HLA-II genes are associated with outcomes of specific immunotherapy for allergic rhinitis

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Background: **Although the precise mechanisms underlying the efficacy of allergen-specific immunotherapy (AIT) are not clear, some evidence suggests that this may be linked to polymorphisms in HLA-II gene. We aimed to investigate the correlation between HLA-II gene polymorphisms and house dust mite (HDM)-specific immunotherapy efficacy, and evaluate specific polymorphisms as potential biomarkers in allergic rhinitis (AR) patients who would benefit most from AIT.**

Methods: **Fifty-one Han Chinese patients with AR receiving HDM AIT were recruited. Genomic DNA was extracted from venous blood samples and genotyped for HLA-DRB1 and HAL-DQB1 alleles using the polymerase chain reaction sequence-based genotyping method. Nasal and eye symptoms were investigated based on visual analogue scale and rhinoconjunctivitis quality of life.**

Results: **Allele DRB1*04:06; DRB1*14:05 showed a positive correlation with improvements in nasal blockage, nasal itching, eye itching, and activities. Similarly, DQB1*03:02:01; DQB1*05:03: 01 was positively correlated with improvements in nose blocking, nasal itching, eye itching, behavioral problems, and nasal symptoms scores; and DRB1*03:01; DRB1*04:06 positively correlated with nasal symptoms scores. In contrast, DRB1*07:01:01; DRB1*11:01 was negatively correlated with non-pollen symptoms, behavioral problems, and nasal symptoms.**

Conclusion: **HLA-DRB1 and HLA-DQB1 gene polymorphism are associated with AIT efficacy in HDM-sensitive Chinese patients with AR, of which DRB1*03:01; DRB1*04:06 and DQB1*03:02:01; DQB1*05:03:01 may be useful biomarkers of AR patient candidacy for effective AIT.** © 2019 ARS-AAOA, LLC.

Key Words:
allergic rhinitis; house dust mites; allergen-specific immunotherapy; human leukocyte antigen; HLA-DQB1; HLA-DRB1; polymorphism

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Allergic rhinitis (AR), a globally increasing disease, is estimated to affect approximately 8.7% to 24.1% of the population in the major cities in mainland China.[1] AR is characterized by nasal congestion, itching, rhinorrhea, and sneezing, which are manifested as a consequence of inappropriate immune responses mediated by allergen-specific immunoglobulin E (IgE) antibodies toward otherwise harmless antigens such as pollen and house dust mite (HDM). The uncontrolled symptoms of AR impair patients' quality of life (QOL), including physical and social functioning, disturbed sleep, daytime somnolence and fatigue, irritability, depression, and attention, learning, and memory deficits.[2] The management of AR encompasses tertiary environmental control, pharmacotherapy, and allergen-specific immunotherapy (AIT).[3] However, total avoidance

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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is often not feasible for public health and efficacy of medications may differ between patients.[4] Therefore, AIT is often the choice of treatment when AR cannot be well controlled by allergen avoidance and pharmacotherapy because of its confirmed efficacy and safety.[5,6]

AIT has been used for more than 100 years, with a progressive increase in the understanding of the mechanisms of immune regulation in allergic diseases. The basic mechanism includes modulation of T-cell and B-cell responses, production of antibody isotypes, and related inhibition of migration and activation of eosinophils, basophils, and mast cells to tissues. The human leukocyte antigen class II (HLA-II) molecules are mainly expressed on antigen-presenting cells such as B lymphocytes, macrophages, dendritic cells, and endothelial cells, and present peptides of antigen to $CD4^+$ T cells for initiating the process of adaptive immunity. Indeed, the possibility that HLA-II molecules are likely to be involved in the regulation of inflammatory diseases[7] has been demonstrated by a consistent finding for the association between the presence of asthma and atopy phenotype with HLA-DRB1 and HLADQB1 genes in several independent studies.[8] We have recently demonstrated an association between different DQB1 and DRB1 alleles and HDM-sensitive AR in Han Chinese subjects[9]; however, the particular alleles involved have varied between studies. Therefore, the aim of the present study was to evaluate HLA-DRB1 and HLA-DQB1 polymorphisms, which might be associated with successful outcome of HDM-specific immunotherapy in Chinese subjects with AR. In this regard we demonstrated that DRB1*03:01; DRB1*04:06 and DQB1*03:02:01; DQB1*05:03:01 were associated with successful AIT in these patients, and therefore may be potential biomarkers of AR patient candidacy for effective AIT.

Patients and methods

Ethics statement and patients

The study was approved by Beijing Institute of Otolaryngology Ethics Committee and written informed consent was obtained from all the participants or their legal guardians prior to entry into the study. All experiments were carried out in accordance with local guidelines and regulations and complied with the declaration of Helsinki and the Good Clinical Practice guidelines. Patients had blood drawn for specific IgE (sIgE) and DNA extraction at their first clinic visit before receiving AIT. All the patients enrolled in the study were treated using a cluster immunotherapy schedule as reported by Zhang et al.[10]

Overall, 55 patients were recruited initially, 4 of which did not complete the initial phase and were excluded from subsequent analysis. Three of the 4 patients dropped out of the study because of difficulty with traveling to the immunotherapy unit for scheduled treatment, and 1 withdrew because of pregnancy. Finally, a total of 51 patients with AR (26 male and 25 female), aged 18 to 62 years (mean ± standard deviation [SD]: 30 ± 9.9 years), who had received maintenance immunotherapy with *Dermatophagoides pteronyssinus* extract for 1 year were enrolled in this study. All patients were of northern Chinese Han ethnicity, and diagnosed with HDM-sensitive AR according to Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines,[3] based on clinical symptoms of sneezing, watery rhinorrhea, congestion, as well as sensitization to only *D. pteronyssinus* (Der p) or *Dermatophagoides farinae* (Der f) or to both, as determined by both serum-specific IgE and skin-prick testing (SPT). Patients with allergic dermatitis and asthma were excluded.

HDM allergen-specific IgE determination

Serum samples from all patients were tested for the presence of specific-IgE against a standard panel of common inhaled allergens using the UniCAP250 fluoroenzyme immunoassay (FEIA) system, according to the manufacturer's instructions (Pharmacia Upjohn, Uppsala, Sweden). The standard panel of common inhaled allergens included dust mite (Der p and Der f); autumn pollens (*Artemisia argyi*, ragweed, Humulus, and *Chenopodium album*); spring pollens produced by trees (*Salix caprea*, *Populus deltoides*, *Betula verrucose*, and *Ulmus americana*) and weeds (*Robinia pseudoacacia* and *Fraxinus chinensis*); animal hair (dog and cat); molds (indoor and outdoor mustiness or of floriculture); and cockroach. In order to minimize the impact of the coexistence of pollen allergies on the immunotherapy of HDM, we screened both the spring and autumn pollens that almost covered all the common pollens existing in northern regions in China. Values greater than 0.35 kU/L were considered as positive.

SPTs

All AR patients underwent SPTs according to established guidelines. None of the patients had taken antihistamines of any type for at least 1 week before the SPT and were tested for skin wheal reactions against a panel of common aeroallergens similar to that used for specific IgE in serum (Allergopharma, Reinbek, Germany). In the case of HMD (Der p and Der f), allergen extracts containing 5000 standardized biological units/mL were used for testing. A positive (10 mg/mL histamine) and a negative (saline solution) control were also employed as part of the test panel. Fifteen minutes after application, the mean diameter of the wheal produced by each test solution was measured to assess the skin reaction. When the size of the wheal was equal to or larger than one-half of the diameter of the histamine control and at least 3 mm larger than the diameter of the negative control, the SPT was considered to be positive.[11]

Immunotherapy schedules

All patients were treated using a cluster immunotherapy schedule, as reported by Zhang et al.[10] Briefly, AIT was administered with a commercial standardized depot

preparation of *D. pteronyssinus* extract (Alutard SQ; ALK-Abelló, Hørsholm, Denmark) that was adsorbed onto aluminum hydroxide and prepared as standardized solution with an allergenic activity of 100,000 standardized quality (SQ) units/mL (containing 9.8 g/mL *D. pteronyssinus*). Three injections with different concentration of 10 SQ/mL, 100 SQ/mL, and 1000 SQ/mL were given for the first visit and then 2 injections with gradually increased dose were given for each subsequent visit. The injections were administered at least half an hour apart, and the patient was observed for at least another half hour following the last injection. The patient returned to the clinic at weekly intervals for 6 weeks, during which the AIT dose was gradually increased to a maximum dose of 100,000 SQ at week 6. The dosing interval was gradually increased to 6 weeks and maintained until the end of the first year. At these visits the AIT dose was administered as 2 injections given half an hour apart, with an additional half-hour for observation. The immunotherapy schedules are detailed in Supporting Table 1.

Assessment of nasal and eye symptoms

At the beginning and after 1 year of AIT a horizontal visual analogue scale (VAS) ranging from 0 to 10 cm was used to assess the severity of nasal and eye symptoms, including nasal obstruction, itchy nose, watery rhinorrhea, sneezing, itchy eyes, eye swollen , eye sore, and lacrimation.[12] The VAS is a straight line, the end anchors of which are labeled as the extreme boundaries of the sensation, feeling, or response to be measured. The VAS to measure severity of nasal and eye symptoms was labeled "not at all bothersome" (0 cm) on one end and "intolerable bothersome" (10 cm) on the other. The VAS is scored by measuring the distance from one end of the scale to the subject's mark on the line.

Assessment of QOL

The questionnaire developed by Juniper and Guyatt[13] was used to assess the QOL of patients at baseline (the beginning of AIT) and after 1 year of AIT.

DNA extraction and HLA typing

Genomic DNA was extracted from venous blood sample of each participant, using the DNA Isolation Kit for Mammalian Blood (Roche, Indianapolis, IN). HLA-DRB1 and HLA-DQB1 gene typing was performed by a polymerase chain reaction sequence-based typing (PCR-SBT) method, using Big Dye^{TM} Terminator v3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA) on an ABI 3730XL Sequencer (Applied Biosystems). ABI-ATF1.0: Conexio Genomics was used for the analysis of typing results.

Statistical analysis

The symptom VAS difference between baseline and 1 year after AIT was selected to evaluate the efficacy of AIT. Frequencies of HLA were estimated using the R statistical analysis package (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/). The association between AIT efficacy and HLA alleles were analyzed by logistic regression using R package. For multiple allelic frequency comparisons, Bonferroni's correction was applied to avoid an alpha inflation and the corrected p value (pc) at the level of significance was set at $p = 0.05$. Epi-Info program was used to calculate odds ratio (OR), confidence interval (CI), and p values.

