risk
SE	Shared epitope
SNP	Single nucleotide polymorphisms
T1DGC	Type 1 Diabetes Genetics Consortium
TCR	T-cell receptor
TNF	Tumor necrosis factor
UTR	Untranslated region

1. Background

1.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that is believed to have a complex etiology involving environmental and genetic factors.[1] The prevalence of RA differs geographically, ranging from 0.5% to 1%, and it is two to three times more frequent in women as compared to men.[2] A twin study indicated that heritability accounted for approximately 65% of RA, by comparing the concordance rates among monozygotic twins with dizygotic twins.[3] Despite the findings in genome-wide association (GWA) studies, rheumatoid arthritis is still regarded as a complex disease in that the T cell-mediated immune regulation can be stimulated by environmental factors.[4,5] The overexpression of tumor necrosis factor (TNF) is suggested to be the main cause for synovial inflammation and joint destruction.[6] However, the etiology of RA remains unclear, especially how genetic factors may interact with environmental factors in immune responses that consequently cause the inflammation and damage of the joints in the body.

1.2 Subtypes of rheumatoid arthritis

Previous study indicated that the diagnosis of "rheumatoid arthritis" was a set of diseases with different etiology but similar symptoms.[1] Thus, it is natural to consider distinct types of the disease simultaneously when it comes to the pathogenesis of RA, through integrating environmental and genetic risk factors.

A recent subdivision is based on the presence of antibodies against cyclic citrullinated peptide (anti-CCP), or anti-citrullinated peptide antigens (ACPA) in the blood. ACPA is an anti-body targeting citrullinated peptide, while citrullination is a product of a posttranslational modification of the amino acid arginine. This subdivision has been proved to have high specificity regarding RA.[7] Presence of ACPA is considered to be stable over time in this subgroup of RA patients. Approximately 70% of RA patients have anti-citrullinated peptide antigens.[1] Also, antibodies to the immune dominant citrullinated α-enolase CEP-1 epitope, which is a subset of the ACPA group, have been reported to be associated with the gene-environment interaction.[8] Besides the previously described groups, there are some other

traditional subdivisions, such as separating RA based on the presence of an antibody complex called rheumatoid factor (RF).

1.3 Predictors for rheumatoid arthritis

Several environmental exposures with increased risk for RA have been identified such as smoking, parity, exposure to mineral oil, and exposure to silica.[9,10,11,12] Among those, smoking is the most established one, and has been associated with certain types of RA, with an observed relative risk up to 2.[13]

On the other hand, over fifty genetic risk loci have been discovered through genome-wide approach as well as candidate-gene approach.[14,15,16] A recent GWA study indicated that the strong association between the major histocompatibility complex (MHC) and ACPA-positive disease could be explained by amino acids in human leukocyte antigen molecule (HLA) proteins located in peptide-binding grooves.[17] The gene coding for HLA in chromosome 6 is believed to play an important role in the immune system as a presenter of foreign substances as well as autogenic substances. However, the main genetic effects of single nucleotide polymorphisms (SNPs) do not take into account gene-environment interactions that are considered to be important for the occurrence of complex diseases.

So far, a strong interaction between smoking and HLA-DRB1 “shared epitope” (SE) alleles has been observed in relation to ACPA-positive RA susceptibility.[18,19] These studies used a candidate-gene approach, but still less is known about the gene-environment interaction on a genome-wide level. A recent published abstract described the gene-environment interaction between smoking and SNPs concerning two subsets of RA in a genome-wide scale.[20] The findings show that all SNPs interacting with smoking are located in the HLA region, especially the HLA class II region. In the light of these findings, we can narrow down our initial scope to chromosome 6, where MHC and HLA are located, and thus apply a genome-wide analysis approach to a candidate region.

1.4 HLA and autoimmune diseases

The human leukocyte antigen (HLA) genes are the genetic basis of the major histocompatibility complex (MHC) molecules, located in chromosome 6

and traditionally have three classifications: HLA-class I, class II, and class III genes. Among those, the class II genes include HLA-DP, -DQ, -DR (Fig 1a). HLA class II molecules, the expression products of class II genes, have functions in recognizing and binding peptides on the surface of antigen-presenting cells (APCs) (Fig 1b). As long as a peptide is engaged with MHC molecule, simultaneously binding to T-cell receptor (TCR), the 'first signal' (MHC-Ag-TCR) of T-cell activation is evoked (Fig 1c). Normally, matured T-cell response has a tolerance for auto-antigen, however in RA patients, this tolerance has been destroyed and the T-cell mediates self-active signals. Consequently, the immune system is attacking the own tissues as if they were foreign antigens.

1.5 Methods for gene-environment interactions

When estimating interaction we need to take into account the diverse definitions of interaction. In this study, we primarily use additive interaction to evaluate the interaction between amino acid polymorphisms and smoking, as suggested by Rothman.[21] The attributable proportion (AP) owing to interaction is calculated in order to quantify the amount of excess risk for RA. Attributable proportion is the proportion of the incidence among persons exposed to two interacting factors that is attributable to the interaction per se. That means, AP reflects their joint effect beyond the sum of their independent effects.

There are mainly two strategies in the context of gene environment interaction studies.[22] One strategy is the parametric or semi-parametric approach, which requires intrinsical models, for instance, a regression framework. This approach is usually chosen when researchers aim to screen for unknown interaction factors, to test for marginal effects, or to test for interaction per se. An alternative strategy is the agnostic approach. This model-free approach is released from classical hypothesis testing procedure, and many data-mining approaches are borrowed to fit the high-dimensionality and large-scale data collections. In the current study, we utilized the regression model to scan for possible interacting effects, in order to allow for the inclusion of matching variables, confounders and effect modifiers.

2. Aims

In this study, we take a genome-wide analysis approach in chromosome six aiming to examine the interactions involving imputed amino acid polymorphisms in HLA proteins and smoking in the development of serologically defined subtypes of rheumatoid arthritis.

The research questions are: 1) Is there any interaction between imputed amino acids in HLA and smoking regarding risk of developing rheumatoid arthritis; 2) Is there any difference in HLA amino acids and smoking interactions between ACPA-positive and ACPA-negative RA cases; 3) Is there any difference in HLA amino acids and smoking interactions if we use different genetic models (dominant, recessive, and co-dominant models); 4) Is there any independent interaction within HLA conditioning on HLA-DRB1 shared epitope (SE) alleles?

3. Methods

3.1 Data

This study was based on the Epidemiological Investigation of Rheumatoid Arthritis (EIRA), which was a large population-based epidemiological study conducted in Sweden. EIRA was a case-control study including newly diagnosed individuals aged 18-70 since May 1996 and still ongoing, and consisting of two sets of participants --- EIRA I and EIRA II. Cases were defined as individuals newly diagnosed with RA according to the American College of Rheumatology (ACR) criteria of 1987, while controls were randomly selected from a national population register to match cases in terms of age, gender and residential area at the time of diagnosis.[23] For EIRA I all the controls were individually matched, and for EIRA II they were probabilistically matched. By this approach, adjusted odds ratios can be interpreted as estimates of incidence rate ratio, since incident cases and population based controls were recruited as soon as a new case occurred in the source population. Details about the study design have been reported elsewhere.[13]

In this study, we included all individuals recruited in EIRA until 2009 comprising two subgroups of the two generations of EIRA studies. The first material included a total number of 3000 individuals. 1921 individuals newly diagnosed with RA were selected as cases and 1079 healthy individuals were selected as controls. The second material included 4337

individuals, among which 2481 were cases and 1856 were controls. Quality control has been done to exclude individuals with for instance disorder sex information or outlying missing genotyping rates. There was no significant difference between individuals that were included and were removed from the study in some important characteristics.

3.2 Biological parameters and imputation

Biological data including ACPA status and chromosome six genotypic sequences were obtained. Serum antibodies were analyzed through using ELISA (Immuno-scan CCPlus, Euro-Diagnostica) to determine ACPA status. 25 U/ml was set as the cut-off for ACPA positivity. Genotyping for HLA sequences was conducted using blood sample through the sequence-specific primer polymerase chain reaction (PCR) method, as described in previous publication.[18] Shared epitope alleles were defined as DRB1*01, DRB1*04, and DRB1*10.[24] These alleles that are associated with ACPA-positive RA were denoted as 'shared epitope', in that they share a common amino acid sequence (^{70}QRRAA^{74}, ^{70}RRRAA^{74}, or ^{70}QKRAA^{74}) within the HLA-DRB1 region.[25]

However, pinpointing the candidate loci within HLA is challenging due to the structural complexity and the extensive linkage disequilibrium (LD) characteristic of the MHC.[26] Hence, we imputed classical HLA alleles and the corresponding amino acid sequences utilizing reference data collected by the Type 1 Diabetes Genetics Consortium (T1DGC) based on European decent. For the first material of 3000 individuals, we used a set of genome-wide dense markers from a genome-wide association study. For the second material of 4337 individuals, we utilized the Immunochip markers, which were concentrated on immunologic interested regions based on observations from different autoimmune diseases such as RA, Multiple sclerosis (MS) and others. If we use capital letters (A) to denote major alleles and use lowercase letters (a) to denote minor alleles, we can obtain probabilities that take the uncertainty in the imputation procedure into account for each of the three genotypes: the homozygous reference genotype (A/A), the heterozygous genotype (A/a), and the homozygous variant genotype (a/a). A threshold was decided to determine the imputed genotypes of each marker. We encoded exhaustive groups of loci with high polymorphisms in the reference panel as biallelic markers. Imputation was performed through using BEAGLE.[27]

Cases and controls were imputed together for each material. Imputation accuracy and genotype rate were assessed.

Data quality assessment and control were carried out among both samples and markers in order to minimized false positives. We used the following criteria to filter out low-quality markers: marker call rates less than 95% in either cases or controls; minor allele frequency (MAF) less than 0.01 in either cases or controls; Hardy-Weinberg equilibrium p-value less than 1×10^{-5} in controls. Meanwhile, we removed subjects with posterior probability of genotype < 0.99, showing evidence of relatedness, showing evidence of possible DNA contamination, and with non-European ancestry. All the quality control procedures were performed in PLINK (version 1.07).[28]

3.3 Smoking and covariates information

Information regarding lifestyle factors including smoking was obtained through self-reported questionnaire. There were five categories for cigarette smoking: never smokers; current smokers; ex-smokers; non-regular smokers; and other types of smokers. Only participants of "never smokers" were considered as "never smoker", and other participants were classified as "ever smokers". Exposures were only considered before the first RA symptoms occurred among cases, and the same time period was applied to the corresponding controls. Baseline characteristics including age, sex, and living area were also collected through questionnaires. Age was collected as continuous, and divided into 10 categories. Living area had 20 categories in the original data, and was classified as either 'Stockholm' or 'Outside Stockholm'.

3.4 Genetic models

Now that genotypes were obtained from imputation, we applied genetic models in which genotypes were observed as alleles, and further related to phenotypes. Given that single major locus was considered as a functional unit, three genetic models were performed to each marker: dominant, recessive, and co-dominant model. Assuming minor alleles (a) represented risk factors for RA, a dominant mode indicates that subjects carrying either one or two copies of minor allele (A/a; a/a) would be classified as present of a specific genetic risk factor. In the

recessive model, only subjects with two copies of minor allele (a/a) would be classified as present of genetic risk factor. Then, in the co-dominant model, each additional copy of minor alleles would be regarded as genetic risk factor, as compared to the homozygous reference group (A/A).

3.5 Statistical analysis

DNA samples and markers that may introduce bias were identified and removed as described above. A chi-square test was performed to evaluate the association of selected HLA allelic genotypes and their corresponding amino acid sequences in relation to ACPA-positive and ACPA-negative RA respectively.

We used logistic regression models to test the multiplicative interaction between HLA allelic genotypes and smoking in relation to the development of RA. Log odds can be calculated for each biallelic marker in the following model:

$$logit(Allele_{\alpha}) = \theta + \beta_{G,\alpha} \cdot G_{\alpha} + \beta_{E,\alpha} \cdot E + \beta_{I,\alpha} \cdot G_{\alpha} \cdot E + \beta_{Cov} \cdot Cov$$

where α indicates the specific allele being tested; $\beta_{G,\alpha}$ is the parameter for allele additive effect, while $\beta_{E,\alpha}$ is the parameter for environmental effect, and $\beta_{I,\alpha}$ for gene-environment interaction effect. G_{α} means the dosage of allele α. E equals 1 in the presence of smoking history, and 0 otherwise. Covariates that were included in the model were age, sex, and living area. The logistic regression model was applied to each biallelic marker. The null hypothesis is that $\beta_{I,\alpha} = 0$. Correction effects were added to the model at later stage.

Then we tested additive interaction by measuring the attributable proportion (AP) together with 95% CI as follows:

$$RERI = RR_{11} - RR_{10} - RR_{01} + 1,$$

$$AP = RERI/RR_{11}$$

RR_{11} represents the relative risk when both genetic and environmental risk factors are present; RR_{10} means the relative risk in the presence of genetic factor while in the absence of environmental factor; and RR_{01} correspondingly means the relative risk in the absence of genetic factor while in the presence of environmental factor. We assume the baseline situation in which both factors are unexposed to be $RR_{00} = 1$. Different genetic models were applied as described above. The null hypothesis is that AP = 0. All the interaction tests were performed

in ACPA-positive and ACPA-negative RA respectively. Adjustment was made for age, sex, and living area. Because so many tests were performed, we corrected for multiple testing through Bonferroni correction. P-values were adjusted using Bonferroni correction, and we used 0.05 divided by the number of markers in the test as the p-value threshold for significance. We excluded markers with cell frequency less than 5, in order to minimize the potential false positive.

HLA-DRB1 shared epitope (SE) alleles that confer susceptibility to RA, are strongly linked with adjacent alleles, due to the unique biochemical structure of HLA class II region (DR, DQ, DP). Hence, we further assessed the independent effects through conditioning the logistic models on shared epitope in HLA-DRB1. The dichotomized status of sheared epitope alleles used a dominant genetic model. Information regarding shared epitope was included as covariate in the model.

