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HLA-DQ Haplotypes Differ by Ethnicity in Patients with Childhood-onset Diabetes

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Abstract

Aim—To understand the etiology of childhood-onset diabetes, we examined genetic risk markers, autoantibodies (AB), and β -cell function in a mixed-race group of young patients.

Methods—145 patients aged 0–17 at diagnosis (54% African American, 22% Caucasian, 16% Latino, 8% Mixed-Other) were studied at mean duration 6.9 ± 5.7 (range 0.1–28.5) years, including HLA-DQA1-DQB1 genotyping, stimulated C-peptide (CP), GAD and IA-2 antibodies (AB). Based on no residual β -cell function (CP–) and islet autoantibodies (AB+), 111 patients were classified with type 1 diabetes (T1DM); 22 were CP+ and AB– and thus considered to have type 2 diabetes (T2DM); 12 patients had features of both T1DM and T2DM, or mixed phenotype.

Results—Based on the presence of two high-risk HLA-DQA1/B1 haplotypes, 39% of African Americans, 81% of Caucasians, 70% of Latinos, and 67% of Mixed-Others, were at high genetic risk. In T1DM patients, 41% of African Americans, 80% of Caucasians, 73% of Latinos, and 63% of Mixed-Others were genetically susceptible. 31% of African Americans, including 29% of those with T1DM, could not be characterized because their haplotypes had unknown T1DM associations. These unusual haplotypes comprised 11% in T1DM, 14% in T2DM, and 8% of haplotypes in mixed phenotype patients.

Conclusions—59% of childhood-onset T1DM patients were identified with high genetic risk based on known HLA-DQA1/B1 associations. Many non-Caucasian patients carry HLA-DQ alleles whose association with T1DM is undetermined. Genetic approaches can provide insights into the etiology and appropriate treatment of childhood-onset diabetes, but only if sufficient data are available in diverse ethnic groups.

Keywords

Diabetes Type 1; Diabetes Type 2; Children and adolescents; Ethnic differences; African Americans; Caucasians; Latinos; Epidemiology; Phenotypes; HLA-DQA1-DQB1

Background - Introduction

Diabetes is one of the most common chronic diseases of childhood. Although in recent years it has become obvious that childhood-onset diabetes is heterogeneous in etiology, it is primarily comprised of the autoimmune-mediated, insulin-deficient type 1 phenotype. By far the strongest genetic determinants of type 1 diabetes risk are located in the major

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histocompatibility region (MHC) on chromosome 6p21, with the most robust associations with the human leukocyte antigen (HLA) class II genes DRB1 and DQB1. Historically, cross-population comparisons have allowed major insights into the genetic basis for disease, including type 1 diabetes (1,2). While MHC genes account for approximately 40% of type 1 diabetes risk, it has long been recognized that other regions of the genome also confer susceptibility or resistance to beta-cell autoimmunity and type 1 diabetes (3–5). Currently, studies comparing type 1 diabetes genetics across ethnic lines have focused on these non-HLA associations (2,6,7), confirming associations with insulin gene (INS) polymorphisms and variants at CTLA4, and PTPN22, among others. Unfortunately, few data, even on the older HLA associations, are currently available for African-origin or indigenous American groups.

Over the past 1–2 decades there has been a steady increase in childhood diabetes incidence of approximately 3% per annum across the world (8,9). Major secular changes in the environmental-behavioral determinants of diabetes etiology, specifically overnutrition and physical inactivity, are also occurring at this time. Furthermore, recent epidemiologic data show that the risk for type 1 diabetes in non-Caucasian children is roughly equivalent to that in non-Hispanic whites (9,10), while the risk for non-type 1 phenotypes is roughly double that for Caucasian young people (9, 11–13). However, important disparities in diabetes outcomes have been demonstrated between Caucasian and non-Caucasian children in the United States (14–16). This is probably rooted in social, not biological, causes, i.e. lack of adequate health care, but if the etiology of diabetes in non-Caucasian children is not well understood, then inappropriate treatment could also be contributing to the documented ethnic disparities. It is essential to decipher the genetic and nongenetic contributions to the etiology of childhood diabetes, not only to develop appropriate treatments, but also to correctly identify patients for inclusion in future research.