Results

Association of DQB1 and DRB1 alleles with nose symptoms

A total of 36 DQB1 and 40 DRB1 alleles were found among the patients (Table 1), of which several alleles demonstrated significant positive or negative associations with individual nasal symptoms, following immunotherapy for 1 year (Table 2). In particular, DRB1*04:06;DRB1*14:05 and DQB1*03:02:01;DQB1*05:03:01 were associated with significant improvements in nasal obstruction, whereas DRB1*08:03:02;DRB1*13:02:01 demonstrated a significantly negative association. Similarly, DRB1*04:06; DRB1*14:05, DQB1*03:01:01;DQB1*06:09 and DQB1*03:02:01;DQB1*05:03:01 showed significant positive associations with alleviation of itchy nose, whereas DRB1*04:03:01; DRB1*07:01:01 showed a negative association. Although alleviation of sneezing was not associated with any particular allele, DQB1*02:02; DQB1*03:02:01, DQB1*03:03:02; DQB1*03:03:02, and DQB1*06:01:01; DQB1*06:04:01 all showed negative associations with sneezing. In contrast, rhinorrhea was not found to be positively or negatively associated with any allele. However, assessment of total nasal symptoms scores indicated significant positive associations with alleles DRB1*03:01; DRB1*04:06, DRB1*04:06; DRB1*14:05, DQB1*02:01:01; DQB1*03:02:01, and DQB1*03:02:01; DQB1*05:03:01, and significant negative associations with allele DRB1*07:01:01; DRB1*11:01. The alleles found to have no significant association with improvement in nose symptoms are shown in Supporting Table 2.

Association with eye symptoms

Six alleles were found to be associated with improvement of itchy eyes (Table 3) and 1 allele, DQB1*03:02; DQB1*06:03, was negatively association with lacrimation. Although improvement in eye sore was associated with alleles DRB1*04:06; DRB1*13:01:01 and DQB1*03:02; DQB1*06:03, DRB1*13:02:01; DRB1*14:05:01, DRB1*15:02:01; DRB1*16:02:01, and DQB1*05:01:01; DQB1*05:02:01 showed negative associations. In contrast, eye swelling was not associated with any gene polymorphism. The alleles found to have no significant association with improvement eye symptoms are shown in Supporting Table 3.

TABLE 1. Distribution of DQB1 and DRB1 genotypes

Frequency (%)	Genotypes			
2.9	DQB1*02:01:01;DQB1*03:02:01	DQB1*03:03:02;DQB1*05:02:01	DRB1*04:03:01;DRB1*07:01:01	DRB1*07:01:01;DRB1*14:03:01
	DQB1*02:01:01;DQB1*06:02:01	DQB1*02:01:01;DQB1*02:02	DRB1*04:05;DRB1*07:01:01	DRB1*09:01:02;DRB1*16:02:01
	DQB1*02:02;DQB1*03:02:01	DQB1*05:01:01;DQB1*05:02:01	DRB1*04:05:01;DRB1*09:01:02	DRB1*08:03:02;DRB1*09:01:02
	DQB1*02:02;DQB1*04:01:01	DQB1*05:01:01;DQB1*06:02:01	DRB1*11:01;DRB1*13:02:01	DRB1*07:01:01;DRB1*09:01:02
	DQB1*02:02;DQB1*06:04:01	DQB1*05:02:01;DQB1*05:02:01	DRB1*12:02:01;DRB1*14:54	DRB1*07:01:01;DRB1*11:01
	DQB1*02:01:01;DQB1*03:03:02	DQB1*05:03:01;DQB1*06:04:01	DRB1*13:02:01;DRB1*14:05:01	DRB1*09:01:02;DRB1*13:02:01
	DQB1*03:01:01;DQB1*06:09	DQB1*06:01:01;DQB1*06:02:01	DRB1*13:02:01;DRB1*15:01	DRB1*04:06;DRB1*13:01:01
	DQB1*03:02;DQB1*06:03	DQB1*06:01:01;DQB1*06:04:01	DRB1*08:03:02;DRB1*13:02:01	DRB1*04:06;DRB1*14:05
	DQB1*03:02:01;DQB1*05:03:01	DQB1*06:09;DQB1*06:10	DRB1*08:03:02;DRB1*15:01	DRB1*15:02:01;DRB1*16:02:01
	DQB1*03:03:02;DQB1*03:03:02	DRB1*03:01;DRB1*15:01	DRB1*09:01:02;DRB1*09:01:02	DRB1*01:01;DRB1*15:01
	DQB1*03:03:02;DQB1*04:01:01	DRB1*09:01:02;DRB1*14:05:01	DRB1*09:01:02;DRB1*11:01	DRB1*14:54;DRB1*15:06
	DQB1*03:03:02;DQB1*05:03:01	DRB1*03:01;DRB1*04:05:01	DRB1*13:12:01;DRB1*16:02:01	
	DQB1*03:03:02;DQB1*06:01:01	DRB1*03:01;DRB1*04:06	DRB1*03:01;DRB1*09:01:02	
	DQB1*02:01:01;DQB1*04:01:01	DRB1*03:01;DRB1*07:01:01	DRB1*01:01:01;DRB1*11:01	
3.9	DQB1*02:01:01;DQB1*06:01:01	DQB1*03:03;DQB1*06:02	DRB1*08:03:02;DRB1*11:01	DQB1*03:01:01;DQB1*05:02:01
	DQB1*02:02;DQB1*02:02	DQB1*03:03;DQB1*06:03	DRB1*09:01:02;DRB1*12:02:01	DQB1*03:01:01;DQB1*06:01:01
	DQB1*02:02;DQB1*03:01:01	DQB1*03:03:02;DQB1*06:09	DRB1*09:01:02;DRB1*13:01:01	DRB1*07:01:01;DRB1*15:01
	DQB1*02:02;DQB1*03:03:02	DRB1*03:01;DRB1*08:03:02	DRB1*09:01:02;DRB1*15:01	DRB1*15:01;DRB1*15:01
	DQB1*02:02;DQB1*06:02:01	DRB1*07:01:01;DRB1*13:02:01	DRB1*10:01;DRB1*11:01	DQB1*03:01;DQB1*06:02
5.9	DQB1*03:01:01;DQB1*05:01:01	DQB1*03:01:01;DQB1*03:03:02	DRB1*07:01:01;DRB1*07:01:01	

TABLE 2. Association of DRB1 and DQB1 gene polymorphisms with improvement of nose symptoms

Symptoms	Alleles	Beta	SE	T	*p*
Nasal obstruction	DRB1*04:06;DRB1*14:05	8.3	2.863	2.900	0.015
	DRB1*08:03:02;DRB1*13:02:01	−7.6	2.863	−2.655	0.022
	DQB1*03:02:01;DQB1*05:03:01	8.9	3.413	2.608	0.020
Itchy nose	DRB1*04:03:01;DRB1*07:01:01	−8.9	3.477	−2.560	0.027
	DRB1*04:06;DRB1*14:05	8.1	3.477	2.330	0.040
	DQB1*03:01:01;DQB1*06:09	9.8	3.385	2.895	0.011
	DQB1*03:02:01;DQB1*05:03:01	11.2	3.385	3.309	0.005
Sneezing	DQB1*02:02;DQB1*03:02:01	−7.8	3.264	−2.390	0.030
	DQB1*03:03:02;DQB1*03:03:02	−8.2	3.264	−2.512	0.024
	DQB1*06:01:01;DQB1*06:04:01	−7.6	3.264	−2.328	0.034
Nose symptoms	DRB1*03:01;DRB1*04:06	4.00	1.37	2.926	0.014
	DRB1*04:06;DRB1*14:05	3.70	1.37	2.706	0.020
	DRB1*07:01:01;DRB1*11:01	−5.0	1.37	−3.657	0.004
	DQB1*02:01:01;DQB1*03:02:01	7.0	2.14	3.266	0.005
	DQB1*03:02:01;DQB1*05:03:01	6.7	2.14	3.126	0.007

Beta = logistic regression coefficients; SE = standard error; T = *t* statistic.

TABLE 3. Association of DRB1 and DQB1 gene polymorphisms with improvement of eye symptoms

Symptoms	Alleles	Beta	SE	T	*p*
Itchy eyes	DRB1*01:01:01;DRB1*11:01	9.5	3.191	2.977	0.013
	DRB1*04:06;DRB1*13:01:01	13.7	3.191	4.293	0.001
	DRB1*04:06;DRB1*14:05	15.2	3.191	4.763	0.001
	DRB1*07:01:01;DRB1*15:01	6.45	2.764	2.334	0.040
	DRB1*14:54;DRB1*15:06	7.7	3.191	2.413	0.034
	DQB1*03:02:01;DQB1*05:03:01	8.7	3.81	2.282	0.038
Lacrimation	DQB1*03:02;DQB1*06:03	8.4	3.71	2.263	0.039
Eye sore	DRB1*04:06;DRB1*13:01:01	9.2	3.10	2.967	0.013
	DRB1*13:02:01;DRB1*14:05:01	−7.0	3.10	−2.257	0.045
	DRB1*15:02:01;DRB1*16:02:01	−1.5	3.10	−4.837	0.001
	DQB1*03:02;DQB1*06:03	9.2	3.48	2.646	0.018
	DQB1*05:01:01;DQB1*05:02:01	−15.0	3.48	−4.313	0.001

Beta = logistic regression coefficients; SE = standard error; T = t statistic.

TABLE 4. Effect of immunotherapy on the QOL items*

QOL	W0	W52	*p*
Activities	3.2 (2.5–4.0)	2.1 (1.0–3.0)	<0.001
Sleep	2.4 (1.0–3.9)	1.0 (0.0–1.4)	<0.001
Non–hay fever symptoms	2.3 (1.0–3.1)	1.0 (0.0–1.7)	<0.001
Practical problems	2.8 (1.7–4.0)	1.5 (0.0–2.3)	<0.001
Nasal symptoms	3.0 (2.2–4.0)	1.5 (0.0–2.5)	<0.001
Eye symptoms	1.8 (0.2–2.8)	0.7 (0.0–1.3)	<0.001
Emotions	2.2 (0.4–3.2)	0.8 (0.0–1.3)	<0.001
Overall QOL	2.5 (1.5–3.7)	1.2 (0.4–1.9)	<0.001

*Data are shown as median scores with interquartile ranges in parentheses.
QOL = quality of life; W0 = baseline at initiation of immunotherapy; W52 = after 1 year of treatment.

Association with QOL

The overall QOL and all domain scores were significantly improved from baseline after immunotherapy for 1 year (Table 4). Assessment of associations between DRB1 and DQB1 gene polymorphisms and QOL items following immunotherapy are shown in Table 5. In particular, DRB1*01:01:01; DRB1*11:01 and DRB1*04:06; DRB1*14:05 were positively correlated with improvements in activities, whereas DQB1*02:02; DQB1*03:02:01 was negatively correlated with sleep. Similarly, DRB1*07:01:01; DRB1*11:01 showed a negative correlation with non–hay fever symptoms (tired, fatigue, worn out, reduced productivity, poor concentration, thirst), whereas DRB1*03:01;DRB1*15:01, DRB1*07:01:01; DRB1*11:01, DRB1*08:03:02;DRB1*13:02:01, and DQB1*02:01:01; DQB1*06:02:01 were negatively correlated with the majority of practical problems (need to blow nose repeatedly, need to rub nose/eyes, inconvenience of having to carry tissues or handkerchief). Only allele DQB1*03:02:01;DQB1*05:03:01 showed a positive association for practical problems.

Discussion

AIT is an effective treatment that leads to significant improvement in symptoms, medication needs, and QOL of patients.[14] The mechanism of AIT involves multiple pathways including regulating T cell and B cell responses, decreasing mediator release and migration of inflammatory cells.[15–17] Currently, several well-standardized allergen extracts, including HDM[18] grass, tree, venoms, and weed (ragweed and mugwort) pollens,[19,20] are available for use in the clinic. Although AIT has been used for more than a century in clinical practice, its underlying mechanisms remain unclear. Indeed, AIT is not effective in all allergic individuals and is not equally effective in the treatment of different allergen-sensitive patients.[21] Thus, there is a need to find a reliable biomarker that could identify patients who would benefit most from AIT.

