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Human Leukocyte Antigen Class I B and C Loci Contribute to Type 1 Diabetes (T1D) Susceptibility and Age at T1D Onset

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Abstract

Alleles of human leukocyte antigen (HLA) class II genes are well known to affect susceptibility to type 1 diabetes (T1D), but less is known about the contribution of HLA class I alleles to T1D susceptibility. In this study, molecular genotyping was performed at the HLA-B and HLA-C loci for 283 multiplex Caucasian families, previously typed for HLA-A and the class II loci. Allele frequencies were compared between affected siblings and affected family-based controls. Linkage disequilibrium coefficients were calculated for HLA-B–HLA-C haplotypes and for class I–class II haplotypes. After adjustment for linkage disequilibrium, the following alleles remain associated with T1D: B*1801, B*3906, B*4403, C*0303, C*0802, and C*1601. B and C allele associations were tested for certain T1D-associated DRB1–DQB1 haplotypes, with the following results: B*3801 is protective on DRB1*0401–DQB1*0302 haplotypes, both C*0701 and C*0702 are predisposing on DRB1*0404–DQB1*0302 haplotypes, and B*3906 is predisposing on DRB1*0801–DQB1*0402 haplotypes. As with previous results for HLA-A, HLA-B and HLA-C are associated with age at T1D onset (mean 11.6 ± 0.3 years). The protective allele B*4403 was associated with older age at onset (15.1 years; $p < 0.04$), and the predisposing alleles C*0702 and B*3906 were associated with younger age at onset (9.5 years, $p < 0.001$; and 7.8 years, $p < 0.002$, respectively). These data support a role for HLA class I alleles in susceptibility to and age at onset of T1D.

Keywords

type 1 diabetes; HLA class I; HLA-B; HLA-C; age at onset

INTRODUCTION

Type 1 diabetes (T1D) is a multifactorial autoimmune disease resulting from the destruction of insulin-producing β cells in the pancreas by autoreactive T cells. Such destruction results in clinically insufficient insulin production and in a dysregulation of glucose homeostasis [1, 2]. About 50% of the familial clustering for T1D is attributed to genes within the human leukocyte antigen (HLA) region [3]. Several studies have revealed that the HLA-linked

susceptibility to T1D is determined by multiple components. Although the strongest contribution is widely recognized to come from the class II DRB1 and DQB1 genes, various reports have indicated that DPB1, another locus within class II [4–7], class I [8–10], and class III regions [11] modify susceptibility to this disease.

Evidence for a role of major histocompatibility complex (MHC) class I alleles in diabetes susceptibility comes from studies of animal models. Some common MHC class I variants, when coexpressed with other susceptibility genes, aberrantly mediate autoreactive CD8 T-cell responses essential to T1D development [12]. Evidence from nonobese diabetic mice reveals that MHC class I and class II variants interactively regulate not only the development of diabetogenic T cells, but also the T-cell receptor promiscuity of autoreactive effectors; further evidence indicates an effect on disease susceptibility of allelic variation at the class I K locus [13].

Class I polymorphisms have been associated with susceptibility to T1D in humans as well [5, 8–10]. In addition, polymorphisms in nonclassical class I loci, such as the A4 and A5 alleles and the MHC class I chain-related gene A (MICA), have been found to be increased in patients with T1D relative to controls in Italian and Korean populations, respectively [14, 15].

In humans, the presence of HLA-A24 has been demonstrated to correlate with little or no residual β -cell activity in patients with T1D [9]. In addition, a role for A24 in disease susceptibility in the Finnish population was also reported by Fennessy *et al.* [16]. Associations with age at onset for T1D have been reported for several HLA class I polymorphisms, including A*2402 [17–19]. Human leukocyte antigen class I molecules function as antigen presenting cells for CD8⁺ cytotoxic T lymphocytes, and they play a role in determining the antigen specificity of the cytotoxic T lymphocyte-mediated destruction of islet cells. Consequently, HLA class I function is consistent with the observed associations of HLA-A alleles with age at T1D onset.

In a study of multiplex Caucasian families from the United States [8], associations of HLA-A alleles with T1D susceptibility that persisted after adjusting for linkage disequilibrium (LD) with class II alleles were reported. The data revealed increased T1D susceptibility for A*2402 and A*3002 and decreased susceptibility for A*0101 or A*1101. The associations with A*2402 (predisposing) and A*1101 (protective) were later confirmed in a Filipino case-control study [5] in which a predisposing effect for A*2402 and A*2403 (but not A*2407) was not accounted for by LD with class II haplotypes.

Few reported studies address the role of HLA class I B and C alleles in T1D susceptibility, although specific alleles of these genes (*e.g.*, B18) are known to modify the effect of the DR3 haplotype on T1D susceptibility [20, 21]. In the Filipino population mentioned above [5], C*0102 (increased) and C*1502 (decreased) remained significantly associated with T1D, even after accounting for LD with class II DRB1-DQB1 haplotypes. No significant HLA-B associations that were not attributable to LD with class II were seen in the Filipino data; however, in a Finnish population, Pitkaniemi *et al.* [22] found that B62 was predisposing to T1D after accounting for haplotype effects.

This report illustrates T1D associations for HLA class I B and C alleles in a set of 283 Caucasian, multiplex T1D families. These families were previously genotyped for all HLA class II loci and for HLA-A, allowing analysis of the HLA-B and HLA-C data in the context of the remainder of the HLA alleles on the chromosome and adjustment of the association data based on LD of class I alleles with HLA DRB1-DQB1 haplotypes. Associations are seen for individual alleles and haplotypes, even after correction for LD. In addition, DRB1-DQB1 haplotype-specific effects are evident for HLA-B and HLA-C alleles, as is an association of some alleles with age at T1D onset.

MATERIALS AND METHODS

Subjects

DNA samples from 283 Caucasian, multiplex families were obtained from the collection of the Human Biological Data Interchange (HBDI, Philadelphia, PA). The HBDI is a repository for cell lines derived from T1D families and was established in part for the purpose of mapping T1D-associated genes by linkage analysis. Most of the HBDI families are nuclear families with unaffected parents and at least two affected siblings (multiplex). Only two affected siblings from each family have been included in this analysis.

Genotyping Methods

Molecular HLA typing data were generated with polymerase chain reaction–sequence-specific oligonucleotide probe linear array technology, similar to previously described methodology for genotyping the HLA-A locus [23].

Statistical Analysis

Control haplotypes ($n = 399$) were determined on the basis of the affected family-based control (AFBAC) method [24]. The transmission of overall haplotypes at all four loci (DRB1, DQB1, HLA-B, and HLA-C) was used to determine AFBAC haplotypes, and recombinants were excluded. The statistical significance of differences in allele frequencies between T1D cases and AFBACs was assessed by Pearson χ^2 test. In addition, the percentage of times that an HLA-B or HLA-C allele was transmitted from a heterozygous parent to an affected offspring was computed.

