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HLA-Associated Phenotypes in Youth with Autoimmune Diabetes

Mary Helen Black, Ph.D.[1], **Jean M. Lawrence, Sc.D., M.P.H., M.S.S.A.**[1], **Catherine Pihoker, M.D.**[2], **Lawrence M. Dolan, M.D.**[3], **Andrea Anderson, M.S.**[4], **Beatriz Rodriguez, M.D., Ph.D.**[5], **Santica M. Marcovina, Ph.D., Sc.D.**[6], **Elizabeth J. Mayer-Davis, Ph.D.**[7], **Giuseppina Imperatore, MD, Ph.D.**[8], and **Dana Dabelea, M.D., Ph.D.**[9] for the SEARCH for Diabetes in Youth Study Group

[1]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, California

[2]Department of Pediatric Endocrinology, Children's Hospital & Regional Medical Center, Seattle, Washington

[3]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[4]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina

[5]University of Hawaii at Manoa, Honolulu, Hawaii

[6]Department of Medicine, Northwest Lipid Research Laboratories, Seattle, Washington

[7]Department of Nutrition, University of North Carolina, Chapel Hill, North Carolina

[8]Division of Diabetes Translation, Centers for Diseases Control and Prevention, Atlanta, GA

[9]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO

Abstract

Objectives—To examine *HLA* DRB1-DQB1 haplotypes within a multi-ethnic cohort and assess their association with characteristics of diabetes onset.

Methods—The sample included 1,662 participants from the SEARCH for Diabetes in Youth Study who tested positive for GADA and/or IA-2A autoantibodies. Blood drawn at the study visit was used to measure fasting C-peptide and genotype *HLA* DRB1 and DQB1 loci. Diabetic ketoacidosis (DKA) at diagnosis was determined from medical records. Multivariable linear and logistic regression models stratified by race/ethnicity were used to assess associations with DRB1-DQB1 haplotypes.

Results—The frequency of DRB1*03 susceptibility haplotypes ranged 27.5–28.9% in all racial/ethnic groups. The frequency of susceptibility DRB1*04-DQB1*0302 was higher in non-Hispanic white (NHW; 34.1%) and Hispanic (38.9%) compared to non-Hispanic black (NHB; 20.8%) youth. Neutral and protective haplotypes were low frequency in all groups. DBR1*03 haplotypes were associated with younger age at diagnosis in NHW and positivity for multiple autoantibodies in Hispanics. DRB1*04-DQB1*0302 haplotypes were associated with multiple autoantibody

Corresponding Author: Mary Helen Black, PhD, Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles, 2nd floor, Pasadena CA 91101, Telephone 626-564-3553; Facsimile 626-564-7872, MaryHelen.X.Black@kp.org.

positivity in NHW and Hispanics, and lower fasting C-peptide and higher odds of DKA in Hispanics only. Although protective DRB1*04-DQB1*0301 haplotypes were associated with older age at diagnosis in NHW, they were also associated with multiple autoantibody positivity in these youth. Protective DRB1*13 haplotypes were associated with decreased odds of multiple autoantibody positivity in NHB youth.

Conclusions—The distribution of DRB1-DQB1 haplotypes and their association with onset-related characteristics of autoimmune diabetes varies across major racial/ethnic groups in the United States. This may contribute to variation in clinical presentation of autoimmune diabetes by race/ethnicity.

Keywords

HLA; type 1 diabetes; autoantibodies; diabetic ketoacidosis; fasting C-peptide

INTRODUCTION

Type 1 diabetes mellitus is a chronic autoimmune disease characterized by progressive beta cell destruction and subsequent insulin deficiency. Onset typically occurs in childhood or adolescence, concomitant with the presence of autoantibodies such as glutamic acid decarboxylase-65 (GADA) and insulinoma-associated antigen 2 (IA-2A) (1,2). First-degree relatives of individuals with autoimmune diabetes are more likely to express these autoantibodies and are at increased risk for developing type 1 diabetes, which indicates a role for genetic factors in the etiology of the disease (3,4).

Key genetic determinants of the autoimmune component of type 1 diabetes have been identified in the major histocompatibility class II regions of chromosome 6, such as Human Leukocyte Antigen (*HLA*) DRB1 and DQB1 (5–11). Although susceptibility and resistance to type 1 diabetes have mapped to these loci, studies reporting these associations were conducted primarily in Caucasian populations (6,7,9,10). Few studies have investigated the race/ethnicity-specific distribution of alleles at these *HLA* loci in black (5,12) or Hispanic populations (11–13). Moreover, the joint effect of these loci on specific clinical characteristics of onset and severity, especially in these minority populations, is not well understood.

