Associations between HLA class II alleles and IgE sensitization to allergens in the Qatar Biobank cohort

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Background: Allergic disorders are the consequence of IgE sensitization to allergens. Population studies have shown that certain human leukocyte antigen (HLA) alleles are associated with increased or decreased risk of developing allergy.
Objective: We aimed to characterize the relationship between HLA class II allelic diversity and IgE sensitization in an understudied Arab population.
Methods: We explored associations between IgE sensitization to 7 allergen mixes and mesquite (comprising 41 food or aeroallergens) and 45 common classical HLA class II alleles in a well-defined cohort of 797 individuals representing the general adult population of Qatari nationals and long-term residents. To do so, we performed HLA calling from whole genome sequencing data at 2-field resolution using 2 independent algorithms. We then applied 3 different regression models to assess either each allergen mix independently, in the context of IgE sensitization to other allergens tested, or polysensitization.
Results: More than half (n = 447) of the study participants showed IgE sensitization to at least 1 allergen, most of them (n = 400) to aeroallergens (Phadiatop). We identified statistically significant negative and positive associations with 24 HLA class II alleles. These have been reported to confer risk or protection from variety of diseases; however, only a few have previously been associated with allergy in other populations.
Conclusions: Our study reveals several new risk and protective genetic markers for allergen-specific IgE sensitization. This is a first and essential step toward a better understanding of the origins of allergic diseases in this understudied population. (J Allergy Clin Immunol Global 2023;2:100117.)

Key words: *Allergens, association study, IgE sensitization, Qatar Biobank*

Allergic IgE sensitization is a prerequisite and first step in the development of clinical type 1 hypersensitivity/allergic disorders.[1] Such sensitization is characterized by allergen-specific IgE in the serum or plasma, or an immediate weal and flare reaction on skin prick testing that exceeds clinically defined thresholds. IgE-associated allergy affects approximately a third of the human population and comprises a spectrum of immune disorders of varying severity, including allergic rhinitis and conjunctivitis (ie, hay fever), allergic asthma, atopic dermatitis, food allergy, oral allergy syndrome, acute urticaria/angioedema, and anaphylaxis (eg, to medications, venoms).[2,3]

Despite its prevalence, the underlying pathophysiology, mechanisms, and contributing factors of IgE-associated allergy are incompletely understood.[3] At the molecular level, primary allergic sensitization is characterized by allergen exposure and human leukocyte antigen (HLA) class II–dependent presentation of allergen-derived peptides by antigen presenting cells to naive T lymphocytes, followed by loss of tolerance of these cells to otherwise benign antigens followed by their differentiation into T_H2 cells. These allergen-specific T_H2 cells then promote B-cell activation, differentiation, and class switching, resulting in the production of allergen-specific IgE.[3] Upon reexposure of sensitized individuals to the allergen, which may occur at any age, allergen binding to these IgE antibodies can then lead to more aggressive and rapid histamine-mediated responses, which underpin the clinical manifestations of an allergic response through the activation of basophils and tissue-resident mast cells.[4] While this host defence mechanism has evolved to protect against parasitic infections and venoms of arthropods, other invertebrates, or vertebrates,[5,6] in modern-day human life, seemingly maladaptive IgE-mediated immune responses to otherwise benign allergens have become more prevalent, negatively affecting human health and quality of life. A variety of factors have been postulated to explain the recent increase in prevalence of allergic diseases, including urbanization and pollution, the hygiene hypothesis, different dietary exposure/habits, altered early life feeding, and changes in the microbiome.[7]

Given the critical role of the HLA class II glycoproteins in primary allergic sensitization and the high level of genetic diversity of these genes among the human population,[8] it is not surprising that associations between certain HLA types and responsiveness toward allergens were identified even before the completion of the Human Genome Project.[9,10] Nonetheless, previous genetic association studies have predominantly been conducted in populations of European ancestry, while studies in other populations are still significantly underpowered.[11] Here, we leveraged data from 800 adults in the Qatar Biobank (QBB) cohort study. This population-based long-term study aims to collect high-quality biological samples and curated data to

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Received for publication July 6, 2022; revised January 16, 2023; accepted for publication February 5, 2023.
Available online May 18, 2023.
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The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections
2772-8293

https://doi.org/10.1016/j.jacig.2023.100117

support biomedical research with the goal of improving the health of the population of Qatar and the larger Middle East and North Africa region. Thus, a subset of this well-defined cohort was selected to represent the general Arab population, which primarily included Qatari nationals as well as a small number of long-term residents of Qatar. This largely understudied population has more limited genetic diversity compared to populations of European ancestry and is primarily composed of individuals with Arab, Persian, North African, and South Asian ancestry.[12-14] We conducted a systematic candidate gene association study focused on classical HLA class II genes and IgE sensitization to 41 food and inhaled allergens. Such associations may be used in the future to identify individuals at risk who may benefit from interventions even before they develop clinical symptoms.