An European Academy of Allergy and Clinical Immunology (EAACI) position paper has recently reported on some candidate biomarkers used in clinical trials of AR patients with/without asthma, and grouped the biomarkers into 7 domains: including (1) IgE, (2) IgG-subclasses, (3) serum inhibitory activity for IgE, (4) basophil activation, (5) cytokines and chemokines, (6) cellular markers, and (7) in vivo biomarkers.[22] Although all of these markers were shown to have advantages as well as their respective drawbacks, it was recommended that the use of allergen-specific

TABLE 5. Association of DRB1 and DQB1 gene polymorphisms with improvement of quality of life items

	Alleles	Beta	SE	T	*p*
Activities	DRB1*01:01:01;DRB1*11:01	6.0	1.74	3.441	0.006
	DRB1*04:06;DRB1*14:05	5.0	1.74	2.867	0.015
Sleep	DQB1*02:02;DQB1*03:02:01	−5.6	2.497	−2.243	0.041
Non-hay-fever symptoms	DRB1*07:01:01;DRB1*11:01	−5.0	1.86	−2.684	0.021
Practical problems	DRB1*03:01;DRB1*15:01	−5.7	1.90	−2.998	0.012
	DRB1*07:01:01;DRB1*11:01	−5.7	1.90	−2.998	0.012
	DRB1*08:03:02;DRB1*13:02:01	−4.7	1.90	−2.472	0.031
	DQB1*02:01:01;DQB1*06:02:01	−4.7	1.799	−2.613	0.020
	DQB1*03:02:01;DQB1*05:03:01	4.0	1.799	2.224	0.042

Beta = logistic regression coefficients; SE = standard error; T = *t* statistic.

IgG4 as a biomarker for compliance should be explored further. Moreover, sIgE/total IgE and IgE-facilitated allergen binding (IgE-FAB) were considered as potential surrogate candidate biomarkers. sIgE and sIgG4 are the most commonly studied biomarkers in AIT trials. Although sIgE is transiently increased during AIT, no functional relevance or severe allergic reactions have been associated with this increase in sIgE.[23] In contrast, studies have demonstrated correlation between allergen-specific sIgG4 and clinical outcomes, but not between quantitative levels of sIgG4 antibodies and clinical efficacy.[24] Thus, current guidelines do not recommend any validated and generally accepted candidate biomarkers assessed only quantitatively as predictors of clinical and immunological responses.[25]

HLA II proteins play a pivotal role in the adaptive immune system, by presenting peptides on the cell surface for recognition by T cells. In this regard, peptide–HLA class II (pHLAII) complexes-activated CD4+ cells mediate the coordination and regulation of effector cells and produce large amounts of different cytokines responsible for the initiation and maintenance of allergic inflammation. More than 200 HLA genes have been identified to be associated with various immune-mediated diseases.[26] Indeed, a recent study by Jones et al.[27] has highlighted the role of HLA in the development of AR. The authors showed that maternal anti-HLA class II antibodies were associated with significantly less atopy and seasonal rhinitis in the offspring at age 8 years. Similarly, associations between of HLA and HDM allergen have been reported in many studies; with 1 gene linkage study specifically showing significant linkage of HDM-specific, but not grass or birch pollen-specific, IgE response to HLA–DQB and HLA–DRB.[28] Other studies have reported HLADRB1*1101,[29] HLADRB1*04, and HLA-DQA1*0301[30] to be associated with atopic asthma in HDM-sensitized individuals of different ethnicities.

However, few studies have reported on association between the effectiveness of immunotherapy for AR and HLA expression. One study investigated the relationship between HLA molecules and the positive or negative response of multisensitized patients to grass pollen immunotherapy.[31] The authors showed that the frequency of B14 and DRB1*1101-4 antigens/alleles, as well as the A2B5DR11 haplotype were significantly higher in patients who responded to immunotherapy, whereas DR3 antigen and the A1B8 haplotype were significantly higher in patients who did not respond to immunotherapy. Comparably, here we only investigated the association between AIT efficiency and HLA polymorphisms among subjects with HDM allergy and further allergen specific association study should be addressed in patients with multiple sensitizations. In this respect, to the best of our knowledge, the present study is the first to assess associations of HLA gene polymorphisms with effectiveness of specifically HDM-AIT in HDM-sensitized AR patients. In this study, we initially divided the group data into 2 separate groups, based on the different evaluation scales, and found that 11, 10, and 8 different alleles, respectively, had significant associations with nose symptoms, eye symptoms, and QOL, respectively. It is worth noting that alleles DRB1*04:06; DRB1*14:05 and DQB1*03:02:01; DQB1*05:03:01 showed a positive association in all 3 evaluated scales. Moreover, DRB1*04:06; DRB1*14:05 was positively associated with improvement of nasal obstruction, itchy eyes, itchy nose, nose symptoms, and activities, suggesting that AR patients with this HLA allele could benefit more from immunotherapy-mediated improvements in symptoms. Indeed, Kim et al.[32] have reported that frequencies of HLA-DRB1*04 and HLA-DRB1*14 are decreased in the *D. pteronyssinus*–sensitive subjects compared with control subjects, and suggested that these alleles may have a protective effect upon the development of Der p sensitization.

We found that DQB1*03:02:01; DQB1*05:03:01 was also positively associated with improvement of nasal obstruction, itchy eyes, itchy nose, nose symptoms, and practical problems. Interestingly, DQB1*03 has been reported in 1 study as the most frequent major histocompatibility

complex (MHC) class II allele in both patients with allergic fungal rhinosinusitis and patients with hypertrophic sinus disease.[33] However, no correlation was found between specific HLA-DRB1 or HLA-DQB1 alleles and total serum IgE levels, or type I immediate hypersensitivity skin tests to common aeroallergens in patients with AFS. Patients with HSD did not have a predominance of HLA-DQB1*0301 and HLA-DQB1*0302 allelic variants over that seen in healthy control subjects.[33] These conflicting findings with the findings from the present study may be a consequence of differences in ethnic backgrounds of the patients investigated, phenotyping definitions and HLA typing methods employed. It is noteworthy, however, that compared with earlier serological methods, PCR sequence specific oligonucleotid probes (PCR-SSOP), PCR sequence specific primer (PCR-SSP) and PCR single strand conformational polymorphism (PCR-SSCP), in the present study we used the polymerase chain reaction sequence-based typing (PCR-SBT) method, which has many advantages over the earlier methods, in particular greater accuracy in gene typing, higher resolution, and possibility of finding new alleles.

This study is somewhat limited in that the follow-up period was relatively short, compared to the 3 to 5 years that is generally attributable to AIT. Thus, it is possible that some of these alleles may have demonstrated improvements in symptoms and QOL of patients later than 1 year. In this sense, it would be very interesting to see if other HLA markers specifically correlate with long-term response to immunotherapy.

Conclusion

This study showed that several HLA alleles are positively associated with efficacy of HDM AIT in HDM-AR patients. In particular, DRB1*04:06; DRB1*14:05 and DQB1*03:02:01; DQB1*05:03:01, may be potential biomarkers of successful HMD AIT. However, due to small study population investigated, it was not possible to collect enough information about the patients' treatment dosage for further analysis. Therefore, we consider that an increased sample size and well-documented longer treatment schedules are necessary to confirm these findings and also assess the role of other HLA markers over the long term.

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Supplementary Table 1. Cluster AIT dosage schedules

Week	Dose SQ units	Week	Dose SQ units
0	10	4	20000
	100		40000
	1000	5	40000
1	2000		60000
	4000	6	100000
2	5000	8	100000
	10000	12	100000
3	10000	18	100000
	20000	24	100000

Supplementary Table 2. DRB1 and DQB1 gene polymorphisms not associated with improvement of nose symptoms.

Symptoms	Alleles	Beta	SE	T	P
Nasal obstruction	DRB1*01:01:01DRB1*11:01	0.2	2.863	0.070	0.946
	DRB1*03:01DRB1*04:05:01	-0.7	2.863	-0.245	0.811
	DRB1*03:01DRB1*04:06	-0.5	2.863	-0.175	0.865
	DRB1*03:01DRB1*07:01:01	-0.6	2.863	-0.210	0.838
	DRB1*03:01DRB1*08:03:02	2.2	2.479	0.887	0.394
	DRB1*03:01DRB1*09:01:02	5.3	2.863	1.852	0.091
	DRB1*03:01DRB1*15:01	-2.8	2.863	-0.978	0.349
	DRB1*04:03:01DRB1*07:01:01	-6.1	2.863	-2.131	0.057
	DRB1*04:05DRB1*07:01:01	-1.7	2.863	-0.594	0.565
	DRB1*04:05:01DRB1*09:01:02	-3.8	2.863	-1.328	0.211
	DRB1*04:06DRB1*13:01:01	0.4	2.863	0.140	0.891
	DRB1*07:01:01DRB1*07:01:01	-0.2	2.337	-0.100	0.922
	DRB1*07:01:01DRB1*09:01:02	-0.1	2.863	-0.035	0.973
	DRB1*07:01:01DRB1*11:01	-4.7	2.863	-1.642	0.129
	DRB1*07:01:01DRB1*13:02:01	0.7	2.479	0.282	0.783
	DRB1*07:01:01DRB1*14:03:01	-0.6	2.863	-0.210	0.838
	DRB1*07:01:01DRB1*15:01	-1.0	2.479	-0.403	0.694
	DRB1*08:03:02DRB1*09:01:02	-5.3	2.863	-1.852	0.091
	DRB1*08:03:02DRB1*11:01	-0.5	2.479	-0.182	0.859
	DRB1*08:03:02DRB1*15:01	-0.3	2.863	-0.105	0.918
	DRB1*09:01:02DRB1*09:01:02	-0.5	2.863	-0.175	0.865
	DRB1*09:01:02DRB1*11:01	-4.0	2.863	-1.397	0.190
	DRB1*09:01:02DRB1*12:02:01	-0.6	2.479	-0.242	0.813
	DRB1*09:01:02DRB1*13:01:01	-0.5	2.479	-0.182	0.859
	DRB1*09:01:02DRB1*13:02:01	-5.4	2.863	-1.886	0.086
	DRB1*09:01:02DRB1*14:05:01	-0.7	2.863	-0.245	0.811
	DRB1*09:01:02DRB1*15:01	-0.6	2.479	-0.222	0.829
	DRB1*09:01:02DRB1*16:02:01	0.7	2.863	0.245	0.811
	DRB1*10:01DRB1*11:01	-2.1	2.479	-0.847	0.415
	DRB1*11:01DRB1*13:02:01	3.8	2.863	1.328	0.211
	DRB1*12:02:01DRB1*14:54	-0.2	2.863	-0.070	0.946
	DRB1*13:02:01DRB1*14:05:01	0.5	2.863	0.175	0.865
	DRB1*13:02:01DRB1*15:01	-3.2	2.863	-1.118	0.287
	DRB1*13:12:01DRB1*16:02:01	-0.3	2.863	-0.105	0.918
	DRB1*14:54DRB1*15:06	-0.2	2.863	-0.070	0.946
	DRB1*15:01DRB1*15:01	-3.2	2.479	-1.271	0.230
	DRB1*15:02:01DRB1*16:02:01	0.6	2.863	0.210	0.838
	DQB1*02:01:01DQB1*03:02:01	0.1	3.413	0.029	0.977
	DQB1*02:01:01DQB1*03:03:02	5.9	3.413	1.729	0.104
	DQB1*02:01:01DQB1*04:01:01	-0.1	3.413	-0.029	0.977
	DQB1*02:01:01DQB1*06:01:01	2.8	2.956	0.947	0.359