Adjustment for LD With Class II Haplotypes

The expected allele frequencies were computed, given LD and haplotype relative penetrances. Briefly, the null hypothesis (H_0) in this case is that HLA-B or -C allele frequencies will differ between patients and controls (1) caused by LD between HLA-B, HLA-C, or HLA-B–HLA-C haplotypes and DRB1-DQB1 haplotypes, and (2) from chance (sampling), thus implying that HLA-B, HLA-C, or HLA-B–HLA-C haplotypes are neutral relative to disease predisposition.

Under H_0 , the expected allele frequencies at HLA-B or C can be computed by the equation derived by Thomson (1984):

$$\bar{q}_{Bj} = p_{Bj} + \sum_i^k D_{ij} \frac{q_{DR-DQi}}{p_{DR-DQi}}$$

where D_{ij} indicates pairwise LD between the i th DR-DQ haplotype and the j th HLA-B or -C allele in the control sample, q indicates frequency in patients, and p indicates frequency in controls. This method relies on sampling estimates of pairwise LD between HLA-B, HLA-C, or HLA-B–HLA-C haplotypes and DRB1-DQB1 and estimates of the patient and control frequencies derived from the samples under study. Thus, a sampling error will be associated with the computed value for expected HLA-B, HLA-C, or HLA-B–HLA-C allele and haplotype frequencies. The larger the control sample, the smaller this error. This has been taken into account in our statistical tests, which were carried out as previously described [8].

HLA-B and -C Associations Within Specific Class II Haplotypes

A transmission disequilibrium test [25] was carried out on DRB1-DQB1 heterozygous parents carrying at least one of the following well-established T1D risk haplotypes: DRB1*0301-DQB1*02, DRB1*0401-DQB1*0302, DRB1*0404-DQB1*0302, DRB1*0801-DQB1*0402, and DRB1*0101-DQB1*0501, referred to here as DR3, DR4(1), DR4(4), DR8, and DR1, respectively. Because lack of Hardy-Weinberg equilibrium can potentially introduce a bias to this type of analysis, the Hardy-Weinberg proportions of HLA parental genotypes were assessed by an exact Markov chain procedure (as implemented by Arlequin 1.1, Excoffier, University of Geneva, Geneva, Switzerland), which resulted in $p = 0.168$. Under the null hypothesis that no other loci within the HLA region modify the effect on T1D susceptibility of these haplotypes, the transmission proportion of HLA-B and -C alleles to T1D affected offspring should not vary among alleles. Deviations from such random expectation were assessed by χ^2 test.

For selected alleles, an analysis of variance was carried out with age at onset as the outcome variable and the presence of at least one copy of an allele (1) or zero copies of an allele (0) as the independent variable. Age at onset was not available for 14 of 566 affected individuals genotyped for HLA-B and HLA-C. The F -statistic, derived from the analysis of variance and carried out by S-Plus 6.1 (Insightful, Seattle, WA) therefore has (1, 551) degrees of freedom.

RESULTS

Allele and Haplotype Frequencies in T1D Cases and Controls

Differences in allele frequencies between T1D-affected individuals and AFBACs at the HLA-B and HLA-C loci in the HBDI families are listed in Table 1 (HLA-B) and Table 2 (HLA-C). These results are not adjusted for LD with HLA class II haplotypes. The strongest associations observed at the B locus were seen for B*0801, B*1501, and B*3906 (predisposing) and for B*0702, B*4403, and B*5701 (protective). For the C locus, the most significant associations were seen for C*0303, C*0304, and C*0701 (predisposing) and for C*0602, C*0702, C*0802, and C*1601 (protective).

The frequencies of 11 HLA-B–HLA-C haplotypes were significantly different between AFBACs and cases (Table 3). Six haplotypes appeared protective for T1D, including B*0702-C*0702 (odds ratio [OR] = 0.43), B*3502-C*0401 (OR = 0.05), B*5701-C*0602 (OR = 0.08), B*4403-C*1601 (OR = 0.22), B*1402-C*0802 (OR = 0.32), and B*5101-C*1502 (OR = 0.31). Five haplotypes appeared predisposing for T1D, including B*0801-C*0701 (OR = 2.60), B*1801-C*0501 (OR = 5.62), B*3906-C*0702 (OR = 4.96), B*1501-C*0304 (OR = 3.21), and B*1501-C*0303 (OR = 4.37).

LD

The HLA region has one of the highest levels of LD in the human genome. HLA-B and HLA-C alleles exhibit very strong LD, as measured in the control samples (AFBAC; Table 4). The most common haplotype combinations (haplotype frequency >5%) were B*0702-C*0702, B*0801-C*0701, B*4001-C*0304, B*4402-C*0501, and B*3501-C*0401. Sixteen other haplotypes have an LD coefficient that differs significantly from zero.

The genes encoding the HLA class II molecules DR and DQ have the strongest effect on T1D susceptibility and are in such strong LD with each other that a recombinant event between the DRB1 and DQB1 loci is almost never seen. Alleles in both the HLA-B and the HLA-C loci are in LD with DRB1-DQB1 haplotypes. Tables 5 and 6 illustrate the LD between HLA class II DRB1-DQB1 haplotypes and HLA-B and HLA-C alleles, respectively. Fifteen combinations of DRB1-DQB1 haplotypes with HLA-B alleles (Table 5) and 16 combinations of DRB1-DQB1 haplotypes with HLA-C alleles (Table 6) exhibit LD coefficients that differ significantly from zero.

Table 7 lists the LD coefficients for combinations of class II DRB1-DQB1 haplotypes with class I HLA-B–HLA-C haplotypes. The observation that 16 of these combined haplotypes exhibit LD coefficients that vary significantly from zero underscores the extent of LD in the HLA region, and thus the complexity of interpretation of T1D associations for any single HLA locus.

Adjustment for LD Between Class I and II

Some of the differences between cases and AFBACs listed in Table 4 may be attributable to LD of HLA-B–HLA-C haplotypes with predisposing or protective HLA-DRB1-DQB1 haplotypes. For example, haplotypes B*0702-C*0702 and B*5701-C*0602 are both in strong LD with the highly protective haplotypes DRB1*1501-DQB1*0602 and DRB1*0701-DQB1*0303, respectively (Table 7). On the other hand, haplotypes B*0801-C*0701 and B*1801-C*0501 are both in strong LD with DRB1*0301-DQB1*02, a highly predisposing haplotype. However, no clear LD pattern can account for the large differences between cases and AFBACs for some haplotypes, including B*3906-C*0702.

Tables 8 (HLA-B) and 9 (HLA-C) list the allelic T1D associations that remain after observed allele frequencies are compared with expected frequencies, estimated by conditioning on the LD coefficient with DRB1-DQB1 haplotypes and on the effect on disease susceptibility of the class II haplotypes in the present data set. The allele frequencies of three B alleles exhibited significant deviations from expected values after this correction. Notably, the allele B*1801, thought to mark predisposing DR3 haplotypes, is not

significantly increased in cases without adjustment for LD (Table 1), but appears significantly predisposing after the correction (Table 8). The predisposing effect of B*3906 and the protective effect of B*4403 remain significant after the adjustment for LD. Three HLA-C alleles (Table 9), including C*0303 (predisposing), C*0802 (protective), and C*1601 (protective), remain significantly associated with T1D after LD adjustment.