METHODS

Study cohort

The study subjects included 800 adult Qatari nationals and long-term residents of Qatar, who were randomly selected from the larger QBB cohort[15] as described previously.[14,16] Their relevant demographic data are shown in Table E1 in this article's Online Repository (available at www.jaci-global.org) and have been described previously.[16]

Our human subject research was approved by the institutional research ethics boards of Sidra Medicine and QBB. This included the receipt of written informed consent from all study participants at the recruitment site, QBB.

Inference of HLA class II alleles from whole genome sequence data

Whole genome sequencing data with 30× minimum average coverage were obtained as described previously.[12,14,17] Only alleles from classical HLA class II genes were considered for our downstream association studies. HLA-DRA alleles were excluded because of the absence of polymorphisms in sequences encoding the peptide-binding groove.[8] To mitigate a possible effect of HLA typing errors, 2 independent methods were used, namely HLA*LA[18] and HLA-HD (v1.4.0),[19] and the HLA types for each individual at 2-field resolution (ie, the protein sequence) was inferred. For both methods, an updated HLA allele dictionary from the IPD-IMGT/HLA Database (v3.45) was used with default options, as described in the respective repositories.[20,21] Alleles with discordant HLA typing results obtained using the 2 methods (ie, alleles for which the allele frequency deviated by >5%), as well as rare alleles with a minor allele frequency (MAF) <1, were excluded. On the basis of these criteria, a total of 45 alleles from the 5 HLA class II genes (Table I) were retained for downstream association studies.

Measurement of allergen-specific, and total IgE

Allergen-specific serum IgE levels were measured by fluorescent enzyme immunoassay using a Phadia 250 analyzer (Thermo Fisher Scientific, Waltham, Mass). For each study subject, allergen-specific IgE responses to 7 allergen mixes and mesquite tree pollen, comprising 41 food and inhaled allergens in total (Table II), were measured. An IgE level of >0.34 kUA/L was considered positive for sensitization of a given study subject to an allergen mix. The total IgE levels in each sample were also measured using the Invitrogen eBioscience Human IgE ELISA Ready-SET-Go! Kit (Thermo Fisher Scientific) in accordance with the manufacturer's recommendations.

Statistical analysis

A Pearson correlation analysis was used to test for associations between IgE sensitization to the different allergen mixes among the study subjects in our cohort. Associations between sensitization to allergens and HLA class II alleles were assessed by logistic regression using age, sex, the first 4 genetic principal components and normalized IgE levels as covariates. The first 4 genetic principal components were computed from common variants (MAF >5%) detected in the whole genome sequences of the study subjects using PLINK (v1.9).[22] Three association models were used to explore relationships between HLA class II types and IgE sensitization to allergens. In the first model, each HLA class II allele that met the criteria described above served as the dependent variable. Positive or negative test results for each individual and allergen test served as independent categorical variables,[23] thereby allowing for an independent assessment of IgE sensitization to specific types of allergens (Table II). The following equation was applied:

$$\text{allele}_{i=[1-45]} = \beta_{allergen\ mix=[1-8]} * allergen\ mix_{i=[1-8]} + \beta_{\text{cov}} * \text{cov}ariates + \in_1$$

Alleles were assigned a binary value (ie, "0" if absent in a given individual, or "1" if present, irrespective of zygosity). $\beta_{allergen\ mix=[1-8]}$ represents the coefficient of association for each allergen mix and ε_1 an intercept of the logistic regression model.

Alternatively, we used a multinomial logistic regression model, where each allele was treated as a dependent variable and IgE sensitization to each allergen mix was treated as a nominal outcome variable. This model allowed us to examine genetic associations with IgE sensitization to each allergen mix in the context of IgE sensitization to other allergens tested. In this way, possible effects from correlations between IgE sensitization to different mixes that either share an allergen component (eg, both food mixes fx1 and fx5 contain peanut as an allergen component; Table II), or were due to cross-sensitization to related allergens (eg, food mixes fx1 and fx22 are both nut mixes but do not share an allergen component) could be controlled for. The following equation was used:

$$\begin{aligned} allele_{i=[1-45]} = {} & \beta_{fx1} * fx1 + \beta_{fx2} * fx2 + \beta_{fx5} * fx5 \\ & + \beta_{fx22} * fx22 + \beta_{wx1} * wx1 + \beta_{gx2} * gx2 \\ & + \beta_{t20} * t20 + \beta_{phad} * phad + \beta_{\text{cov}} * \text{cov}ariates + \in_1 \end{aligned}$$

Finally, associations between HLA class II alleles and IgE polysensitization to allergens, irrespective of the type of allergen, were assessed by utilizing a multivariate logistic regression model. A polysensitization score per individual was used as the outcome variable. This score was calculated by dividing the total number of positive IgE sensitization tests per individual by 8 as the number of tests performed for each individual sample. The following equation was used:

TABLE I. Common HLA class II alleles assessed in this study (n = 45)