Genetic data were analyzed using Haploview 4.2, and R package car.[29,30] Statistical software including R (version 2.14.1) and SAS (version 9.2) were used to perform statistical analysis. AP was calculated by the GEIRA program, a published program for calculating gene-environment and gene-gene interaction.[31]

4 Ethical considerations

This study analyses existing data collected as part of EIRA. A most visualized risk is the physical harm caused in the process of biological data collection. Sera and cells of participants were used for serologic analysis and DNA genotyping. Biological samples were obtained from cases during their first visit to the rheumatology department; while for controls, they were obtained from local health care units. Trained nurses were recruited to perform the work, and during the whole process, standard hygiene was monitored and ensured.

Concerns about data safety should be mentioned. A chain of strict instructions was followed to ensure the data safety. Data were preserved in a way that only limited people had the access to it, and researchers had no access to personal identity numbers, name, address or any other information that could link the characteristics to a certain individual.

Psychological risk come from the questionnaire was limited, since the questions only covered lifestyle questions. Despite that one may answer differently if he or she was accompanied by someone, it was unlikely to cause any psychological or emotional risks. Information in this study is collected using an extensive questionnaire and blood samples. Hence, our application of data in this study will not cause any extra burden for participants.

Informed consents were obtained from all subjects. This study was approved by Regional Ethics Committee of Stockholm (DNR 96-174, 2006/476-31/4).

5 Results

5.1 Baseline and clinical characteristics

After quality control of genotyping data, we imputed binary 8961 SNP markers across MHC, including nucleotides, amino acid residues, and groups of nucleotides or amino acid residues. A total number of 1815 cases (60.5%) in the GWAS material, of which 1101 (36.7%) were APCA-positive RA cases. In the Immunochip material, a total of 2481 cases (57.2%) were used, of which 1590 (36.7%) were APCA-positive cases. A description on characteristics of all participants is provided in Table 1. No significant differences were found among participant categories in terms of sex, age, or living area. Smoking showed an increased risk for rheumatoid arthritis (GWAS material: $p = 0.0007$; Immunochip material: $p < 0.0001$). Shared epitope status was also different depending on subtypes of RA (GWAS material: $p < 0.0001$; Immunochip material: $p < 0.0001$).

5.2 Genotypes and RA association tests

We first wanted to estimate the major genetic effect within HLA region in chromosome 6 in relation to ACPA status of RA. Each allele was used as a unit of analysis. In the GWAS material, strong associations were found between HLA genotypes and ACPA-positive RA, but not ACPA-negative RA. The markers with high associations were concentrated around HLA-DRB1 region (Fig 2a-b). On the other hand, in the Immunochip material, associations were found in both ACPA-positive and ACPA-negative RA cases. These identified markers mainly range from HLA-C to HLA-DRB1 region in chromosome 6 (Fig 2c-d). We used

genotypes with major allele frequencies as reference, and the odds ratios corresponding to genotypes with minor allele frequencies appeared both above and below 1, which indicating protective effects as well as increased risks among genotypes with minor allele frequencies. The most significant association for ACPA-positive RA was observed in HLA-DRB1 position 13 (OR: 2.925, $p = 2.616\times10^{-104}$); while the most significant association for ACPA-negative RA showed in rs9268861 (OR: 1.433, $p = 1.512\times10^{-8}$).

5.3 Multiplicative interactions between genotypes and smoking

When we used the model framework described above to test for interactions in multiplicative scale, no markers were found to interact with smoking in ACPA-positive and ACPA-negative RA after Bonferroni correction, neither in GWAS data nor the Immunochip data (Fig 2).

5.4 Additive interactions between genotypes and smoking

First we tested for additive interactions from the dominant model. In the GWAS data, 103 markers were detected in ACPA-positive RA, among which 45 were amino acid markers corresponding to 17 amino acids in HLA, including 16 amino acids in HLA-DRB1 and 1 amino acid in HLA-DQA1: HLA-DRB1 position -25, -24, -16, 10, 11, 12, 13, 33, 37, 47, 96, 120, 149, 180, 233; HLA-DQA1 position 34 (Table 2, Appendix Table). More markers were identified in the Immunochip data. 237 markers including 58 amino acid markers and 179 SNPs were significant in the dominant model. These amino acids markers correspond to 22 amino acid positions: HLA-DRB1 position -25, -16, 10, 11, 12, 13, 32, 37, 47, 67,70, 73, 74, 96, 120, 149, 233; HLA-DQA1 position 34, 47, 56,76; HLA-DQB1 position 71 (Table 2, Appendix Table). All tests were adjusted for sex, age, and living area, and corrected for multiple testing.

When we applied the recessive model to the GWAS material, 282 markers showed significant among ACPA-positive RA after Bonferroni correction, and 96 amino acid markers were corresponding to as many as 38 amino acids in HLA-DRB1, HLA-DQA1, and HLA-DQB1: HLA-DRB1 position -24, 10, 11, 12, 13, 33, 37, 70, 74, 96, 98, 104, 120, 149, 180, 233; HLA-DQA1 position 26, 40, 47, 50, 51, 53, 56, 76, 187, 215; HLA-DQB1 position -10, 28, 30, 37, 46, 47, 52, 55, 71, 74, 140, 182 (Table 2, Appendix Table). Similarly, recessive

model showed more markers in Immunochip material, especially in DQA1 and DQB1. 56 amino acid markers out of 207 significant markers were identified, corresponding to 34 amino acid positions: HLA-DRB1 position -24, 11, 13, 33, 37, 67, 70, 73, 74, 96, 120, 180; HLA-DQA1 position 26,34, 40, 47, 50, 51, 53, 56, 76, 187; HLA-DQB1 position -10, 28, 30, 37, 46, 47, 52, 55, 66, 67, 71, 74.

And in the co-dominant model, 34 amino acids were identified within HLA among ACPA-positive RA in GWAS material: HLA-DRB1 position -25, -24, -16, 10, 11, 12, 13, 32, 33, 37, 47, 70, 74, 96, 98, 104, 120, 149, 180, 233; HLA-DQA1 position 26, 34, 47, 50, 53, 56, 76, 175, 187, 215; HLA-DQB1 position 30, 55, 140, 182 (Table 2, Appendix Table). In Immunochip material, co-dominant model covered almost all the markers identified in two previous models. A total number of 356 markers including 96 amino acid markers were found, and corresponding to 42 amino acids: HLA-DRB1 position -25, -24,-16, 10, 11, 12, 13, 32, 33, 37, 47, 67, 70, 73, 74, 96, 120, 149, 180, 233; HLA-DQA1 position 26,34, 40, 47, 50, 51, 53, 56, 76, 187; HLA-DQB1 position -10, 28, 30, 37, 46, 47, 52, 55, 66, 67, 71, 74. The highest attributable proportion was observed in HLA-DRB1*0401 (AP: 0.814, 95% CI: 0.630 - 0.998, $p = 3.635\times10^{-18}$), when co-dominant model was applied to the GWAS data.

Interestingly, we observed 3 SNPs only showing effects with ACPA-positive RA when interaction with smoking was considered (rs2235498, rs2844455, rs9277756). That means they were not associated with ACPA-positive RA on their own. We further explored whether any interacting effects with ACPA-negative RA, and no such effects were observed within selected HLA region in this study.

5.5 Conditional tests on HLA-DRB1 shared epitope (SE) alleles

HLA-DRB1 shared epitope information was included in the model as a covariate, so that we were able to assess potential independent effects. Interaction effects from dominant model completely vanished after corrected for shared epitope alleles, and interacting amino acids from recessive and co-dominant models also decreased dramatically.

In the GWAS material, no interacting SNPs remained in the dominant model after the inclusion of ‘any shared epitope’ as a covariate. A total number of 22 amino acid positions were observed in the co-dominant model: HLA-DRB1 position -24, 11, 13, 33, 37, 96, 98,

104, 120, 180; HLA-DQA1 position 26, 47, 50, 53, 56, 76, 187, 215; HLA-DQB1 30, 55, 140, 182. Besides, 12 out of these 22 amino acids were also observed in the recessive model. Similar results were found in the Immunochip material that none interacting SNPs remained in the dominant model. 12 amino acids were observed in the co-dominant model: HLA-DRB1 position -24, 11, 13, 33, 96, 120, 180; HLA-DQA1 position 26, 47, 56, 76, 187, including 5 observed amino acid positions demonstrated in the recessive model (Table 2).

Still, the highest attributable proportion appeared in HLA-DRB1*0401 (AP: 0.807, 95% CI: 0.621 - 0.993, $p = 1.767\times10^{-17}$), even if *0401 per se is defined as part of shared epitope in DRB1. All interacting markers outside SE were also associated with ACPA-positive RA.

6 Discussion

6.1 Main findings

In this study, we confirmed the association between HLA regions and ACPA-positive RA. Genetic effects were observed in both ACPA-positive and ACPA-negative cases from the Immunochip material. The GWAS data showed similar patterns of association within the HLA region, but the genetic effects were comparatively weaker. The finding is consistent with previous association studies, in which HLA-DRB1, HLA-B, and HLA-DPB1 were found to explain most of the of the MHC associations with ACPA-positive RA, while HLA-DRB1 and HLA-B explain associations with ACPA-negative RA.[17,20, 32]

There are three main findings presented in this study. First, we demonstrated a strong additive interaction between amino acids in HLA proteins and smoking in ACPA-positive RA, but not in ACPA-negative RA. This also coincides with previous evidences that ACPA-positive and ACPA-negative RA are distinct diseases with respective unique mechanisms. The SNPs demonstrating highest suggestive associations with ACPA-negative RA were found in chromosome 2 and 7, which is out of the scope of the current study.[33] Second, different subgroups of HLA class II region showed diverse favor in genetic models. Most HLA-DR alleles could be detected by all three genetic models, and co-dominant model almost covers all the HLA-DR alleles. That means alleles in HLA-DR region primarily follow a co-dominant model. On the contrary, dominant model could hardly detect HLA-DQ alleles,

which indicates a recessive tendency, as well as a higher tolerance for heterozygous variants in HLA-DQ region. These observed preferences in genetic models may provide us with insight in potential genetic mechanisms. Third, shared epitope alleles explain most of the interacting effects from heterozygous variants, while HLA class II alleles outside the shared epitope region still have independent interacting effects due to homozygous variants. Additionally, we found three SNPs showing effects with ACPA-positive RA only when considering interaction with smoking. Among those, rs9277756 is located in HLA-DPB2 region; rs2844455 is an intron variant located in zinc finger domain, and may have function in 5'-UTR. It is a novel finding that might give rise to the exploration of translational regulation in HLA class II region.

Although the overall performances are similar in both materials, more markers were found to be associated with RA in the Immunochip data in each genetic model (Fig 2). This is no surprising because the marker selection in the Immunochip data is less random, based on earlier findings and hypothesis suggesting potential immune roles of regions, and with much higher density.

6.2 Strengths and limitations

The current study has several strengths. Almost all the results observed in the GWAS data are also detected in the Immunochip material, which indicates that the false positive findings in this study are limited. We imputed genotypes from a large reference panel, so that despite the missing alleles of potential importance in the original marker set, alleles in the imputed marker set can still be detected. This will increase the ability to identify true biological effects. The EIRA study covers pure Caucasians with European ancestry. Therefore, unlike other genome-wide studies, correction for population stratification is not necessary for our study. Approaches such as principle component analysis could cause problems like over-adjustment, since principle components per se explain the genetic effects, and thus the true effects will be underestimated, especially in the Immunochip data where alleles are picked on a priori basis. The utilization of EIRA sample successfully avoids this contradictory situation. Besides, as a national-based study, EIRA has covered a wide range of geographical areas in Sweden, which allow us to generalize the findings to the Swedish population. Furthermore,

three genetic models were applied in parallel, which maximized the ability to detect underlying interacting effects. It also demonstrated genetic patterns of preferences in different genetic models as described above. Despite diverse methods and strategies that used in gene-environment interaction studies, we used the deviation from additivity of effects (additive interaction). This measurement of additive scale reflects the biological interactions better than methods based on multiplicative scale, and with higher sensitivity (Fig 3-5).

Several limitations have to be mentioned. There underlies a recall bias, since the smoking status was assessed after diagnosis, and this sort of bias could be differential among cases and controls. The dichotomized environmental exposure is rough compared to genetic exposures. We included only pure non-smokers as 'never smokers', and all the rest were defined as 'ever smokers'. Nevertheless, we did not take into account any dosage, duration, or smoking patterns of 'ever smokers'. This misclassification might cause an underestimation of the effects caused by smoking, especially in the light of a previous study where a dose dependent effect of smoking was observed.[34] Similarly, even if serum ACPA was measured as continuous, it was stratified to a binary status. Previous studies suggest heterogeneity among ACPA-negative RA subjects due to lack of a specific test for ACPA-negative RA. For instance, ACPA-positive RA individuals fail to be detected in anti-CCP test will be included as ACPA-negative RA cases, and this can be a source of bias for tests regarding ACPA-negative RA.[32,35] If there were any interacting effects from ACPA-negative RA however did not show in this study, one possible explanation is that the heterogeneity among ACPA-negative RA diluted the effects. Also, we cannot exclude the possibility of gene-gene interactions, since smoking habits might to some extent be genetically driven.[36]

Preceding studies used formulas developed by Hosmer and Lemeshow to calculate a symmetrical confidence interval of AP. The excess risk for disease, however, is usually not symmetrical about the estimate. A rigid application of symmetrical AP would be problematic. For example, the higher bound of 95% confidence interval might exceed 1. Although this type of irrational results did not appear in the current study, we may still have a doubt about the potential bias when measuring confidence interval of AP.

Shared epitope alleles were classified using 2-digit and 4-digit DRB1 classical alleles, as described above. Nevertheless, the imputed markers in our study are largely related with

shared epitope alleles, or even based on them, such as DRB1*0401. When we explored the independent risk conditional on SE, the true effects might be over-adjusted, which is a source of underestimation. Furthermore, we found the highest AP in DRB1*0401 after conditioned on SE, despite *0401 is within DRB1 SE region. This coincides with previously reported results that *0401 has the highest relative risk among SE allele groups.[37] Alternatively, it might be due to the low resolution of 'with any shared epitope' variable. That means we primarily found other alleles than *0401 when subjects were classified. One option to avoid over-adjustment is to stratify for shared epitope status; however it requires larger sample size.