SEARCH for Diabetes in Youth (SEARCH) is a large multi-center observational study among a racial/ethnically diverse population of children and adolescents with diabetes. We describe the distribution of DRB1-DQB1 haplotypes in non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanic youth with autoantibody-positive type 1 diabetes, and examine the associations between these haplotypes and clinical characteristics of diabetes, such as age at diagnosis, presence of diabetic ketoacidosis (DKA) at onset, multiple autoantibody positivity, and fasting C-peptide (FCP) levels.

METHODS

Population and Data Sources

SEARCH began conducting population-based ascertainment of youth with clinically diagnosed diabetes < 20 years of age in 2001 and continues to enroll youth with newly-diagnosed (incident) diabetes (14). SEARCH participants who completed an initial survey were asked to participate in an in-person study visit. At the time of the visit, informed consent and assent (when applicable) were obtained, health questionnaires administered, anthropometrics measured, and blood samples drawn from metabolically stable participants (no episodes of DKA during the previous month) after a minimum 8-hour overnight fast. All measures were conducted by trained, certified staff using standardized study protocols.

Blood samples were processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories) for analysis. Institutional review board(s) for each center approved the study protocol.

Demographic and Clinical Characteristics

Race/ethnicity was obtained through self-report using standard census questions (15). Youth who reported Hispanic ethnicity were categorized as Hispanic; non-Hispanic youth who reported more than one race (n=36) were categorized using the National Center for Health Statistics' plurality approach (16). According to this algorithm, youth who self-identified as both black and NHW (n=26), or as black and Asian/Pacific Islander (n=1) were categorized as NHB. Youth who self-identified as NHW and any race/ethnicity other than Hispanic, black or Asian/Pacific Islander, were categorized as NHW (n=9).

Height and weight were used to calculate BMI (kg/m^2). Age- and sex-specific BMI z-scores were derived from the Centers for Disease Control and Prevention national standards, and used to define BMI categories: "underweight or normal weight" if < 85th percentile, "overweight" if between 85th and 95th percentiles, and "obese" if > 95th percentile (17). DKA at onset was determined by one of the following: (1) blood bicarbonate < 15 mmol/l or pH < 7.25 (venous) or <7.30 (arterial or capillary); (2) ICD-9 code 250.1 at discharge; and (3) diagnosis of DKA in the medical record (18).

Blood samples were analyzed for GADA and IA-2A autoantibodies using a standardized protocol and common serum calibrator developed by the NIDDK-sponsored standardization group (19). The cutoff values for positivity were 33 NIDDKU/ml for GADA and 5 NIDDKU/ml for IA-2A. The calculated specificity and sensitivity were 97% and 76%, respectively, for GADA and 99% and 64%, respectively, for IA-2A (19). FCP was measured by a two-site immunoenzymetric assay (TOSOH Bioscience, Inc., San Francisco, CA) with sensitivity of 0.05 ng/ml, and inter-assay coefficient of variation in quality control samples of 3.8%, 1.6% and 1.8% for low, medium and high levels of FCP, respectively. Hemoglobin A1C (A1c) was measured by a dedicated ion exchange high performance liquid chromatography instrument (TOSOH, Bioscience, Inc., San Francisco, CA). All assays were performed at Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, which serves as the central laboratory for the Search Study.

Molecular Analysis

HLA class II genotyping was performed with a PCR-based sequence-specific oligonucleotide probe system. Oligonucleotide probes corresponding to known polymorphic sequence motifs in *HLA* DRB1 and DQB1 loci were immobilized on nylon membranes. The polymorphic second exons of DQB1 and DRB1 were amplified using labeled primers (biotinylated), denatured, and hybridized to the immobilized probe array. Preliminary genotype data were imported into Sequence Compilation and Rearrangement Evaluation (SCORE) software for final genotype determination (9). DRB1-DQB1 haplotypes were inferred by visual inspection of individual DRB1 and DQB1 genotypes, based on well-established patterns of linkage disequilibrium (9).