Haplotype-Specific Associations

The previous results average the effects of B and C alleles over all possible DRB1-DQB1 combinations and do not account for the possibility of haplotype-specific deviations from expected values. To investigate this possibility, transmission proportions of HLA-B and HLA-C alleles from parents to affected offspring were examined in the context of the most common DRB1-DQB1 haplotype classes found in patients with T1D in the study sample. These haplotypes are DRB1*0301-DQB1*02, DRB1*0401-DQB1*0302, DRB1*0404-DQB1*0302, DRB1*0801-DQB1*0402, and DRB1*0101-DQB1*0501, and are abbreviated as DR3, DR4(1) DR4(4), DR8, and DR1, respectively. The results are listed in Table 10. A particularly notable result was observed for the allele C*0702. C*0702 is in strong positive LD with the protective haplotype DRB1*1501-DQB1*0602 (Table 6), and, averaging over all haplotypes, does not appear significantly associated with T1D susceptibility. However, when individual haplotypes are examined, an increased transmission of C*0702 was observed for DR3 ($p < 0.09$), DR4(4) ($p < 0.05$), and DR8 ($p < 0.06$) haplotypes (Table 10). In addition, the allele C*0303 appears to reverse the disease susceptibility effect of the haplotype DRB1*1101-DQB1*0302. Overall, DRB1*1101-DQB1*0302 haplotypes were transmitted from heterozygote parents to affected offspring 17.3% of the time (of 52 informative transmissions). DRB1*1101-DQB1*0302-C*0303 haplotypes ($n = 4$ informative transmissions) were transmitted 75% of the time. Although the numbers are small, a Fisher exact test reveals that this difference in transmission proportions is statistically significant ($p = 0.014$, data not shown) and supports the hypothesis that alleles at the class I loci can modify T1D susceptibility effects of DRB1-DQB1 haplotypes.

B*1801 was overtransmitted in DR3 haplotypes, and the slight overtransmission of C*0501 in DR3 haplotypes may solely result from LD with B18. This B18 effect appears to be limited to DR3 haplotypes as it was not seen in DR4, DR1, or DR8 haplotypes. Another apparent haplotype-specific effect was observed for B*3801 on DR4(1) haplotypes. B*3801 reveals no apparent disease association when averaged over all DRB1-DQB1 haplotypes; however, DR4(1) haplotypes carrying this B*3801 were significantly undertransmitted to patients compared with DR4(1) haplotypes not carrying B*3801. This result is intriguing, although the sample number is small and precludes the drawing of any robust conclusions. Finally, C*0304 was significantly undertransmitted (19%, $p < 0.03$) on DR1 haplotypes, even though C*0304 appeared significantly predisposing in the uncorrected data (Table 2) and appeared only slightly, and nonsignificantly, protective when averaged over all haplotypes after LD adjustment (Table 9). All the other alleles whose frequency deviated within a specific DR-DQ haplotype (e.g., B*3906 with DR8 and DR1, Table 10) were already found to be significantly associated with T1D after adjusting for LD and are seen on more than one class II haplotype.

Age at Onset

Previous data reported for this sample set revealed strong association of HLA-A alleles and age at onset [16]. Given the role of class I molecules in triggering the effector portion of the autoimmune reaction, the B and C loci are logical candidates to be associated with age at onset. Age-at-onset differences were examined only for those alleles with a T1D association not explained by LD with class II alleles.

Individuals carrying allele B*3906 were on average 3.7 years younger at the onset of T1D than patients not carrying this allele ($p < 0.002$, Table 11). Patients carrying C*0702 also had a significantly lower age at onset ($p < 0.001$), whereas patients carrying at least one copy of B*4403 were on average 3.5 older at the onset of the disease than patients with other genotypes ($p < 0.04$, Table 11). The association of C*0702 was only partly a result of its positive LD with B*3906, because a significantly younger age at onset ($p < 0.03$) was observed, even when patients carrying one or two copies of B*3906 were excluded from the analysis (Table 11). These results confirm the importance of class I antigens in modifying age at onset of T1D.

DISCUSSION

This study is the first in Caucasians to investigate the influence of class I alleles on T1D with complete molecular genotyping for both the B and C loci on samples previously typed for HLA-A [8]. Two issues require careful consideration. First, having tested for associations with 49 B-locus alleles and 28 C-locus alleles, the question of multiple comparisons must be addressed. Given the large number of tests carried out, some of the statistically significant results with p values near the cutoff for statistical significance ($p < 0.05$) could be the result of type I error (*i.e.*, false-positive findings). Some tests, however (*e.g.*, B*18), are based on prior hypotheses, so the confidence level is reasonably high that the results represent true associations. For those individual alleles with no prior hypothesis regarding their effect on T1D susceptibility, the results presented here may be spurious or unique to this data set. These results represent a first step toward understanding the role of alleles at the B and C loci; however, they require replication in independent populations before strong conclusions may be drawn from them. The second issue for consideration is that of type II error (*i.e.*, false-negative findings). The extremely large number of four-locus haplotypes results in very sparse data, especially for stratified analyses such as those for specific DR-DQ haplotypes. In that case, the data may be under-powered to detect some true allelic associations because of the small numbers involved. Despite these limitations, the data reveal T1D associations that are worth noting and attempting to replicate in other studies.

These data do not replicate some of the allelic associations reported in the Filipino (C*0102 and C*1502) or Finnish (B62) populations. B62 is absent from our study population, and C*1502 was decreased in patients relative to what would be expected by LD, although this deviation did not achieve statistical significance ($p < 0.14$), and C*1502 is not a common allele in this population (2.5%). The only unexplained inconsistency is the result for C*0102, for which no evidence for T1D association was found.

Two allelic associations, B*4403 (protective) and B*3906 (predisposing), warrant additional discussion. The predisposing effect of B*3906 was particularly dramatic for the DR8 haplotype. For B*4403 (protective), the association with susceptibility was accompanied by a significant increase in age at onset, and for B*3906 (predisposing) cases, it was accompanied by a significantly younger age at onset. These associations with both age at onset and disease susceptibility appear to be consistent with the hypothesis that role of class I molecules on T1D susceptibility is a result of their potential influence in the acceleration or delay of the final stage of the autoimmune response (β -cell destruction).

For the C locus, the strongest association, averaging over all DR-DQ haplotypes, was a predisposing effect of C*0303, an allele that is in positive LD with DRB1*1301-DQB1*0603. DRB1*1301-DQB1*0603 is a protective haplotype in this sample, with an OR of 0.12 [3]. As previously observed, the predisposing effect of C*0303 was also seen on the protective haplotype DRB1*1101-DQB1*0301.