6.3 Interpretations and future thoughts

It has been challenging to explain biological mechanisms of gene-environmental interacting effects on complex diseases. In this study, we applied exhausted biallelic markers of loci with high polymorphisms, aiming to accumulate evidences for potential functional links between smoking and HLA proteins. The current findings infer the role of T-cell responses in the initiation of RA.[35] Given the functional elucidation of immunological tolerance at molecule level, further studies can be focused on how these loci trigger T-cell activation differently in the present or absent of smoking. Alternatively, a deeper understanding of functional mechanisms of interacting effects with smoking might be achieved in the light of information on secondary or higher structure of HLA proteins.

6.4 Public health implications

To date, patients with RA still suffer a higher mortality rate than the general population, and it is related with a great underlying social loss.[38] Approximately one third of RA patients cannot continue their work within two years of the disease onset. What's more, life expectancy has been reduced by 7 years in men and 3 years in women, as a result of systematic complications and RA itself.[1] Conventional therapies aim at clinical remission, however is lacking in molecular remission. Sustained remission would be expected to maintain through novel therapeutics that may provide the promise of higher therapeutic responses and the rebuilt of auto-immunologic tolerance.[39]

This work is a combination of molecular and public health data regarding an investigation of a complex disease which have the potential to find important mechanisms that may offer the perspective of the formation of future prevention strategies. Genetic screening for risk loci among general population is becoming feasible, achieved by the introduction of high-throughput sequencing. As genetic risk and lifestyle information integrated, a revolution of disease prevention is predictable. Even if a genetic background with increased risk is doomed, one can still get personalized advice such as smoking cessation, both before and at the early stage of disease onset.

7 Conclusion

This study is consistent with previous results that smoking interacting with genotypic variants in HLA proteins in relation to the risk of ACPA-positive RA, and the interacting effects remain after controlling for DRB1 shared epitope alleles. We narrowed down the scope to HLA class II region, and further discovered a total number of 48 amino acid positions within HLA-DRB1, DQA1, and DQB1 showing interactions with smoking, 22 remained after correction for SE. We did not observe any evidence for gene-smoking interaction with regard to ACPA-negative RA. The study provides evidence for gene-smoking interaction mechanisms in ACPA-positive RA, so as to bridge the gap from understanding the disease at the nucleotide level to a higher functional level.

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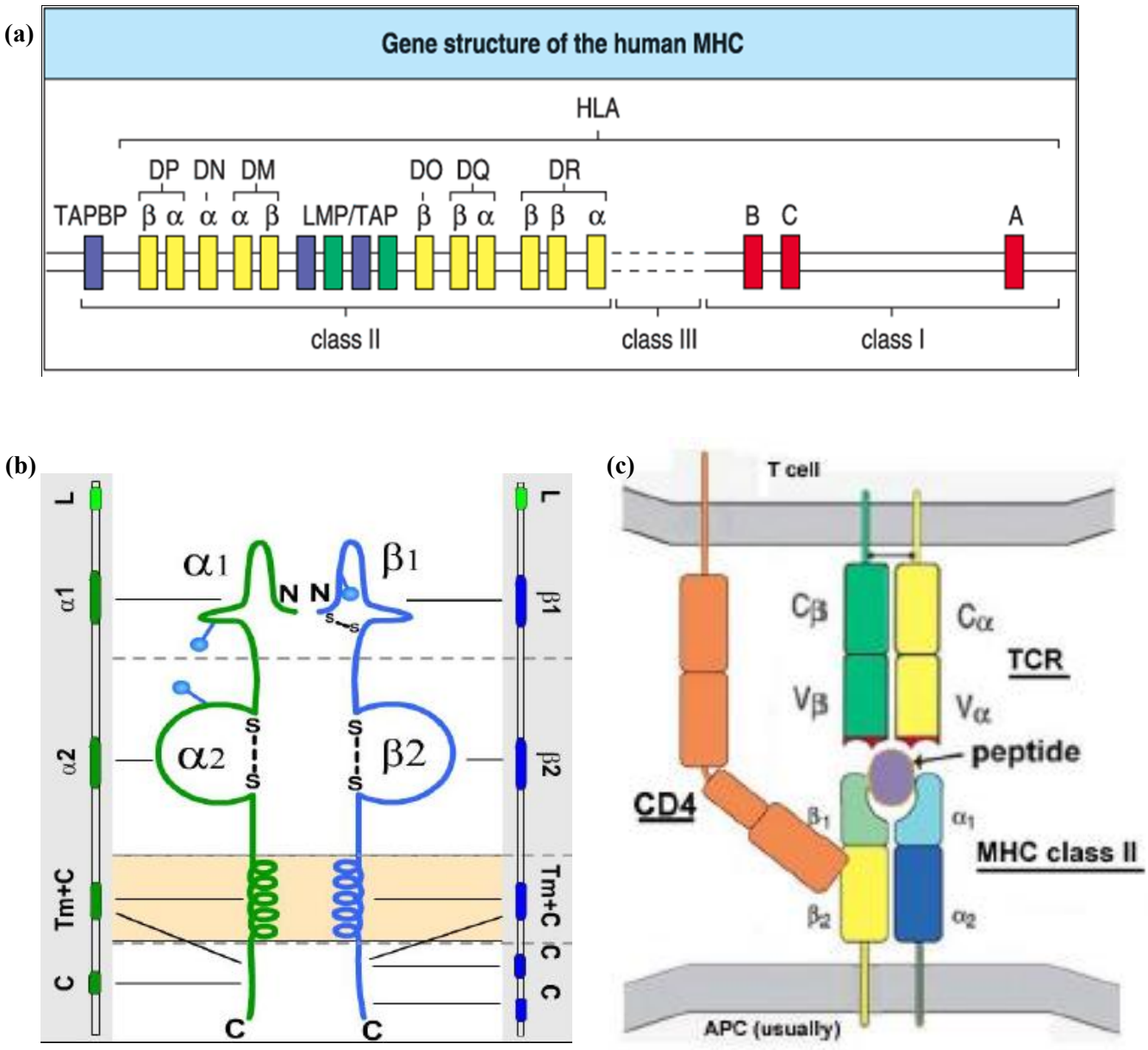
Table 1. Characteristic description of rheumatoid arthritis statue stratified by ACPA

	GWAS data			Immunochip data		
	RA ACPA-positive cases n (%) N=1,101	RA ACPA-negative cases n (%) N=714	RA controls n (%) N=1,079	RA ACPA-positive cases n (%) N=1,590	RA ACPA-negative cases n (%) N=891	RA controls n (%) N=1,856
EIRA						
EIRA I	1,067 (96.9)	699 (97.9)	1,067 (98.9)	1,074 (67.5)	634 (71.2)	971 (52.3)
EIRA II	34 (3.1)	15 (2.1)	0	516 (32.5)	257 (28.8)	885 (47.7)
NA	0	0	12 (1.1)	0	0	0
Sex						
Male	318 (28.9)	212 (29.7)	299 (27.7)	1,119 (70.4)	631 (70.8)	1,370 (73.8)
Female	783 (71.1)	502 (70.3)	768 (71.2)	471 (29.6)	260 (29.2)	486 (26.2)
NA	0	0	12 (1.1)	0	0	0
Age, mean± sd (years)	51.3 ± 12.0	51.5 ± 13.1	52.9 ± 11.6	51.2 ± 12.3	52.9 ± 11.7	54.2 ± 11.1
Living area						
Stockholm	622 (56.5)	377 (52.8)	581 (53.8)	882 (55.5)	480 (53.9)	1016 (54.7)
Outside Stockholm	477 (43.3)	337 (47.2)	485 (44.9)	708 (44.5)	411 (46.1)	840 (45.3)
NA	2 (0.2)	0	13 (1.2)	0	0	0
Cigarette smoking						
Never smokers	279 (25.3)	276 (38.7)	392 (36.3)	430 (27.1)	340 (38.2)	746 (40.2)
Ever smokers	821 (74.6)	434 (60.8)	670 (62.1)	1,064 (66.9)	493 (55.3)	994 (53.6)
NA	1 (0.1)	4 (0.5)	17 (1.6)	96 (6.0)	58 (6.5)	116 (6.2)
Shared epitope						
Any shared epitope	918 (83.4)	393 (55.0)	416 (38.5)	1,236 (77.7)	430 (48.2)	890 (48.0)
None shared epitope	159 (14.4)	314 (44.0)	427 (39.6)	220 (13.9)	374 (42.0)	758 (40.8)
NA	24 (2.2)	7 (1.0)	236 (21.9)	134 (8.4)	87 (9.8)	208 (11.2)

Table 2. Additive interaction comparison across materials

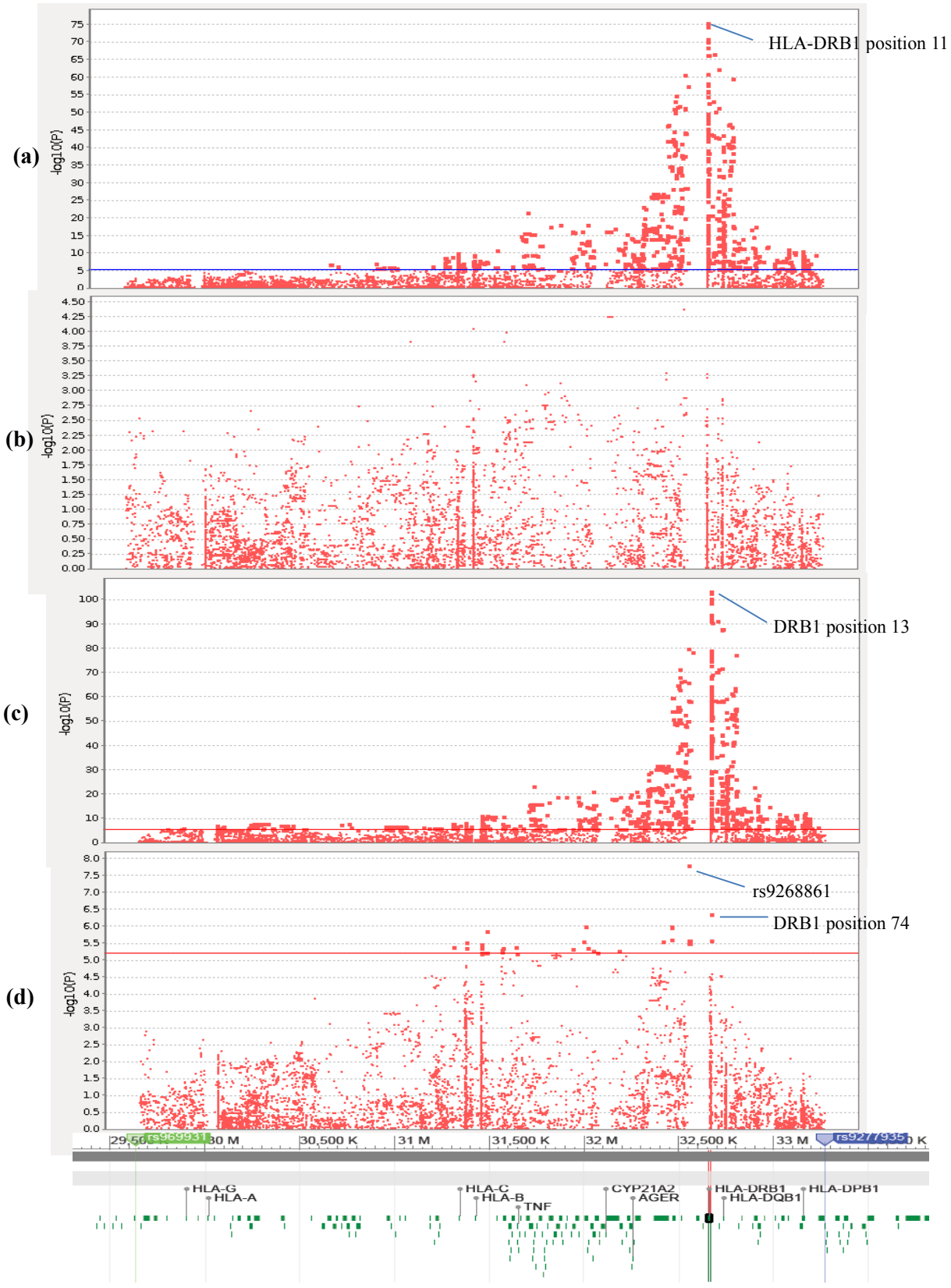
HLA region	Position	Additive interaction in GWAS data		Additive interaction in Immunochip Data	
		Interaction effect only	Condition on SE	Interaction effect only	Condition on SE
DRB1	-25	Yes		Yes	
	-24	Yes	Yes	Yes	Yes
	-16	Yes		Yes	
	10	Yes		Yes	
	11	Yes	Yes	Yes	Yes
	12	Yes		Yes	
	13	Yes	Yes	Yes	Yes
	32	Yes		Yes	
	33	Yes	Yes	Yes	
	37	Yes	Yes	Yes	
	47	Yes		Yes	
	67			Yes	
	70	Yes		Yes	
	73			Yes	
	74	Yes		Yes	
	96	Yes	Yes	Yes	Yes
	98	Yes	Yes		
	104	Yes	Yes		
	120	Yes	Yes	Yes	Yes
	149	Yes		Yes	
	180	Yes	Yes	Yes	Yes
	233	Yes		Yes	
DQA1	26	Yes	Yes	Yes	Yes
	34	Yes		Yes	
	40	Yes		Yes	
	47	Yes	Yes	Yes	Yes
	50	Yes	Yes	Yes	
	51	Yes		Yes	
	53	Yes	Yes	Yes	
	56	Yes	Yes	Yes	Yes
	76	Yes	Yes	Yes	Yes
	175	Yes			
	187	Yes	Yes	Yes	Yes
	215	Yes	Yes		
DQB1	-10	Yes		Yes	
	28	Yes		Yes	
	30	Yes	Yes	Yes	
	37	Yes		Yes	
	46	Yes		Yes	
	47	Yes		Yes	
	52	Yes		Yes	
	55	Yes	Yes	Yes	
	66			Yes	
	67			Yes	
	71	Yes		Yes	
	74	Yes		Yes	
	140	Yes	Yes		
	182	Yes	Yes		

Fig 1. HLA and immune recognition.[40]