Statistical Analysis

Youth with newly diagnosed diabetes in 2002–2006 from five centers who were at least 3 years of age and completed a SEARCH visit were considered for inclusion in these analyses. Among these 3,128 youth, we hierarchically excluded those with a health care provider diagnosis other than type 1 diabetes (n=461), those who did not test positive for GADA or IA-2A autoantibodies at the initial study visit (n=836), and those without complete *HLA* genotyping (n=127). Given that we aimed to examine clinical characteristics and haplotype

distributions by race/ethnicity, we further excluded Asian/Pacific Islanders (n=29), Native Americans (n=5) and other race/ethnicities (n=8) due to small sample size, resulting in a final cohort of 1,662 youth for these analyses.

We present arithmetic means for normally distributed continuous demographic and clinical characteristics and geometric means for those that were log-transformed. ANOVA was used to determine significant differences in mean continuous characteristics among the three racial/ethnic groups. Chi-square was used to assess differences in proportions of categorical traits. DRB1-DQB1 haplotype frequencies, which are based on the occurrence of a given haplotype out of the total number of haplotypes (2N), were computed for all observed haplotypes in the SEARCH sample, by race/ethnicity. Haplotypes with frequencies > 1% in at least one racial/ethnic group are presented in Table 2. Chi-square was used to determine significant differences in haplotype frequencies among the groups. Frequencies for all observed haplotypes are listed in Supplemental Table 1. We categorized haplotypes as "susceptibility", "neutral" and "protective" with respect to risk for type 1 diabetes (8) and for the purposes of this analysis, combined haplotypes according to these risk categories. Susceptibility haplotypes were defined as DRB1*03-DQB1*XX, DRB1*04-DQB1*0302 and DRB1*0901-DQB1*02; neutral haplotypes as DRB1*01-DQB1*XX; protective haplotypes as DRB1*04-DQB1*0301, DRB1*0701-DQB1*XX and DRB1*13-DQB1*XX. We examined associations between haplotypes (presence/absence) and clinical characteristics by race/ethnicity. Odds ratios and 95% CI for association with categorical traits were computed with multivariable logistic regression. Multivariable linear regression was used to determine haplotype associations with continuous traits, with nominal p-values (p<0.05) reported. Multivariable models for traits assessed at onset were adjusted for sex and age at diagnosis (where appropriate); traits measured at the study visit were adjusted for age at diagnosis, sex and duration of diabetes. Statistical analyses were performed using SAS version 9.2 (SAS Institute).

RESULTS

The study sample consisted of 1,662 youth with autoimmune diabetes (49% female), ranging in age from 3 to 21 years, of whom 77% were NHW, 10% NHB and 13% Hispanic (Table 1). The majority of NHW youth (99.3%) reported NHW as their only race/ethnicity. Among NHB youth, 83.7% self-identified as black or African American only, 15.7% as both black and NHW, and 0.6% as both black and Asian/Pacific Islander. Most Hispanic youth self-identified as Mexican or Mexican American (71.1%); others reported Puerto Rican (4.7%), Cuban (1.0%), Central American (3.8%), South American (3.0%), European Spanish (5.7%), or "Latino" or "Hispanic" only (10.7%).

Although mean age at diagnosis and mean age at study visit were similar among all racial/ethnic groups, NHB and Hispanic youth had a slightly longer duration of diabetes at the time of the visit. NHB youth were also more likely to test positive for GADA than either NHW or Hispanic youth. NHW and Hispanics were more likely to test positive for IA-2A, and among all youth who tested positive for IA-2A, had significantly higher mean IA-2A titers than NHB. NHB and Hispanic youth were more likely to present with DKA at diabetes onset than NHW youth. Although both NHB and Hispanics had a higher prevalence of overweight and obesity than NHW, they had similar FCP levels at the study visit.