Gene	Allele	Allele frequency	
		HLA-HD	HLA-LA
DPA1	DPA1*02:02	0.070	0.063
DPB1	DPB1*01:01	0.037	0.037
DPB1	DPB1*02:01	0.181	0.181
DPB1	DPB1*04:02	0.034	0.048
DPB1	DPB1*09:01	0.018	0.018
DPB1	DPB1*10:01	0.023	0.023
DPB1	DPB1*13:01	0.052	0.054
DPB1	DPB1*14:01	0.073	0.076
DPB1	DPB1*17:01	0.024	0.026
DQA1	DQA1*01:01	0.032	0.073
DQA1	DQA1*01:03	0.056	0.056
DQA1	DQA1*02:01	0.176	0.176
DQA1	DQA1*03:01	0.116	0.148
DQA1	DQA1*04:01	0.016	0.017
DQB1	DQB1*03:01	0.103	0.116
DQB1	DQB1*03:02	0.123	0.123
DQB1	DQB1*03:03	0.011	0.011
DQB1	DQB1*04:02	0.025	0.025
DQB1	DQB1*05:01	0.063	0.063
DQB1	DQB1*05:02	0.154	0.154
DQB1	DQB1*05:03	0.014	0.014
DQB1	DQB1*06:01	0.024	0.024
DQB1	DQB1*06:02	0.049	0.049
DQB1	DQB1*06:03	0.040	0.040
DQB1	DQB1*06:04	0.029	0.029
DRB1	DRB1*01:01	0.021	0.021
DRB1	DRB1*01:02	0.014	0.014
DRB1	DRB1*03:01	0.159	0.159
DRB1	DRB1*03:02	0.016	0.016
DRB1	DRB1*04:02	0.046	0.042
DRB1	DRB1*04:03	0.058	0.054
DRB1	DRB1*04:05	0.019	0.017
DRB1	DRB1*07:01	0.181	0.151
DRB1	DRB1*08:04	0.012	0.012
DRB1	DRB1*10:01	0.026	0.026
DRB1	DRB1*11:01	0.039	0.038
DRB1	DRB1*11:04	0.029	0.029
DRB1	DRB1*13:01	0.035	0.035
DRB1	DRB1*13:02	0.040	0.040
DRB1	DRB1*13:03	0.013	0.013
DRB1	DRB1*15:01	0.056	0.056
DRB1	DRB1*15:02	0.018	0.018
DRB1	DRB1*15:03	0.012	0.012
DRB1	DRB1*16:01	0.027	0.027
DRB1	DRB1*16:02	0.114	0.105

$$allele_{i=[1-45]} = \beta_{score} * score + \beta_{\mathrm{cov}} * \mathrm{cov}ariates + \in_1$$

P values were corrected for multiple testing using the Holm method.[24] Stringent thresholds were selected to filter for statistically and biologically meaningful associations, considering both the magnitude of the association ($|\beta| \geq 0.68$; ie, the natural log-transformed representation of an odds ratio of >2 or <0.5) and significance ($P \leq .005$). For each association model, possible class imbalance was taken into account by leveraging a combined method for over- and undersampling using the synthetic minority oversampling technique (SMOTE) as well as the edited nearest neighbors (ENN) method to reduce the noise from oversampling events.[25-27] A cross-validation with 100-fold bootstrapping for each association model was also performed. Associations that did not remain statistically significant in ≥90% of the iterations with at least 1 HLA typing method were disregarded. Significant associations were reported as median values of β and the corrected *P* values. All statistical analyses and data visualizations were performed using in-house Python (v3.9) scripts with Statsmodels (v0.14) for regression and multiple testing (https://www.statsmodels.org). Imbalance-learn (v0.8.1) was used for class resampling (https://imbalanced-learn.org), and graphical and statistical packages, such as Matplotlib (v3.4.3), Seaborn (v0.11), and Altair (v4.1), were used to generate figures.

TABLE II. IgE sensitization to allergens in QBB cohort (n = 797)

Allergen-specific IgE (no. of allergens per test, abbreviation)*	No. (%)
Phadiatop aeroallergen mix including cat, dog, horse dander, house dust mite, flour mite, *Cladosporium herbarum*, timothy grass, silver birch, olive, mugwort, and nettle pollens (n = 11, phad)	358 (44.9)
Mixed weeds including *Chenopodium album*, plantago, *Salsola kali*, artemisia, and ambrosia (n = 5, wx1)	200 (25.1)
Seafood mix including cod,‡ tuna, shrimp, mussel, and salmon (n = 5, fx2)	151 (18.9)
Mixed grasses including Bermuda grass, rye, timothy, meadow, Johnson, and Bahia (n = 6, gx2)	92 (11.5)
Food allergen mix including milk, peanut,† soya, wheat, cod,‡ and egg white (n = 6, fx5)	84 (10.5)
Mesquite pollen (n = 1, t20)	72 (9.0)
Nut mix including pistachio, cashew, pecan, and walnut (n = 4, fx22)	51 (6.4)
Nut mix including Brazil nut, almond, peanut,† hazelnut, and coconut (n = 5, fx1)	29 (3.6)

*Positive allergen-specific IgE test result was defined as >0.34 kUA/L.
†Peanut is a component of 2 allergen mixes, fx5 and fx1.
‡Cod is a component of 2 allergen mixes, fx5 and fx2.