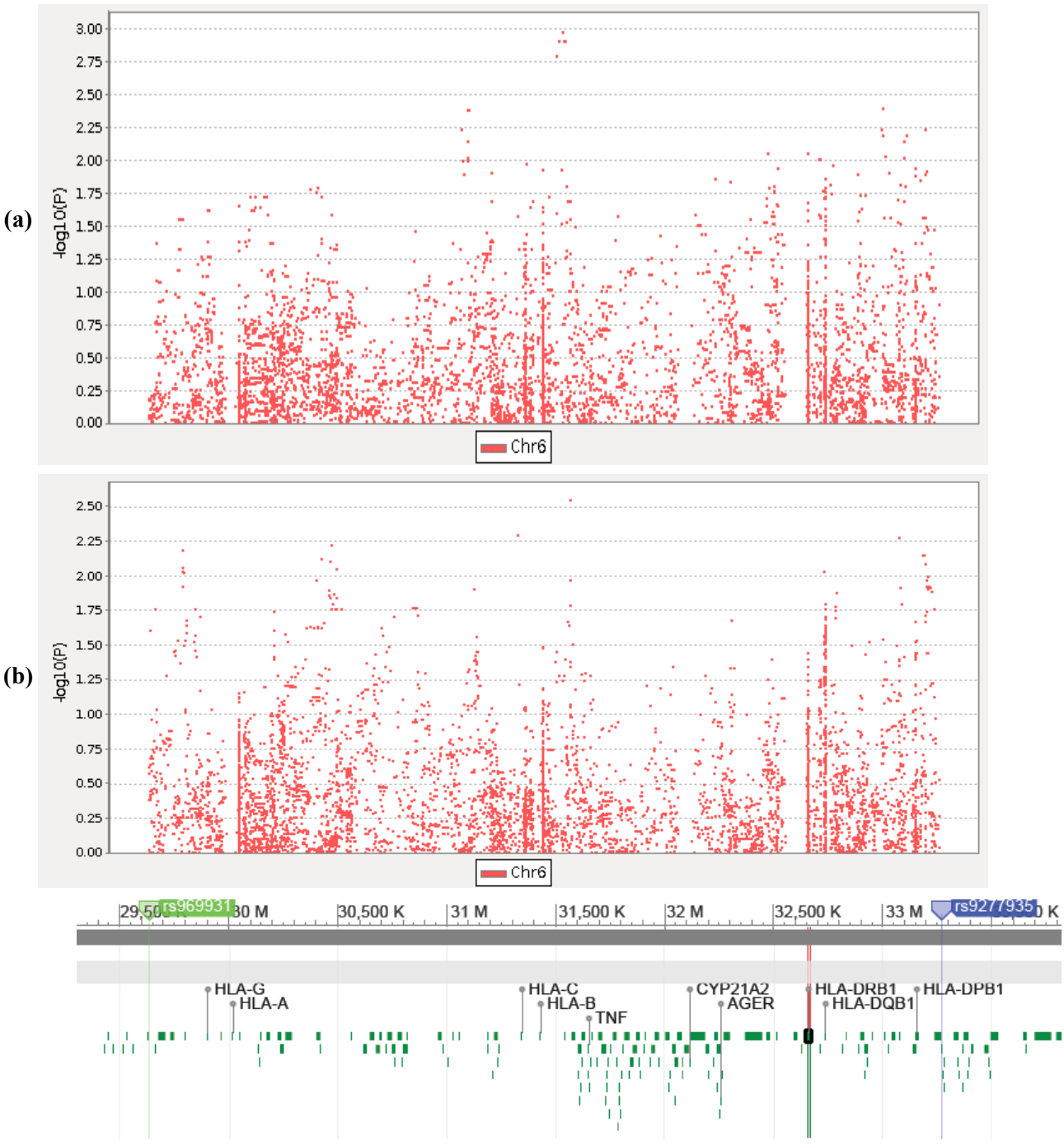
(a) HLA structure. (b) HLA class II molecule structure. (c) The role of HLA class II molecule in T-cell activation.

Fig 2. Association between SNPs within HLA and rheumatoid arthritis.



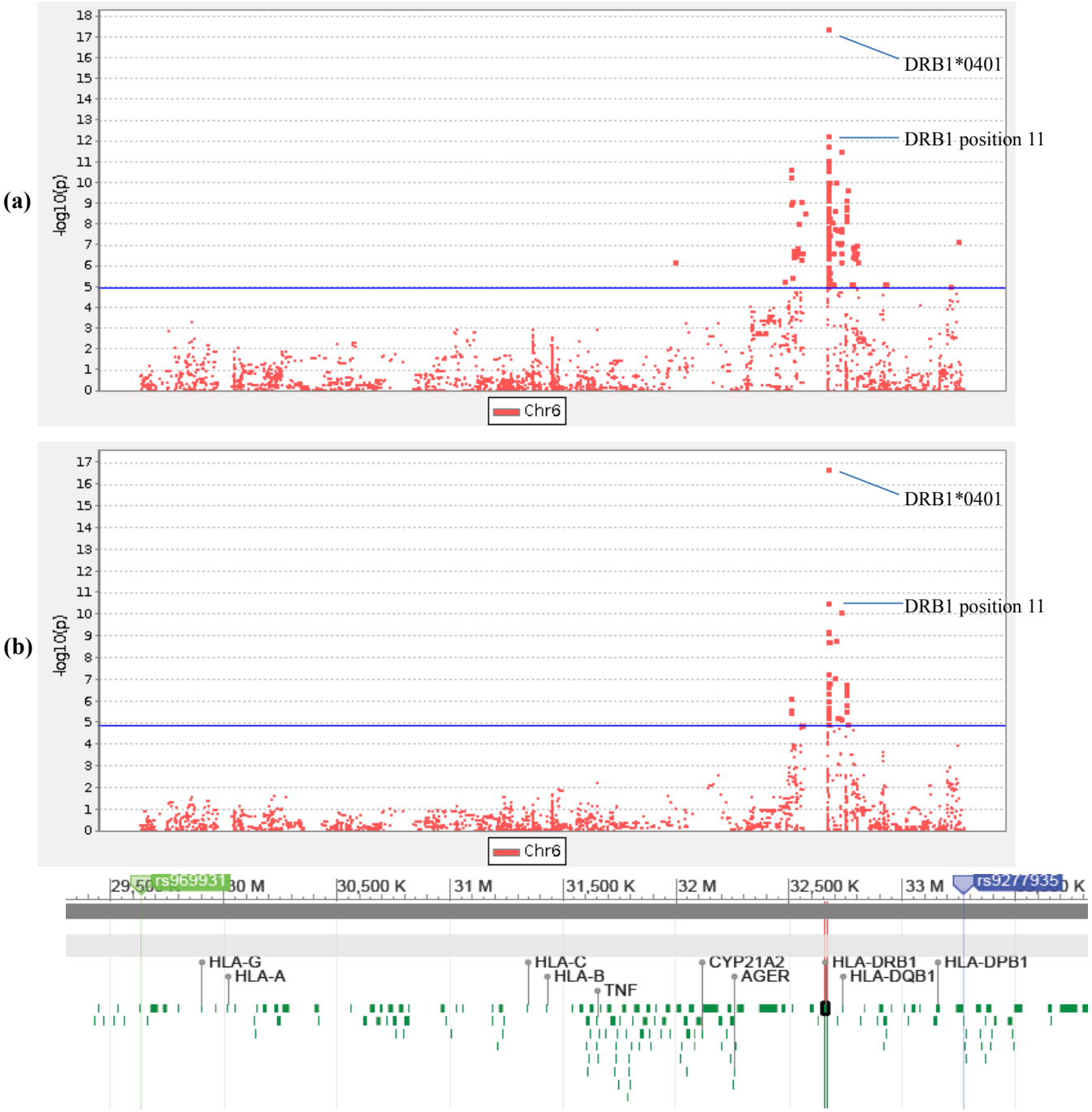
(a) GWAS data association tests for ACPA-positive and (b) APCA-negative RA.
(c) Immunochip data association tests for ACPA-positive and (d) ACPA-negative RA.

Fig 3. Multiplicative interaction between SNPs in HLA and smoking in relation to APCA+ rheumatoid arthritis, adjusted for sex, age, living area.



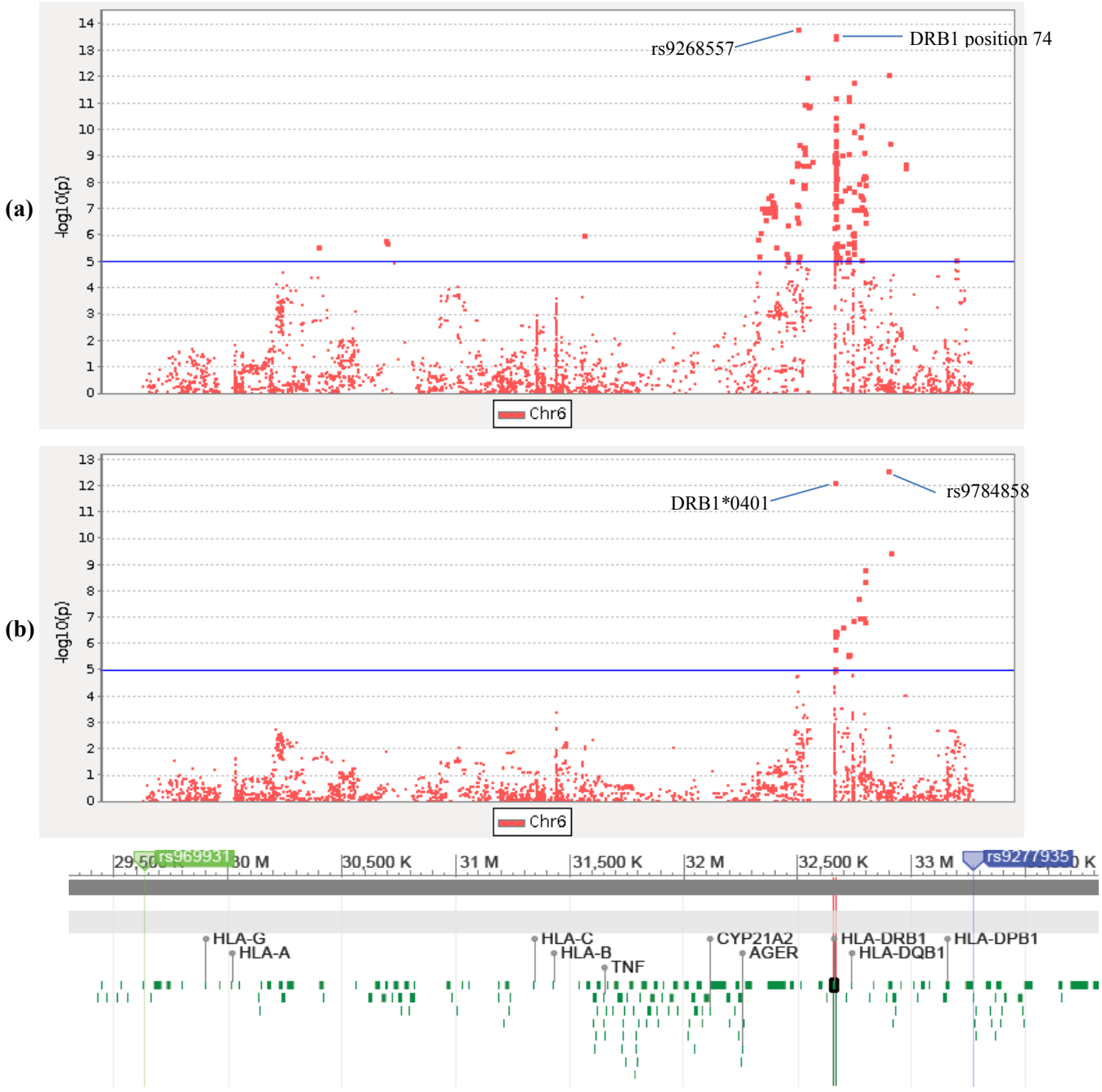
(a) GWAS data interacting effects in multiplicative scale. (b) Immunochip data interacting effects in multiplicative scale.

Fig 4. GWAS material additive interaction between SNPs in HLA and smoking in relation to ACPA-positive rheumatoid arthritis in additive model, adjusted for sex, age, living area.



(a) Interacting effects. (b) Interacting effects after controlling for SE alleles.

Fig 5. Immunochip material additive interaction between SNPs in HLA and smoking in relation to ACPA-positive rheumatoid arthritis in additive model, adjusted for sex, age, living area.



(a) Interacting effects. (b) Interacting effects after controlling for SE alleles.

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Appendix Table. Additive interacting effects from co-dominant model in GWAS material and Immunochip material. For each marker showing interacting effects with smoking in relation to ACPA-positive RA unconditional for shared epitope alleles, we listed the corresponding association test statistics. Allele frequency rates among cases and controls are also listed. Loci with high polymorphisms have been exhaustively grouped. Results from association test and interacting test in GWAS material are presented in Appendix Table a; results from association test and interacting test in Immunochip material are presented in Appendix Table b.

Appendix Table a.