We used samples from 145 patients derived from a family study in the Chicago metropolitan area to evaluate genetic associations with apparent type 1, type 2, and mixed diabetes phenotypes. All patients were initially diagnosed between the ages of 0–17, and 54% were African American in ancestry (Table 1). Phenotyping was based on physical findings after, on average, seven years' duration of diabetes. This work was undertaken to address the hypothesis that the genetic profile of children with type 1 diabetes is different than those of children with type 2 or mixed forms of diabetes, among both Caucasian and non-Caucasian populations. Specifically, we hypothesized that a) The prevalence of type 1 diabetes-associated HLA haplotypes will be lower among patients with youth-onset diabetes exhibiting mixed features or those of type 2 diabetes, than among patients with “true” type 1 diabetes, irrespective of ethnicity; and b) The frequency of high-risk HLA-DQA1/B1 haplotypes would be similar among Caucasian type 1 patients and those of other ethnic backgrounds.

Methods

Subjects

Patients (n=150) were recruited from clinics or by mail, if they were aged 0–17 years at initial diagnosis of diabetes, and if the diabetes was not secondary to another medical condition. Patients were excluded based on insufficient HLA data (n=2) or inability to determine their phenotype at the time of examination (n=3), leaving a final study sample of 145 patients. Clinical studies were conducted in the Clinical Research Centers at the University of Illinois at Chicago and the University of Chicago, and in participants' homes. Human Subjects Research committees at the University of Illinois at Chicago and the University of Chicago approved the study protocol. Written informed consent was obtained

from participants prior to the interview and clinical studies; those currently aged 12–17 were asked to give written assent, and parental consent was obtained.

Patients were examined 6.9 ± 5.7 (mean $\pm$ SD); range 0.1–28.5; years after their initial diagnosis. Information on family history and clinical characteristics was gathered in detailed interviews. Ethnicity was defined as having at least three grandparents with the same ethnic origin according to the proband or a family informant. In addition to genetic studies, physical measures were taken and islet cell autoantibodies (insulinoma-associated antigen 2, or IA-2; glutamic acid decarboxylase, or GAD) and β -cell function were tested.

Phenotyping

We determined the phenotypes of patients using information from their physical examinations and questionnaires. Patients with <2 years' duration who were autoantibody positive and using insulin alone, or those with no detectable post-challenge C-peptide and a disease duration >2 years, i.e. no endogenous insulin production, were classified as having 'true' type 1 diabetes ($n=111$). Patients with residual β -cell function, no islet autoantibodies, and either not using insulin at all, or using ≥ 2 insulin shots/day (with or without oral antidiabetic agents), were classified as having type 2 diabetes ($n=22$). Fifteen of these individuals were using oral agents or diet alone. We observed a substantial fraction of patients who had to be categorized as having 'mixed' phenotype ($n=12$); these patients had either a) residual β -cell function and autoantibodies ($n=10$); or b) measurable C-peptide, but reporting an acute outcome, i.e. DKA, when stopping insulin therapy ($n=2$).

Autoantibodies

Antibodies to radiolabelled recombinant human GAD65 (whole) and human IA-2 (349 AA cytoplasmic portion) were quantified by fluid-phase immunoprecipitation assay (17). These antigens were cloned from human islets and human glioblastoma, respectively, and are expressed in recombinant form by coupled in-vitro transcription and translation in the presence of ^{35}S -methionine. After incubation with subject serum in separate triplicate wells, immune complexes are precipitated using Protein A, washed, and counted for bound radioactivity. Using the mean of triplicates on each index serum and each unknown serum, an antibody "index" is calculated as: Index = (Unknown Serum-Index Negative)/(Index Positive-Index Negative). The WHO/JDF standard serum for GAD antibody and IA-2 were used in each assay. The assays were 94% and 80% sensitive, and 94% and 95% specific, for GAD and IA-2, respectively, in the 2005 Diabetes Autoantibody Standardization Program sponsored by the Centers for Disease Control & Prevention and the Immunology of Diabetes Society.