Overall, 85% of youth in the study were carriers of at least one DRB1*03, DRB1*04 or DRB1*09 haplotype for susceptibility to type 1 diabetes. However, the distribution of many specific DRB1-DQB1 haplotypes varied by race/ethnicity (Table 2). While the DRB1*0301-DQB1*0201 susceptibility haplotype did not differ in frequency among the racial/ethnic groups, the frequency of the DRB1*0401-DQB1*0302 susceptibility haplotype was

substantially higher in NHW than NHB or Hispanic youth. DRB1*0405-DQB1*0302 was more frequent in NHB and Hispanic than NHW youth, while DRB1*0407-DQB1*0302 was more frequent in Hispanic youth only. The frequencies of susceptibility DRB1*0901-DQB1*0201 and DRB1*0901-DQB1*0202 haplotypes were significantly higher in NHB than NHW and Hispanic youth. In general, frequencies of the neutral haplotypes either did not differ among racial/ethnic groups, or were higher in NHW compared to NHB and Hispanic youth (e.g. DRB1*0101-DQB1*0501). As expected, haplotypes shown to be protective for type 1 diabetes were of low frequency among all groups. In fact, the most protective haplotypes including DRB1*11, DRB1*14, DRB1*15 and DRB1*16 alleles typically had frequencies 1% in all racial/ethnic groups (Supplementary Table 1). The protective haplotype DRB1*0401-DQB1*0301 was more frequent in NHW, while frequency of modestly protective DRB1*0701-DQB1*0202 was higher among NHB.

While the frequency of susceptibility haplotypes DRB1*03-DQB1*XX were similar among all racial/ethnic groups, associations with characteristics of diabetes onset were not observed across all race/ethnicities. DRB1*03-DQB1*XX haplotypes were significantly associated with positive titers for both GADA and IA-2A in Hispanic youth only (Table 3); Hispanic youth carrying haplotypes with a DRB1*03 allele had 82% greater odds of testing positive for both GADA and IA-2A than non-carriers (OR: 1.82, 95% CI: 1.05–3.15). NHW youth carrying haplotypes with this allele had significantly younger mean age of diabetes onset compared to non-carriers (9.9 ± 0.2 vs. 10.5 ± 0.2 years; p=0.011) (Supplemental Figure 1). The susceptibility haplotype DRB1*04-DQB1*0302 was also significantly associated with positive titers for multiple autoantibodies in Hispanic youth; carriers of this haplotype were more than twice as likely to test positive for both GADA and IA-2A as non-carriers (OR: 2.13, 95% CI: 1.15–3.94) (Table 3). Hispanic carriers of this haplotype were also more than twice as likely to have had DKA at onset (OR: 2.38, 95% CI: 1.07–5.31) (Table 3) and significantly lower mean FCP at the study visit (0.45 ± 0.03 vs. 0.67 ± 0.08 ng/ml, p=0.007) compared to non-carriers (Supplemental Figure 2).

While neutral haplotypes did not appear to significantly alter risk for multiple autoantibody positivity, they appeared to have race/ethnicity-specific effects on other characteristics of diabetes onset. NHB youth with haplotypes containing a DRB1*01 allele were more than three times as likely to have had DKA at onset (OR= 3.62, 95% CI: 1.18–11.06) (Table 3), while NHW youth carrying this allele had significantly older age of onset (10.7 ± 0.2 vs. 10.1 ± 0.2 years; p=0.037) compared to non-carriers (Supplemental Figure 1). Interestingly, the modestly protective haplotypes, DRB1*04-DQB1*0301 and DRB1*0701-DQB1*XX were associated with increased odds of positive titers for multiple autoantibodies in NHW (OR= 1.98, 95% CI: 1.32–2.97 and OR=1.51, 95% CI: 1.05–2.17, respectively) (Table 3). DRB1*04-DQB1*0301 was also associated with older age of onset in NHW youth (11.0 ± 0.3 vs. 10.1 ± 0.1 years; p=0.017) (Supplemental Figure 1). Protective and neutral haplotypes containing the DRB1*13 allele were generally more frequent in NHB and NHW youth, and appeared to have a protective effect for multiple autoantibody positivity and DKA at onset. NHB youth carrying a DRB1*13 allele were 57% less likely to test positive for both GADA and IA-2A compared to non-carriers (OR= 0.43, 95% CI: 0.19–0.95). DRB1*13 may also confer protection from DKA at onset in NHB youth (OR= 0.40, 95% CI: 0.13–1.19) (Table 3).

DISCUSSION

In this diverse sample of 1,662 youth with diabetes, we found the distribution of *HLA* DRB1-DQB1 haplotypes to vary by race/ethnicity. DRB1-DQB1 associations with characteristics of diabetes onset and severity also varied by race/ethnicity, although not always in accordance with race/ethnicity-specific haplotype frequencies. Moreover, a few

haplotypes previously shown to be "neutral" or "protective" with respect to risk for type 1 diabetes were associated with diabetes-related characteristics in some groups. As such, these findings may explain some of the variation in clinical presentation of autoimmune diabetes by race/ethnicity.