RESULTS

Sensitization to allergens in the QBB cohort

In our first set of analyses, we assessed the prevalence of IgE sensitization in a subset of the QBB cohort, representing adults of a largely understudied general population in the greater Middle East.[15,28] We successfully tested 797 study subjects of the QBB cohort for IgE sensitization to 7 different allergen mixes and mesquite tree (Table II; we had to exclude data from 3 subjects as a result of insufficient quantity of serum samples for allergen-specific IgE testing). Of these individuals, 98% (n = 780) were Qatari nationals (Table E1). Of the successfully tested subjects, 51.7% (n = 412) showed IgE sensitization to at least 1 allergen (Fig 1, *A*). A small fraction (1.7%, n = 14) of individuals showed sensitization to all the food and inhaled allergen mixes tested (Fig 1, *A*). Among the sensitized individuals, most had IgE antibodies against the Phadiatop (phad) aeroallergen mix (n = 358), followed by a weed mix (wx1; n = 200) and the seafood allergens (fx2; n = 151) (Table II and Table E1). As expected, sensitization to nut allergen mixes (fx1 and fx22) was highly correlated (Pearson correlation >0.8) and to a lesser extent with IgE sensitization to a food allergen mix (fx5) including milk, peanut, soya, wheat, cod, and egg white. Similarly, IgE sensitization to mesquite pollen allergen (t20) and mixed weeds (wx1) were highly correlated. In contrast, sensitization to mixed grass

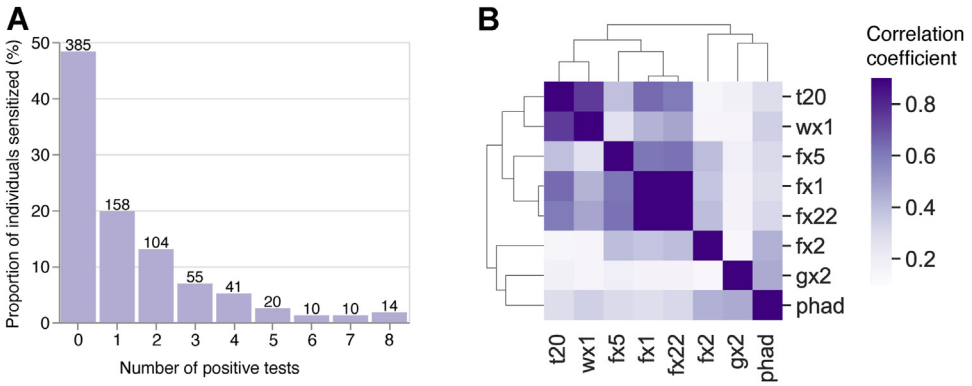

FIG 1. Proportion of individuals with allergen-specific IgE sensitization and correlations among positive test results. **A,** Bar diagram depicting proportion of individuals that either showed no IgE sensitization, or individuals who showed IgE sensitization to 1 or more allergen mixes (total numbers per group are shown on *top of each bar*). **B,** Pearson correlation among positive tests in tested individuals.

(gx2) was only weakly correlated with sensitization to the phad mix, and even less so to the other allergen mixes tested (Fig 1, *B*).

Associations between total IgE levels and allergen-specific IgE sensitization

Having identified a relatively high prevalence of IgE sensitization among our general adult population cohort, we next explored relationships between IgE sensitization status to the allergen mixes assessed in this study as the response variable and variables such as sex, age, total IgE levels, and the first 4 genetic principal components (which we assessed to account for possible effects of the population genetic structure) as explanatory variables using a linear regression model. As expected, total IgE levels were significantly associated with allergen sensitization; we did not find any significant associations for other regressors (see Table E2 in the Online Repository at www.jaci-global.org). We also examined the associations between the proportions of positive test results for IgE sensitization to the tested allergen mixes per individual (nominal response variable) and the same set of explanatory variables using a generalized linear model, thereby allowing us to test for associations with polysensitization. Again, only total IgE levels were significantly and positively associated with IgE polysensitization (Table E2).