	DQB1*02:01:01DQB1*06:02:01	-2.2	3.413	-0.645	0.529
	DQB1*02:02DQB1*02:02	1.1	2.956	0.372	0.715
	DQB1*02:02DQB1*03:01:01	-2.1	2.956	-0.694	0.499
	DQB1*02:02DQB1*03:02:01	-5.5	3.413	-1.611	0.128
	DQB1*02:02DQB1*03:03:02	-0.3	2.956	-0.101	0.921
	DQB1*02:02DQB1*04:01:01	-1.1	3.413	-0.322	0.752
	DQB1*02:02DQB1*06:02:01	-0.4	2.956	-0.135	0.894
	DQB1*02:02DQB1*06:04:01	-1.1	3.413	-0.322	0.752
	DQB1*03:01DQB1*06:02	-2.6	2.956	-0.863	0.402
	DQB1*03:01:01DQB1*03:03:02	-1.1	2.787	-0.407	0.690
	DQB1*03:01:01DQB1*05:01:01	-0.7	2.787	-0.263	0.796
	DQB1*03:01:01DQB1*05:02:01	0.4	2.956	0.118	0.907
	DQB1*03:01:01DQB1*06:01:01	0.2	2.956	0.051	0.960
	DQB1*03:01:01DQB1*06:09	4.4	3.413	1.289	0.217
	DQB1*03:02DQB1*06:03	1.0	3.413	0.293	0.774
	DQB1*03:03DQB1*06:02	0.1	2.956	0.017	0.987
	DQB1*03:03DQB1*06:03	0.2	2.956	0.051	0.960
	DQB1*03:03:02DQB1*03:03:02	0.1	3.413	0.029	0.977
	DQB1*03:03:02DQB1*04:01:01	-3.2	3.413	-0.938	0.363
	DQB1*03:03:02DQB1*05:02:01	1.3	3.413	0.381	0.709
	DQB1*03:03:02DQB1*05:03:01	-0.1	3.413	-0.029	0.977
	DQB1*03:03:02DQB1*06:01:01	-4.7	3.413	-1.377	0.189
	DQB1*03:03:02DQB1*06:09	-0.6	2.956	-0.186	0.855
	DQB1*05:01:01DQB1*05:02:01	1.2	3.413	0.352	0.730
	DQB1*05:01:01DQB1*06:02:01	0.6	3.413	0.176	0.863
	DQB1*05:02:01DQB1*05:02:01	0.4	3.413	0.117	0.908
	DQB1*05:03:01DQB1*06:04:01	1.1	3.413	0.322	0.752
	DQB1*06:01:01DQB1*06:02:01	0.3	3.413	0.088	0.931
	DQB1*06:01:01DQB1*06:04:01	-7.0	3.413	-2.051	0.058
	DQB1*06:09DQB1*06:10	-2.6	3.413	-0.762	0.458
Itchy nose	DRB1*01:01:01DRB1*11:01	1.3	3.477	0.374	0.716
	DRB1*03:01DRB1*04:05:01	-1.0	3.477	-0.288	0.779
	DRB1*03:01DRB1*04:06	-2.2	3.477	-0.633	0.540
	DRB1*03:01DRB1*07:01:01	-3.1	3.477	-0.892	0.392
	DRB1*03:01DRB1*08:03:02	1.3	3.011	0.432	0.674
	DRB1*03:01DRB1*09:01:02	-1.9	3.477	-0.546	0.596
	DRB1*03:01DRB1*15:01	-2.9	3.477	-0.834	0.422
	DRB1*04:03:01DRB1*07:01:01	-8.9	3.477	-2.560	0.027
	DRB1*04:05DRB1*07:01:01	-2.7	3.477	-0.777	0.454
	DRB1*04:05:01DRB1*09:01:02	-5.8	3.477	-1.668	0.124
	DRB1*04:06DRB1*13:01:01	-2.0	3.477	-0.575	0.577
	DRB1*04:06DRB1*14:05	8.1	3.477	2.330	0.040
	DRB1*07:01:01DRB1*07:01:01	-1.6	2.839	-0.564	0.584
	DRB1*07:01:01DRB1*09:01:02	-5.5	3.477	-1.582	0.142
	DRB1*07:01:01DRB1*11:01	-4.8	3.477	-1.381	0.195
	DRB1*07:01:01DRB1*13:02:01	0.5	3.011	0.166	0.871

DRB1*07:01:01DRB1*14:03:01	-0.6	3.477	-0.173	0.866
DRB1*07:01:01DRB1*15:01	-3.7	3.011	-1.229	0.245
DRB1*08:03:02DRB1*09:01:02	-3.9	3.477	-1.122	0.286
DRB1*08:03:02DRB1*11:01	-1.3	3.011	-0.415	0.686
DRB1*08:03:02DRB1*13:02:01	0.3	3.477	0.086	0.933
DRB1*08:03:02DRB1*15:01	-1.5	3.477	-0.431	0.675
DRB1*09:01:02DRB1*09:01:02	-5.4	3.477	-1.553	0.149
DRB1*09:01:02DRB1*11:01	-4.5	3.477	-1.294	0.222
DRB1*09:01:02DRB1*12:02:01	-0.4	3.011	-0.133	0.897
DRB1*09:01:02DRB1*13:01:01	-2.2	3.011	-0.731	0.480
DRB1*09:01:02DRB1*13:02:01	-0.8	3.477	-0.230	0.822
DRB1*09:01:02DRB1*14:05:01	-1.5	3.477	-0.431	0.675
DRB1*09:01:02DRB1*15:01	-0.6	3.011	-0.199	0.846
DRB1*09:01:02DRB1*16:02:01	-1.8	3.477	-0.518	0.615
DRB1*10:01DRB1*11:01	-2.0	3.011	-0.664	0.520
DRB1*11:01DRB1*13:02:01	6.7	3.477	1.927	0.080
DRB1*12:02:01DRB1*14:54	-0.5	3.477	-0.144	0.888
DRB1*13:02:01DRB1*14:05:01	-1.0	3.477	-0.288	0.779
DRB1*13:02:01DRB1*15:01	-7.0	3.477	-2.013	0.069
DRB1*13:12:01DRB1*16:02:01	-2.8	3.477	-0.805	0.438
DRB1*14:54DRB1*15:06	-4.7	3.477	-1.352	0.204
DRB1*15:01DRB1*15:01	-4.0	3.011	-1.328	0.211
DRB1*15:02:01DRB1*16:02:01	2.0	3.477	0.575	0.577
DQB1*02:01:01DQB1*03:02:01	0.9	3.385	0.266	0.794
DQB1*02:01:01DQB1*03:03:02	1.2	3.385	0.355	0.728
DQB1*02:01:01DQB1*04:01:01	2.1	3.385	0.620	0.544
DQB1*02:01:01DQB1*06:01:01	4.4	2.931	1.501	0.154
DQB1*02:01:01DQB1*06:02:01	0.2	3.385	0.059	0.954
DQB1*02:02DQB1*02:02	2.6	2.931	0.887	0.389
DQB1*02:02DQB1*03:01:01	0.4	2.931	0.136	0.893
DQB1*02:02DQB1*03:02:01	-5.8	3.385	-1.714	0.107
DQB1*02:02DQB1*03:03:02	-1.6	2.931	-0.529	0.605
DQB1*02:02DQB1*04:01:01	0.4	3.385	0.118	0.908
DQB1*02:02DQB1*06:02:01	-0.6	2.931	-0.205	0.841
DQB1*02:02DQB1*06:04:01	1.2	3.385	0.355	0.728
DQB1*03:01DQB1*06:02	-0.9	2.931	-0.307	0.763
DQB1*03:01:01DQB1*03:03:02	1.3	2.764	0.482	0.636
DQB1*03:01:01DQB1*05:01:01	2.2	2.764	0.796	0.438
DQB1*03:01:01DQB1*05:02:01	1.5	2.931	0.495	0.628
DQB1*03:01:01DQB1*06:01:01	1.9	2.931	0.631	0.537
DQB1*03:01:01DQB1*06:09	9.8	3.385	2.895	0.011
DQB1*03:02DQB1*06:03	1.1	3.385	0.325	0.750
DQB1*03:02:01DQB1*05:03:01	11.2	3.385	3.309	0.005
DQB1*03:03DQB1*06:02	2.5	2.931	0.853	0.407
DQB1*03:03DQB1*06:03	0.9	2.931	0.307	0.763
DQB1*03:03:02DQB1*03:03:02	-2.3	3.385	-0.680	0.507

	DQB1*03:03:02DQB1*04:01:01	-2.7	3.385	-0.798	0.438
	DQB1*03:03:02DQB1*05:02:01	1.3	3.385	0.384	0.706
	DQB1*03:03:02DQB1*05:03:01	1.6	3.385	0.473	0.643
	DQB1*03:03:02DQB1*06:01:01	-0.8	3.385	-0.236	0.816
	DQB1*03:03:02DQB1*06:09	4.2	2.931	1.416	0.177
	DQB1*05:01:01DQB1*05:02:01	5.1	3.385	1.507	0.153
	DQB1*05:01:01DQB1*06:02:01	3.1	3.385	0.916	0.374
	DQB1*05:02:01DQB1*05:02:01	-1.6	3.385	-0.473	0.643
	DQB1*05:03:01DQB1*06:04:01	2.1	3.385	0.620	0.544
	DQB1*06:01:01DQB1*06:02:01	1.6	3.385	0.473	0.643
	DQB1*06:01:01DQB1*06:04:01	3.4	3.385	1.004	0.331
	DQB1*06:09DQB1*06:10	-3.9	3.385	-1.152	0.267
Sneezing	DRB1*01:01:01DRB1*11:01	-2.1	3.701	-0.567	0.582
	DRB1*03:01DRB1*04:05:01	-2.3	3.701	-0.621	0.547
	DRB1*03:01DRB1*04:06	-2.2	3.701	-0.594	0.564
	DRB1*03:01DRB1*07:01:01	0.4	3.701	0.108	0.916
	DRB1*03:01DRB1*08:03:02	1.9	3.205	0.577	0.576
	DRB1*03:01DRB1*09:01:02	1.4	3.701	0.378	0.713
	DRB1*03:01DRB1*15:01	-2.1	3.701	-0.567	0.582
	DRB1*04:03:01DRB1*07:01:01	-7.4	3.701	-1.999	0.071
	DRB1*04:05DRB1*07:01:01	-3.1	3.701	-0.838	0.420
	DRB1*04:05:01DRB1*09:01:02	-5.6	3.701	-1.513	0.159
	DRB1*04:06DRB1*13:01:01	0.7	3.701	0.189	0.853
	DRB1*04:06DRB1*14:05	7.0	3.701	1.891	0.085
	DRB1*07:01:01DRB1*07:01:01	-1.8	3.022	-0.607	0.556
	DRB1*07:01:01DRB1*09:01:02	-6.2	3.701	-1.675	0.122
	DRB1*07:01:01DRB1*11:01	-6.3	3.701	-1.702	0.117
	DRB1*07:01:01DRB1*13:02:01	-0.3	3.205	-0.078	0.939
	DRB1*07:01:01DRB1*14:03:01	-2.4	3.701	-0.648	0.530
	DRB1*07:01:01DRB1*15:01	-1.5	3.205	-0.468	0.649
	DRB1*08:03:02DRB1*09:01:02	-3.4	3.701	-0.919	0.378
	DRB1*08:03:02DRB1*11:01	-1.2	3.205	-0.374	0.715
	DRB1*08:03:02DRB1*13:02:01	-7.2	3.701	-1.945	0.078
	DRB1*08:03:02DRB1*15:01	-5.6	3.701	-1.513	0.159
	DRB1*09:01:02DRB1*09:01:02	-7.8	3.701	-2.107	0.059
	DRB1*09:01:02DRB1*11:01	-4.3	3.701	-1.162	0.270
	DRB1*09:01:02DRB1*12:02:01	-1.7	3.205	-0.530	0.606
	DRB1*09:01:02DRB1*13:01:01	-2.8	3.205	-0.858	0.409
	DRB1*09:01:02DRB1*13:02:01	1.2	3.701	0.324	0.752
	DRB1*09:01:02DRB1*14:05:01	-1.6	3.701	-0.432	0.674
	DRB1*09:01:02DRB1*15:01	-3.1	3.205	-0.951	0.362
	DRB1*09:01:02DRB1*16:02:01	-1.0	3.701	-0.270	0.792
	DRB1*10:01DRB1*11:01	0.4	3.205	0.125	0.903
	DRB1*11:01DRB1*13:02:01	2.1	3.701	0.567	0.582
	DRB1*12:02:01DRB1*14:54	-1.6	3.701	-0.432	0.674
	DRB1*13:02:01DRB1*14:05:01	-2.1	3.701	-0.567	0.582