C*0702, on the other hand, did not appear significantly increased in patients relative to its expected value. In fact, before adjusting for LD this allele appears to be protective because of its LD with DRB1*1501-DQB1*0602. However, when this allele occurred in the same chromosome as predisposing DR-DQ haplotypes (DR3, DR4, and DR8), it was transmitted more often than expected to affected offspring, and the effect was significant for the DR4(4) haplotype. The excess transmission may, in some cases, result from LD between C*0702 and B*3906 (*e.g.*, in the context of DR8 and DR1), but in the case of DR4 and DR3 haplotypes, these two alleles may have independent effects on susceptibility. A predisposing effect of C*0702 seems to be supported by its strong association with younger age at onset, which persists even when individuals carrying B*3906 were excluded from the analysis.

Again, the importance of assessing the effect of these alleles in other independent data sets must be stressed. Nevertheless, this study should serve as a reference for future research studies in which associations of HLA-B and HLA-C alleles with T1D susceptibility and age at onset can be tested and perhaps replicated in other populations.

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ABBREVIATIONS

AFBAC	affected family-based control
HBDI	Human Biological Data Interchange
HLA	human leukocyte antigen
LD	linkage disequilibrium
OR	odds ratio
T1D	type 1 diabetes

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TABLE 1

HLA-B allele frequencies among T1D cases (transmitted) and controls (AFBAC) and proportion transmitted from heterozygote parents to T1D cases

HLA-B	Controls (AFBAC) (%)	T1D (%)	Odds ratio	95% CI	p Value	Transmitted (%)
0702	16.5	8.0	0.44	(0.30–0.66)	1.E-04	37.0
0704	0.3	0.0	—	—	NS	0.0
0705	0.3	1.0	3.91	(0.46–33.02)	NS	68.8
0801	9.3	21.8	2.73	(1.84–4.04)	3.E-06	63.1
1302	1.5	0.7	0.47	(0.13–1.66)	NS	36.4
1401	0.8	0.7	0.94	(0.21–4.22)	NS	44.4
1402	3.3	1.1	0.34	(0.13–0.89)	0.023	29.5
1501	4.0	12.5	3.43	(1.96–6.00)	1.E-05	68.9
1503/7/8/10/24 ^a	0.3	0.9	—	—	NS	65.0
1517	0.3	0.4	1.77	(0.17–18.02)	NS	50.0
1518	0.8	0.0	—	—	NS	0.0
1801	5.8	8.7	1.57	(0.94–2.61)	NS	62.7
2702	0.5	0.1	0.18	(0.01–3.90)	NS	16.7
2703	2.3	4.2	1.92	(0.88–4.17)	NS	58.5
3501	7.3	3.8	0.50	(0.28–0.89)	0.020	35.3
3502	2.3	0.4	0.19	(0.05–0.79)	0.011	20.8
3503	1.0	1.1	1.15	(0.33–4.01)	NS	50.0
3508	0.3	0.4	1.41	(0.13–15.62)	NS	66.7
3701	0.8	0.6	0.82	(0.17–3.86)	NS	37.5
3801	2.8	1.9	0.67	(0.28–1.57)	NS	38.0
3901	1.3	1.3	1.06	(0.34–3.31)	NS	50.0
3903	0.3	0.0	—	—	NS	0.0
3906	0.8	3.8	5.21	(1.55–17.56)	0.003	86.0
4001	6.5	7.2	1.11	(0.66–1.84)	NS	52.6
4002	1.0	0.7	0.70	(0.17–2.83)	NS	40.9
4101	0.3	0.9	3.55	(0.41–30.48)	NS	62.5
4202	0.3	0.0	—	—	NS	0.0
4402	7.5	6.8	0.90	(0.55–1.47)	NS	47.0
4403	4.8	1.8	0.36	(0.17–0.78)	0.008	29.4
4404	0.0	0.1	—	—	NS	50.0
4501	0.3	0.6	2.48	(0.27–22.94)	NS	58.3
4701	0.3	0.4	1.77	(0.17–18.02)	NS	62.5
4801	0.0	0.1	—	—	NS	50.0
4901	0.8	1.1	1.41	(0.35–5.69)	NS	54.5
5001	1.3	1.6	1.27	(0.42–3.83)	NS	50.0
5002	0.3	0.0	—	—	NS	0.0
5101	4.0	2.7	0.65	(0.32–1.33)	NS	45.5

HLA-B	Controls (AFBAC) (%)	T1D (%)	Odds ratio	95% CI	p Value	Transmitted (%)
5108	0.3	0.1	0.35	(0.01–10.52)	NS	25.0
5201	0.5	0.4	0.70	(0.10–5.02)	NS	40.0
5301	1.0	0.3	0.26	(0.04–1.72)	NS	25.0
5501	1.5	0.6	0.41	(0.11–1.53)	NS	31.8
5601	1.0	0.6	0.61	(0.15–2.59)	NS	38.9
5701	5.3	0.4	0.08	(0.02–0.30)	2.E-06	9.3
5703	0.3	0.2	0.70	(0.04–11.30)	NS	50.0
5801	0.8	0.0	—	—	NS	0.0

Abbreviations: AFBAC = affected family-based control; CI = confidence interval; HLA = human leukocyte antigen; NS = not significant; T1D = type 1 diabetes.

^a These low-frequency alleles were grouped together for brevity.

TABLE 2

HLA-C allele frequencies among T1D cases (transmitted) and controls (AFBAC) and proportion transmitted from heterozygote parents to T1D cases

HLA-C	Controls (%)	T1D (%)	Odds ratio	95% CI	p Value	Transmitted (%)
0102	2.3	2.3	1.02	(0.43–2.41)	NS	46.3
0202	4.5	3.3	0.72	(0.37–1.39)	NS	41.3
0206	0.3	0.2	0.70	(0.04–11.30)	NS	50.0
0302	0.5	0.0	—	—	NS	0.0
0303	2.5	6.3	2.60	(1.27–5.31)	0.008	63.4
0304	9.0	14.1	1.66	(1.09–2.52)	0.024	59.0
0305	0.0	0.1	—	—	NS	50.0
0314	0.0	0.2	—	—	NS	100.0
0401	10.5	6.8	0.62	(0.39–0.98)	0.049	40.5
0501	7.8	11.0	1.46	(0.93–2.29)	NS	57.2
0602	10.0	3.8	0.35	(0.21–0.61)	2.E-04	29.5
0606	0.0	0.1	—	—	NS	50.0
0701	13.0	25.6	2.30	(1.62–3.25)	2.E-05	61.5
0702	18.5	12.5	0.63	(0.44–0.90)	0.018	44.7
0704	1.8	1.1	0.60	(0.20–1.80)	NS	43.3
0801	0.0	0.1	—	—	NS	50.0
0802	4.3	1.6	0.36	(0.16–0.82)	0.013	31.7
1202	0.5	0.4	0.70	(0.10–5.02)	NS	40.0
1203	6.5	5.4	0.82	(0.48–1.40)	NS	46.9
1402	0.5	0.8	1.59	(0.30–8.46)	NS	57.1
1403	0.3	0.0	—	—	NS	0.0
1502	2.5	1.0	0.38	(0.13–1.09)	NS	32.4
1504	0.0	0.2	—	—	NS	50.0
1505	0.3	0.8	3.19	(0.36–27.95)	NS	75.0
1601	3.8	1.3	0.34	(0.14–0.83)	0.015	30.0
1602	0.3	0.4	1.41	(0.13–15.62)	NS	50.0
1604	0.0	0.1	—	—	NS	50.0
1701	0.5	0.7	1.41	(0.26–7.75)	NS	44.4

See Table 1 for abbreviations.