Association of HLA class II alleles with IgE sensitization to allergens

Next, we explored the relationships between a total of 45 HLA class II alleles (Table I) and IgE sensitization to the allergens described above. First, we explored relationships between the selected HLA class II alleles and IgE sensitization to each specific allergen mix separately. We identified 37 significant associations between 20 HLA class II alleles and IgE sensitization to 6 allergen mixes (phad, wx1, fx2, fx5, t20, and gx2) (Fig 2, *A,* and see Table E3 in the Online Repository at www.jaci-global.org). Most of these associations (n = 30) were statistically significant after cross-validation, regardless of the HLA typing method used (Fig 2, *A,* and Table E3). In accordance with the larger number of individuals sensitized to aeroallergens and mixed weeds as described above, significant genetic associations were most frequently found with IgE sensitization to these 2 allergen mixes (wx1 and phad), revealing both risk alleles (eg, DQB1*06:03, DQB1*06:04, DRB1*01:02, DRB1*13:01 and DRB1*13:02) and protective alleles (eg, DQB1*05:03, DRB1*11:04 and DRB1*13:03). Of note, some alleles (eg, DRB1*01:02, DRB1*08:04 and DRB1*10:01) seemed to confer protection against IgE sensitization to one allergen mix and at the same time represent a risk allele in the context of IgE sensitization to another allergen mix (Fig 2, *A*). Significant associations between HLA class II alleles and the other allergen mixes were less frequent, in line with the smaller proportion of sensitized individuals. Some associations (eg, with the seafood mix) were less robust because our stringent criteria for statistical significance were only met based on the results of one of the HLA typing methods used, and therefore may also be a spurious association resulting from a typing error (Fig 2, *A*).

Next, we examined IgE sensitization to each allergen mix in the context of IgE sensitization to the other allergen mixes tested using a second, multinomial logistic regression model and the same covariates as used in our first regression model. We observed 30 significant associations between 18 HLA class II alleles and IgE sensitization to 6 allergen mixes, of which 21 associations were statistically significant regardless of the HLA typing method used (Fig 2, *B,* and see Table E4 in the Online Repository at www.jaci-global.org). In accordance with the previous model, we identified multiple risk alleles (eg, DQB1*06:04, DRB1*01:02, and DRB1*10:01) that correlated positively with IgE sensitization to the Phadiatop aeroallergen mix and mixed weeds (wx1). Alleles with a protective role in IgE sensitization to various allergens (eg, DPB1*09:01, DPB1*17:01, DRB1*11:04, DRB1*13:03, and DRB1*15:03) were also identified. Notably, we found 10 associations between a specific HLA class II allele and allergen mix that were significant in both models applied, and regardless of the HLA typing method used (Table E4).

Using a third regression model, we assessed associations between HLA class II alleles and IgE polysensitization to allergens, irrespective of the type of allergen. Using this approach, we found 7 HLA class II alleles that were significantly associated with polysensitization, including 5 protective alleles (DPB1*09:01, DPB1*10:01, DRB1*11:04, DRB1*13:03, and DRB1*16:01) and 2 risk alleles (DRB1*01:02 and DRB1*13:01) (Fig 2, *C,* and see Table E5 in the Online

