Table 1. HLA class II susceptibility to IDDM in Japanese patients

	Total IDDM (n = 178)	Fast progressive IDDM Onset			Slowly progressive	
		< 15 year (n = 52)	15–30 year (n = 39)	> 30 year (n = 39)	IDDM (n = 48)	Control (n = 279)
DRB1*0405	53.4[a]	50.0[a]	56.4[a]	53.8[a]	54.2[a]	22.9
DRB1*0802	21.3[b]	30.8[b]	23.1	15.4	14.6	10.4
DQA1*0301-DQB1*0302	11.8	17.3[b]	12.8	7.7	8.3	3.4 (5/149)
DQA1*0401-DQB1*0302	3.4	7.7	2.6	0.0	2.1	1.3 (2/149)
DQA1*0401-DQB1*0402	5.6	3.8	7.7	7.7	4.2	4.7 (7/149)
DRB1*0901	43.3	36.5	43.6	59.0[b]	37.5	30.1

Frequencies (%) of alleles or haplotypes are presented. [a] $pc < 0.002$, [b] $pc < 0.05$

betes, since it was not significantly increased in patients with slowly progressing disease (Table 1) [9]. Interactions between this haplotype and later age-specific environmental factors, or later-age operative genetic factors, may be involved in the disease development, but obviously further studies are necessary to confirm and clarify this observation.

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High frequency of HLA DQA1*0301 in Yakuts: no correlation with IDDM incidence

Dear Sir,

Products of HLA DQA1 and HLA DQB1 genes are considered to directly participate in the development of insulin-dependent diabetes mellitus (IDDM). HLA DQA1 Arg52 alleles (mainly 0301 allele) and non-Asp-57 alleles of the HLA DQB1 gene are associated with IDDM in different populations [1]. Moreover, incidence of the disease correlates with the frequency of "diabetogenic" alleles of the DQB1 gene in different populations [2]. The DQA1 gene has not been investigated as frequently from this point of view. Products of HLA DQB1 and DQA1 genes (DQβ and DQα chains, respectively) form a heterodimer molecule and it could be assumed that both genes are important for development of IDDM, and that frequency of HLA DQA1*0301 should also correlate with IDDM incidence.

We compared HLA DQA1 allele frequencies in Russian (IDDM incidence is 6.3 [3]) and Yakut populations with a low IDDM incidence (Table 1). The incidence IDDM in Saha Republic (Yakutia) calculated from the data of Ministry of Health and demographic data [4] is 2.7. A vast majority of the diabetic subjects are patients of Slavonic or Jewish origin, thus IDDM frequency in Yakuts should actually be considerably lower. This small-scale investigation shows an unexpectedly high frequency of the 0301 allele of the HLA DQA1 gene in Yakuts that does not correlate with a low IDDM incidence.

Table 1. Frequency of HLA DQA1 allele carriers in Yakuts and Russians

Allele	Yakuts		Russians	
	No. subjects	Frequency	No. subjects	Frequency
0101/0102	12	0.48	27	0.47
0103	8	0.32	9	0.16
0201	4	0.16	18	0.31
0301	15	0.60	13	0.23
0401	3	0.12	4	0.07
0501	5	0.20	29	0.50
0601	0	0	1	0.02

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We determined alleles of HLA DQA1 locus by the amplification/restriction procedure described previously [5] with some modifications. This method allowed us to distinguish seven alleles or allele sets (Table 1).

The most "diabetogenic" DQA1*0301 allele is more frequent in Yakuts (18 from 50 chromosomes) than in Russians (14 from 114 chromosomes). Investigation of Yakut patients with Viliuisk encephalomyelitis uncovered even greater frequency of this allele. Our unpublished investigations together with other data support the idea that presence of DQA1*0301 allele in one of the homologous chromosomes is sufficient for diabetes susceptibility. Thus, comparison of "diabetogenic" allele carrier numbers is probably more informative than comparison of allele frequencies (Table 1).

The difference between frequencies of DQA1*0301 allele carriers in Yakuts and Russians is reliable ($p < 0.05$ after correction for multiple comparisons) and the data are in accordance with investigations of HLA DQA1 alleles in Japanese and Chinese, who also have a high frequency of the HLA DQA1*0301 allele and a low incidence of IDDM [6, 7]. It is possible that role of the DQα chain is less than is proposed here. However there is no reason to reject the hypothesis of a functional role for DQ loci in diabetes susceptibility. Moreover, there is an association of IDDM with the DQA1*0301 allele in Japanese subjects. More important are exclusions from the correlation between IDDM incidence and non-Asp57 allele frequency of DQB1 in different populations [6, 8]. IDDM is a multifactorial disease, and another genetic or environmental factor could play a key role in its resistance in Yakut and other populations. Unusual data concerning the role of DQ genes in diabetes susceptibility are mainly derived from investigations of Mongoloid populations living in a quite different environment. It appears that another race-specific genetic factor is responsible for incidence of IDDM in different populations. In any case further population study of IDDM susceptibility genes is important for better understanding of IDDM aetiology.

Sincerely yours,
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HLA-A alleles and susceptibility to IDDM

Dear Sir,
We were interested to read "A gene in the HLA class I region contributes to susceptibility to IDDM in the Finnish population?" [1]. Data from such a large, well-characterized population are extremely valuable in the study of the contribution of HLA genes to insulin-dependent diabetes mellitus (IDDM). We believe, however, that considerable caution should be exercised in the interpretation of the results.

The authors show that of the four Cw1, B56, DR4, DQ8 haplotypes identified, only the A2-associated haplotype was significantly associated with IDDM (82 of 1492 diabetic haplotypes were A2, Cw1, B56, DR4, DQ8 compared with 14 of 1254 control haplotypes). This finding is taken as evidence that the HLA class I region contributes to diabetes susceptibility. It should be noted, however, that the three non-A2, Cw1, B56, DR4, DQ8 haplotypes are very uncommon, together constituting only 7 of 1492 diabetic haplotypes and 2 of 1254 control haplotypes. This study population, although large, is too small to exclude a disease-predisposing effect of the non-A2 haplotypes. If the distribution of the A2-positive and A2-negative Cw1, B56, DR4, DQ8 haplotypes is examined as in Table 1, one finds that the frequency of A2 does not differ significantly between the diabetic and control haplotypes. These data, therefore, do not suggest that the HLA class I region makes a particular contribution to susceptibility to IDDM.

Table 1. Distribution of Cw1, B56, DR4, DQ8 haplotypes between diabetic and control subjects

	Diabetic haplotypes $n = 89$	Control haplotypes $n = 16$
A2 haplotypes	82	14
Non-A2 haplotypes	7	2

$\chi^2 = 0.016$ (Yates' correction), not significant

The authors also point out that certain Cw3, B62, DR4, DQ8 haplotypes and certain Cw7, B8, DR3, DQ2 haplotypes are significantly associated with IDDM but others are not, depending on the allele at the HLA-A locus. It should be noted, however, that those haplotypes which are not associated with diabetes are uncommon, each non-associated haplotype constituting less than 1 % of both the diabetic and control populations. A similar comparison to that made in Table 1 of the distribution between the diabetic and control subjects of the disease-associated Cw3, B62, DR4, DQ8 haplotypes (A2, A3 and A24) with those which are not (A1, A11 and A28) gives a

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