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Human leukocyte antigen associations in Finnish liver transplantations due to primary sclerosing cholangitis and primary biliary cirrhosis

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Abstract: A genetic predisposition has been suggested in primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). The aim of the study was to evaluate human leukocyte antigen (HLA) frequencies and HLA associations in Finnish PSC and PBC patients. The relative frequencies of HLA-A, -B, and -DR antigens were compared between patients with PSC (n=50), or PBC (n=89), transplanted due to end-stage liver disease, and healthy members in the Finnish bone marrow donor registry (n=10000). Prevalence differences, prevalence ratios and the associated large-sample significance probabilities (2-sided P-values) and 95% confidence intervals were calculated.

We found a strong positive association between PSC and HLA-B8 and -DR3, and a weak positive association between HLA-A1 and PSC. HLA-DR3 also had a weak positive association with PBC, and a weak negative association between HLA-DR5 and PBC was found. In conclusion, HLA-B8, and –DR3 are susceptible for progressive liver disease in PSC, and HLA-DR3 may also be susceptible for disease progression in PBC. HLA-DR5 may be protective against severe PBC.

Keywords: Human leukocyte antigen, liver transplantation, primary biliary cirrhosis, primary sclerosing cholangitis

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1 Introduction

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the biliary system in which the intrahepatic and extrahepatic bile ducts are progressively destroyed. The clinical course of the disease is heterogeneous and PSC may be asymptomatic for years in some patients. PSC may also lead to liver cirrhosis and chronic liver failure or eventually cholangiocarcinoma [1–3]. In PSC, human leukocyte antigen (HLA) class II expression has been found in liver tissue (bile ducts, Kuppfer cells, arterial and venous endothelium) [4] and genetic factors have been proposed to contribute to the pathogenesis of PSC [5].

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by destruction of intrahepatic bile ducts and the presence of circulating autoantibodies to mitochondrial, smooth muscle cell, and nuclear antigens [6]. Both PSC and PBC have been shown to display significant and consistent HLA associations [7]. Also in PBC HLA class II expression has been found in bile ducts [8].

In a small study population, positive and negative association with HLA-B8 and HLA-B12, respectively, with PSC was found [9]. An increased frequency of the allele DRB1*0301, which encodes the serological determinant HLA-DR3, and the allele DRB1*1301 encoding the serological determinant HLA-DR6, have reproducibly been shown to be associated with PSC [10–12]. The association of DRB1*0301 with PSC has been replicated in other studies [13, 14]. In a study of 265 PSC patients from five European countries, HLA-DR3, -DQ2 heterozygous genotype associated with a more rapid progression of PSC [15]. When secondary HLA associations were sought by eliminating all of the patients and controls positive for the primary associated allele or alleles and reanalysing the data, increased HLA-DR2 (DRB1*1501 allele) frequency was observed in PSC patients [11, 14]. HLA-DR4 has been found to negatively associate with PSC [10, 11, 13, 14], suggesting a protective effect of this allele, but, on the contrary, rapid disease progression has been observed in a study in HLA-DR4 positive PSC patients [14].

Thus far any significant associations between PBC and HLA-A or HLA-B antigens have not been found. Previous studies have reported an increased frequency of HLA-DR8 [16–22] and HLA-DR3 [20, 23] in PBC patients compared to referent persons. In one study [16], HLA-DR5 had decreased frequency in PBC as compared to referent persons, and in another study [22], HLA DRB1*1302 (DR6) and HLA DRB1*1501 (DR2) were found to be negatively associated with PBC.

The aim of this study was to examine HLA frequencies and HLA associations in Finnish PSC and PBC patients with end stage liver disease.

2 Statistical methods and Experimental Procedures

2.1 Patients and controls

Fifty patients with PSC (31 females and 19 males) and 89 patients with PBC (12 females and 77 males) transplanted during the years 1982-2002 due to end stage liver disease were included in the study, and, consequently, represent severe forms of these diseases. The diagnoses of PSC and PBC were based on generally accepted clinical, cholangiographic, and histologic criteria. Most of the PSC patients had inflammatory bowel disease either ulcerative colitis or Crohn's disease and all PSC patients had typical findings in ERC. Patients who were anti-mitochondrial antibody (AMA)-negative and had mixed overlapping type of autoimmune hepatitis were excluded from the PBC patient group.