Of the susceptibility haplotypes, the combined frequency of those containing at least one DRB1*03 allele ranged from 27.5% in Hispanic youth, to 28.8% and 28.9% in NHW and NHB youth, respectively. The frequency of susceptibility haplotypes DRB1*03-DQB1*0201 and DRB1*04-DQB1*0302 (28.4% and 34.5%, respectively) in our NHW sample were slightly lower than those reported by the Type 1 Diabetes Genetics Consortium (T1DGC) (34.1% and 39.4%, respectively) and other Caucasian samples (6,9,20). Additionally, the frequency of neutral DRB1*01-DQB1*XX and protective DRB1*04-DQB1*0301, DRB1*0701-DQB1*XX and DRB1*13-DQB1*XX haplotypes (8.9%, 4.8%, 5.5%, and 6.6%, respectively) were slightly higher than those previously reported in the T1DGC (7.5%, 1.7%, 3.6%, and 3.1%, respectively) (9). This variation may be due to differences in the geographic location of proband ascertainment, and/or enrichment of family members with type 1 diabetes in the T1DGC. Scant data exist on the frequency of these haplotypes in Hispanic or black individuals with diabetes for comparison, although others have noted higher frequencies of DQB1*0302 among NHW and Hispanic youth and DQB1*02XX among black youth with type 1 diabetes, which are consistent with our findings (12).

Few studies have examined associations between DRB1-DQB1 haplotypes and clinical characteristics of diabetes onset or severity, especially in black or Hispanic populations. While the frequency of haplotypes containing a DRB1*03 allele was similar among all racial/ethnic groups, we found the presence of these haplotypes to be significantly associated with multiple autoantibody positivity among Hispanic youth only. DRB1*04-DQB1*0302 haplotypes, which were more frequent in NHW and Hispanics, were associated with multiple autoantibody positivity in both groups. DRB1*04-DQB1*0302 was also significantly associated with increased risk for DKA in Hispanic youth, which may indicate a role for this particular set of haplotypes in severity of onset in Hispanics. Interestingly, despite their "protective" designations, we also found DRB1*04-DQB1*0301 and DRB1*0701-DQB1*XX to be associated with multiple autoantibody positivity in NHW youth. This finding is supported by a study conducted in northern European children and adolescents with type 1 diabetes, which reported both DRB1*04 and DRB1*07 associations with IA-2A positivity (21). Moreover, Noble *et al.* recently reported that the effect of DRB1*0701-DQB1*0201, which was the highest frequency DRB1*07 haplotype in our sample, particularly among NHB youth, varies by DQA1 allele (22). The presence of European-derived DQA1*0201 on the haplotype confers protection, while the presence of DQA1*0301, linked to African ancestry, confers susceptibility to type 1 diabetes (22). Although DQA1 was not typed in our sample, it is possible that the association observed with increased autoantibody positivity is due to a greater presence of DQA1*0301 than DQA1*0201.

We acknowledge the limitations of our investigation. GADA and IA-2A were the only autoantibodies measured from blood samples drawn at the SEARCH study visit. Therefore, in restricting our analyses to youth who tested positive for at least one of the two autoantibodies measured, we excluded those who may have been positive for other diabetes-related autoantibodies in the absence of GADA or IA-2A. Self-reported race/ethnicity precluded us from accounting for racial/ethnic admixture in the estimation of haplotype frequencies and their effects on diabetes-related characteristics. Moreover, the modest sample sizes for NHB and Hispanic youth precluded us from examining DRB1-DQB1 haplogenotypes in more detail, and limited our power to detect association with some traits;

most associations observed at a nominal significance level (p<0.05) would not survive correction for multiple testing. Despite these limitations, our population-based approach combined with the multi-ethnic composition of this cohort allowed for exploration of *HLA*-associated phenotypes in major racial/ethnic groups largely understudied. SEARCH participants are also well characterized in terms of traits associated with diabetes onset.