SNP	χ^2	log10(p)	Allele Frequency		AP (95%CI)	log10(p)
			Cases	Controls		
rs2844455	19.7	-5.05	0.2184	0.1654	0.664 (0.404-0.924)	-6.24
rs3117099	75.5	-17.44	0.1417	0.2456	0.462 (0.263-0.660)	-5.29
rs9268528	143.9	-32.43	0.5409	0.3601	0.572 (0.402-0.743)	-10.29
rs9268542	140.2	-31.61	0.5409	0.3624	0.578 (0.408-0.747)	-10.67
rs9268543	247.0	-54.92	0.4201	0.1997	0.664 (0.450-0.877)	-8.97
rs9268556	140.2	-31.61	0.5409	0.3624	0.578 (0.408-0.747)	-10.67
rs2395163	231.4	-51.53	0.4432	0.2257	0.579 (0.334-0.823)	-5.46
rs9268557	176.9	-39.65	0.3215	0.5204	0.510 (0.347-0.672)	-9.11
rs2187818	151.1	-34.01	0.5368	0.3517	0.511 (0.314-0.708)	-6.44
rs9268585	152.0	-34.21	0.5354	0.3499	0.515 (0.32-0.711)	-6.61
rs9268589	148.2	-33.36	0.5359	0.3526	0.516 (0.324-0.710)	-6.80
rs9268606	148.2	-33.36	0.5359	0.3526	0.516 (0.324-0.710)	-6.80
rs7773756	148.2	-33.36	0.5359	0.3526	0.516 (0.324-0.710)	-6.80
rs9268615	146.7	-33.03	0.5436	0.3610	0.506 (0.313-0.70)	-6.53
rs14004	153.2	-34.46	0.5395	0.3531	0.515 (0.320-0.710)	-6.63
rs9268645	147.4	-33.20	0.5354	0.3526	0.515 (0.321-0.708)	-6.71
rs9268657	151.3	-34.05	0.5350	0.3499	0.513 (0.317-0.710)	-6.51
rs7192	167.9	-37.67	0.2675	0.4560	0.452 (0.283-0.620)	-6.82
rs7195	167.9	-37.67	0.2675	0.4560	0.452 (0.283-0.620)	-6.82
rs2213586	167.9	-37.67	0.2675	0.4560	0.452 (0.283-0.620)	-6.82
rs2213585	168.8	-37.86	0.2670	0.4560	0.453 (0.284-0.621)	-6.88
rs2227139	168.8	-37.86	0.2670	0.4560	0.453 (0.284-0.621)	-6.88
rs3763327	168.8	-37.86	0.2670	0.4560	0.453 (0.284-0.621)	-6.88
rs7754768	165.0	-37.03	0.2761	0.4639	0.480 (0.317-0.643)	-8.08
rs9268832	167.5	-37.58	0.2702	0.4588	0.501 (0.341-0.660)	-9.10
rs9268853	198.1	-44.26	0.5041	0.2952	0.537 (0.328-0.745)	-6.36
rs9268923	197.3	-44.08	0.5036	0.2952	0.543 (0.338-0.749)	-6.67

rs2395185	197.3	-44.08	0.5036	0.2952	0.543 (0.338-0.749)	-6.67
rs9268969	197.3	-44.08	0.5036	0.2952	0.543 (0.338-0.749)	-6.67
rs9368726	197.3	-44.08	0.5036	0.2952	0.543 (0.338-0.749)	-6.67
rs9405108	197.3	-44.08	0.5036	0.2952	0.543 (0.338-0.749)	-6.67
rs1964995	258.7	-57.48	0.3392	0.5820	0.515 (0.345-0.684)	-8.54
AA_DRB1_233_32656004_R	165.0	-37.04	0.1948	0.3698	0.464 (0.298-0.630)	-7.35
AA_DRB1_233_32656004_T	190.2	-42.53	0.2216	0.4161	0.495 (0.340-0.650)	-9.44
SNP_DRB1_32656004	165.0	-37.04	0.1948	0.3698	0.464 (0.298-0.630)	-7.35
SNP_DRB1_32656559	316.8	-70.14	0.5799	0.3119	0.557 (0.362-0.752)	-7.67
SNP_DRB1_32657334	260.7	-57.91	0.3383	0.5820	0.512 (0.341-0.683)	-8.36
AA_DRB1_180_32657338_L	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_180_32657338_V	251.0	-55.80	0.4623	0.2335	0.630 (0.418-0.843)	-8.23
SNP_DRB1_32657339	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
SNP_DRB1_32657430	199.2	-44.50	0.2225	0.4222	0.500 (0.347-0.652)	-9.90
AA_DRB1_149_32657431_H	199.2	-44.50	0.2225	0.4222	0.500 (0.347-0.652)	-9.90
AA_DRB1_149_32657431_Q	199.2	-44.50	0.2225	0.4222	0.500 (0.347-0.652)	-9.90
SNP_DRB1_32657475	199.2	-44.50	0.2225	0.4222	0.500 (0.347-0.652)	-9.90
AA_DRB1_120_32657518_N	320.1	-70.85	0.4609	0.2053	0.674 (0.476-0.872)	-10.59
AA_DRB1_120_32657518_S	320.1	-70.85	0.4609	0.2053	0.674 (0.476-0.872)	-10.59
SNP_DRB1_32657518	320.1	-70.85	0.4609	0.2053	0.674 (0.476-0.872)	-10.59
SNP_DRB1_32657526	172.4	-38.67	0.2439	0.4319	0.466 (0.302-0.63)	-7.56
AA_DRB1_104_32657566_A	197.1	-44.04	0.5000	0.2919	0.550 (0.348-0.754)	-6.98
AA_DRB1_104_32657566_S	197.1	-44.04	0.5000	0.2919	0.550 (0.348-0.754)	-6.98
SNP_DRB1_32657567	197.1	-44.04	0.5000	0.2919	0.550 (0.348-0.754)	-6.98
AA_DRB1_98_32657584_E	197.1	-44.04	0.5000	0.2919	0.550 (0.348-0.754)	-6.98
AA_DRB1_98_32657584_K	197.1	-44.04	0.5000	0.2919	0.550 (0.348-0.754)	-6.98
SNP_DRB1_32657585	197.1	-44.04	0.5000	0.2919	0.550 (0.348-0.754)	-6.98
AA_DRB1_96_32657590_H	252.2	-56.06	0.2829	0.5185	0.518 (0.36-0.676)	-9.85
AA_DRB1_96_32657590_HE	195.8	-43.76	0.5767	0.3652	0.576 (0.408-0.743)	-10.83
AA_DRB1_96_32657590_HQ	316.8	-70.14	0.5799	0.3119	0.557 (0.362-0.752)	-7.67
AA_DRB1_96_32657590_Hx	252.2	-56.06	0.2829	0.5185	0.518 (0.36-0.676)	-9.85
AA_DRB1_96_32657590_QY	195.8	-43.76	0.5767	0.3652	0.576 (0.408-0.743)	-10.83
AA_DRB1_96_32657590_Y	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_96_32657590_YE	316.8	-70.14	0.5799	0.3119	0.557 (0.362-0.752)	-7.67
AA_DRB1_96_32657590_Yx	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
SNP_DRB1_32657591_A	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
SNP_DRB1_32657591_G	316.8	-70.14	0.5799	0.3119	0.557 (0.362-0.752)	-7.67
AA_DRB1_74_32659926_A	90.2	-20.67	0.1812	0.3044	0.448 (0.263-0.632)	-5.71

AA_DRB1_74_32659926_AE	77.8	-17.95	0.1512	0.259	0.509 (0.318-0.701)	-6.71
SNP_DRB1_32659926_G	90.2	-20.67	0.1812	0.3044	0.448 (0.263-0.632)	-5.71
SNP_DRB1_32659927	77.8	-17.95	0.1512	0.2590	0.509 (0.318-0.701)	-6.71
SNP_DRB1_32659937	161.4	-36.25	0.1889	0.3605	0.450 (0.294-0.606)	-7.78
AA_DRB1_70_32659938_D	161.4	-36.25	0.1889	0.3605	0.450 (0.294-0.606)	-7.78
AA_DRB1_70_32659938_Q	150.4	-33.86	0.2352	0.4087	0.389 (0.217-0.561)	-5.04
SNP_DRB1_32659939	161.4	-36.25	0.1889	0.3605	0.450 (0.294-0.606)	-7.78
AA_DRB1_47_32660007	198.3	-44.32	0.2906	0.4991	0.429 (0.248-0.610)	-5.46
SNP_DRB1_32660007	198.3	-44.32	0.2906	0.4991	0.429 (0.248-0.610)	-5.46
AA_DRB1_37_32660037_NF	187.7	-42.01	0.1998	0.3888	0.463 (0.300-0.627)	-7.58
AA_DRB1_37_32660037_NL	131.8	-29.78	0.1599	0.3068	0.493 (0.319-0.667)	-7.54
AA_DRB1_37_32660037_NS	115.9	-26.30	0.3996	0.5626	0.488 (0.311-0.666)	-7.20
AA_DRB1_37_32660037_SY	189.2	-42.33	0.2162	0.4092	0.458 (0.294-0.623)	-7.31
AA_DRB1_37_32660037_Y	202.8	-45.29	0.5277	0.3146	0.582 (0.398-0.766)	-9.22
AA_DRB1_37_32660037_YF	121.5	-27.53	0.4160	0.5829	0.516 (0.346-0.686)	-8.60
AA_DRB1_37_32660037_YL	193.2	-43.19	0.5441	0.3350	0.532 (0.334-0.729)	-6.87
SNP_DRB1_32660038_A	131.8	-29.78	0.1599	0.3068	0.493 (0.319-0.667)	-7.54
HLA_DRB1_04	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
HLA_DRB1_0401	197.5	-44.15	0.3088	0.1321	0.814 (0.63-0.998)	-17.44
SNP_DRB1_32660045	245.8	-54.68	0.3174	0.5528	0.500 (0.331-0.669)	-8.19
AA_DRB1_33_32660049	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
SNP_DRB1_32660050	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_32_32660052	123.2	-27.90	0.1771	0.3225	0.462 (0.276-0.648)	-5.94
SNP_DRB1_32660053	123.2	-27.90	0.1771	0.3225	0.462 (0.276-0.648)	-5.94
SNP_DRB1_32660090	217.0	-48.39	0.5213	0.3017	0.560 (0.367-0.753)	-7.90
AA_DRB1_13_32660109_H	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_13_32660109_HF	336.5	-74.42	0.6153	0.3378	0.568 (0.391-0.744)	-9.55
AA_DRB1_13_32660109_HG	220.0	-49.04	0.4805	0.2632	0.582 (0.368-0.796)	-7.01
AA_DRB1_13_32660109_HY	203.2	-45.37	0.4855	0.2757	0.575 (0.372-0.778)	-7.55
AA_DRB1_13_32660109_RH	175.7	-39.37	0.5554	0.3554	0.547 (0.366-0.729)	-8.46
AA_DRB1_13_32660109_SFG	119.9	-27.17	0.3987	0.5644	0.479 (0.297-0.662)	-6.60
AA_DRB1_13_32660109_SG	198.2	-44.28	0.223	0.4222	0.499 (0.347-0.652)	-9.87
AA_DRB1_13_32660109_SR	211.9	-47.28	0.2979	0.5144	0.461 (0.284-0.637)	-6.52
AA_DRB1_13_32660109_SRF	148.4	-33.41	0.5263	0.3434	0.489 (0.278-0.699)	-5.28
AA_DRB1_13_32660109_SRG	259.7	-57.69	0.3388	0.5820	0.511 (0.340-0.682)	-8.31
AA_DRB1_13_32660109_SRY	275.3	-61.09	0.3438	0.5945	0.495 (0.313-0.677)	-7.000
AA_DRB1_13_32660109_SY	210.5	-46.97	0.2280	0.4347	0.482 (0.325-0.639)	-8.75
AA_DRB1_13_32660109_SYF	130.8	-29.57	0.4037	0.5769	0.480 (0.294-0.666)	-6.38

AA_DRB1_13_32660109_SYG	251.1	-55.81	0.2688	0.5023	0.528 (0.377-0.680)	-11.11
SNP_DRB1_32660109_GC	259.7	-57.69	0.3388	0.5820	0.511 (0.340-0.682)	-8.31
SNP_DRB1_32660109_T	203.2	-45.37	0.4855	0.2757	0.575 (0.372-0.778)	-7.55
SNP_DRB1_32660110_A	130.8	-29.57	0.4037	0.5769	0.480 (0.294-0.666)	-6.38
SNP_DRB1_32660110_AC	175.7	-39.37	0.5554	0.3554	0.547 (0.366-0.729)	-8.46
SNP_DRB1_32660110_AT	220.0	-49.04	0.4805	0.2632	0.582 (0.368-0.796)	-7.01
SNP_DRB1_32660110_G	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
SNP_DRB1_32660111	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_12_32660112	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
SNP_DRB1_32660112	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
AA_DRB1_11_32660115_PV	195.8	-43.76	0.5767	0.3652	0.576 (0.408-0.743)	-10.83
AA_DRB1_11_32660115_S	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
AA_DRB1_11_32660115_SD	196.8	-43.99	0.2375	0.4384	0.492 (0.336-0.648)	-9.22
AA_DRB1_11_32660115_SG	251.1	-55.81	0.2688	0.5023	0.528 (0.377-0.680)	-11.11
AA_DRB1_11_32660115_SGD	251.2	-55.84	0.2834	0.5185	0.517 (0.358-0.675)	-9.79
AA_DRB1_11_32660115_SGL	192.2	-42.98	0.5913	0.3814	0.584 (0.426-0.743)	-12.30
AA_DRB1_11_32660115_SL	135.8	-30.66	0.3629	0.5385	0.510 (0.345-0.676)	-8.81
AA_DRB1_11_32660115_SLD	137.7	-31.07	0.3774	0.5547	0.511 (0.342-0.680)	-8.54
AA_DRB1_11_32660115_SP	259.7	-57.69	0.3388	0.5820	0.511 (0.340-0.682)	-8.31
AA_DRB1_11_32660115_SPD	262.2	-58.24	0.3533	0.5982	0.518 (0.344-0.691)	-8.29
AA_DRB1_11_32660115_SPG	336.5	-74.42	0.6153	0.3378	0.568 (0.391-0.744)	-9.55
AA_DRB1_11_32660115_SPL	217.0	-48.39	0.5213	0.3017	0.560 (0.367-0.753)	-7.90
AA_DRB1_11_32660115_V	320.1	-70.85	0.4609	0.2053	0.674 (0.476-0.872)	-10.59
AA_DRB1_11_32660115_VD	309.1	-68.47	0.4755	0.2215	0.669 (0.483-0.854)	-11.75
AA_DRB1_11_32660115_VG	223.0	-49.71	0.5068	0.2854	0.582 (0.389-0.775)	-8.48
AA_DRB1_11_32660115_VL	341.8	-75.59	0.6008	0.3216	0.565 (0.379-0.751)	-8.55
SNP_DRB1_32660115_A	341.8	-75.59	0.6008	0.3216	0.565 (0.379-0.751)	-8.55
SNP_DRB1_32660115_G	259.7	-57.69	0.3388	0.5820	0.511 (0.340-0.682)	-8.31
SNP_DRB1_32660115_GC	336.5	-74.42	0.6153	0.3378	0.568 (0.391-0.744)	-9.55
SNP_DRB1_32660115_GT	262.2	-58.24	0.3533	0.5982	0.518 (0.344-0.691)	-8.29
SNP_DRB1_32660116_A	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
SNP_DRB1_32660116_C	217.0	-48.39	0.5213	0.3017	0.560 (0.367-0.753)	-7.90
SNP_DRB1_32660117	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
AA_DRB1_10_32660118_Q	171.6	-38.47	0.2443	0.4319	0.466 (0.301-0.630)	-7.53
AA_DRB1_10_32660118_Y	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
SNP_DRB1_32660119_A	198.2	-44.28	0.2230	0.4222	0.499 (0.347-0.652)	-9.87
SNP_DRB1_32660119_G	171.6	-38.47	0.2443	0.4319	0.466 (0.301-0.630)	-7.53
SNP_DRB1_32665401	152.1	-34.21	0.2216	0.3939	0.433 (0.255-0.612)	-5.73