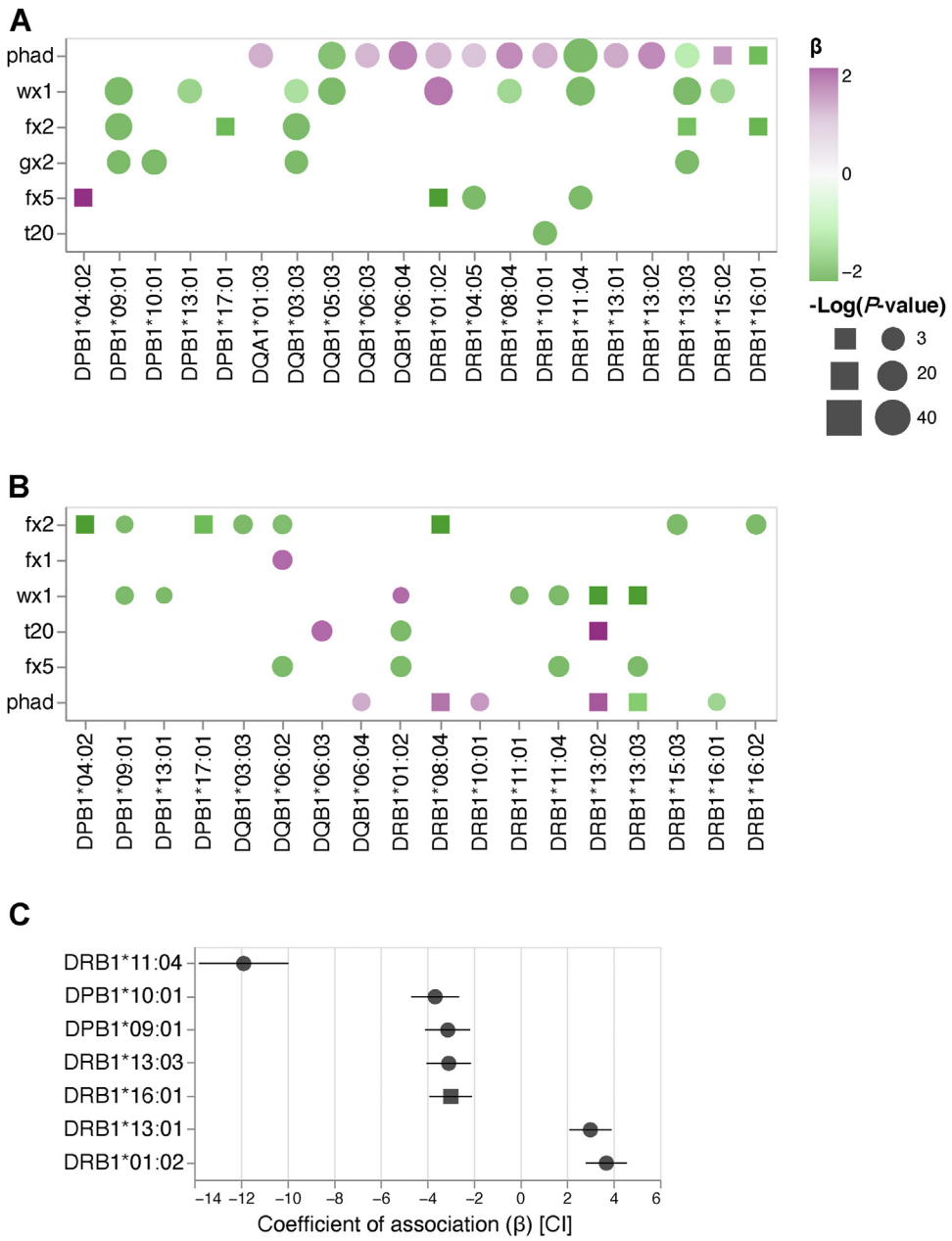

FIG 2. Significant associations between HLA class II alleles and IgE sensitization to inhaled and food allergens. **A** and **B,** Heat maps depicting significant associations between alleles listed in Table I and IgE sensitization to allergen mixes listed in Table II, either determined by logistic regression (model 1) assessing each specific allergen mix separately *(A)* or using a multinomial logistic regression model (model 2) *(B).* **C,** Forest plot depicting significant associations between HLA class II alleles and IgE polysensitization to allergens, irrespective of type of allergen (model 3). In *(A)* and *(B),* coefficient (β) and direction of associations are indicated by *color gradient* for each symbol. *Symbol size* depicts $-\log_{10}$ (adjusted *P* value) of association. *Round symbols* show aggregated *P* values for associations that remained statistically significant after cross-validation and regardless of HLA typing method used. *Square symbols* show *P* values when associations reached statistical significance with only 1 of 2 HLA typing methods used (ie, either HLA*LA or HLA-HD). Only significant associations are shown. Error bars in *(C)* depict 95% confidence interval (95% CI).

Repository at www.jaci-global.org). Of note, all these alleles were also associated with IgE sensitization to individual allergen mixes, as described above.

Finally, we compared the MAFs of all HLA class II alleles for which no association was found with the MAFs of those HLA class II alleles for which we had identified a significant association with IgE sensitization using at least 1 of the 3 regression models we used. Interestingly, we found a statistically significant bias ($P < .001$) toward lower MAF among the group of alleles associated with IgE sensitization (Fig 3).

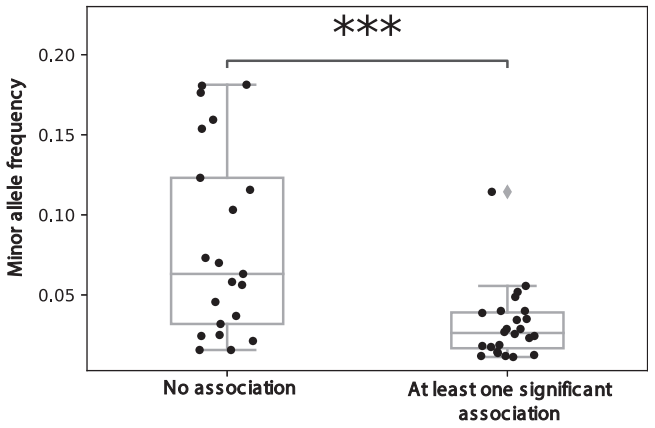

FIG 3. Relationship between allele frequency and IgE sensitization to allergens. Box blot showing minor allele frequency of 45 alleles assessed in this study, stratified into 2 groups: *(i)* alleles for which no significant associations with IgE sensitization to allergens were identified; and *(ii)* alleles for which our regression analyses revealed at least 1 statistically significant association. Both groups were compared by Mann-Whitney-Wilcoxon test (2 sided) with Bonferroni correction. Error bars represent minimum and maximum values, respectively. ***$P < .001$.