In conclusion, the frequencies of DRB1-DQB1 haplotypes and their association with clinical features of autoimmune diabetes vary across major racial/ethnic groups in the United States. Our findings also suggest a role for "neutral" and "protective" haplotypes in the severity of diabetes onset that has not been previously explored, particularly in racial/ethnic minority groups. Taken together, these findings may explain, in part, the variation in clinical presentation of autoimmune diabetes within and across racial/ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

ABBREVIATIONS

GADA

IA-2A

HLA

NHW

NHB

DKA

FCP

BMI

A1c

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Table 1

SEARCH Participant Characteristics

	Non-Hispanic White (n=1,285)	Non-Hispanic Black (n=166)	Hispanic (n=211)	p-value[*]
Mean Age at Diagnosis ± SE [yrs]	10.2 ± 0.1	9.8 ± 0.3	10.1 ± 0.3	0.51
Mean Age at Initial Visit ± SE [yrs]	11.4 ± 0.1	11.1 ± 0.3	11.4 ± 0.3	0.76
Mean Diabetes Duration ± SE [months]	9.8 ± 0.2 [§]	11.0 ± 0.5	11.3 ± 0.4 [†]	0.001
Sex (%)				0.014
Female	612 (47.6)	99 (59.6)	103 (48.8)	
Male	673 (52.4)	67 (40.4)	108 (51.2)	
Weight Status (%)				< 0.001
Underweight	68 (5.3)	6 (3.7)	14 (6.8)	
Normal Weight	811 (63.6)	81 (49.4)	98 (47.3)	
Overweight	242 (19.0)	33 (20.1)	58 (28.0)	
Obese	155 (12.1)	44 (26.8)	37 (17.9)	
Mean BMI z-score ± SE	0.53 ± 0.03 [‡]	0.93 ± 0.08 [†]	0.70 ± 0.08	< 0.001
Mean A1c % ± SE	7.6 ± 0.04 [‡]	8.6 ± 0.18 [†,§]	7.9 ± 0.12 [‡]	< 0.001
Type of Autoantibody Present (%)				
GADA	870 (67.7)	131 (78.9)	149 (70.6)	0.011
IA-2A	1067 (83.0)	122 (73.5)	174 (82.5)	0.010
Number of Autoantibodies (%)				0.77
GADA or IA-2A only	633 (49.3)	79 (47.6)	99 (46.9)	
Both GADA and IA-2A	652 (50.7)	87 (52.4)	112 (53.1)	
Mean Titers GADA ± SE [//]	239.6 ± 9.2	293.2 ± 28.8	240.7 ± 22.7	0.16
Mean Titers IA-2A ± SE [//]	214.9 ± 7.2 [‡]	125.2 ± 15.2 [†,§]	182.1 ± 15.8 [†]	< 0.001
Mean Fasting C-peptide ± SE [ng/mL] [//]	0.49 ± 0.01	0.50 ± 0.04	0.51 ± 0.04	0.92
DKA at onset [¶] (%)				0.031
No	709 (72.9)	81 (63.8)	104 (65.8)	
Yes	264 (27.1)	46 (36.2)	54 (34.2)	

[*] P-values derived from ANOVA for continuous traits or chi-square for categorical traits

[†] significantly different than Non-Hispanic White (p < 0.05)

[‡] significantly different than Non-Hispanic Black (p < 0.05)

[§] significantly different than Hispanic (p < 0.05)

[//] Values shown are geometric means with SE calculated using the Delta Method

[¶] DKA at onset available for 1,258 youth.

Table 2

HLA DRB1-DQB1 Haplotype Frequencies[*] by Race/Ethnicity

DRB1	DQB1	Effect on Risk for Type 1 Diabetes[†]	Non-Hispanic White (n=1,285)	Non-Hispanic Black (n=166)	Hispanic (n=211)	p-value[‡]
0101	0501	Neutral	7.24	3.92	2.37	<0.001
0102	0501	Neutral	0.82	2.71	1.42	0.009
0301	0201	Susceptibility	28.44	28.31	27.01	0.841
0401	0301	Protective	4.44	1.20	2.61	0.003
0401	0302	Susceptibility	22.45	7.83	6.40	<0.001
0402	0302	Susceptibility	2.06	0.30	4.03	0.001
0403	0302	Protective	0.35	0.00	1.42	0.013
0404	0302	Susceptibility	7.59	4.82	9.24	0.065
0405	0302	Susceptibility	1.52	7.83	9.00	<0.001
0407	0302	Susceptibility	0.35	0.00	8.77	<0.001
0701	0202	Protective	4.98	9.34	5.21	0.007
0801	0402	Neutral	2.26	0.00	1.66	0.004
0802	0402	Neutral	0.16	0.30	2.84	<0.001
0901	0201	Susceptibility	0.00	4.82	0.47	<0.001
0901	0202	Susceptibility	0.00	2.11	0.24	<0.001
0901	0303	Neutral	1.67	0.60	0.71	0.156
1101	0301	Protective	1.21	0.30	1.42	0.273
1102	0301	Protective	0.19	1.51	0.47	0.003
1201	0501	Undetermined	0.00	1.51	0.00	<0.001
1301	0603	Protective	1.87	0.60	0.71	0.068
1302	0501	Undetermined	0.04	1.20	0.24	<0.001
1302	0604	Neutral	3.70	4.22	1.90	0.113
1601	0502	Neutral	1.01	0.60	0.71	0.855