End-stage liver disease was defined as a condition with cirrhosis and one or more of the following symptoms and signs present: disordered blood coagulation, hepatic encephalopathy, ascites, variceal bleeding and/or hepatorenal syndrome [24]. All liver transplantation patients in this study were of Finnish origin. A total of 10000 healthy voluntary bone marrow donors registered with the Finnish Bone Marrow Donor Registry were used as healthy controls [25].

2.2 HLA data

HLA data of the patients was obtained from the Finnish Liver Transplantation Registry and these HLA frequencies were compared to those demonstrated in the Finnish bone marrow donor registry [25]. HLA-A, -B, and -DR typing of the liver transplant recipients and Finnish bone marrow donors was performed using a complement dependent lymphocytotoxicity test on peripheral lymphocytes [25]. HLA-DR typing of the patients was verified by PCR-SSOP method since 1998. The HLA results of bone marrow donors were available only at the serological level, and therefore we used the serological nomenclature following the standard system determined in International Histocompatibility Workshops. Tissue typing of the patients and bone marrow donors had originally been performed in the Tissue Typing Department of the Finnish Red Cross Blood Transfusion Service. Associations between HLA-A, -B, and -DR antigens and PSC and PBC were studied and compared to previously reported results.

2.3 Statistical analysis

To compare the relative frequencies or prevalence of HLA antigens between PSC or PBC patients and the Finnish healthy bone marrow donors we assumed a model of two independent binomial samples. Restricted likelihood score (standardized) test statistic-based unconditional estimates of the differences and ratios of prevalence as well as their 95% large sample (asymptotic) confidence intervals were obtained using the unconditional chi square test-based procedure proposed by Miettinen and Nurminen [26] and implemented

in the StatXact [27] statistical software.

Table 1A Comparison of observed HLA-A, HLA-B and HLA-DR prevalences in a population sample of healthy Finnish bone marrow donors and Finnish liver transplantation patients due to primary sclerosing cholangitis (PSC) in terms of the prevalence difference and prevalence ratio as well the associated large-sample significance probabilities (2-sided P-values) and 95% confidence intervals (lower and upper limits). Comparisons involving zero prevalences in both series are deleted.