TABLE 3

HLA-B and HLA-C haplotype frequencies among T1D cases (transmitted) and controls (AFBAC) and proportion transmitted from heterozygote parents to T1D cases (only haplotypes with frequencies above 0.5% in either T1D cases or controls are shown)

HLA-B	HLA-C	Controls (AFBAC) (%)	T1D (%)	Odds ratio	95% CI	p Value	Transmitted (%)
0702	0702	16.5	7.9	0.43	(0.29–0.65)	9.E-05	36.5
0705	1505	0.3	0.8	3.19	(0.36–27.95)	NS	75.0
0801	0701	9.3	21.0	2.60	(1.76–3.86)	8.E-06	63.0
1302	0602	1.5	0.7	0.47	(0.13–1.66)	NS	36.4
1401	0802	0.8	0.5	0.70	(0.14–3.50)	NS	43.8
1402	0802	3.3	1.1	0.32	(0.12–0.84)	0.017	28.6
1501	0303	1.0	4.2	4.37	(1.51–12.70)	0.004	74.2
1501	0304	2.3	6.9	3.21	(1.54–6.70)	0.001	69.6
1501	0401	0.5	0.6	1.24	(0.22–7.05)	NS	58.3
1801	0501	1.0	5.4	5.62	(1.97–16.08)	4.E-04	80.3
1801	0701	1.8	1.7	0.96	(0.36–2.56)	NS	55.9
1801	1203	2.0	1.4	0.70	(0.26–1.88)	NS	44.4
2703	0102	0.5	1.1	2.13	(0.43–10.59)	NS	60.0
2703	0202	1.8	2.4	1.37	(0.54–3.44)	NS	54.0
3501	0401	5.5	3.8	0.68	(0.37–1.24)	NS	41.8
3502	0401	1.8	0.1	0.05	(0.00–0.88)	0.004	6.3
3503	0401	0.5	0.8	1.59	(0.30–8.46)	NS	57.1
3701	0602	0.8	0.5	0.70	(0.14–3.50)	NS	35.7
3801	1203	2.5	1.9	0.74	(0.31–1.77)	NS	41.3
3901	0702	0.8	0.3	0.35	(0.05–2.50)	NS	25.0
3901	1203	0.5	1.0	1.95	(0.38–9.88)	NS	68.8
3906	0702	0.8	3.6	4.96	(1.47–16.78)	0.005	85.4
4001	0304	6.5	6.5	1.00	(0.60–1.69)	NS	50.7
4002	0202	1.0	0.3	0.26	(0.04–1.72)	NS	25.0
4402	0501	6.5	5.5	0.83	(0.49–1.42)	NS	46.3
4402	0704	0.8	0.9	1.18	(0.28–4.95)	NS	55.6
4403	0401	1.0	0.4	0.44	(0.09–2.14)	NS	25.0
4403	1601	3.5	0.8	0.22	(0.08–0.64)	0.003	22.5
4901	0701	0.8	1.0	1.30	(0.32–5.32)	NS	54.5
5001	0602	1.3	1.2	0.99	(0.31–3.13)	NS	46.7
5101	1402	0.5	0.7	1.41	(0.26–7.75)	NS	66.7
5101	1502	2.5	0.8	0.31	(0.10–0.96)	0.033	28.1
5301	0401	1.0	0.3	0.26	(0.04–1.72)	NS	25.0
5501	0303	1.3	0.6	0.49	(0.12–1.93)	NS	35.0
5601	0102	0.8	0.6	0.82	(0.17–3.86)	NS	43.8
5701	0602	5.0	0.4	0.08	(0.02–0.32)	5.E-06	9.6

See Table 1 for abbreviations.

TABLE 4

Linkage disequilibrium between HLA-B and HLA-C alleles among control haplotypes

HLA-B	HLA-C	Haplotype frequency (%)	D_{ij}	D'	p Value
0702	0702	16.5	0.1347	1.00	2.E-77
0801	0701	9.3	0.0806	1.00	4.E-61
4001	0304	6.5	0.0593	1.00	6.E-63
4402	0501	6.5	0.0593	0.86	3.E-63
3501	0401	5.5	0.0475	0.73	1.E-32
5701	0602	5.0	0.0448	0.95	1.E-40
4403	1601	3.5	0.0333	0.93	1.E-60
1402	0802	3.3	0.0312	1.00	1.E-67
3801	1203	2.5	0.0233	0.90	1.E-30
5101	1502	2.5	0.0241	1.00	2.E-55
1501	0304	2.3	0.0189	0.52	2.E-11
1801	1203	2.0	0.0163	0.30	2.E-08
1801	0701	1.8	0.0100	0.20	0.011
2703	0202	1.8	0.0165	0.77	9.E-27
3502	0401	1.8	0.0152	0.75	3.E-11
1302	0602	1.5	0.0135	1.00	1.E-13
5001	0602	1.3	0.0113	1.00	2.E-11
5501	0303	1.3	0.0122	0.83	3.E-37
1501	0303	1.0	0.0090	0.37	4.E-09
1801	0501	1.0	0.0055	0.10	NS
4002	0202	1.0	0.0096	1.00	2.E-20
4403	0401	1.0	0.0050	0.12	NS
5301	0401	1.0	0.0090	1.00	5.E-09

See Table 1 for abbreviations.

TABLE 5

Linkage disequilibrium between class II DRB1-DQB1 haplotypes and class I HLA-B alleles among controls