	DRB1*13:02:01DRB1*15:01	-5.6	3.701	-1.513	0.159
	DRB1*13:12:01DRB1*16:02:01	-3.3	3.701	-0.892	0.392
	DRB1*14:54DRB1*15:06	-6.4	3.701	-1.729	0.112
	DRB1*15:01DRB1*15:01	-5.3	3.205	-1.638	0.130
	DRB1*15:02:01DRB1*16:02:01	-4.7	3.701	-1.270	0.230
	DQB1*02:01:01DQB1*03:02:01	-2.6	3.264	-0.797	0.438
	DQB1*02:01:01DQB1*03:03:02	1.0	3.264	0.306	0.764
	DQB1*02:01:01DQB1*04:01:01	-2.7	3.264	-0.827	0.421
	DQB1*02:01:01DQB1*06:01:01	1.5	2.827	0.513	0.616
	DQB1*02:01:01DQB1*06:02:01	-2.5	3.264	-0.766	0.456
	DQB1*02:02DQB1*02:02	-1.1	2.827	-0.371	0.716
	DQB1*02:02DQB1*03:01:01	-4.8	2.827	-1.680	0.114
	DQB1*02:02DQB1*03:02:01	-7.8	3.264	-2.390	0.030
	DQB1*02:02DQB1*03:03:02	-5.6	2.827	-1.981	0.066
	DQB1*02:02DQB1*04:01:01	-3.5	3.264	-1.072	0.301
	DQB1*02:02DQB1*06:02:01	-1.9	2.827	-0.672	0.512
	DQB1*02:02DQB1*06:04:01	-2.5	3.264	-0.766	0.456
	DQB1*03:01DQB1*06:02	-5.7	2.827	-1.999	0.064
	DQB1*03:01:01DQB1*03:03:02	-3.0	2.665	-1.113	0.283
	DQB1*03:01:01DQB1*05:01:01	-0.8	2.665	-0.313	0.759
	DQB1*03:01:01DQB1*05:02:01	-2.9	2.827	-1.008	0.329
	DQB1*03:01:01DQB1*06:01:01	-1.6	2.827	-0.566	0.580
	DQB1*03:01:01DQB1*06:09	1.7	3.264	0.521	0.610
	DQB1*03:02DQB1*06:03	0.3	3.264	0.092	0.928
	DQB1*03:02:01DQB1*05:03:01	6.6	3.264	2.022	0.061
	DQB1*03:03DQB1*06:02	-3.5	2.827	-1.220	0.241
	DQB1*03:03DQB1*06:03	-3.2	2.827	-1.114	0.283
	DQB1*03:03:02DQB1*03:03:02	-8.2	3.264	-2.512	0.024
	DQB1*03:03:02DQB1*04:01:01	-6.0	3.264	-1.838	0.086
	DQB1*03:03:02DQB1*05:02:01	-1.4	3.264	-0.429	0.674
	DQB1*03:03:02DQB1*05:03:01	-2.0	3.264	-0.613	0.549
	DQB1*03:03:02DQB1*06:01:01	-3.8	3.264	-1.164	0.263
	DQB1*03:03:02DQB1*06:09	1.0	2.827	0.354	0.728
	DQB1*05:01:01DQB1*05:02:01	-5.1	3.264	-1.562	0.139
	DQB1*05:01:01DQB1*06:02:01	-0.4	3.264	-0.123	0.904
	DQB1*05:02:01DQB1*05:02:01	-6.8	3.264	-2.083	0.055
	DQB1*05:03:01DQB1*06:04:01	-2.5	3.264	-0.766	0.456
	DQB1*06:01:01DQB1*06:02:01	-6.0	3.264	-1.838	0.086
	DQB1*06:01:01DQB1*06:04:01	-7.6	3.264	-2.328	0.034
	DQB1*06:09DQB1*06:10	-6.0	3.264	-1.838	0.086
Nose symptoms	DRB1*01:01:01DRB1*11:01	-0.1	1.367	-0.073	0.943
	DRB1*03:01DRB1*04:05:01	0.0	1.367	0.000	1.000
	DRB1*03:01DRB1*04:06	4.0	1.367	2.926	0.014
	DRB1*03:01DRB1*07:01:01	-3.0	1.367	-2.194	0.051
	DRB1*03:01DRB1*08:03:02	-0.5	1.184	-0.422	0.681
	DRB1*03:01DRB1*09:01:02	-2.5	1.367	-1.828	0.095

DRB1*03:01DRB1*15:01	-2.5	1.367	-1.828	0.095
DRB1*04:03:01DRB1*07:01:01	-3.0	1.367	-2.194	0.051
DRB1*04:05DRB1*07:01:01	-1.5	1.367	-1.097	0.296
DRB1*04:05:01DRB1*09:01:02	-0.5	1.367	-0.366	0.722
DRB1*04:06DRB1*13:01:01	-1.3	1.367	-0.951	0.362
DRB1*04:06DRB1*14:05	3.7	1.367	2.706	0.020
DRB1*07:01:01DRB1*07:01:01	-0.7	1.116	-0.597	0.562
DRB1*07:01:01DRB1*09:01:02	-1.2	1.367	-0.878	0.399
DRB1*07:01:01DRB1*11:01	-5.0	1.367	-3.657	0.004
DRB1*07:01:01DRB1*13:02:01	0.4	1.184	0.296	0.773
DRB1*07:01:01DRB1*14:03:01	0.8	1.367	0.585	0.570
DRB1*07:01:01DRB1*15:01	-0.8	1.184	-0.633	0.539
DRB1*08:03:02DRB1*09:01:02	0.0	1.367	0.000	1.000
DRB1*08:03:02DRB1*11:01	-0.4	1.184	-0.338	0.742
DRB1*08:03:02DRB1*13:02:01	-1.8	1.367	-1.317	0.215
DRB1*08:03:02DRB1*15:01	0.5	1.367	0.366	0.722
DRB1*09:01:02DRB1*09:01:02	-2.5	1.367	-1.828	0.095
DRB1*09:01:02DRB1*11:01	2.3	1.367	1.682	0.121
DRB1*09:01:02DRB1*12:02:01	-0.7	1.184	-0.549	0.594
DRB1*09:01:02DRB1*13:01:01	-0.7	1.184	-0.549	0.594
DRB1*09:01:02DRB1*13:02:01	-2.0	1.367	-1.463	0.172
DRB1*09:01:02DRB1*14:05:01	-1.0	1.367	-0.731	0.480
DRB1*09:01:02DRB1*15:01	-1.3	1.184	-1.056	0.314
DRB1*09:01:02DRB1*16:02:01	1.3	1.367	0.951	0.362
DRB1*10:01DRB1*11:01	-0.3	1.184	-0.211	0.837
DRB1*11:01DRB1*13:02:01	0.5	1.367	0.366	0.722
DRB1*12:02:01DRB1*14:54	-1.0	1.367	-0.731	0.480
DRB1*13:02:01DRB1*14:05:01	0.5	1.367	0.366	0.722
DRB1*13:02:01DRB1*15:01	0.0	1.367	0.000	1.000
DRB1*13:12:01DRB1*16:02:01	0.9	1.367	0.658	0.524
DRB1*14:54DRB1*15:06	1.0	1.367	0.731	0.480
DRB1*15:01DRB1*15:01	0.3	1.184	0.211	0.837
DRB1*15:02:01DRB1*16:02:01	-0.5	1.367	-0.366	0.722
DQB1*02:01:01DQB1*03:03:02	0.5	2.143	0.233	0.819
DQB1*02:01:01DQB1*04:01:01	3.0	2.143	1.400	0.182
DQB1*02:01:01DQB1*06:01:01	2.5	1.856	1.347	0.198
DQB1*02:01:01DQB1*06:02:01	0.5	2.143	0.233	0.819
DQB1*02:02DQB1*02:02	2.0	1.856	1.077	0.298
DQB1*02:02DQB1*03:01:01	0.9	1.856	0.485	0.635
DQB1*02:02DQB1*03:02:01	0.0	2.143	0.000	1.000
DQB1*02:02DQB1*03:03:02	2.4	1.856	1.293	0.216
DQB1*02:02DQB1*04:01:01	1.5	2.143	0.700	0.495
DQB1*02:02DQB1*06:02:01	2.3	1.856	1.212	0.244
DQB1*02:02DQB1*06:04:01	4.2	2.143	1.959	0.069
DQB1*03:01DQB1*06:02	3.3	1.856	1.751	0.100
DQB1*03:01:01DQB1*03:03:02	3.3	1.750	1.905	0.076

DQB1*03:01:01DQB1*05:01:01	2.8	1.750	1.600	0.130
DQB1*03:01:01DQB1*05:02:01	3.0	1.856	1.589	0.133
DQB1*03:01:01DQB1*06:01:01	2.6	1.856	1.401	0.182
DQB1*03:01:01DQB1*06:09	3.5	2.143	1.633	0.123
DQB1*03:02DQB1*06:03	1.7	2.143	0.793	0.440
DQB1*03:02:01DQB1*05:03:01	6.7	2.143	3.126	0.007
DQB1*03:03DQB1*06:02	1.8	1.856	0.943	0.361
DQB1*03:03DQB1*06:03	2.4	1.856	1.266	0.225
DQB1*03:03:02DQB1*03:03:02	0.5	2.143	0.233	0.819
DQB1*03:03:02DQB1*04:01:01	2.5	2.143	1.166	0.262
DQB1*03:03:02DQB1*05:02:01	4.3	2.143	2.006	0.063
DQB1*03:03:02DQB1*05:03:01	2.0	2.143	0.933	0.366
DQB1*03:03:02DQB1*06:01:01	3.0	2.143	1.400	0.182
DQB1*03:03:02DQB1*06:09	1.8	1.856	0.943	0.361
DQB1*05:01:01DQB1*05:02:01	2.5	2.143	1.166	0.262
DQB1*05:01:01DQB1*06:02:01	3.0	2.143	1.400	0.182
DQB1*05:02:01DQB1*05:02:01	4.0	2.143	1.866	0.082
DQB1*05:03:01DQB1*06:04:01	3.5	2.143	1.633	0.123
DQB1*06:01:01DQB1*06:02:01	3.5	2.143	1.633	0.123
DQB1*06:01:01DQB1*06:04:01	1.2	2.143	0.560	0.584
DQB1*06:09DQB1*06:10	3.0	2.143	1.400	0.182

Beta: Logistic regression coefficients; SE: standard error; T: t statistic

Supplementary Table 3. DRB1 and DQB1 gene polymorphisms not associated with improvement of eye symptoms.

