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HLA-DRB1*0403 is associated with dominant protection against IDDM in the general Dutch population and subjects with high-risk DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 genotype

Key words:

insulin-dependent diabetes mellitus; HLA-DRB1*0403; autoimmune disease; susceptibility

Acknowledgments:

We thank the regional pediatricians for supply of blood samples of families with type 1 diabetes patients. This study was supported by the Diabetes Fonds Nederland. Dr. Roep was supported by the Royal Academy of Arts and Sciences, The Netherlands.

Abstract: Insulin-dependent (Type 1) diabetes mellitus (IDDM) is a genetically controlled T-cell mediated autoimmune disease. Recently, subtyping of HLA-DRB1*04 identified the HLA-DRB1*0403 allele to be associated with protection in Caucasoids with the highest risk heterozygous genotype DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201. Some studies confirmed this finding, but other reports were not consistent with a dominantly protective trait. We here report the frequency of HLA-DRB1*0403 in a large cohort ($n=200$) of Dutch patients with IDDM, their first-degree family members ($n=370$), and random controls ($n=420$) of the general population in The Netherlands. We found that HLA-DRB1*0403 is strongly associated with dominant protection against development of IDDM in unrelated subject, even in the context of the highest risk HLA-DQ phenotypes and HLA-DR4-DQB1*0302 ($P<0.0001$).

Insulin-dependent (Type 1) diabetes mellitus (IDDM) is a genetically controlled T-cell mediated autoimmune disease in which the insulin-producing β -cells in pancreatic islets of Langerhans are irreversibly destroyed (1). Although the genetic association is diverse (2), the major histocompatibility complex (MHC) region on chromosome 6 is most strongly associated with both susceptibility and protection to IDDM. This region, designated IDDM-1, has at least two separate regions that are associated with predisposition (3). The consensus is that combinations of HLA-DR en -DQ alleles or haplotypes, rather than particular alleles or loci confer the highest genetic risk to IDDM (4–7). Recently, subtyping of HLA-DRB1*04 identified the HLA-DRB1*0403 allele to be associated with protection in Caucasoids with the highest risk heterozygous genotype DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 (8). Other studies confirmed these findings (3, 5, 7, 9), but not all studies were consistent with a dominantly protective trait. In the Chinese population, no independent association of HLA-DRB1*0403 with predisposition to type 1 diabetes was found (10, 11), while in Caucasians, non-significant

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Received 3 February,
accepted for publication 30 March 1999

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Tissue Antigens . ISSN 0001-2815

Tissue Antigens 1999; 54: 88–90
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Comparison of IDDM patients vs. control subjects for presence of HLA-DRB1*0403**Table 1**

	HLA-DRB1*0403-positive	HLA-DRB1*0403-negative	P-value
<i>General population</i>			
IDDM patients	0	200	0.02
General population	10	410	
<i>High-risk HLA-DR/DQ phenotypes</i>			
IDDM patients	0	120	0.000081
General population	8	49	
<i>HLA-DRB1*04-DQB1*0302</i>			
IDDM patients	0	141	0.000087
General population	8	59	
<i>Families with IDDM</i>			
IDDM patients	0	200	Not significant
Parents	1	227	
Siblings	2	140	

trends towards decreased prevalence of DRB1*0403 in IDDM patients have also been reported (4, 12, 13). In some cases, the lack of significance may be explained by the limited numbers of subjects studied.

We here report the frequency of HLA-DRB1*0403 in a large cohort ($n=200$) of Dutch patients with IDDM that were collected consecutively upon diagnosis by pediatricians in the southwestern part of The Netherlands (Table 1). This frequency was compared to the frequency of HLA-DRB1*0403 in random controls ($n=420$) of the general population in The Netherlands (Table 1) (14). HLA-DRB1, DQA1 and DQB1 polymorphism was tested by polymerase chain reaction using sequence-specific oligonucleotide probes (PCR-SSOP) on locus specifically amplified DNA (15).

Our results confirm the findings in Belgium, Sweden and Sardinia showing a dominant strong protective association. We extended our analyses to high-risk subjects and first-degree relatives of the IDDM patients studied here. Even in subjects with the highest genetic risk HLA-DR/DQ phenotypes (DR3-DQA1*0501-DQB1*0201 homozygotes, DR3-DQA1*0501-DQB1*0201/DR4-DQA1*0301-DQB1*0302, DR4-DQA1*0301-DQB1*0302 homozygotes, DR4-DQA1*0301-DQB1*0302/DR1- or DR10-DQA1*0101-DQB1*0501, DR4-DQA1*0301-DQB1*0302/DR6-DQA1*0102-DQB1*0604, DR4-DQA1*0301-DQB1*0302/DR8-DQA1*0401-DQB1*0402) and sub-

jects with the predisposing high-risk HLA-DRB1*04-DQB1*0302 haplotype we found that HLA-DRB1*0403 was associated with dominant protection against development of IDDM. In families of our IDDM patients, DRB1*0403 had never been inherited by diabetic offspring, while two non-diabetic siblings of IDDM patients inherited this allele (not significant (NS)).

HLA-DRB1*0406, which only differs from HLA-DRB1*0403 by codon 37 (Ser) that does not affect the peptide binding motif of the DR molecule (7), was not found in either patients or controls. Interestingly, HLA-DRB1*0407, which codes for a DR molecule that differs from that of HLA-DRB1*0403 by a single amino acid residue on position 86 of the β -chain, did not display dominant protection (1/114 IDDM patients vs. 8/420 control subjects; NS). In Belgian subjects, the DRB1*0407 allele conferred dominant protection in DR3/4-positive Caucasoids, while in DQ2/8-positive subjects it was not significantly associated with protection to IDDM (8). HLA-DRB1*0407 codes for a DR molecule that differs from that of DRB1*0403 in peptide binding motif in the first pocket only (large aromatic residues in stead of Val, Ile or Leu) (7).

We conclude that in the Dutch population, HLA-DRB1*0403 is strongly associated with dominant protection against development of IDDM, even in the context of the highest risk HLA-DQ phenotype.

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