DISCUSSION

Nationals and residents of Qatar represent an understudied population of the greater Middle East; the origins of allergy and asthma in this and other populations remain incompletely understood. In this study, we used a systematic, unbiased approach to explore the relationships between classical HLA class II alleles and IgE sensitization to a broad panel of inhaled and food allergens. To do so, we leveraged available samples and genomic data from a subset of the well-defined QBB cohort.[15,28] Of these individuals, 51.7% showed IgE sensitization to at least 1 allergen. This prevalence rate is consistent with a previous study of young adult blood donors showing atopic sensitization in 50.2% in Kuwaiti nationals.[29] To mitigate spurious associations, we performed rigorous regression analyses based on alleles inferred by 2 independent HLA typing methods. Furthermore, we used 3 different regression models to explore relationships between the selected HLA class II alleles and IgE sensitization, by one of assessing each allergen mix independently (model 1), in the context of IgE sensitization to other allergens tested (model 2), or polysensitization (model 3). Interestingly, of the significant associations that we identified between specific HLA class II alleles and IgE sensitization to individual allergen mixes either by using models 1 or 2, or both, most alleles were negatively associated with IgE sensitization. These findings suggest that these alleles play a protective role in the context of allergy and asthma.

Nonetheless, a small number of the tested HLA class II alleles were significantly and positively associated with IgE sensitization to selected allergens. These alleles represent risk alleles for allergic diseases. All 24 alleles that we found to be associated with IgE sensitization to allergens have been previously associated with risk and/or protection from various clinical conditions, including systemic autoimmune and inflammatory diseases, congenital disorders, chronic viral infection, and vaccine responses (Table III).[30-79] However, only a few have already been demonstrated to be associated with allergic diseases and asthma in other populations. For example, HLA-DQB1*06:03 has been shown to be a risk factor for peanut allergy;[80] while DRB1*04:05 and HLA-DQB1*03:03 are risk factors for shrimp and peach allergy, respectively.[81] In addition, a haplotype encoding DQB1*06:04 has been reported to confer protection from asthma.[82] We identified DQB*06:02 as a risk allele for IgE sensitization to the nut allergen mix fx1, although no associations with nut allergen mix fx22 were detected, possibly because of the small proportion of individuals in our cohort who were sensitized to these allergens.

A study of a European cohort demonstrated that DQB1*05:01, DQA1*01:01, and DRB1*01:01 were strongly and positively associated with IgE sensitization to pollen allergens, particularly to mugwort pollen (Art v 1).[23] While our study did not reveal similar associations in the QBB cohort, we identified several other risk alleles for IgE sensitization to the Phadiatop aeroallergen mix, which contained mugwort pollen. Direct comparisons between different cohort studies remain difficult for several reasons. Apart from the obvious geographic (ie, environmental) and ethnic (ie, population genetic and cultural) differences, compared to our cohort, the French cohort assessed by Gheerbrant et al[23] comprised participants who were selected by using a diagnosis of asthma or familial relationship with asthma cases as a specific inclusion criterion. In contrast, the adult participants assessed in our study were primarily recruited on the basis of Qatari nationality or long-term residency in Qatar, without considering any clinical and phenotypic features or familial relationships as inclusion criteria. Notwithstanding these important differences, it is interesting to note that most associations we identified between HLA class II alleles and IgE sensitization were negative (ie, may play a protective role), whereas associations identified by Gheerbrant et al were predominantly positive. Because our cohort is more representative of the general adult population (with Arab ancestry), it is tempting to speculate that IgE sensitization to allergens is a strong driver of balancing selection and that both favorable as well as seemingly disadvantageous HLA class II alleles have arisen during hominine evolution. Interestingly, of all the HLA class II alleles assessed in the present study, significant associations were primarily found with less common alleles (Fig 3), suggesting a role of negative frequency-dependent selection (also referred to as rare allele advantage) against overt IgE sensitization as a mechanism for balancing the selection of different HLA alleles.[8,83]

It is also important to highlight limitations of our study. Allergic diseases are a consequence of gene–environment interactions, and not all sensitized individuals develop allergic diseases. Nonetheless, a recent cross-sectional study[84] revealed that the prevalence of diagnosed asthma, lifetime allergic rhinitis, and diagnosed eczema among children in Qatar was as high as 34.6%, 30.9%, and 37.4%, respectively. These findings suggest that a considerable proportion of the sensitized individuals assessed in this present study may also have clinical signs of allergic disease. However, it was not possible for us to test for disease associations in our cohort because robust data on asthma and allergy status of the assessed participants were unavailable. Moreover, HLA typing methods from whole genome sequencing data are prone to error[85,86] and may give rise to spurious associations. We attempted to overcome this limitation by utilizing 2 of the most popular and independent methods, namely HLA*LA and HLA-HD, along with an up-to-date allele dictionary from the IPD-IMGT/HLA Database. Another weakness of our study is that we tested for associations

TABLE III. Alleles associated with IgE sensitization to allergens and their associations with disease susceptibility or protection, as reported elsewhere