Symptoms	Alleles	Beta	SE	T	P
Itchy eyes	DRB1*03:01DRB1*04:05:01	6.5	3.191	2.037	0.066
	DRB1*03:01DRB1*04:06	6.5	3.191	2.037	0.066
	DRB1*03:01DRB1*07:01:01	6.5	3.191	2.037	0.066
	DRB1*03:01DRB1*08:03:02	4.3	2.764	1.556	0.148
	DRB1*03:01DRB1*09:01:02	6.1	3.191	1.912	0.082
	DRB1*03:01DRB1*15:01	6.5	3.191	2.037	0.066
	DRB1*04:03:01DRB1*07:01:01	2.0	3.191	0.627	0.544
	DRB1*04:05DRB1*07:01:01	6.5	3.191	2.037	0.066
	DRB1*04:05:01DRB1*09:01:02	-0.9	3.191	-0.282	0.783
	DRB1*07:01:01DRB1*07:01:01	4.0	2.606	1.522	0.156
	DRB1*07:01:01DRB1*09:01:02	0.6	3.191	0.188	0.854
	DRB1*07:01:01DRB1*11:01	2.2	3.191	0.689	0.505
	DRB1*07:01:01DRB1*13:02:01	4.7	2.764	1.701	0.117
	DRB1*08:03:02DRB1*09:01:02	3.4	3.191	1.065	0.309
	DRB1*08:03:02DRB1*11:01	4.0	2.764	1.429	0.181
	DRB1*08:03:02DRB1*13:02:01	6.5	3.191	2.037	0.066
	DRB1*08:03:02DRB1*15:01	3.7	3.191	1.159	0.271
	DRB1*09:01:02DRB1*09:01:02	3.1	3.191	0.971	0.352
	DRB1*09:01:02DRB1*11:01	0.4	3.191	0.125	0.903
	DRB1*09:01:02DRB1*12:02:01	5.5	2.764	1.972	0.074
	DRB1*09:01:02DRB1*13:01:01	3.9	2.764	1.411	0.186
	DRB1*09:01:02DRB1*13:02:01	1.9	3.191	0.595	0.564
	DRB1*09:01:02DRB1*14:05:01	5.4	3.191	1.692	0.119
	DRB1*09:01:02DRB1*15:01	3.2	2.764	1.158	0.271
	DRB1*09:01:02DRB1*16:02:01	6.5	3.191	2.037	0.066
	DRB1*10:01DRB1*11:01	3.5	2.764	1.266	0.232
	DRB1*11:01DRB1*13:02:01	6.5	3.191	2.037	0.066
	DRB1*12:02:01DRB1*14:54	2.7	3.191	0.846	0.416
	DRB1*13:02:01DRB1*14:05:01	2.5	3.191	0.783	0.450
	DRB1*13:02:01DRB1*15:01	5.6	3.191	1.755	0.107
	DRB1*13:12:01DRB1*16:02:01	3.1	3.191	0.971	0.352
	DRB1*15:01DRB1*15:01	4.7	2.764	1.683	0.121
	DRB1*15:02:01DRB1*16:02:01	5.0	3.191	1.567	0.145
	DQB1*02:01:01DQB1*03:02:01	0.0	3.813	0.000	1.000
	DQB1*02:01:01DQB1*03:03:02	-0.4	3.813	-0.105	0.918
	DQB1*02:01:01DQB1*04:01:01	0.0	3.813	0.000	1.000
	DQB1*02:01:01DQB1*06:01:01	-2.2	3.302	-0.666	0.515
	DQB1*02:01:01DQB1*06:02:01	0.0	3.813	0.000	1.000
	DQB1*02:02DQB1*02:02	-1.7	3.302	-0.515	0.614
	DQB1*02:02DQB1*03:01:01	-2.1	3.302	-0.621	0.544
	DQB1*02:02DQB1*03:02:01	-4.5	3.813	-1.180	0.256

	DQB1*02:02DQB1*03:03:02	-5.1	3.302	-1.529	0.147
	DQB1*02:02DQB1*04:01:01	0.0	3.813	0.000	1.000
	DQB1*02:02DQB1*06:02:01	-0.1	3.302	-0.015	0.988
	DQB1*02:02DQB1*06:04:01	-3.4	3.813	-0.892	0.387
	DQB1*03:01DQB1*06:02	-1.9	3.302	-0.560	0.584
	DQB1*03:01:01DQB1*03:03:02	-2.7	3.113	-0.878	0.394
	DQB1*03:01:01DQB1*05:01:01	-1.0	3.113	-0.321	0.753
	DQB1*03:01:01DQB1*05:02:01	-3.6	3.302	-1.090	0.293
	DQB1*03:01:01DQB1*06:01:01	-2.6	3.302	-0.772	0.452
	DQB1*03:01:01DQB1*06:09	0.0	3.813	0.000	1.000
	DQB1*03:02DQB1*06:03	7.2	3.813	1.888	0.079
	DQB1*03:03DQB1*06:02	-3.3	3.302	-0.999	0.334
	DQB1*03:03DQB1*06:03	-2.6	3.302	-0.787	0.443
	DQB1*03:03:02DQB1*03:03:02	-3.4	3.813	-0.892	0.387
	DQB1*03:03:02DQB1*04:01:01	-7.4	3.813	-1.941	0.071
	DQB1*03:03:02DQB1*05:02:01	0.0	3.813	0.000	1.000
	DQB1*03:03:02DQB1*05:03:01	-1.1	3.813	-0.288	0.777
	DQB1*03:03:02DQB1*06:01:01	-3.1	3.813	-0.813	0.429
	DQB1*03:03:02DQB1*06:09	-2.4	3.302	-0.727	0.479
	DQB1*05:01:01DQB1*05:02:01	-1.5	3.813	-0.393	0.700
	DQB1*05:01:01DQB1*06:02:01	-6.5	3.813	-1.705	0.109
	DQB1*05:02:01DQB1*05:02:01	1.2	3.813	0.315	0.757
	DQB1*05:03:01DQB1*06:04:01	-4.0	3.813	-1.049	0.311
	DQB1*06:01:01DQB1*06:02:01	-2.8	3.813	-0.734	0.474
	DQB1*06:01:01DQB1*06:04:01	0.0	3.813	0.000	1.000
	DQB1*06:09DQB1*06:10	-0.9	3.813	-0.236	0.817
Eye swollen	DRB1*01:01:01DRB1*11:01	5.4	3.942	1.370	0.198
	DRB1*03:01DRB1*04:05:01	0.0	3.942	0.000	1.000
	DRB1*03:01DRB1*04:06	0.0	3.942	0.000	1.000
	DRB1*03:01DRB1*07:01:01	0.0	3.942	0.000	1.000
	DRB1*03:01DRB1*08:03:02	-2.3	3.414	-0.659	0.523
	DRB1*03:01DRB1*09:01:02	-1.9	3.942	-0.482	0.639
	DRB1*03:01DRB1*15:01	0.0	3.942	0.000	1.000
	DRB1*04:03:01DRB1*07:01:01	-1.3	3.942	-0.330	0.748
	DRB1*04:05DRB1*07:01:01	0.0	3.942	0.000	1.000
	DRB1*04:05:01DRB1*09:01:02	0.0	3.942	0.000	1.000
	DRB1*04:06DRB1*13:01:01	5.0	3.942	1.268	0.231
	DRB1*04:06DRB1*14:05	4.7	3.942	1.192	0.258
	DRB1*07:01:01DRB1*07:01:01	-0.7	3.219	-0.228	0.824
	DRB1*07:01:01DRB1*09:01:02	-2.6	3.942	-0.660	0.523
	DRB1*07:01:01DRB1*11:01	-4.3	3.942	-1.091	0.299
	DRB1*07:01:01DRB1*13:02:01	-3.1	3.414	-0.893	0.391
	DRB1*07:01:01DRB1*14:03:01	0.2	3.942	0.051	0.960
	DRB1*07:01:01DRB1*15:01	0.0	3.414	0.000	1.000
	DRB1*08:03:02DRB1*09:01:02	0.0	3.942	0.000	1.000
	DRB1*08:03:02DRB1*11:01	-2.6	3.414	-0.747	0.471

DRB1*08:03:02DRB1*13:02:01	0.0	3.942	0.000	1.000
DRB1*08:03:02DRB1*15:01	-6.0	3.942	-1.522	0.156
DRB1*09:01:02DRB1*09:01:02	0.0	3.942	0.000	1.000
DRB1*09:01:02DRB1*11:01	-3.4	3.942	-0.862	0.407
DRB1*09:01:02DRB1*12:02:01	0.2	3.414	0.044	0.966
DRB1*09:01:02DRB1*13:01:01	-2.7	3.414	-0.791	0.446
DRB1*09:01:02DRB1*13:02:01	0.0	3.942	0.000	1.000
DRB1*09:01:02DRB1*14:05:01	-1.2	3.942	-0.304	0.767
DRB1*09:01:02DRB1*15:01	0.3	3.414	0.088	0.932
DRB1*09:01:02DRB1*16:02:01	0.3	3.942	0.076	0.941
DRB1*10:01DRB1*11:01	-1.0	3.414	-0.293	0.775
DRB1*11:01DRB1*13:02:01	-2.2	3.942	-0.558	0.588
DRB1*12:02:01DRB1*14:54	3.2	3.942	0.812	0.434
DRB1*13:02:01DRB1*14:05:01	-3.3	3.942	-0.837	0.420
DRB1*13:02:01DRB1*15:01	-3.2	3.942	-0.812	0.434
DRB1*13:12:01DRB1*16:02:01	-3.4	3.942	-0.862	0.407
DRB1*14:54DRB1*15:06	1.2	3.942	0.304	0.767
DRB1*15:01DRB1*15:01	-3.6	3.414	-1.040	0.321
DRB1*15:02:01DRB1*16:02:01	-6.2	3.942	-1.573	0.144
DQB1*02:01:01DQB1*03:02:01	0.0	4.346	0.000	1.000
DQB1*02:01:01DQB1*03:03:02	-1.9	4.346	-0.437	0.668
DQB1*02:01:01DQB1*04:01:01	0.0	4.346	0.000	1.000
DQB1*02:01:01DQB1*06:01:01	-2.3	3.764	-0.598	0.559
DQB1*02:01:01DQB1*06:02:01	0.0	4.346	0.000	1.000
DQB1*02:02DQB1*02:02	1.0	3.764	0.266	0.794
DQB1*02:02DQB1*03:01:01	-2.1	3.764	-0.545	0.594
DQB1*02:02DQB1*03:02:01	-1.3	4.346	-0.299	0.769
DQB1*02:02DQB1*03:03:02	-3.4	3.764	-0.903	0.381
DQB1*02:02DQB1*04:01:01	0.0	4.346	0.000	1.000
DQB1*02:02DQB1*06:02:01	0.0	3.764	0.000	1.000
DQB1*02:02DQB1*06:04:01	-2.8	4.346	-0.644	0.529
DQB1*03:01DQB1*06:02	-3.6	3.764	-0.943	0.361
DQB1*03:01:01DQB1*03:03:02	-1.0	3.548	-0.291	0.775
DQB1*03:01:01DQB1*05:01:01	1.1	3.548	0.319	0.754
DQB1*03:01:01DQB1*05:02:01	-0.1	3.764	-0.027	0.979
DQB1*03:01:01DQB1*06:01:01	-2.6	3.764	-0.678	0.508
DQB1*03:01:01DQB1*06:09	-2.2	4.346	-0.506	0.620
DQB1*03:02DQB1*06:03	5.0	4.346	1.150	0.268
DQB1*03:02:01DQB1*05:03:01	4.7	4.346	1.081	0.297
DQB1*03:03DQB1*06:02	0.3	3.764	0.080	0.938
DQB1*03:03DQB1*06:03	-2.7	3.764	-0.717	0.484
DQB1*03:03:02DQB1*03:03:02	0.0	4.346	0.000	1.000
DQB1*03:03:02DQB1*04:01:01	0.0	4.346	0.000	1.000
DQB1*03:03:02DQB1*05:02:01	0.3	4.346	0.069	0.946
DQB1*03:03:02DQB1*05:03:01	-1.2	4.346	-0.276	0.786
DQB1*03:03:02DQB1*06:01:01	0.0	4.346	0.000	1.000