HLA Genotyping

HLA-DQA1 and -DQB1 typing was conducted in the laboratory of Dr. William Hagopian at the Pacific Northwest Research Institute, using extracted DNA ($n=39$) or dried bloodspot samples applied to Schleicher & Schuell 903 paper ($n=109$). Genotyping at HLA-DQB1 (high resolution) and HLA-DQA1 (moderate resolution) used published PCR primers (18). and standard SSOP techniques, supplemented by direct sequencing on an ABI310 automated sequencer as needed. Results were used to generate extended haplotypes for assignment of type 1 diabetes risk according to published multi-ethnic data (19–21). We considered the following HLA-DQA1-DQB1 haplotypes to confer susceptibility to type 1 diabetes: 0201-0302, 0301-0201, 0301-0302, 030x-0302, 0302-0303, 030x-0303, 0401-0301, 0401-0402 (in Caucasians), 0501-0201/2, 050x-0201/2. Neutral haplotypes were identified as: 0101-0501, 010x-0501, 0101/4-0503, 0101-0604, 0101-0609, 0102-0502, 0102-0604, 0102-0609; haplotypes that were classified as resistant were: 0102-0602, 0103-0603, 0201-0201, 0201-0201/2, 0201-0303, 0301-0301, 030x-0301, 0401-0402 (in African Americans), 0501-0301, 0601-0301. There were several additional haplotypes whose

association with type 1 diabetes risk has not yet been decisively identified. Based on both HLA-DQA1-DQB1 haplotypes, we considered those with one susceptible haplotype paired with either a susceptible, neutral, or unknown haplotype to be at high genetic risk for type 1 diabetes. Similarly, those with at least one resistant haplotype paired with either a resistant, neutral, or unknown haplotype to have a low genetic risk for type 1 diabetes. Intermediate type 1 risk was assumed for those with a neutral haplotype paired with either an unknown or a neutral haplotype, or those with one susceptible and one resistant haplotype. There were 113 of the 145 subjects with HLA typing who were able to be classified in this manner; the remaining 32 subjects carried two haplotypes with undetermined risk status.

C-Peptide

All assays were conducted in the Diabetes Research and Training Center Ligand Assay Core laboratory at the University of Chicago. For participants examined before 2004 (n=39), plasma C-peptide was measured using a previously described immunoassay (22). The lower limit of sensitivity of this assay was 0.02 nmol/L and the intra-assay CV averaged 6%. C-peptide for participants seen after 2004 (n=106) was measured with a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products Corporation, Biermann GmbH, Bad Nauheim, Germany) in the same laboratory (23). A modified assay was substituted by the manufacturer in October 2007 (Immulite 1000). The lower limit of detection for both Immulite assays was 0.17 nmol/L and the intra-assay coefficient of variation was 8% on average. For purposes of this study, we defined residual β -cell function as a C-peptide value ≥ 0.05 nmol/L using the pre-2004 assay, and as ≥ 0.17 nmol/L in the newer assays (22–24).

Statistical Methods

Univariate analyses, t-tests or Chi-square tests as appropriate, were conducted to compare variables across ethnic groups. P-values were not corrected for multiple comparisons. Due to small numbers, we chose not to construct multivariable models. All analyses were conducted using SPSS version 16 (Chicago, IL).

Results

The study group included 83 females, with 78 patients of non-Hispanic black (African American) origin, 32 non-Hispanic whites (Caucasians), 23 Latinos and 12 patients of other or mixed ethnicity, primarily Asian (Table 1). Caucasians had somewhat shorter disease duration at the time of examination, 5.4 years vs. 7.5, 6.8, and 7.0 years for African Americans, Latinos, and Mixed-Other groups, respectively. Fewer Caucasians, 16%, than African Americans (33%), Latinos (24%), or Mixed-Others (27%) had a first-degree relative with diabetes, though neither of these comparisons was statistically significant (Table 1). Islet autoantibodies (GAD +/- IA-2) were detectable in 87 (60%) of the patients, including 69% of type 1 and 83% of mixed phenotype patients; by definition type 2 diabetes patients were antibody negative. Among the type 1 patients there were no ethnic differences in the prevalence of antibody positivity (Table 1); there were too few Caucasian and Latino mixed phenotype patients to allow significance testing of antibody positivity by ethnicity in that subgroup.