DRB1	DQB1	HLA-B	DR-DQ frequency (%)	HLA-B frequency (%)	DR-DQ-B frequency (%)	D_{ij}	D'	p Value
1501	0602	0702	15.79	16.54	9.27	0.067	0.506	1.8E-16
0301	02	0801	9.52	9.27	6.77	0.059	0.701	6.9E-36
0701	02	4403	10.28	4.76	3.51	0.030	0.707	6.6E-18
0101	0501	3501	7.52	7.27	1.75	0.012	0.180	1.1E-03
0701	02	1302	10.28	1.50	1.50	0.013	1.000	7.1E-12
0401	0302	1501	3.51	4.01	1.50	0.014	0.405	3.9E-13
1501	0602	1801	15.79	5.76	1.50	0.006	0.122	NS
1302	0604	4001	3.26	6.52	1.50	0.013	0.424	2.2E-08
0404	0302	4001	3.26	6.52	1.50	0.013	0.424	2.2E-08
0401	0301	4402	4.51	7.52	1.50	0.012	0.279	6.5E-05
0101	0501	0702	7.52	16.54	1.25	0.000	0.002	NS
1104	0301	1801	3.26	5.76	1.25	0.011	0.347	9.1E-07
1301	0603	3801	5.76	2.76	1.25	0.011	0.421	4.2E-08
0101	0501	4001	7.52	6.52	1.25	0.008	0.127	2.9E-02
0301	02	1801	9.52	5.76	1.00	0.005	0.087	NS
1101	0301	3501	4.76	7.27	1.00	0.007	0.149	2.6E-02
1101	0301	5101	4.76	4.01	1.00	0.008	0.213	2.1E-04
1302	0604	0702	3.26	16.54	0.75	0.002	0.078	NS
0701	02	1402	10.28	3.26	0.75	0.004	0.143	NS
0701	02	3501	10.28	7.27	0.75	0.000	0.001	NS
0401	0301	4001	4.51	6.52	0.75	0.005	0.109	NS
1501	0602	4402	15.79	7.52	0.75	-0.004	-0.367	NS
1301	0603	4402	5.76	7.52	0.75	0.003	0.060	NS
1201	0301	4402	1.75	7.52	0.75	0.006	0.382	6.5E-04
1501	0602	5101	15.79	4.01	0.75	0.001	0.035	NS

See Table 1 for abbreviations.

TABLE 6

Linkage disequilibrium between class II DRB1-DQB1 haplotypes and class I HLAC alleles among controls^a

DRB1	DQB1	HLA-C	DR-DQ frequency (%)	HLA-C frequency (%)	DR-DQ-C frequency (%)	D_{ij}	D'	p Value
1501	0602	0702	15.8	18.5	9.52	0.066	0.513	1.3E-14
0301	02	0701	9.5	13.0	7.02	0.058	0.698	3.7E-25
0701	02	1601	10.3	3.8	3.26	0.029	0.851	2.6E-20
0701	02	0602	10.3	10.0	2.51	0.015	0.164	0.004
0101	0501	0401	7.5	10.5	2.01	0.012	0.181	0.006
1302	0604	0304	3.3	9.0	1.50	0.012	0.408	8.2E-06
0401	0302	0304	3.5	9.0	1.50	0.012	0.372	2.5E-05
0404	0302	0304	3.3	9.0	1.50	0.012	0.408	8.2E-06
0101	0501	0304	7.5	9.0	1.50	0.008	0.121	0.045
0401	0301	0501	4.5	7.8	1.50	0.012	0.277	9.9E-05
0101	0501	0702	7.5	18.5	1.50	0.001	0.018	NS
1501	0602	1203	15.8	6.5	1.50	0.005	0.087	NS
0701	02	0401	10.3	10.5	1.25	0.002	0.019	NS
0701	02	0802	10.3	4.3	1.25	0.008	0.214	0.014
1501	0602	0401	15.8	10.5	1.00	-0.007	-0.395	NS
1501	0602	0501	15.8	7.8	1.00	-0.002	-0.181	NS
0301	02	0501	9.5	7.8	1.00	0.003	0.038	NS
1301	0603	1203	5.8	6.5	1.00	0.006	0.116	0.041
0402	0302	1203	2.3	6.5	1.00	0.009	0.406	8.2E-06
1101	0301	0102	4.8	2.3	0.75	0.006	0.300	8.5E-05
1301	0603	0303	5.8	2.5	0.75	0.006	0.257	0.002
0401	0301	0304	4.5	9.0	0.75	0.003	0.084	NS
0701	02	0304	10.3	9.0	0.75	-0.002	-0.187	NS
1101	0301	0401	4.8	10.5	0.75	0.003	0.059	NS
1301	0603	0401	5.8	10.5	0.75	0.001	0.028	NS
1301	0603	0501	5.8	7.8	0.75	0.003	0.057	NS
1501	0602	0602	15.8	10.0	0.75	-0.008	-0.524	NS
1501	0602	0701	15.8	13.0	0.75	-0.013	-0.634	NS
0101	0501	0701	7.5	13.0	0.75	-0.002	-0.231	NS
1104	0301	0701	3.3	13.0	0.75	0.003	0.116	NS
0401	0301	0702	4.5	18.5	0.75	-0.001	-0.099	NS
1302	0604	0702	3.3	18.5	0.75	0.001	0.056	NS
1104	0301	1203	3.3	6.5	0.75	0.005	0.177	0.019
1101	0301	1203	4.8	6.5	0.75	0.004	0.099	NS

See Table 1 for abbreviations.

^a Only haplotypes with a frequency of at least 0.75% in controls are shown.

TABLE 7

Linkage disequilibrium between class II DRB1-DQB1 haplotypes and class I HLA-B-HLA-C haplotypes among controls

DRB1	DQB1	HLA-B	HLA-C	DR-DQ frequency (%)	B-C frequency (%)	DR-DQ-B-C frequency (%)	D_{ij}	D'	p Value
0101	0501	0702	0702	7.5	16.5	1.3	0.0001	0.002	NS
0101	0501	3501	0401	7.5	5.5	1.8	0.0134	0.263	3.2E-05
0101	0501	4001	0304	7.5	13.0	1.3	0.0027	0.042	NS
0102	0501	1402	0802	1.0	3.3	1.0	0.0097	1.000	8.3E-27
0301	02	0801	0701	9.5	9.3	6.8	0.0588	0.701	6.9E-36
0301	02	1801	0501	9.5	1.0	1.0	0.0091	1.000	4.5E-09
0401	0301	4001	0304	4.5	13.0	0.8	0.0016	0.042	NS
0401	0301	4402	0501	4.5	13.0	1.5	0.0092	0.233	0.017
0401	0302	1501	0304	3.5	2.3	1.3	0.0117	0.539	7.7E-17
0404	0302	4001	0304	3.3	13.0	1.5	0.0108	0.381	9.4E-04
0701	02	1302	0602	10.3	1.5	1.5	0.0135	1.000	7.1E-12
0701	02	1402	0802	10.3	3.3	0.8	0.0042	0.143	NS
0701	02	3501	0401	10.3	5.5	0.8	0.0019	0.037	NS
0701	02	4403	1601	10.3	3.5	3.0	0.0265	0.841	1.3E-18
0701	0303	5701	0602	4.0	5.0	3.3	0.0306	0.803	3.0E-42
1104	0301	1801	0701	3.3	1.8	0.8	0.0069	0.409	6.5E-09
1301	0603	3801	1203	5.8	2.5	1.0	0.0086	0.363	6.5E-06
1301	0603	4402	0501	5.8	13.0	0.8	0.0000	0.000	NS
1302	0604	0702	0702	3.3	16.5	0.8	0.0021	0.078	NS
1302	0604	4001	0304	3.3	13.0	1.5	0.0108	0.381	9.4E-04
1302	0609	1402	0802	1.5	3.3	0.8	0.0070	0.483	2.3E-10
1401	0503	0702	0702	3.3	16.5	0.8	0.0021	0.078	NS
1501	0602	0702	0702	15.8	16.5	9.3	0.0666	0.506	1.8E-16
1501	0602	1801	1203	15.8	2.0	1.3	0.0094	0.555	8.8E-04
1501	0602	4402	0501	15.8	13.0	0.8	-0.0131	-0.635	NS

See Table 1 for abbreviations.