AA_DRB1_-16_32665457_A	171.6	-38.47	0.2443	0.4319	0.466 (0.301-0.630)	-7.53
AA_DRB1_-16_32665457_V	144.3	-32.52	0.2166	0.3832	0.422 (0.241-0.602)	-5.32
SNP_DRB1_32665457	171.6	-38.47	0.2443	0.4319	0.466 (0.301-0.630)	-7.53
AA_DRB1_-24_32665481_F	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_-24_32665481_L	236.3	-52.61	0.4673	0.2442	0.630 (0.419-0.842)	-8.31
SNP_DRB1_32665482	298.9	-66.24	0.4396	0.1956	0.679 (0.474-0.885)	-10.04
AA_DRB1_-25_32665484_K	171.6	-38.47	0.2443	0.4319	0.466 (0.301-0.630)	-7.53
AA_DRB1_-25_32665484_R	144.3	-32.52	0.2166	0.3832	0.422 (0.241-0.602)	-5.32
SNP_DRB1_32665484	171.6	-38.47	0.2443	0.4319	0.466 (0.301-0.630)	-7.53
rs477515	196.5	-43.92	0.4900	0.2831	0.582 (0.385-0.780)	-8.12
rs2858867	91.0	-20.83	0.2330	0.3652	0.419 (0.237-0.601)	-5.19
rs482044	102.4	-23.35	0.5436	0.3906	0.496 (0.308-0.684)	-6.63
rs660895	238.7	-53.11	0.4637	0.2400	0.631 (0.425-0.836)	-8.72
rs522308	195.0	-43.58	0.4886	0.2827	0.577 (0.378-0.777)	-7.84
rs521539	238.7	-53.11	0.4637	0.2400	0.631 (0.425-0.836)	-8.72
rs3104413	301.2	-66.73	0.4401	0.1951	0.680 (0.474-0.885)	-10.06
rs6931277	301.2	-66.73	0.4401	0.1951	0.680 (0.474-0.885)	-10.06
rs9271488	192.4	-43.03	0.5005	0.2947	0.552 (0.352-0.752)	-7.17
rs9271588	226.0	-50.36	0.3233	0.5491	0.492 (0.321-0.663)	-7.78
rs3104389	192.4	-43.03	0.5005	0.2947	0.552 (0.352-0.752)	-7.17
rs9272105	114.6	-26.01	0.3828	0.5445	0.481 (0.306-0.656)	-7.11
SNP_DQA1_32713273	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
HLA_DQA1_03	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
HLA_DQA1_0301	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717072	123.0	-27.85	0.5027	0.3369	0.521 (0.324-0.717)	-6.67
SNP_DQA1_32717084	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717108	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717120	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
AA_DQA1_26_32717128	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717128	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717147	150.2	-33.82	0.5236	0.3397	0.508 (0.308-0.708)	-6.19
SNP_DQA1_32717151	230.1	-51.24	0.3302	0.5584	0.494 (0.322-0.667)	-7.69
AA_DQA1_34_32717152	230.1	-51.24	0.3302	0.5584	0.494 (0.322-0.667)	-7.69
SNP_DQA1_32717159	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717190_C	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81
AA_DQA1_47_32717191_Q	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
AA_DQA1_47_32717191_RC	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
AA_DQA1_47_32717191_RQ	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81

SNP_DQA1_32717191	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717199	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
AA_DQA1_50_32717200_L	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717205	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
AA_DQA1_53_32717209_R	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717209	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717217_A	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717217_x	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81
AA_DQA1_56_32717218_R	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
AA_DQA1_56_32717218_x	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81
SNP_DQA1_32717219_A	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717219_x	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81
SNP_DQA1_32717277_C	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81
SNP_DQA1_32717277_G	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
AA_DQA1_76_32717278_L	96.3	-22.00	0.2121	0.3452	0.493 (0.322-0.664)	-7.81
AA_DQA1_76_32717278_V	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32717833	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717986	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32717987_G	150.2	-33.82	0.5236	0.3397	0.508 (0.308-0.708)	-6.19
AA_DQA1_175_32717988_E	150.2	-33.82	0.5236	0.3397	0.508 (0.308-0.708)	-6.19
AA_DQA1_175_32717988_QK	150.2	-33.82	0.5236	0.3397	0.508 (0.308-0.708)	-6.19
SNP_DQA1_32718379	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
AA_DQA1_187_32718380_A	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
AA_DQA1_187_32718380_T	280.6	-62.25	0.4541	0.2146	0.672 (0.484-0.861)	-11.56
SNP_DQA1_32718381	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32718456	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32718459	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
AA_DQA1_215_32718464_F	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
AA_DQA1_215_32718464_L	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQA1_32718465	191.6	-42.85	0.5000	0.2947	0.551 (0.351-0.752)	-7.14
SNP_DQB1_32737124	141.1	-31.81	0.5577	0.3781	0.531 (0.355-0.707)	-8.45
AA_DQB1_182_32737742_N	141.1	-31.81	0.5577	0.3781	0.531 (0.355-0.707)	-8.45
AA_DQB1_182_32737742_S	142.5	-32.12	0.5590	0.3786	0.537 (0.363-0.712)	-8.82
SNP_DQB1_32737742	141.1	-31.81	0.5577	0.3781	0.531 (0.355-0.707)	-8.45
SNP_DQB1_32737837	195.3	-43.65	0.2593	0.4625	0.475 (0.315-0.635)	-8.21
AA_DQB1_140_32737868_A	142.5	-32.12	0.5590	0.3786	0.537 (0.363-0.712)	-8.82
AA_DQB1_140_32737868_T	141.1	-31.81	0.5577	0.3781	0.531 (0.355-0.707)	-8.45
SNP_DQB1_32737869	141.1	-31.81	0.5577	0.3781	0.531 (0.355-0.707)	-8.45

SNP_DQB1_32737933	141.1	-31.81	0.5577	0.3781	0.531 (0.355-0.707)	-8.45
HLA_DQB1_03	174.8	-39.19	0.5336	0.3350	0.561 (0.38-0.743)	-8.89
AA_DQB1_55_32740672_P	174.1	-39.02	0.5332	0.3350	0.559 (0.377-0.741)	-8.73
SNP_DQB1_32740672_G	174.1	-39.02	0.5332	0.3350	0.559 (0.377-0.741)	-8.73
SNP_DQB1_32740722	174.1	-39.02	0.5332	0.3350	0.559 (0.377-0.741)	-8.73
AA_DQB1_30_32740747_Y	81.8	-18.82	0.3347	0.4690	0.522 (0.356-0.688)	-9.19
SNP_DQB1_32740748_A	81.8	-18.82	0.3347	0.4690	0.522 (0.356-0.688)	-9.19
SNP_DQB1_32742296_C	161.5	-36.27	0.1730	0.3411	0.500 (0.346-0.654)	-9.67
rs9275141	113.3	-25.74	0.4024	0.5635	0.436 (0.246-0.626)	-5.16
rs4642516	113.3	-25.74	0.4024	0.5635	0.436 (0.246-0.626)	-5.16
rs9275224	208.3	-46.48	0.2761	0.4884	0.454 (0.285-0.622)	-6.87
rs2858324	182.7	-40.9	0.2448	0.4388	0.436 (0.268-0.604)	-6.47
rs5000634	143.1	-32.25	0.5609	0.3800	0.500 (0.315-0.685)	-6.93
rs6457617	209.1	-46.66	0.2816	0.4949	0.457 (0.288-0.626)	-6.95
rs6457620	209.1	-46.66	0.2816	0.4949	0.457 (0.288-0.626)	-6.95
rs7745040	143.1	-32.25	0.5609	0.3800	0.500 (0.315-0.685)	-6.93
rs2647012	181.9	-40.72	0.2448	0.4384	0.440 (0.273-0.606)	-6.65
rs1612904	161.5	-36.27	0.2334	0.4133	0.441 (0.274-0.607)	-6.67
rs2856717	178.7	-40.04	0.2443	0.4361	0.435 (0.267-0.603)	-6.43
rs9275516	206.1	-46.02	0.2688	0.4791	0.456 (0.288-0.624)	-7.00
rs6932517	206.0	-46.00	0.2693	0.4796	0.448 (0.278-0.617)	-6.65
rs9275596	161.5	-36.27	0.2334	0.4133	0.429 (0.261-0.598)	-6.22
rs3819721	75.9	-17.52	0.3915	0.2674	0.535 (0.301-0.768)	-5.14
rs9357155	37.7	-9.08	0.2134	0.1423	0.693 (0.39-0.995)	-5.14
rs9277756	16.2	-4.25	0.2148	0.1668	0.653 (0.365-0.941)	-5.05
rs2235498	8.4	-2.42	0.2003	0.1664	0.706 (0.451-0.962)	-7.23

Appendix Table b.

SNP	χ^2	log10(p)	Allele Frequency		AP (95%CI)	log10(p)
			Cases	Controls		
rs261945	22.1	-5.58	0.4965	0.4399	0.444 (0.258-0.629)	-5.57
rs1264423	30.7	-7.53	0.3877	0.4539	0.447 (0.265-0.629)	-5.81
rs1264419	31.0	-7.60	0.3874	0.4539	0.443 (0.261-0.625)	-5.72
rs2844503	44.9	-10.68	0.5324	0.4515	0.452 (0.271-0.633)	-6.01
rs412657	95.4	-21.81	0.2717	0.3828	0.390 (0.232-0.549)	-5.87
rs6936204	114.5	-26.00	0.2503	0.3704	0.380 (0.215-0.544)	-5.21
rs3130320	129.0	-29.16	0.2610	0.3901	0.390 (0.235-0.545)	-6.10
rs3115569	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs9268055	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3115563	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3132928	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3096681	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3132931	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs3115560	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3096673	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3096674	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs3132945	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3096677	96.8	-22.12	0.1463	0.241	0.449 (0.283-0.615)	-6.94
rs3115557	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs1559873	97.8	-22.34	0.1487	0.2466	0.441 (0.273-0.608)	-6.59
rs1559874	96.0	-21.93	0.1469	0.2411	0.450 (0.283-0.616)	-6.94
rs3130340	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3115553	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs9268125	99.7	-22.74	0.1465	0.2427	0.453 (0.292-0.615)	-7.43
rs9268131	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs9268135	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs9268137	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs7751896	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs6935269	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs3749966	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs7750783	100.4	-22.91	0.1466	0.2433	0.452 (0.292-0.612)	-7.54
rs6909427	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs7775332	98.8	-22.55	0.1535	0.2505	0.442 (0.281-0.603)	-7.14
rs7742654	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs3864299	92.5	-21.17	0.1525	0.2460	0.451 (0.288-0.613)	-7.28

rs3864300	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs9268165	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs9268166	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs9268167	98.6	-22.51	0.1538	0.2508	0.441 (0.279-0.602)	-7.07
rs6457536	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs9268176	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs7341328	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs9268192	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs9268197	97.3	-22.24	0.1462	0.2411	0.448 (0.282-0.615)	-6.91
rs9268198	91.8	-21.02	0.1528	0.2460	0.450 (0.288-0.612)	-7.25
rs3864302	97.9	-22.36	0.1541	0.2508	0.453 (0.290-0.617)	-7.25
rs9268202	96.8	-22.13	0.1462	0.2408	0.452 (0.285-0.620)	-6.90
rs6934429	91.3	-20.92	0.1528	0.2457	0.454 (0.290-0.617)	-7.24
rs6934776	96.8	-22.13	0.1462	0.2408	0.452 (0.285-0.620)	-6.90
rs6939410	96.4	-22.02	0.1462	0.2406	0.449 (0.280-0.618)	-6.74
rs1018434	88.0	-20.19	0.1544	0.2457	0.461 (0.293-0.630)	-7.10
rs1018433	90.8	-20.81	0.1528	0.2454	0.451 (0.286-0.616)	-7.09
rs1018430	97.6	-22.29	0.1538	0.2503	0.441 (0.278-0.605)	-6.91
rs9268212	96.4	-22.02	0.1462	0.2406	0.449 (0.280-0.618)	-6.74
rs9268213	90.8	-20.81	0.1528	0.2454	0.451 (0.286-0.616)	-7.09
rs9268215	90.8	-20.81	0.1528	0.2454	0.451 (0.286-0.616)	-7.09
rs6909790	90.8	-20.81	0.1528	0.2454	0.451 (0.286-0.616)	-7.09
rs6915455	90.8	-20.81	0.1528	0.2454	0.451 (0.286-0.616)	-7.09
rs521828	92.6	-21.2	0.1767	0.2745	0.431 (0.251-0.611)	-5.56
rs3129924	67.9	-15.77	0.1182	0.1907	0.443 (0.254-0.633)	-5.33
rs3129925	67.9	-15.77	0.1182	0.1907	0.443 (0.254-0.633)	-5.33
rs3129926	67.9	-15.77	0.1182	0.1907	0.443 (0.254-0.633)	-5.33
rs2143461	67.9	-15.77	0.1182	0.1907	0.443 (0.254-0.633)	-5.33
rs3129939	67.9	-15.77	0.1182	0.1907	0.443 (0.254-0.633)	-5.33
rs3129942	80.3	-18.48	0.161	0.2489	0.426 (0.238-0.615)	-5.04
rs3129943	73.5	-16.99	0.1698	0.2551	0.435 (0.246-0.624)	-5.19
rs2050190	106.0	-24.12	0.1984	0.3071	0.417 (0.256-0.579)	-6.41
rs3117099	121.6	-27.55	0.1415	0.2478	0.464 (0.306-0.621)	-8.07
rs3129963	133.7	-30.19	0.1123	0.2169	0.475 (0.302-0.647)	-7.18
rs9268528	178.3	-39.95	0.5327	0.3723	0.451 (0.281-0.621)	-6.73
rs6930571	127.6	-28.87	0.1097	0.2109	0.518 (0.349-0.686)	-8.77
rs9268530	126.0	-28.51	0.1097	0.2101	0.517 (0.349-0.686)	-8.74
rs9268534	126.0	-28.51	0.1097	0.2101	0.517 (0.349-0.686)	-8.74