We defined an overall level of genetic risk for type 1 diabetes based on two HLA-DQA1/B1 haplotypes with known risk status. We found that 39% of African Americans, 81% of Caucasians, 70% of Latinos, and 67% of Mixed-others carried a high level of genetic risk; while 24%, 9%, 4% and 17% were at intermediate risk, and 6%, 6%, 4%, and none were at low risk, respectively (p=0.005; Table 1). Among type 1 patients, 41% of African Americans, 80% of Caucasians, 73% of Latinos, and 63% of Mixed-others carried a high

level of genetic risk ($p=0.02$). 31% of African American patients, including 29% of those with type 1 diabetes, could not be characterized in terms of overall genetic risk based on HLA because they carried HLA-DQA1/B1 haplotypes of unknown association. This was also the case for Latino and mixed race patients, where 22% and 17%, respectively, could not be assigned an HLA-based genetic risk, including 23% of Latino type 1 patients (Table 1). In contrast, only one Caucasian subject was not able to be characterized because this type 1 patient carried undefined haplotypes.

Comparing overall HLA-based genetic risk across phenotypes, we found that 59% of type 1 patients displayed a susceptible (high risk) profile, compared with 32% of type 2 and 58% of mixed phenotype patients. Among African Americans, 41% of type 1 patients displayed a susceptible HLA profile, as did 24% of type 2 and 50% of mixed phenotype patients. The proportions of African Americans who displayed a resistant HLA profile were 6% of type 1, 12% of type 2, and none of the mixed phenotype patients. Among Caucasians, 80% of type 1 patients carried a susceptible HLA profile, as did the single type 2 patient and the single mixed phenotype patient. Among Latinos, 73% of type 1 patients displayed a susceptible HLA-DQA1/DQB1 profile; the single Latino type 2 patient displayed a neutral risk profile. Among the 12 mixed/other race patients who were studied, the majority of both type 1 patients (5/8) and type 2 patients (2/3) displayed a susceptible genetic risk profile based on two HLA-DQA1/B1 haplotypes.

There appear to be relatively large deviations from predicted frequencies for the type 1-associated HLA-DQA1/B1 haplotypes (Table 2). There were 290 haplotypes for evaluation in the 145 patients, of which 167 (58%) were defined as type 1 diabetes susceptibility haplotypes, 42 (15%) were neutral, 50 (17%) have been reported to confer resistance to type 1 diabetes, and 33 (11%) were undefined in terms of their risk association.

Among the 222 haplotypes in those patients who had type 1 diabetes, 143 haplotypes (64%) carried type 1 susceptibility, 26 (12%) were neutral, 30 (14%) were resistant, and 25 (11%) were undefined. Among the 102 haplotypes in African American type 1 patients, 52% were susceptible, 13% were neutral, 20% were resistant, and fully 18% were not yet defined in terms of their type 1 diabetes risk association. In the 60 haplotypes from Caucasian patients with type 1 diabetes, 73% carried type 1 diabetes susceptibility, 15% were neutral, 10% were resistant, and one was undefined. In 44 haplotypes of Latino type 1 patients, 75% were susceptible, 9% were neutral, 5% were resistant, and 11% were undefined. Thirteen of the 16 haplotypes carried by mixed-other race type 1 patients were susceptible, while just one was undefined in terms of its type 1 diabetes association.

Discussion

We explored the extent of genetic variation at HLA-DQA1 and -DQB1 among patients diagnosed in childhood, in whom the inborn components of diabetes risk are likely to be of greatest importance. Our sample represents a diversity of ethnic origins, and phenotype was determined as precisely as possible within the constraints of research among otherwise healthy, free-living individuals. We found that the prevalence of type 1 diabetes-associated HLA haplotypes was lower among patients with youth-onset diabetes exhibiting features of type 2 diabetes, than among patients with “true” type 1, irrespective of ethnicity. However, the frequency of high-risk HLA-DQA1/B1 haplotypes was considerably lower among African American patients, compared to those of Caucasian ancestry, even among those who clearly demonstrated a type 1 phenotype. This effect was largely accounted for by the much higher frequency among African Americans and Latinos of haplotypes that have not yet been characterized in terms of their type 1 diabetes risk. This observation is consistent with the report of Antal, et al. (25) who examined HLA class I supertypes in minority type 1

patients, and found that 65% did not belong to the A2 supertype, which is the most commonly associated with type 1 in Caucasians.

