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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 $\pm$ 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. *Human Immunology 66, 301–313 (2005).* © American Society for Histocompatibility and Immunogenetics, 2005. Published by Elsevier Inc.

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

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

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].

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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
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.

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