	DQB1*03:03:02DQB1*06:09	-1.7	3.764	-0.438	0.667
	DQB1*05:01:01DQB1*05:02:01	-6.2	4.346	-1.427	0.174
	DQB1*05:01:01DQB1*06:02:01	0.0	4.346	0.000	1.000
	DQB1*05:02:01DQB1*05:02:01	1.2	4.346	0.276	0.786
	DQB1*05:03:01DQB1*06:04:01	-3.3	4.346	-0.759	0.459
	DQB1*06:01:01DQB1*06:02:01	-6.0	4.346	-1.381	0.188
	DQB1*06:01:01DQB1*06:04:01	0.0	4.346	0.000	1.000
	DQB1*06:09DQB1*06:10	-3.2	4.346	-0.736	0.473
Lacrimation	DRB1*01:01:01DRB1*11:01	5.4	3.975	1.358	0.202
	DRB1*03:01DRB1*04:05:01	0.0	3.975	0.000	1.000
	DRB1*03:01DRB1*04:06	0.0	3.975	0.000	1.000
	DRB1*03:01DRB1*07:01:01	0.0	3.975	0.000	1.000
	DRB1*03:01DRB1*08:03:02	-0.5	3.443	-0.145	0.887
	DRB1*03:01DRB1*09:01:02	-6.1	3.975	-1.534	0.153
	DRB1*03:01DRB1*15:01	0.0	3.975	0.000	1.000
	DRB1*04:03:01DRB1*07:01:01	-1.3	3.975	-0.327	0.750
	DRB1*04:05DRB1*07:01:01	0.0	3.975	0.000	1.000
	DRB1*04:05:01DRB1*09:01:02	-7.4	3.975	-1.861	0.090
	DRB1*04:06DRB1*13:01:01	8.4	3.975	2.113	0.058
	DRB1*04:06DRB1*14:05	4.7	3.975	1.182	0.262
	DRB1*07:01:01DRB1*07:01:01	0.0	3.246	0.010	0.992
	DRB1*07:01:01DRB1*09:01:02	-3.7	3.975	-0.928	0.373
	DRB1*07:01:01DRB1*11:01	-4.3	3.975	-1.082	0.303
	DRB1*07:01:01DRB1*13:02:01	-0.7	3.443	-0.203	0.843
	DRB1*07:01:01DRB1*14:03:01	0.2	3.975	0.050	0.961
	DRB1*07:01:01DRB1*15:01	0.0	3.443	0.000	1.000
	DRB1*08:03:02DRB1*09:01:02	0.0	3.975	0.000	1.000
	DRB1*08:03:02DRB1*11:01	-2.6	3.443	-0.741	0.474
	DRB1*08:03:02DRB1*13:02:01	0.0	3.975	0.000	1.000
	DRB1*08:03:02DRB1*15:01	1.2	3.975	0.302	0.768
	DRB1*09:01:02DRB1*09:01:02	-2.4	3.975	-0.604	0.558
	DRB1*09:01:02DRB1*11:01	-2.7	3.975	-0.679	0.511
	DRB1*09:01:02DRB1*12:02:01	0.1	3.443	0.029	0.977
	DRB1*09:01:02DRB1*13:01:01	-2.3	3.443	-0.654	0.527
	DRB1*09:01:02DRB1*13:02:01	0.0	3.975	0.000	1.000
	DRB1*09:01:02DRB1*14:05:01	-1.3	3.975	-0.327	0.750
	DRB1*09:01:02DRB1*15:01	-1.5	3.443	-0.436	0.672
	DRB1*09:01:02DRB1*16:02:01	0.1	3.975	0.025	0.980
	DRB1*10:01DRB1*11:01	0.0	3.443	0.000	1.000
	DRB1*11:01DRB1*13:02:01	-0.8	3.975	-0.201	0.844
	DRB1*12:02:01DRB1*14:54	3.1	3.975	0.780	0.452
	DRB1*13:02:01DRB1*14:05:01	-3.0	3.975	-0.755	0.466
	DRB1*13:02:01DRB1*15:01	-3.3	3.975	-0.830	0.424
	DRB1*13:12:01DRB1*16:02:01	0.0	3.975	0.000	1.000
	DRB1*14:54DRB1*15:06	0.3	3.975	0.075	0.941
	DRB1*15:01DRB1*15:01	-3.4	3.443	-0.988	0.345

	DRB1*15:02:01DRB1*16:02:01	-1.3	3.975	-0.327	0.750
	DQB1*02:01:01DQB1*03:02:01	0.0	3.712	0.000	1.000
	DQB1*02:01:01DQB1*03:03:02	-6.1	3.712	-1.643	0.121
	DQB1*02:01:01DQB1*04:01:01	0.0	3.712	0.000	1.000
	DQB1*02:01:01DQB1*06:01:01	-0.5	3.214	-0.156	0.879
	DQB1*02:01:01DQB1*06:02:01	0.0	3.712	0.000	1.000
	DQB1*02:02DQB1*02:02	2.0	3.214	0.622	0.543
	DQB1*02:02DQB1*03:01:01	-2.1	3.214	-0.638	0.533
	DQB1*02:02DQB1*03:02:01	-1.3	3.712	-0.350	0.731
	DQB1*02:02DQB1*03:03:02	-3.8	3.214	-1.181	0.256
	DQB1*02:02DQB1*04:01:01	0.0	3.712	0.000	1.000
	DQB1*02:02DQB1*06:02:01	0.0	3.214	0.000	1.000
	DQB1*02:02DQB1*06:04:01	0.0	3.712	0.000	1.000
	DQB1*03:01DQB1*06:02	-3.4	3.214	-1.058	0.307
	DQB1*03:01:01DQB1*03:03:02	-0.8	3.031	-0.275	0.787
	DQB1*03:01:01DQB1*05:01:01	1.8	3.031	0.594	0.561
	DQB1*03:01:01DQB1*05:02:01	1.6	3.214	0.482	0.637
	DQB1*03:01:01DQB1*06:01:01	-2.6	3.214	-0.793	0.440
	DQB1*03:01:01DQB1*06:09	-0.8	3.712	-0.216	0.832
	DQB1*03:02:01DQB1*05:03:01	4.7	3.712	1.266	0.225
	DQB1*03:03DQB1*06:02	-1.5	3.214	-0.467	0.648
	DQB1*03:03DQB1*06:03	-2.3	3.214	-0.700	0.495
	DQB1*03:03:02DQB1*03:03:02	-2.4	3.712	-0.647	0.528
	DQB1*03:03:02DQB1*04:01:01	-7.4	3.712	-1.994	0.065
	DQB1*03:03:02DQB1*05:02:01	0.1	3.712	0.027	0.979
	DQB1*03:03:02DQB1*05:03:01	-1.3	3.712	-0.350	0.731
	DQB1*03:03:02DQB1*06:01:01	0.0	3.712	0.000	1.000
	DQB1*03:03:02DQB1*06:09	-0.7	3.214	-0.218	0.831
	DQB1*05:01:01DQB1*05:02:01	-1.3	3.712	-0.350	0.731
	DQB1*05:01:01DQB1*06:02:01	0.0	3.712	0.000	1.000
	DQB1*05:02:01DQB1*05:02:01	0.3	3.712	0.081	0.937
	DQB1*05:03:01DQB1*06:04:01	-3.0	3.712	-0.808	0.432
	DQB1*06:01:01DQB1*06:02:01	1.2	3.712	0.323	0.751
	DQB1*06:01:01DQB1*06:04:01	0.0	3.712	0.000	1.000
	DQB1*06:09DQB1*06:10	-3.3	3.712	-0.889	0.388
Eye sore	DRB1*01:01:01DRB1*11:01	5.4	3.101	1.741	0.109
	DRB1*03:01DRB1*04:05:01	0.0	3.101	0.000	1.000
	DRB1*03:01DRB1*04:06	0.0	3.101	0.000	1.000
	DRB1*03:01DRB1*07:01:01	0.0	3.101	0.000	1.000
	DRB1*03:01DRB1*08:03:02	-1.2	2.686	-0.447	0.664
	DRB1*03:01DRB1*09:01:02	-5.1	3.101	-1.645	0.128
	DRB1*03:01DRB1*15:01	0.0	3.101	0.000	1.000
	DRB1*04:03:01DRB1*07:01:01	-3.4	3.101	-1.096	0.296
	DRB1*04:05DRB1*07:01:01	0.0	3.101	0.000	1.000
	DRB1*04:05:01DRB1*09:01:02	0.0	3.101	0.000	1.000
	DRB1*04:06DRB1*14:05	4.7	3.101	1.516	0.158