The relatively small number of non- type 1 patients, particularly among Caucasians and Latinos, limited the statistical power of this analysis. In fact, the value of this manuscript is that it is the first description of frequencies of these variants in an ethnically diverse sample with well-characterized diabetic phenotypes, rather than its statistical robustness. Clearly, if we had conducted HLA-DR typing in addition to the DQA1-DQB1 analysis, it would have allowed greater insight into the type 1 diabetes risk associations (20). We hope that further studies of the HLA-DR-DQ loci in non-European type 1 patients will soon emerge in response to this manuscript which highlights the dearth of such information that now exists.

We used a straightforward approach to determining the phenotype of patients at follow-up, yet the possibility of misclassification cannot be altogether ruled out. We did not test for the zinc transporter 8 autoantibody which was relatively recently identified as a marker of type 1 risk, and thus may have allowed us to more precisely classify phenotype. Certainly, some “true” type 1 patients may continue to demonstrate residual β -cell function for many years. It is also possible that glucose toxicity associated with extremely poor glycemic control could mask the ability to produce insulin in those who would otherwise have been classified as type 2 patients. Among the 95 type 1 patients in our study who had no detectable C-peptide, there were 28 (30%) in very poor metabolic control (HbA1c $\geq 10\%$), a proportion not different among those with mixed or type 2 phenotype. Thus, we remain confident that the type 1 diabetes group in this analysis is largely homogeneous. Finally, this cohort, though grossly representative of the ethnic and socioeconomic distribution of young people in the Chicago metropolitan area, was not randomly selected, but instead consisted of patients whose families were able to be contacted under recently-adopted stringent legal constraints, and who agreed to be examined. Nonetheless, this study does represent a large group of young diabetes patients with careful attention to phenotyping and HLA results, and it includes a substantial number of minority patients.

In summary, fewer than expected of the HLA-DQA1/B1 haplotypes in patients with childhood-onset diabetes conferred high risk for type 1 diabetes, particularly among those from non-Caucasian backgrounds. Studies across racial groups using sufficiently large numbers of samples carry the potential to identify causal variants. Future exploration of the role of genetic variation in diabetes risk among young people should include determination of HLA class II associations in a variety of ethnic groups, as well as meticulous attention to determining phenotype. This is a crucial step in preparing for future etiologic and prevention research, as well as in identifying the appropriate treatment plan for all young diabetes patients.

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Abbreviations

AB	antibodies
CP	C-peptide
DKA	diabetic ketoacidosis

GAD	glutamic acid decarboxylase
HbA1c	hemoglobin A1c
HLA	human leukocyte antigen
IA-2	insulinoma-associated antigen 2
MDM	mixed diabetic phenotype
MHC	major histocompatibility complex
PCOS	polycystic ovarian syndrome
T1DM	type 1 diabetes
T2DM	type 2 diabetes

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Table 1
 Characteristics of 145 Childhood-onset Diabetes Patients with HLA DQA1-DQB1 Typing, by Patients' Ethnicity