TABLE 8

Expected and observed T1D HLA-B allele frequencies, adjusting for linkage disequilibrium with class II DRB1-DQB1 haplotypes

HLA B	Observed T1D frequency ^a (%)	Expected T1D frequency (adjusting for LD with DR-DQ) ^b	χ^2	<i>p</i> Value
0702	8.04	11.72	3.28	NS
0705	0.97	0.00	—	—
0801	21.82	19.04	0.88	NS
1302	0.71	1.34	—	—
1401	0.71	0.72	—	—
1402	1.15	2.79	3.44	NS
1501	12.54	10.48	0.85	NS
1801	8.75	5.09	4.32	0.038
2703	4.24	1.96	3.69	NS
3501	3.80	6.09	2.58	NS
3502	0.44	1.96	—	—
3503	1.15	0.93	—	—
3701	0.62	0.62	—	—
3801	1.86	2.37	0.30	NS
3901	1.33	1.13	0.07	NS
3906	3.80	0.62	9.51	0.002
4001	7.16	8.24	0.36	NS
4002	0.71	0.93	—	—
4101	0.88	0.00	—	—
4402	6.80	6.40	0.06	NS
4403	1.77	4.02	4.41	0.036
4901	1.06	0.72	0.29	NS
5001	1.59	2.04	0.27	NS
5101	2.65	3.55	0.63	NS
5301	0.27	0.93	1.92	NS
5501	0.62	1.34	—	—
5601	0.62	1.21	—	—
5701	0.44	1.75	—	—

See Table 1 for abbreviations.

^a Observed allele frequency among T1D-affected individuals.

^b Expected frequency under linkage disequilibrium (LD) estimated from affected family based controls using equation 1.

TABLE 9

Expected and observed T1D HLA-C allele frequencies, adjusting for linkage disequilibrium with class II DRB1-DQB1 haplotypes

HLA-C	Observed T1D frequency ^a (%)	Expected T1D frequency (adjusting for LD with DR-DQ) ^b	χ^2	<i>p</i> Value
0102	2.3	2.2	0.02	NS
0202	3.3	3.8	0.19	NS
0303	6.3	2.2	8.69	0.0032
0304	14.1	16.0	0.54	NS
0401	6.8	8.7	1.14	NS
0501	11.0	8.1	1.98	NS
0602	3.8	5.6	1.75	NS
0701	25.6	22.2	1.10	NS
0702	12.5	15.3	1.29	NS
0704	1.1	1.5	0.43	NS
0802	1.6	3.6	3.87	0.049
1203	5.4	5.4	0.00	NS
1402	0.8	0.0	3.17	NS
1502	1.0	2.2	2.24	NS
1505	0.8	0.0	3.17	NS
1601	1.3	3.2	3.87	0.049
1701	0.7	0.0	2.82	NS

See Table 1 for abbreviations.

^a Observed allele frequency among T1D-affected individuals.

^b Expected frequency under linkage disequilibrium (LD) estimated from affected family-based controls using equation 1.

TABLE 10

HLA-B, HLA-C, and B-C allele frequencies among transmitted and nontransmitted DR3, DR4, DR1, and DR8 haplotypes to patients with T1D

DRB1*0301 total chromosomes HLA-B	DQB1*02 Not trans = 164	trans = 347		Trans% 67.9%		HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans
		Freq NT	Freq trans	p Value	% Trans											
0702	2.4%	5.5%	5.5%	NS	82.6%	0202	1.8%	0.9%	NS	50.0%	0702	0702	2.4%	5.5%	NS	82.6%
0801	69.5%	60.5%	60.5%	NS	64.8%	0303	2.4%	1.7%	NS	60.0%	0801	0701	67.1%	58.2%	NS	64.7%
1501	1.8%	0.9%	0.9%	NS	50.0%	0304	2.4%	2.3%	NS	66.7%	0801	0702	0.6%	1.4%	NS	83.3%
1801	9.8%	19.6%	19.6%	0.010	81.0%	0401	1.2%	2.9%	NS	83.3%	1801	0501	9.1%	17.6%	0.021	80.3%
2703	2.4%	1.2%	1.2%	NS	50.0%	0501	11.0%	18.2%	0.057	77.8%	3501	0401	0.6%	1.4%	NS	83.3%
3501	0.6%	1.4%	1.4%	NS	83.3%	0602	4.3%	4.3%	NS	68.2%	5001	0602	3.7%	2.6%	NS	60.0%
5001	3.7%	2.6%	2.6%	NS	60.0%	0701	68.3%	58.8%	NS	64.6%	—	Other	16.5%	13.3%	—	—
5101	1.2%	1.4%	1.4%	NS	71.4%	0702	3.0%	6.9%	0.087	82.8%	—	—	—	—	—	—
Other	8.5%	6.9%	6.9%	—	—	Other	5.5%	4.0%	—	—	—	—	—	—	—	—

DRB1*0404 total chromosomes HLA-B	DQB1*0302 Not trans = 41, trans = 106	trans = 106		Trans% 72.1%		HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans
		Freq NT	Freq trans	p Value	% Trans											
0702	2.4%	14.2%	14.2%	0.054	93.8%	0202	7.3%	4.7%	NS	62.5%	0702	0702	2.4%	14.2%	0.054	93.8%
0801	0.0%	9.4%	9.4%	0.092	100.0%	0303	14.6%	7.5%	NS	57.1%	0801	0701	0.0%	9.4%	0.095	100.0%
1501	9.8%	7.5%	7.5%	NS	66.7%	0304	41.5%	27.4%	NS	63.0%	1501	0303	9.8%	4.7%	NS	55.6%
2703	9.8%	5.7%	5.7%	NS	60.0%	0401	4.9%	3.8%	NS	66.7%	2703	0202	7.3%	4.7%	NS	62.5%
3906	4.9%	7.5%	7.5%	NS	80.0%	0501	0.0%	7.5%	NS	100.0%	3906	0702	4.9%	7.5%	NS	80.0%
4001	41.5%	28.3%	28.3%	NS	63.8%	0701	0.0%	13.2%	0.038	100.0%	4001	0304	41.5%	26.4%	NS	62.2%
4402	4.9%	7.5%	7.5%	NS	80.0%	0702	7.3%	23.6%	0.043	89.3%	4402	0501	0.0%	7.5%	NS	100.0%
5101	12.2%	6.6%	6.6%	NS	58.3%	1203	2.4%	4.7%	NS	83.3%	5101	1502	12.2%	4.7%	NS	50.0%
Other	14.6%	13.2%	13.2%	—	—	1502	12.2%	4.7%	NS	50.0%	—	Other	22.0%	20.8%	—	—
—	—	—	—	—	—	Other	9.8%	2.8%	—	—	—	—	—	—	—	—