DRB1*07:01:01DRB1*07:01:01	-0.3	2.532	-0.132	0.898
DRB1*07:01:01DRB1*09:01:02	-2.9	3.101	-0.935	0.370
DRB1*07:01:01DRB1*11:01	-5.6	3.101	-1.806	0.098
DRB1*07:01:01DRB1*13:02:01	0.0	2.686	0.000	1.000
DRB1*07:01:01DRB1*14:03:01	0.2	3.101	0.064	0.950
DRB1*07:01:01DRB1*15:01	0.0	2.686	0.000	1.000
DRB1*08:03:02DRB1*09:01:02	0.0	3.101	0.000	1.000
DRB1*08:03:02DRB1*11:01	-3.2	2.686	-1.192	0.259
DRB1*08:03:02DRB1*13:02:01	0.0	3.101	0.000	1.000
DRB1*08:03:02DRB1*15:01	1.2	3.101	0.387	0.706
DRB1*09:01:02DRB1*09:01:02	0.0	3.101	0.000	1.000
DRB1*09:01:02DRB1*11:01	0.0	3.101	0.000	1.000
DRB1*09:01:02DRB1*12:02:01	0.1	2.686	0.037	0.971
DRB1*09:01:02DRB1*13:01:01	-0.6	2.686	-0.223	0.827
DRB1*09:01:02DRB1*13:02:01	0.0	3.101	0.000	1.000
DRB1*09:01:02DRB1*14:05:01	-1.1	3.101	-0.355	0.730
DRB1*09:01:02DRB1*15:01	1.1	2.686	0.391	0.703
DRB1*09:01:02DRB1*16:02:01	0.0	3.101	0.000	1.000
DRB1*10:01DRB1*11:01	0.0	2.686	0.000	1.000
DRB1*11:01DRB1*13:02:01	0.0	3.101	0.000	1.000
DRB1*12:02:01DRB1*14:54	0.9	3.101	0.290	0.777
DRB1*13:02:01DRB1*15:01	0.0	3.101	0.000	1.000
DRB1*13:12:01DRB1*16:02:01	0.0	3.101	0.000	1.000
DRB1*14:54DRB1*15:06	0.3	3.101	0.097	0.925
DRB1*15:01DRB1*15:01	-3.6	2.686	-1.340	0.207
DQB1*02:01:01DQB1*03:02:01	0.0	3.478	0.000	1.000
DQB1*02:01:01DQB1*03:03:02	-5.1	3.478	-1.467	0.163
DQB1*02:01:01DQB1*04:01:01	0.0	3.478	0.000	1.000
DQB1*02:01:01DQB1*06:01:01	-1.2	3.012	-0.398	0.696
DQB1*02:01:01DQB1*06:02:01	0.0	3.478	0.000	1.000
DQB1*02:02DQB1*02:02	0.0	3.012	0.000	1.000
DQB1*02:02DQB1*03:01:01	-2.7	3.012	-0.897	0.384
DQB1*02:02DQB1*03:02:01	-3.4	3.478	-0.978	0.344
DQB1*02:02DQB1*03:03:02	-2.0	3.012	-0.647	0.527
DQB1*02:02DQB1*04:01:01	0.0	3.478	0.000	1.000
DQB1*02:02DQB1*06:02:01	0.0	3.012	0.000	1.000
DQB1*02:02DQB1*06:04:01	0.0	3.478	0.000	1.000
DQB1*03:01DQB1*06:02	-3.6	3.012	-1.195	0.251
DQB1*03:01:01DQB1*03:03:02	0.1	2.839	0.023	0.982
DQB1*03:01:01DQB1*05:01:01	1.8	2.839	0.634	0.536
DQB1*03:01:01DQB1*05:02:01	0.5	3.012	0.149	0.883
DQB1*03:01:01DQB1*06:01:01	-3.2	3.012	-1.063	0.305
DQB1*03:01:01DQB1*06:09	0.0	3.478	0.000	1.000
DQB1*03:02:01DQB1*05:03:01	4.7	3.478	1.352	0.197
DQB1*03:03DQB1*06:02	1.1	3.012	0.349	0.732
DQB1*03:03DQB1*06:03	-0.6	3.012	-0.199	0.845

	DQB1*03:03:02DQB1*03:03:02	0.0	3.478	0.000	1.000
	DQB1*03:03:02DQB1*04:01:01	0.0	3.478	0.000	1.000
	DQB1*03:03:02DQB1*05:02:01	0.0	3.478	0.000	1.000
	DQB1*03:03:02DQB1*05:03:01	-1.1	3.478	-0.316	0.756
	DQB1*03:03:02DQB1*06:01:01	0.0	3.478	0.000	1.000
	DQB1*03:03:02DQB1*06:09	0.0	3.012	0.000	1.000
	DQB1*05:01:01DQB1*06:02:01	0.0	3.478	0.000	1.000
	DQB1*05:02:01DQB1*05:02:01	0.3	3.478	0.086	0.932
	DQB1*05:03:01DQB1*06:04:01	-7.0	3.478	-2.013	0.062
	DQB1*06:01:01DQB1*06:02:01	1.2	3.478	0.345	0.735
	DQB1*06:01:01DQB1*06:04:01	0.0	3.478	0.000	1.000
	DQB1*06:09DQB1*06:10	0.0	3.478	0.000	1.000
Eye symptoms	DRB1*01:01:01DRB1*11:01	-0.9	1.822	-0.494	0.631
	DRB1*03:01DRB1*04:05:01	-0.7	1.822	-0.384	0.708
	DRB1*03:01DRB1*04:06	0.3	1.822	0.165	0.872
	DRB1*03:01DRB1*07:01:01	-1.0	1.822	-0.549	0.594
	DRB1*03:01DRB1*08:03:02	-0.6	1.578	-0.380	0.711
	DRB1*03:01DRB1*09:01:02	-1.4	1.822	-0.768	0.458
	DRB1*03:01DRB1*15:01	0.3	1.822	0.165	0.872
	DRB1*04:03:01DRB1*07:01:01	-3.5	1.822	-1.894	0.085
	DRB1*04:05DRB1*07:01:01	-0.2	1.822	-0.110	0.915
	DRB1*04:05:01DRB1*09:01:02	-1.7	1.822	-0.933	0.371
	DRB1*04:06DRB1*13:01:01	0.3	1.822	0.165	0.872
	DRB1*04:06DRB1*14:05	2.3	1.822	1.263	0.233
	DRB1*07:01:01DRB1*07:01:01	-2.0	1.487	-1.367	0.199
	DRB1*07:01:01DRB1*09:01:02	-1.5	1.822	-0.823	0.428
	DRB1*07:01:01DRB1*11:01	-3.5	1.822	-1.921	0.081
	DRB1*07:01:01DRB1*13:02:01	-1.1	1.578	-0.697	0.500
	DRB1*07:01:01DRB1*14:03:01	0.3	1.822	0.165	0.872
	DRB1*07:01:01DRB1*15:01	-0.1	1.578	-0.063	0.951
	DRB1*08:03:02DRB1*09:01:02	0.3	1.822	0.165	0.872
	DRB1*08:03:02DRB1*11:01	-0.6	1.578	-0.349	0.734
	DRB1*08:03:02DRB1*13:02:01	0.3	1.822	0.165	0.872
	DRB1*08:03:02DRB1*15:01	-1.2	1.822	-0.659	0.524
	DRB1*09:01:02DRB1*09:01:02	-1.7	1.822	-0.933	0.371
	DRB1*09:01:02DRB1*11:01	0.0	1.822	0.000	1.000
	DRB1*09:01:02DRB1*12:02:01	-0.1	1.578	-0.048	0.963
	DRB1*09:01:02DRB1*13:01:01	-1.6	1.578	-0.982	0.347
	DRB1*09:01:02DRB1*13:02:01	-0.9	1.822	-0.494	0.631
	DRB1*09:01:02DRB1*14:05:01	-0.7	1.822	-0.384	0.708
	DRB1*09:01:02DRB1*15:01	-0.1	1.578	-0.032	0.975
	DRB1*09:01:02DRB1*16:02:01	0.6	1.822	0.329	0.748
	DRB1*10:01DRB1*11:01	-1.2	1.578	-0.729	0.481
	DRB1*11:01DRB1*13:02:01	-0.7	1.822	-0.384	0.708
	DRB1*12:02:01DRB1*14:54	-3.9	1.822	-2.141	0.056
	DRB1*13:02:01DRB1*14:05:01	-0.5	1.822	-0.274	0.789

DRB1*13:02:01DRB1*15:01	-0.5	1.822	-0.274	0.789
DRB1*13:12:01DRB1*16:02:01	-0.7	1.822	-0.384	0.708
DRB1*14:54DRB1*15:06	-0.7	1.822	-0.384	0.708
DRB1*15:01DRB1*15:01	-0.5	1.578	-0.285	0.781
DRB1*15:02:01DRB1*16:02:01	-0.5	1.822	-0.274	0.789
DQB1*02:01:01DQB1*03:02:01	1.3	1.917	0.678	0.508
DQB1*02:01:01DQB1*03:03:02	-0.4	1.917	-0.209	0.838
DQB1*02:01:01DQB1*04:01:01	0.3	1.917	0.156	0.878
DQB1*02:01:01DQB1*06:01:01	0.4	1.660	0.241	0.813
DQB1*02:01:01DQB1*06:02:01	1.3	1.917	0.678	0.508
DQB1*02:02DQB1*02:02	-1.3	1.660	-0.783	0.446
DQB1*02:02DQB1*03:01:01	-0.6	1.660	-0.361	0.723
DQB1*02:02DQB1*03:02:01	-2.5	1.917	-1.278	0.221
DQB1*02:02DQB1*03:03:02	-0.5	1.660	-0.301	0.767
DQB1*02:02DQB1*04:01:01	0.8	1.917	0.417	0.682
DQB1*02:02DQB1*06:02:01	0.9	1.660	0.542	0.596
DQB1*02:02DQB1*06:04:01	1.3	1.917	0.678	0.508
DQB1*03:01DQB1*06:02	0.6	1.660	0.331	0.745
DQB1*03:01:01DQB1*03:03:02	1.0	1.566	0.607	0.553
DQB1*03:01:01DQB1*05:01:01	-0.1	1.566	-0.043	0.967
DQB1*03:01:01DQB1*05:02:01	-1.3	1.660	-0.783	0.446
DQB1*03:01:01DQB1*06:01:01	0.5	1.660	0.271	0.790
DQB1*03:01:01DQB1*06:09	0.3	1.917	0.156	0.878
DQB1*03:02DQB1*06:03	1.3	1.917	0.678	0.508
DQB1*03:02:01DQB1*05:03:01	3.3	1.917	1.721	0.106
DQB1*03:03DQB1*06:02	1.0	1.660	0.572	0.576
DQB1*03:03DQB1*06:03	-0.6	1.660	-0.331	0.745
DQB1*03:03:02DQB1*03:03:02	-0.7	1.917	-0.365	0.720
DQB1*03:03:02DQB1*04:01:01	-0.7	1.917	-0.365	0.720
DQB1*03:03:02DQB1*05:02:01	1.6	1.917	0.834	0.417
DQB1*03:03:02DQB1*05:03:01	0.3	1.917	0.156	0.878
DQB1*03:03:02DQB1*06:01:01	1.3	1.917	0.678	0.508
DQB1*03:03:02DQB1*06:09	-0.7	1.660	-0.422	0.679
DQB1*05:01:01DQB1*05:02:01	0.5	1.917	0.261	0.798
DQB1*05:01:01DQB1*06:02:01	1.0	1.917	0.522	0.610
DQB1*05:02:01DQB1*05:02:01	0.3	1.917	0.156	0.878
DQB1*05:03:01DQB1*06:04:01	0.5	1.917	0.261	0.798
DQB1*06:01:01DQB1*06:02:01	-0.2	1.917	-0.104	0.918
DQB1*06:01:01DQB1*06:04:01	1.3	1.917	0.678	0.508
DQB1*06:09DQB1*06:10	0.5	1.917	0.261	0.798

Beta: Logistic regression coefficients; SE: standard error; T: t statistic