	African American	Caucasian	Latino	Mixed-Other Race	P-value
N (males/females)	78 (29/49)	32 (20/12)	23 (10/13)	12 (3/9)	
<i>Diabetes Phenotype</i> [*] , n (%)					0.011
Type 1	51 (65.4)	30 (93.8)	22 (95.7)	8 (66.7)	
Type 2	17 (21.8)	1 (3.1)	1 (4.3)	3 (25.0)	
Mixed	10 (12.8)	1 (3.1)	0	1 (8.3)	
Age at diag., yrs, mean (SD)	9.0 (4.4)	7.7 (4.0)	7.7 (3.8)	9.2 (4.5)	NS ^{**}
DM duration, yrs, mean (SD)	7.5 (5.4)	5.4 (4.4)	6.8 (4.5)	7.0 (4.6)	NS
Parent +/-or sib with DM [†] , n (%)	26 (33.3)	5 (16.1)	5 (23.8)	3 (27.3)	NS
IA-2 +/-or GAD Ab pos, n (%)	45 (57.7)	21 (65.6)	13 (56.5)	8 (66.7)	NS
IA-2 Ab pos, n (%)	29 (37.2)	13 (40.6)	12 (52.2)	3 (25.0)	NS
GAD Ab pos [†] , n (%)	34 (43.6)	15 (48.4)	11 (50.0)	6 (54.5)	NS
Overall type 1 risk, based on two HLA-DQA1/B1 haplotypes, n (%)					0.005
Resistant	5 (6.4)	2 (6.2)	1 (4.3)	0	
Neutral	19 (24.4)	3 (9.4)	1 (4.3)	2 (16.7)	
Susceptible	30 (38.5)	26 (81.2)	16 (69.6)	8 (66.7)	
Unable to determine	24 (30.8)	1 (3.1)	5 (21.7)	2 (16.7)	
<i>In Type 1 patients only,</i>	<i>n=51</i>	<i>30</i>	<i>22</i>	<i>8</i>	
IA-2 +/-or GAD Ab pos, n (%)	37 (72.5)	20 (66.7)	13 (59.1)	7 (87.5)	NS
IA-2 Ab pos, n (%)	26 (51.0)	12 (40.0)	12 (54.5)	3 (37.5)	NS
GAD Ab pos [†] , n (%)	29 (56.9)	15 (51.7)	11 (52.4)	5 (71.4)	NS
Overall type 1 risk, based on two HLA-DQA1/B1 haplotypes, n (%)					0.020
Resistant	3 (5.9)	2 (6.7)	1 (4.5)	0	
Neutral	12 (23.5)	3 (10.0)	0	2 (25.0)	
Susceptible	21 (41.2)	24 (80.0)	16 (72.7)	5 (62.5)	
Unable to determine	15 (29.4)	1 (3.3)	5 (22.7)	1 (12.5)	

^{*} Phenotype: Type 1, absent stimulated C-peptide with >2 years' diabetes duration or positive antibodies and insulin monotherapy with <2 years' duration; Type 2, C-peptide present with >2 years' diabetes duration and no islet autoantibodies; Mixed, either a) residual β -cell function and autoantibodies (n=10), or b) residual β -cell function after >5 years, on insulin monotherapy since diagnosis, and reports developing DKA when discontinuing insulin after the first 6 months of diabetes (n=2).

NS, not statistically significant

Information available for 141 subjects (family history); 142 subjects (GAD antibodies); 108 type 1 subjects (GAD antibodies)

HLA DQA1-DQB1 Haplotypes and Type 1 Diabetes Associations, in 145 Childhood-onset Diabetes Patients, by Ethnicity and Phenotype

Table 2

A. Type 1 Diabetes Patients (n=111)						
Total haplotypes:	Afr Amer	Caucasian	Latino	Mixed-Other	Total	
	102	60	44	16	222	
<i>Type 1 diabetes association:</i>						
<u>Resistant</u>						
0102-0602	1	1	0	1	3	
0103-0603	1	1	0	0	2	
0201-0201/2	11	1	2	0	14	
0201-0303	1	0	0	0	1	
0301/x-0301	1	1	0	1	3	
0401-0402 (African American)	3	-	-	-	3	
0501-0301	2	2	0	0	4	
Resistant haplotypes, n(%)	20(19.6)	6 (10.0)	2 (4.5)	2 (12.5)	30 (13.5)	
<u>Neutral</u>						
0101/x-0501	5	1	4	0	10	
0101/4-0503	2	3	0	0	5	
0101-0604	1	0	0	0	1	
0102-0502	2	0	0	0	2	
0102-0604/9	3	5	0	0	8	
Neutral haplotypes, n(%)	13 (12.7)	9 (15.0)	4 (9.1)	0	26 (11.7)	
<u>Susceptible</u>						
0201-0302	0	0	1	0	1	
0301-0201	5	0	2	0	7	
0301/x-0302	22	19	13	5	59	
0302/x-0303	2	1	1	1	5	
0401-0402 (Caucasian)	-	2	0	1	3	
0501/x-0201/2	24	22	16	6	68	
Susceptible haplotypes, n(%)	53 (52.0)	44 (73.3)	33 (75.0)	13 (81.3)	143 (64.4)	
<u>Undetermined</u>						
010x-0604	0	0	0	1	1	