[*] Haplotypes shown are of 1% frequency in at least one racial/ethnic group.

[†] Based on Thompson *et al.* (ref 8).

[‡] P-values assessed by Pearson's chi-square test

Table 3

HLA DRB1-DQB1 Haplotype Associations* with Clinical Characteristics and Severity of Diabetes Onset

	Non-Hispanic White (n=1,285)		Non-Hispanic Black (n=166)		Hispanic (n=211)	
	AOR	95% CI	AOR	95% CI	AOR	95% CI
Susceptibility Haplotypes						
DRB1*03-DQB1* XX[†]						
Combined Haplotype Frequency (%)	28.8		28.9		27.5	
Number of Autoantibodies (2 vs. 1)	0.83	0.66–1.03	1.32	0.71–2.44	1.82	1.05–3.15
DKA at Onset (yes vs. no)	0.81	0.61–1.07	1.56	0.74–3.27	0.77	0.39–1.50
DRB1*04-DQB1*0302						
Combined Haplotype Frequency (%)	34.5		20.8		38.9	
Number of Autoantibodies (2 vs. 1)	1.29	1.03–1.62	1.46	0.77–2.74	2.13	1.15–3.94
DKA at Onset (yes vs. no)	1.13	0.84–1.51	0.68	0.31–1.47	2.38	1.07–5.31
DRB1*0901-DQB1*02						
Combined Haplotype Frequency (%)	0.0		6.9		0.7	
Number of Autoantibodies (2 vs. 1)	--	--	1.92	0.72–5.07	--	--
DKA at Onset (yes vs. no)	--	--	1.68	0.59–4.79	--	--
Neutral Haplotypes						
DRB1*01-DQB1* XX[†]						
Combined Haplotype Frequency (%)	8.9		6.9		4.0	
Number of Autoantibodies (2 vs. 1)	0.81	0.60–1.09	1.18	0.46–3.03	--	--
DKA at Onset (yes vs. no)	0.97	0.67–1.42	3.62	1.18–11.06	--	--
Protective Haplotypes						
DRB1*04-DQB1*0301						
Combined Haplotype Frequency (%)	4.8		1.2		3.1	
Number of Autoantibodies (2 vs. 1)	1.98	1.32–2.97	--	--	--	--
DKA at Onset (yes vs. no)	0.82	0.49–1.39	--	--	--	--
DRB1*0701-DQB1* XX[†]						
Combined Haplotype Frequency (%)	5.5		9.6		5.2	
Number of Autoantibodies (2 vs. 1)	1.51	1.05–2.17	1.42	0.64–3.12	0.92	0.37–2.29

	Non-Hispanic White (n=1,285)		Non-Hispanic Black (n=166)		Hispanic (n=211)	
	AOR	95% CI	AOR	95% CI	AOR	95% CI
DKA at Onset (yes vs. no)	1.11	0.71–1.73	0.73	0.30–1.81	1.04	0.36–2.99
DRB1*13-DQB1* XX†						
Combined Haplotype Frequency (%)	6.6		11.1		4.1	
Number of Autoantibodies (2 vs. 1)	0.74	0.53–1.03	0.43	0.19–0.95	--	--
DKA at Onset (yes vs. no)	0.82	0.54–1.26	0.40	0.13–1.19	--	--

*
Associations with number of autoantibodies (both GADA65 and IA-2A vs. only one) are adjusted for age at diabetes diagnosis, sex, and duration of diabetes. Associations with DKA at onset are adjusted for age at diabetes diagnosis and sex.

†
DQB1*XX indicates any DQB1 allele