DRB1*0401 total chromosomes HLA-B	DQB1*0302 Not trans = 78, Freq NT	trans = 259		Trans% 76.9%	HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-A	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans
		Freq trans	p Value																			
0702	3.8%	8.9%	NS	88.5%	0102	3.8%	2.3%	NS	66.7%	0702	0702	3.8%	8.1%	NS	87.5%							
0801	1.3%	3.5%	NS	90.0%	0202	0.0%	5.4%	0.075	100.0%	0801	0701	1.3%	3.5%	NS	90.0%							
1302	0.0%	1.9%	NS	100.0%	0303	9.0%	16.2%	NS	85.7%	1302	0602	0.0%	1.9%	NS	100.0%							
1501	43.6%	40.5%	NS	75.5%	0304	38.5%	32.8%	NS	73.9%	1501	0303	7.7%	12.0%	NS	83.8%							
1801	5.1%	3.5%	NS	69.2%	0401	7.7%	3.5%	NS	60.0%	1801	0304	29.5%	25.5%	NS	74.2%							
2703	1.3%	7.3%	0.054	95.0%	0501	11.5%	7.3%	NS	67.9%	2703	1203	1.3%	3.1%	NS	88.9%							
3501	3.8%	1.2%	NS	50.0%	0602	1.3%	3.1%	NS	88.9%	3501	0202	0.0%	4.6%	NS	100.0%							
3801	5.1%	0.8%	0.011	33.3%	0701	6.4%	5.8%	NS	75.0%	3801	0303	1.3%	1.9%	NS	83.3%							
4001	9.0%	8.1%	NS	75.0%	0702	3.8%	9.7%	NS	89.3%	4001	0401	3.8%	1.2%	NS	50.0%							
4402	11.5%	8.9%	NS	71.9%	0704	2.6%	1.5%	NS	66.7%	4402	1203	5.1%	0.8%	0.011	33.3%							
4403	2.6%	3.1%	NS	80.0%	1203	7.7%	5.8%	NS	71.4%	4403	0304	9.0%	7.3%	NS	73.1%							
5101	2.6%	1.5%	NS	66.7%	Other	7.7%	6.6%	—	—	5101	0501	9.0%	7.3%	NS	73.1%							
5601	3.8%	2.3%	NS	66.7%	—	—	—	—	—	5601	0704	2.6%	1.5%	NS	66.7%							
Other	6.4%	8.5%	—	—	—	—	—	—	—	Other	0102	3.8%	2.3%	NS	66.7%							
—	—	—	—	—	—	—	—	—	—	—	Other	21.8%	18.9%	—	—							

DRB1*0801 total chromosomes HLA-B	DQB1*0402 Not trans = 21, Freq NT	trans = 32		Trans% 60.4%	HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-A	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans
		Freq trans	p Value																			
2703	23.8%	15.6%	NS	50.0%	0102	9.5%	12.5%	NS	66.7%	2703	0102	9.5%	12.5%	NS	66.7%							
3906	4.8%	59.4%	0.002	95.0%	0304	14.3%	12.5%	NS	57.1%	3906	0702	4.8%	59.4%	0.002	95.0%							
4001	9.5%	12.5%	NS	66.7%	0401	19.0%	12.5%	NS	50.0%	4001	0304	9.5%	12.5%	NS	66.7%							
Other	61.9%	12.5%	—	—	0702	23.8%	59.4%	0.060	79.2%	Other	Other	76.2%	15.6%	—	—							
—	—	—	—	—	Other	33.3%	3.1%	—	—	—	—	—	—	—	—							

DRB1*0101 total chromosomes HLA-B	DQB1*0501 Not trans = 85, Freq NT	trans = 72		Trans% 45.9%	HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans	HLA-A	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans
		Freq trans	p Value																			
0702	18.8%	11.1%	NS	33.3%	0102	8.2%	5.6%	NS	36.4%	0702	0702	18.8%	11.1%	NS	33.3%							
0801	3.5%	6.9%	NS	62.5%	0304	15.3%	4.2%	0.030	18.8%	0801	0701	3.5%	6.9%	NS	62.5%							
1501	4.7%	5.6%	NS	50.0%	0401	25.9%	18.1%	NS	37.1%	1501	0102	3.5%	8.3%	NS	66.7%							
2703	5.9%	12.5%	NS	64.3%	0501	5.9%	4.2%	NS	37.5%	2703	0202	2.4%	4.2%	NS	60.0%							

DRB1*0101 total chromosomes HLA-B	DQB1*0501 Not trans = 85, Freq NT	trans = 72		Trans% 45.9%	p Value	Trans		p Value	% Trans	HLA-B	HLA-C	Freq NT	Freq trans	p Value	% Trans
		Freq trans	Freq NT			Freq trans	Freq NT								
3501	24.7%	18.1%	NS	38.2%	NS	18.1%	8.2%	2.8%	22.2%	3501	0401	22.4%	18.1%	NS	40.6%
3906	2.4%	11.1%	0.030	80.0%	0.030	11.1%	23.5%	13.9%	33.3%	3906	0702	2.4%	11.1%	0.030	80.0%
4001	12.9%	4.2%	0.067	21.4%	0.067	4.2%	12.9%	51.4%	—	4001	0304	12.9%	4.2%	0.067	21.4%
4402	8.2%	11.1%	NS	53.3%	NS	11.1%	—	—	—	4402	0501	5.9%	4.2%	NS	37.5%
Other	18.8%	19.4%	—	45.9%	—	19.4%	—	—	—	—	Other	28.2%	31.9%	—	—

Abbreviations: Freq NT = frequency nontransmitted; Freq trans = frequency transmitted; HLA = human leukocyte antigen.

TABLE 11

Mean age at onset of disease by genotype for HLA-B and HLA-C alleles associated with T1D susceptibility

Genotype	Age at onset of patients carrying genotype (y)	Standard error	Age at onset of patients not carrying genotype (y)	Standard error	F^a	p Value
All patients	11.55	0.32	—	—	—	—
B*1801 +	10.83	0.80	11.70	0.36	0.99	NS
B*3906+	7.84	1.19	11.85	0.34	10.46	<0.0013
B*4403 +	15.10	1.72	11.42	0.33	4.42	<0.036
C*0303 +	11.59	0.93	11.53	0.35	0.00	NS
C*0701 +	11.57	0.48	11.54	0.44	0.00	NS
C*0702 +	9.54	0.67	12.16	0.37	11.59	<0.0007
C*0702 + B*3906—	10.19	0.81	12.20	0.37	4.99 ^a	<0.026
C*0802	13.26	1.87	11.50	0.33	0.86	NS
C*1601	12.29	2.06	11.53	0.33	0.13	NS

See Table 1 for abbreviations.

^aFor all tests, $F(1,551)$, except C*0702 + B*3906—, for which $F(1,510)$.