A. Type 1 Diabetes Patients (n=111)

Total haplotypes:	Afr Amer	Caucasian	Latino	Mixed-Other	Total
0302-0202	102	60	44	16	222
030x-0201/2	6	0	3	0	9
030x-0301/9	11	0	0	0	11
030x-0304	0	1	0	0	1
040x-0402	0	0	1	0	1
050x-0301/9	1	0	0	0	1
Undetermined haplotypes, n(%)	18 (17.6)	5 (11.4)	1 (6.3)	25 (11.3)	

B. Type 2 Diabetes Patients (n=22)

Total haplotypes:	Afr Amer	Caucasian	Latino	Mixed-Other	Total
0102-0602	4	0	0	0	4
0103-0603	0	0	1	0	1
0201-0201/2	1	0	0	1	2
0401-0402 (African American)	6	-	-	-	6
0501-0301	3	0	0	0	3
0601-0301	1	0	0	0	1
Resistant haplotypes, n(%)	15 (44.1)	0	1 (50.0)	1 (16.7)	17 (38.6)
<u>Neutral</u>					
0101-0501	4	1	0	0	5
0101/4-0503	1	0	0	0	1
0101-0609	2	0	0	0	2
0102-0502	1	0	0	1	2
Neutral haplotypes, n(%)	8 (23.5)	1 (50.0)	0	1 (16.7)	10 (22.7)
<u>Susceptible</u>					
0301-0201	1	0	0	1	2
0301/x-0302	0	0	1	1	2
0302-0303	1	0	0	0	1

B. Type 2 Diabetes Patients (n=22)						
	Afr Amer	Caucasian	Latino	Mixed-Other	Total	
Total haplotypes:	34	2	2	6	44	
0401-0301	1	0	0	0	1	
0501/x-0201	3	1	0	1	5	
Susceptible haplotypes, n(%)	6 (17.6)	1 (50.0)	1 (50.0)	3 (50.0)	11 (25.0)	
<u>Undetermined</u>						
0101-0502	1	0	0	0	1	
0101-0602	1	0	0	0	1	
0102-0501	1	0	0	0	1	
0501-0304	1	0	0	0	1	
0601-0402	1	0	0	0	1	
060x-0301/9	0	0	0	1	1	
Undetermined haplotypes, n(%)	5 (14.7)	0	0	1 (16.7)	6 (13.6)	

C. Mixed Phenotype Diabetes Patients (n=12)						
	Afr Amer	Caucasian	Latino	Mixed-Other	Total	
Total haplotypes:	20	2	0	2	24	
<i>Type 1 diabetes association:</i>						
<u>Resistant</u>						
0102-0602	1	0	-	0	1	
0401-0402 (African American)	1				1	
0501-0301	1	0	-	0	1	
Resistant haplotypes, n(%)	3 (15.0)	0	-	0	3 (12.5)	
<u>Neutral</u>						
0101-0501	2	1	-	0	3	
0101/4-0503	2	0	-	0	2	
0101-0604	1	0	-	0	1	
Neutral haplotypes, n(%)	5 (25.0)	1 (50.0)	-	0	6 (25.0)	
<u>Susceptible</u>						
0301-0201	1	0	-	0	1	
0301/x-0302	3	0	-	1	4	
0501/x-0201/2	6	1	-	1	8 (33.3)	
Susceptible haplotypes, n(%)	10 (50.0)	1 (50.0)	-	2 (100)	13 (54.2)	

C. Mixed Phenotype Diabetes Patients (n=12)						
	Afr Amer	Caucasian	Latino	Mixed-Other	Total	
Total haplotypes:	20	2	0	2	24	
Undetermined						
0101-0602	1	0	-	0	1	
030x-0201/2	1	0	-	0	1	
Undetermined haplotypes, n(%)	2 (10.0)	0	-	0	2 (8.3)	
Total Haplotypes	156	64	46	24	290	
Number of Patients	78	32	23	12	145	