rs6908065	124.5	-28.19	0.1094	0.2091	0.518 (0.348-0.687)	-8.67
rs6930933	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs3135382	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs2001097	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs3135380	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs9268542	171.7	-38.51	0.5330	0.3755	0.444 (0.274-0.615)	-6.51
rs3135378	124.8	-28.25	0.1104	0.2104	-1.13 (-1.63--0.631)	-5.04
rs3135376	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs3135375	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs3135374	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs3135372	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs2187820	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs9268556	171.7	-38.51	0.5330	0.3755	0.444 (0.274-0.615)	-6.51
rs2395161	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs2395162	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs2395164	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs2213580	125.7	-28.45	0.1101	0.2104	0.517 (0.348-0.686)	-8.70
rs9268557	221.8	-49.43	0.3233	0.5008	0.511 (0.381-0.641)	-13.85
rs3135363	132.5	-29.94	0.1739	0.2923	0.464 (0.295-0.633)	-7.12
rs3135356	123.1	-27.87	0.1097	0.2088	-1.112 (-1.592--0.631)	-5.23
rs3135351	123.1	-27.87	0.1097	0.2088	-1.112 (-1.592--0.631)	-5.23
rs2395171	123.7	-28.00	0.1104	0.2099	0.514 (0.353-0.674)	-9.47
rs3135393	124.5	-28.19	0.1119	0.2123	0.474 (0.310-0.638)	-7.84
rs3129884	124.3	-28.13	0.1129	0.2134	0.475 (0.312-0.639)	-7.91
rs3129887	131.3	-29.67	0.1123	0.2158	0.465 (0.305-0.624)	-7.95
rs8084	236.8	-52.72	0.2868	0.4677	0.427 (0.287-0.567)	-8.69
rs2239806	124.3	-28.13	0.1129	0.2134	0.475 (0.312-0.639)	-7.91
rs2239805	124.5	-28.19	0.1119	0.2123	0.474 (0.310-0.638)	-7.84
rs7192	217.9	-48.60	0.2667	0.4378	0.434 (0.297-0.570)	-9.33
rs7195	216.3	-48.23	0.2673	0.4378	0.433 (0.296-0.570)	-9.26
rs1051336	124.3	-28.13	0.1129	0.2134	0.475 (0.312-0.639)	-7.91
rs1041885	124.3	-28.13	0.1129	0.2134	0.475 (0.312-0.639)	-7.91
rs2213586	217.1	-48.41	0.2670	0.4378	0.434 (0.297-0.570)	-9.33
rs2213585	217.1	-48.41	0.2670	0.4378	0.434 (0.297-0.570)	-9.33
rs2227139	217.1	-48.41	0.2670	0.4378	0.434 (0.297-0.570)	-9.33
rs3763327	215.6	-48.09	0.2673	0.4375	0.431 (0.294-0.568)	-9.13
rs3129890	163.1	-36.62	0.1667	0.2980	0.488 (0.348-0.629)	-11.00
rs3129891	128.6	-29.08	0.1264	0.2325	0.490 (0.320-0.659)	-7.84

rs7754768	225.7	-50.28	0.2733	0.4483	0.457 (0.326-0.589)	-10.98
rs9268832	224.7	-50.07	0.2695	0.4437	0.472 (0.342-0.601)	-12.03
rs9268856	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9268861	120.6	-27.33	0.1377	0.2427	0.498 (0.335-0.662)	-8.65
rs9268862	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs4428528	170.2	-38.18	0.1638	0.2977	0.476 (0.338-0.614)	-10.88
rs7766843	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs7747521	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9268878	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9268885	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9268976	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9268977	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9268980	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs9269043	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs2157338	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs2187823	171.1	-38.37	0.1635	0.2977	0.477 (0.340-0.615)	-10.95
rs1964995	355.7	-78.62	0.3365	0.5636	0.450 (0.304-0.596)	-8.80
AA_DRB1_233_32656004_R	232.0	-51.67	0.1891	0.3551	0.368 (0.225-0.512)	-6.33
AA_DRB1_233_32656004_T	273.4	-60.68	0.2214	0.4089	0.420 (0.285-0.554)	-9.03
SNP_DRB1_32656004	231.0	-51.45	0.1929	0.3586	0.394 (0.251-0.536)	-7.23
SNP_DRB1_32656559	419.4	-92.47	0.5772	0.3311	0.516 (0.349-0.684)	-8.80
SNP_DRB1_32657334	354.8	-78.43	0.3370	0.5642	0.452 (0.306-0.597)	-8.89
AA_DRB1_180_32657338_L	419.9	-92.58	0.4329	0.2031	0.618 (0.417-0.819)	-8.80
AA_DRB1_180_32657338_V	329.4	-72.90	0.4527	0.2439	0.511 (0.298-0.724)	-5.60
SNP_DRB1_32657339	419.1	-92.41	0.4329	0.2034	0.618 (0.417-0.819)	-8.81
SNP_DRB1_32657430	274.4	-60.90	0.2240	0.4121	0.420 (0.285-0.554)	-9.06
AA_DRB1_149_32657431_H	272.6	-60.51	0.2218	0.4095	0.419 (0.285-0.553)	-9.04
AA_DRB1_149_32657431_Q	279.9	-62.10	0.2216	0.411	0.419 (0.285-0.552)	-9.08
SNP_DRB1_32657475	274.4	-60.90	0.2240	0.4121	0.420 (0.285-0.554)	-9.06
AA_DRB1_120_32657518_N	455.7	-100.40	0.4517	0.2104	0.579 (0.371-0.788)	-7.26
AA_DRB1_120_32657518_S	454.0	-100.00	0.4522	0.2102	0.581 (0.372-0.789)	-7.31
SNP_DRB1_32657518	454.9	-100.20	0.4518	0.2107	0.580 (0.371-0.788)	-7.27
SNP_DRB1_32657526	233.1	-51.89	0.2440	0.4186	0.420 (0.279-0.560)	-8.33
AA_DRB1_96_32657590_H	343.6	-75.99	0.2867	0.5079	0.442 (0.297-0.586)	-8.69
AA_DRB1_96_32657590_HE	280.4	-62.21	0.5661	0.3634	0.412 (0.233-0.592)	-5.17
AA_DRB1_96_32657590_HQ	417.7	-92.10	0.5787	0.3324	0.516 (0.348-0.684)	-8.78
AA_DRB1_96_32657590_Hx	344.1	-76.10	0.2884	0.5095	0.437 (0.291-0.583)	-8.38
AA_DRB1_96_32657590_Y	420.4	-92.69	0.4331	0.2033	0.618 (0.418-0.819)	-8.83

AA_DRB1_96_32657590_YE	425.9	-93.89	0.5799	0.3312	0.508 (0.338-0.678)	-8.33
AA_DRB1_96_32657590_Yx	419.6	-92.54	0.4342	0.2039	0.618 (0.418-0.819)	-8.83
SNP_DRB1_32657591_A	413.8	-91.27	0.4306	0.2023	0.615 (0.413-0.818)	-8.62
SNP_DRB1_32657591_G	418.3	-92.25	0.5769	0.3311	0.516 (0.348-0.683)	-8.77
AA_DRB1_74_32659926_AE	131.6	-29.73	0.1453	0.2578	0.546 (0.405-0.686)	-13.59
AA_DRB1_74_32659926_AL	94.4	-21.59	0.1586	0.2578	0.498 (0.332-0.664)	-8.36
AA_DRB1_74_32659926_AQ	81.9	-18.85	0.1343	0.2214	0.468 (0.297-0.639)	-7.10
AA_DRB1_74_32659926_RQ	93.1	-21.31	0.1249	0.2135	0.492 (0.322-0.662)	-7.87
SNP_DRB1_32659926_CT	91.2	-20.88	0.1610	0.2589	0.499 (0.331-0.666)	-8.29
SNP_DRB1_32659927	127.9	-28.94	0.1474	0.2589	0.547 (0.405-0.688)	-13.50
AA_DRB1_73_32659929	93.1	-21.31	0.1249	0.2135	0.492 (0.322-0.662)	-7.87
SNP_DRB1_32659929	93.1	-21.31	0.1249	0.2135	0.492 (0.322-0.662)	-7.87
SNP_DRB1_32659937	226.7	-50.51	0.1902	0.3568	0.427 (0.291-0.562)	-9.14
AA_DRB1_70_32659938_D	226.7	-50.51	0.1902	0.3568	0.427 (0.291-0.562)	-9.14
AA_DRB1_70_32659938_Q	198.5	-44.35	0.2369	0.3994	0.414 (0.270-0.557)	-7.76
SNP_DRB1_32659939	226.7	-50.51	0.1902	0.3568	0.427 (0.291-0.562)	-9.14
AA_DRB1_67_32659947_I	186.8	-41.79	0.2344	0.3916	0.409 (0.267-0.551)	-7.81
AA_DRB1_67_32659947_L	276.1	-61.28	0.3103	0.5133	0.451 (0.308-0.595)	-9.14
SNP_DRB1_32659948_G	276.1	-61.28	0.3103	0.5133	0.451 (0.308-0.595)	-9.14
SNP_DRB1_32659948_T	186.8	-41.79	0.2344	0.3916	0.409 (0.267-0.551)	-7.81
AA_DRB1_47_32660007	261.0	-57.99	0.2912	0.4833	0.371 (0.218-0.525)	-5.66
SNP_DRB1_32660007	261.0	-57.99	0.2912	0.4833	0.371 (0.218-0.525)	-5.66
AA_DRB1_37_32660037_N	169.0	-37.91	0.1506	0.2836	0.451 (0.295-0.607)	-7.81
AA_DRB1_37_32660037_NF	243.6	-54.19	0.2093	0.3864	0.465 (0.333-0.598)	-11.22
AA_DRB1_37_32660037_NL	172.0	-38.57	0.1668	0.3050	0.428 (0.275-0.580)	-7.43
AA_DRB1_37_32660037_SY	255.9	-56.88	0.2228	0.4067	0.441 (0.304-0.578)	-9.58
AA_DRB1_37_32660037_Y	289.1	-64.11	0.5114	0.3057	0.463 (0.272-0.653)	-5.69
AA_DRB1_37_32660037_YL	270.2	-60.00	0.5276	0.3276	0.449 (0.263-0.635)	-5.64
SNP_DRB1_32660038_A	176.5	-39.55	0.1644	0.3037	0.428 (0.277-0.580)	-7.53
SNP_DRB1_32660038_T	169.0	-37.91	0.1506	0.2836	0.451 (0.295-0.607)	-7.81
HLA_DRB1_04	419.4	-92.48	0.4339	0.2040	0.619 (0.418-0.819)	-8.85
HLA_DRB1_0401	257.7	-57.27	0.2908	0.1294	0.711 (0.466-0.956)	-7.91
SNP_DRB1_32660045	338.4	-74.84	0.3222	0.5472	0.475 (0.335-0.616)	-10.48
AA_DRB1_33_32660049	419.1	-92.42	0.4331	0.2038	0.619 (0.418-0.819)	-8.85
SNP_DRB1_32660050	419.1	-92.42	0.4331	0.2038	0.619 (0.418-0.819)	-8.85
AA_DRB1_32_32660052	158.0	-35.51	0.1813	0.3159	0.424 (0.265-0.583)	-6.74
SNP_DRB1_32660053	157.6	-35.43	0.1813	0.3157	0.422 (0.263-0.582)	-6.67
AA_DRB1_13_32660109_H	419.1	-92.42	0.4331	0.2038	0.619 (0.418-0.819)	-8.85

AA_DRB1_13_32660109_HF	470.4	-103.60	0.6172	0.3553	0.506 (0.349-0.663)	-9.61
AA_DRB1_13_32660109_HG	290.4	-64.40	0.4751	0.2737	0.486 (0.278-0.694)	-5.35
AA_DRB1_13_32660109_HY	277.4	-61.56	0.4797	0.2844	0.457 (0.258-0.656)	-5.17
AA_DRB1_13_32660109_RH	250.3	-55.65	0.5476	0.3570	0.415 (0.233-0.597)	-5.10
AA_DRB1_13_32660109_S	212.1	-47.32	0.1798	0.3373	0.409 (0.263-0.556)	-7.34
AA_DRB1_13_32660109_SG	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90
AA_DRB1_13_32660109_SR	267.9	-59.48	0.2957	0.4925	0.425 (0.280-0.569)	-8.07
AA_DRB1_13_32660109_SRG	354.1	-78.27	0.3386	0.5660	0.447 (0.299-0.595)	-8.51
AA_DRB1_13_32660109_SRY	358.6	-79.26	0.3424	0.5741	0.485 (0.340-0.631)	-10.18
AA_DRB1_13_32660109_SY	279.3	-61.98	0.2264	0.4192	0.445 (0.311-0.580)	-10.06
AA_DRB1_13_32660109_SYG	354.3	-78.31	0.2706	0.4932	0.443 (0.304-0.582)	-9.42
SNP_DRB1_32660109_G	212.1	-47.32	0.1798	0.3373	0.409 (0.263-0.556)	-7.34
SNP_DRB1_32660109_GC	354.1	-78.27	0.3386	0.5660	0.447 (0.299-0.595)	-8.51
SNP_DRB1_32660109_T	277.4	-61.56	0.4797	0.2844	0.457 (0.258-0.656)	-5.17
SNP_DRB1_32660110_AC	245.0	-54.50	0.5441	0.3561	0.412 (0.229-0.594)	-5.00
SNP_DRB1_32660110_AT	283.4	-62.86	0.4708	0.2725	0.488 (0.281-0.695)	-5.43
SNP_DRB1_32660110_G	419.1	-92.42	0.4331	0.2038	0.619 (0.418-0.819)	-8.85
SNP_DRB1_32660111	419.1	-92.42	0.4331	0.2038	0.619 (0.418-0.819)	-8.85
AA_DRB1_12_32660112	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90
SNP_DRB1_32660112	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90
AA_DRB1_11_32660115_PV	282.0	-62.57	0.5665	0.3642	0.411 (0.232-0.590)	-5.16
AA_DRB1_11_32660115_S	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90
AA_DRB1_11_32660115_SD	264.2	-58.68	0.2416	0.4286	0.418 (0.281-0.555)	-8.65
AA_DRB1_11_32660115_SG	354.3	-78.31	0.2706	0.4932	0.443 (0.304-0.582)	-9.42
AA_DRB1_11_32660115_SGD	344.7	-76.21	0.2881	0.5092	0.440 (0.296-0.585)	-8.64
AA_DRB1_11_32660115_SGL	282.1	-62.58	0.5822	0.3789	0.409 (0.236-0.582)	-5.43
AA_DRB1_11_32660115_SP	354.1	-78.27	0.3386	0.566	0.447 (0.299-0.595)	-8.51
AA_DRB1_11_32660115_SPD	348.1	-76.96	0.3561	0.5820	0.450 (0.297-0.602)	-8.14
AA_DRB1_11_32660115_SPG	466.3	-102.70	0.6148	0.3535	0.508 (0.351-0.666)	-9.58
AA_DRB1_11_32660115_V	454.7	-100.20	0.4518	0.2109	0.580 (0.371-0.789)	-7.28
AA_DRB1_11_32660115_VD	448.6	-98.83	0.4691	0.2268	0.575 (0.382-0.768)	-8.28
AA_DRB1_11_32660115_VL	467.3	-102.90	0.5999	0.3394	0.498 (0.329-0.666)	-8.18
SNP_DRB1_32660115_A	467.3	-102.90	0.5999	0.3394	0.498 (0.329-0.666)	-8.18
SNP_DRB1_32660115_G	354.1	-78.27	0.3386	0.5660	0.447 (0.299-0.595)	-8.51
SNP_DRB1_32660115_GC	466.3	-102.70	0.6148	0.3535	0.508 (0.351-0.666)	-9.58
SNP_DRB1_32660115_GT	348.1	-76.96	0.3561	0.5820	0.450 (0.297-0.602)	-8.14
SNP_DRB1_32660116_A	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90
SNP_DRB1_32660117	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90