Allele	No. of significant associations (positive/negative)†	Previously reported associations with disease susceptibility or protection	
		Disease	Reference
DPB1*04:02	2 (1/1)	HBV infection	30
DPB1*09:01	4 (0/4)	HBV infection, rheumatoid arthritis, systemic sclerosis	30-34
DPB1*10:01	2 (0/2)	Severe aplastic anemia	35
DPB1*13:01	1 (0/1)	Systemic sclerosis, cervical cancer	36,37
DPB1*17:01	1 (0/1)	Behçet disease, primary biliary cholangitis	38,39
DQA1*01:03	1 (1/0)	Immune-mediated thrombotic thrombocytopenic purpura	40
DQB1*03:03	3 (0/3)	Peach allergy, type 1 diabetes, coronary artery disease, antineutrophil cytoplasmic antibody-associated vasculitis, multiple sclerosis, type 1 diabetes	81,41-45
DQB1*05:03	2 (1/1)	Coronary artery disease, idiopathic achalasia, Parkinson's disease, chronic anterior uveitis	42,46-49
DQB1*06:02	3 (1/2)	Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis	50
DQB1*06:03	2 (2/0)	Peanut allergy, Behçet disease, type 1 diabetes	80,39,45
DQB1*06:04	1 (1/0)	Asthma, azoospermia, cervical cancer, HBV vaccine responsiveness, primary biliary cholangitis	82,51-54
DRB1*01:02	5 (3/2)	Pemphigus foliaceus, congenital adrenal hyperplasia	55,56
DRB1*04:05	2 (1/1)	Shrimp allergy, hypersensitivity pneumonitis, rheumatoid arthritis, enteric fever, autoimmune hepatitis	81,57-60
DRB1*08:04	3 (1/2)	Pemphigus vulgaris	55
DRB1*10:01	2 (1/1)	Rheumatoid arthritis, breast cancer, Anti-IgLON5 disease	61-63
DRB1*11:01	1 (0/1)	IJEV-induced neutralizing antibody responses, type 1 diabetes, idiopathic achalasia, breast cancer, primary biliary cirrhosis, recurrent respiratory papillomatosis, hepatitis C virus infection susceptibility, chronic kidney disease, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, colitis-associated colorectal carcinoma	34,45,47,50,59,61,64-68
DRB1*11:04	4 (0/4)	Allergic bronchopulmonary aspergillosis, systemic sclerosis	50,69
DRB1*13:01	2 (2/0)	Systemic sclerosis, hypersensitivity pneumonitis, colorectal carcinoma, type 1 diabetes, Behçet disease, autoimmune hepatitis	39,45,59,66,69-71
DRB1*13:02	3 (2/1)	Azoospermia, cervical cancer, HBV vaccine responsiveness, Hashimoto thyroiditis, rheumatoid arthritis, systemic lupus erythematosus	51,53,54,58,70,72,73
DRB1*13:03	6 (0/6)	Congenital adrenal hyperplasia	56
DRB1*15:02	2 (1/1)	Systemic sclerosis	74
DRB1*15:03	1 (0/1)	Alloantibody development in thalassemia patients, autoimmune bullous disease	75,76
DRB1*16:01	3 (0/3)	Progressive chronic tubulointerstitial disease	77
DRB1*16:02	1 (0/1)	Dapsone hypersensitivity syndrome, autoimmune diseases	78,79

HBV, Hepatitis B virus; *IJEV,* inactivated Japanese encephalitis vaccine.
†Total number of significant HLA associations between 2 variables, as demonstrated in the present study. The association was counted only once if a significant association was found between the same variables by 2 different models; for example, a positive association between DRB1*11:04 and IgE sensitization to the Phadiatop aeroallergen mix was demonstrated by regression models 1 and 2. Polysensitization was considered an independent variable.

between HLA class II alleles and levels of sensitization to allergen mixes rather than single allergens. Unfortunately, insufficient sample volume per study subject, small sample size, and cost of conducting single allergen testing prohibited us from conducting the latter analysis. Notwithstanding these limitations, on the basis of our systematic study of a cohort comprising the general adult Arab population, we report—for the first time in this population—the prevalence of IgE sensitization to a broad panel of allergens. Furthermore, we demonstrate significant associations between 24 common HLA class II alleles and IgE sensitization to various food and inhaled allergens. Only a few of these associations have been reported in other populations. Future targeted genetic association studies (eg, case–control studies) in independent cohorts are needed to affirm the associations between the HLA-DPB1, -DQB1, and -DRB1 alleles reported here with clinical outcomes of allergic diseases, such as asthma, allergic rhinitis, food allergy, anaphylaxis, and eczema.

DISCLOSURE STATEMENT

Supported in part by a grant from the Qatar National Research Fund (PPM1-1220-150017) and by funds from Sidra Medicine (SDR400127).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

We thank all QBB study participants who generously provided samples and data for this study. We also thank the Qatar Genome Programme and QBB staff who participated in the setting of the QBB study, sample collection, and demographic data acquisition; the Integrated Genomics Services team of Sidra Genomics for generating and processing raw whole genome sequencing data of study participants; and Jessica Tamanini (Insight Editing, London) for proofreading and editing the report.

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