AA_DRB1_10_32660118_Q	239.0	-53.19	0.2414	0.4186	0.414 (0.273-0.555)	-8.04
AA_DRB1_10_32660118_Y	275.1	-61.06	0.2242	0.4126	0.417 (0.282-0.551)	-8.90
SNP_DRB1_32660119_A	280.1	-62.14	0.2216	0.411	0.417 (0.283-0.551)	-9.00
SNP_DRB1_32660119_G	233.3	-51.95	0.2443	0.4191	0.417 (0.276-0.558)	-8.20
SNP_DRB1_32665401	192.5	-43.04	0.2237	0.3785	0.395 (0.242-0.548)	-6.37
AA_DRB1_-16_32665457_A	232.7	-51.81	0.2445	0.4190	0.417 (0.276-0.558)	-8.20
AA_DRB1_-16_32665457_V	187.3	-41.90	0.2144	0.3662	0.378 (0.223-0.533)	-5.73
SNP_DRB1_32665457	233.7	-52.03	0.2442	0.4191	0.417 (0.276-0.558)	-8.19
AA_DRB1_-24_32665481_F	411.1	-90.67	0.4286	0.2025	0.617 (0.417-0.818)	-8.79
AA_DRB1_-24_32665481_L	311.9	-69.09	0.4570	0.2527	0.498 (0.283-0.712)	-5.27
SNP_DRB1_32665482	410.8	-90.61	0.4288	0.2029	0.618 (0.417-0.818)	-8.81
AA_DRB1_-25_32665484_K	232.7	-51.81	0.2445	0.4190	0.417 (0.276-0.558)	-8.20
AA_DRB1_-25_32665484_R	187.3	-41.90	0.2144	0.3662	0.378 (0.223-0.533)	-5.73
SNP_DRB1_32665484	233.0	-51.87	0.2445	0.4191	0.417 (0.276-0.558)	-8.20
rs477515	263.9	-58.62	0.4802	0.2899	0.453 (0.256-0.649)	-5.21
rs2858867	131.1	-29.63	0.2318	0.3586	0.420 (0.270-0.570)	-7.36
rs660895	317.8	-70.35	0.4516	0.2473	0.508 (0.297-0.720)	-5.62
rs521539	317.8	-70.35	0.4516	0.2473	0.508 (0.297-0.720)	-5.62
rs3104413	413.4	-91.18	0.4296	0.2029	0.621 (0.422-0.820)	-9.05
rs6931277	413.4	-91.18	0.4296	0.2029	0.621 (0.423-0.820)	-9.07
rs9271588	322.3	-71.33	0.3204	0.5356	0.424 (0.276-0.571)	-7.73
rs9272219	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQA1_32713249	109.7	-24.94	0.1598	0.2640	0.405 (0.233-0.577)	-5.39
HLA_DQA1_03	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
HLA_DQA1_0301	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32717072	187.2	-41.89	0.5000	0.3371	0.443 (0.260-0.625)	-5.70
SNP_DQA1_32717108	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32717120	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
AA_DQA1_26_32717128	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32717128	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32717151	325.3	-72.00	0.3274	0.5440	0.448 (0.305-0.591)	-9.10
AA_DQA1_34_32717152	325.3	-72.00	0.3274	0.5440	0.448 (0.305-0.591)	-9.10
AA_DQA1_40_32717170	108.5	-24.69	0.1604	0.2640	0.397 (0.222-0.571)	-5.08
SNP_DQA1_32717170	108.5	-24.69	0.1604	0.2640	0.397 (0.222-0.571)	-5.08
SNP_DQA1_32717190_C	160.9	-36.14	0.2063	0.3441	0.483 (0.345-0.620)	-11.25
SNP_DQA1_32717190_T	108.5	-24.69	0.1604	0.2640	0.397 (0.222-0.571)	-5.08
AA_DQA1_47_32717191_C	108.8	-24.74	0.1604	0.2642	0.397 (0.223-0.571)	-5.12
AA_DQA1_47_32717191_Q	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85

AA_DQA1_47_32717191_RQ	160.7	-36.10	0.2063	0.3440	0.481 (0.343-0.618)	-11.11
SNP_DQA1_32717192	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
AA_DQA1_50_32717200_V	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQA1_32717201	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQA1_32717202	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
AA_DQA1_51_32717203	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQA1_32717207	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQA1_32717208	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
AA_DQA1_53_32717209_Q	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQA1_32717217_A	397.6	-87.73	0.4469	0.2209	0.580 (0.379-0.780)	-7.84
SNP_DQA1_32717217_x	160.9	-36.14	0.2063	0.3441	0.483 (0.345-0.620)	-11.25
AA_DQA1_56_32717218_R	398.1	-87.86	0.4469	0.2208	0.580 (0.379-0.780)	-7.85
AA_DQA1_56_32717218_x	161.1	-36.18	0.2063	0.3441	0.482 (0.344-0.619)	-11.19
SNP_DQA1_32717219_A	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32717219_x	160.7	-36.10	0.2063	0.3440	0.481 (0.343-0.618)	-11.11
SNP_DQA1_32717277_C	161.9	-36.36	0.2063	0.3445	0.481 (0.344-0.618)	-11.22
SNP_DQA1_32717277_G	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
AA_DQA1_76_32717278_L	161.9	-36.36	0.2063	0.3445	0.481 (0.344-0.618)	-11.22
AA_DQA1_76_32717278_V	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32718379	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
AA_DQA1_187_32718380_A	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
AA_DQA1_187_32718380_T	399.3	-88.11	0.4469	0.2206	0.580 (0.380-0.780)	-7.85
SNP_DQA1_32718414	181.0	-40.54	0.2129	0.3609	0.376 (0.230-0.522)	-6.37
SNP_DQA1_32718423	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
rs9273012	108.5	-24.69	0.1604	0.2640	0.395 (0.220-0.569)	-5.02
SNP_DQB1_32737205	79.8	-18.38	0.1062	0.1828	0.535 (0.322-0.748)	-6.06
SNP_DQB1_32737837	267.7	-59.45	0.2588	0.4490	0.440 (0.306-0.574)	-9.92
HLA_DQB1_02	79.1	-18.22	0.1065	0.1827	0.535 (0.322-0.748)	-6.07
HLA_DQB1_03	241.6	-53.76	0.5239	0.3382	0.444 (0.262-0.625)	-5.79
HLA_DQB1_0302	227.9	-50.76	0.2938	0.1443	0.673 (0.426-0.921)	-7.00
AA_DQB1_74_32740615_A	78.9	-18.19	0.1065	0.1827	0.534 (0.320-0.747)	-6.02
SNP_DQB1_32740623	78.9	-18.19	0.1065	0.1827	0.534 (0.320-0.747)	-6.02
AA_DQB1_71_32740624_K	78.9	-18.19	0.1065	0.1827	0.534 (0.320-0.747)	-6.02
AA_DQB1_71_32740624_KD	110.5	-25.13	0.1300	0.2282	-1.220 (-1.730--0.710)	-5.56
SNP_DQB1_32740624	110.5	-25.13	0.1300	0.2282	-1.220 (-1.730--0.710)	-5.56
AA_DQB1_67_32740636	100.4	-22.91	0.1359	0.2303	-1.258 (-1.797--0.719)	-5.32
SNP_DQB1_32740637	100.4	-22.91	0.1359	0.2303	-1.258 (-1.797--0.719)	-5.32
SNP_DQB1_32740638	100.4	-22.91	0.1359	0.2303	-1.258 (-1.797--0.719)	-5.32

AA_DQB1_66_32740639	100.4	-22.91	0.1359	0.2303	-1.258 (-1.797--0.719)	-5.32
AA_DQB1_55_32740672_L	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
AA_DQB1_55_32740672_P	241.5	-53.73	0.5239	0.3383	0.443 (0.262-0.625)	-5.78
SNP_DQB1_32740672_A	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740672_G	241.5	-53.73	0.5239	0.3383	0.443 (0.262-0.625)	-5.78
AA_DQB1_52_32740681	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740681	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
AA_DQB1_47_32740696	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740696	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
AA_DQB1_46_32740699	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740699	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740722	241.6	-53.75	0.5240	0.3382	0.443 (0.262-0.625)	-5.78
AA_DQB1_37_32740726_I	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740726	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740727_T	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740731	77.9	-17.97	0.1074	0.1833	0.525 (0.317-0.734)	-6.09
AA_DQB1_30_32740747_S	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740747	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740748_T	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
AA_DQB1_28_32740753	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740753	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
SNP_DQB1_32740773_C	113.1	-25.69	0.1285	0.2278	-1.236 (-1.752--0.720)	-5.58
SNP_DQB1_32740773_T	79.1	-18.22	0.1065	0.1827	0.535 (0.321-0.748)	-6.05
AA_DQB1_-10_32742295_A	112.6	-25.59	0.1330	0.2345	0.492 (0.320-0.665)	-7.67
AA_DQB1_-10_32742295_S	79.4	-18.30	0.1064	0.1827	0.536 (0.323-0.748)	-6.09
SNP_DQB1_32742296_A	79.4	-18.30	0.1064	0.1827	0.536 (0.323-0.748)	-6.09
SNP_DQB1_32742296_C	213.8	-47.69	0.1752	0.3306	0.472 (0.341-0.603)	-11.80
rs3891175	79.5	-18.31	0.1063	0.1827	0.536 (0.323-0.748)	-6.09
rs9275184	231.7	-51.60	0.3014	0.1469	0.687 (0.452-0.922)	-7.99
rs9275206	230.2	-51.27	0.2943	0.1441	0.674 (0.426-0.921)	-7.02
rs9275224	277.3	-61.55	0.2767	0.4723	0.438 (0.303-0.573)	-9.74
rs2858324	238.3	-53.03	0.2428	0.4192	0.394 (0.255-0.534)	-7.53
rs6457617	274.5	-60.92	0.2833	0.4784	0.446 (0.312-0.580)	-10.18
rs6457620	274.5	-60.92	0.2833	0.4784	0.446 (0.312-0.580)	-10.18
rs2647012	238.5	-53.08	0.2425	0.4189	0.393 (0.254-0.533)	-7.48
rs9275334	230.2	-51.27	0.2943	0.1441	0.674 (0.426-0.921)	-7.02
rs17427599	49.5	-11.70	0.3390	0.2613	0.485 (0.272-0.698)	-5.10
rs1612904	218.3	-48.68	0.2305	0.3971	0.389 (0.247-0.531)	-7.10

rs2856717	236.3	-52.59	0.2418	0.4173	0.391 (0.251-0.531)	-7.37
rs9275495	230.2	-51.27	0.2943	0.1441	0.674 (0.426-0.921)	-7.02
rs9275516	287.7	-63.81	0.2648	0.4628	0.414 (0.274-0.553)	-8.20
rs9275530	228.2	-50.83	0.2933	0.1439	0.674 (0.426-0.921)	-7.02
rs9275532	230.2	-51.27	0.2943	0.1441	0.674 (0.426-0.921)	-7.02
rs6932517	282.7	-62.72	0.2667	0.4631	0.415 (0.276-0.555)	-8.26
rs7764856	349.1	-77.18	0.3748	0.6006	0.480 (0.328-0.633)	-9.16
rs7454108	226.3	-50.42	0.2915	0.1430	0.693 (0.454-0.931)	-7.91
rs3957146	226.3	-50.42	0.2915	0.1430	0.693 (0.454-0.931)	-7.91
rs9275596	214.6	-47.87	0.2330	0.3984	0.384 (0.241-0.527)	-6.83
rs3998159	228.9	-50.98	0.2925	0.1430	0.697 (0.462-0.932)	-8.22
rs9275599	205.2	-45.81	0.2818	0.1417	0.665 (0.410-0.920)	-6.49
rs9784858	78.4	-18.07	0.2060	0.1269	0.753 (0.547-0.959)	-12.08
rs10484565	77.5	-17.87	0.2025	0.1245	0.732 (0.504-0.961)	-9.49
rs241409	63.1	-14.72	0.1865	0.1180	0.718 (0.482-0.955)	-8.59
rs241407	64.3	-14.97	0.1878	0.1183	0.720 (0.485-0.955)	-8.71
rs9277628	17.8	-4.62	0.1787	0.1405	0.637 (0.356-0.918)	-5.06