HLA locus	Prevalence, %		Prevalence difference, %	Confidence interval		Prevalence ratio	Confidence interval		P-value
	PSC patients	Healthy donors*		Lower limit	Upper limit		Lower limit	Upper limit	
A1	28.0	16.2	11.8	1.3	25.5	1.73	1.08	2.58	0.02
A2	48.0	44.7	3.3	-9.9	16.8	1.07	0.78	1.38	0.64
A3	40.0	37.1	2.9	-9.5	16.8	1.08	0.74	1.45	0.67
A9	18.0	17.2	0.8	-7.5	13.6	1.05	0.57	1.79	0.88
A10	12.0	5.8	6.2	-0.2	18.0	2.07	0.96	4.13	0.06
A11	4.0	7.5	-3.5	-6.5	6.0	0.53	0.15	1.80	0.35
A19	10.0	17.5	-7.5	-13.2	3.9	0.57	0.25	1.22	0.16
A28	14.0	11.3	2.7	-4.4	14.9	1.24	0.61	2.32	0.55
B5	10.0	9.4	0.6	-5.1	12.0	1.06	0.46	2.28	0.88
B7	18.0	24.3	-6.3	-14.6	6.5	0.74	0.40	1.27	0.30
B8	38.0	16.5	21.5	9.3	35.4	2.30	1.56	3.15	< 0.001
B12	8.0	14.3	-6.3	-11.2	4.5	0.56	0.22	1.32	0.20
B13	6.0	6.2	-0.2	-4.2	10.0	0.97	0.33	2.62	0.95
B14	0.0	0.6	-0.6	-0.8	6.5	0.00	0.00	11.94	0.58
B15	26.0	22.4	3.6	-6.6	17.2	1.16	0.71	1.77	0.54
B16	4.0	9.3	-5.3	-8.3	4.2	0.43	0.12	1.45	0.20
B17	8.0	3.1	4.9	0.0	15.7	2.58	1.01	6.12	0.047
B18	4.0	9.5	-5.5	-8.5	4.0	0.42	0.12	1.42	0.19
B21	0.0	0.4	-0.4	-0.5	6.7	0.00	0.00	17.95	0.65
B22	2.0	4.3	-2.3	-4.0	6.2	0.47	0.08	2.45	0.42
B27	18.0	14.4	3.6	-4.7	16.4	1.25	0.68	2.14	0.47
B35	34.0	24.4	9.6	-2.0	23.5	1.39	0.92	1.97	0.12
B37	0.0	1.6	-1.6	-1.9	5.5	0.00	0.00	4.47	0.37
B40	16.0	16.2	-0.2	-7.9	12.3	0.99	0.51	1.76	0.97
B41	0.0	0.9	-0.9	-1.1	6.2	0.00	0.00	7.95	0.50
B47	0.0	1.4	-1.4	-1.7	5.7	0.00	0.00	5.11	0.40
DR1	42.0	29.7	12.3	-0.4	26.1	1.41	0.99	1.88	0.06
DR2	20.0	28.0	-8.0	-16.8	5.1	0.71	0.40	1.18	0.21
DR3	38.0	17.1	20.9	8.7	34.8	2.22	1.51	3.04	< 0.001
DR4	20.0	22.8	-2.8	-11.6	10.3	0.88	0.49	1.45	0.63
DR5	8.0	11.5	-3.5	-8.4	7.4	0.70	0.27	1.64	0.44
DR6	20.0	23.0	-3.0	-11.8	10.1	0.87	0.49	1.44	0.62
DR7	10.0	10.7	-0.7	-6.4	10.7	0.93	0.41	2.00	0.87
DR8	20.0	17.7	2.3	-6.5	15.3	1.13	0.63	1.87	0.67
DR9	2.0	5.6	-3.6	-5.4	4.9	0.27	0.36	0.63	1.88
DR10	0.0	1.7	-1.7	-2.0	5.4	0.00	0.00	4.20	0.35

* Source: M.K. Sirén et al. [25]

Table 1B Comparison of observed HLA-A,HLA-B and HLA-DR prevalences in a population sample of healthy Finnish bone marrow donors and Finnish liver transplantation patients due to primary biliary cirrhosis (PBC) in terms of the prevalence difference and prevalence ratio as well the associated large-sample significance probabilities (2-sided P-values) and 95% confidence intervals (lower and upper limits). Comparisons involving zero prevalences in both series are deleted.

HLA locus	Prevalence, %		Prevalence difference, %	Confidence interval		Prevalence ratio	Confidence interval		P-value
	PBC patients	Healthy donors*		Lower limit	Upper limit		Lower limit	Upper limit	
A1	19.1	16.2	2.9	-4.0	12.3	1.18	0.76	1.76	0.46
A2	47.2	44.7	2.5	-7.6	12.8	1.06	0.83	1.29	0.64
A3	43.8	37.1	6.7	-3.2	17.1	1.18	0.91	1-46	0.19
A9	22.5	17.2	5.3	-2.2	15.0	1.31	0.87	1.88	0.19
A10	2.3	5.8	-3.5	-5.3	2.0	0.39	0.11	1.35	0.15
A11	6.7	7.5	-0.8	-4.4	6.5	0.90	0.42	1.86	0.79
A19	20.2	17.5	2.7	-4.4	12.3	1.16	0.75	1.70	0.50
A28	18.0	11.3	6.7	0.0	15.9	1.59	1.00	2.42	0.048
B5	13.5	9.4	4.1	-1.6	12.7	1.43	0.84	2.36	0.19
B7	24.7	24.3	0.4	-7.4	10.3	1.02	0.70	1.43	0.93
B8	22.5	16.5	6.0	-1.5	15.7	1.36	0.91	1.96	0.13
B12	13.5	14.3	-0.8	-6.5	7.8	0.94	0.55	1.55	0.83
B13	4.5	6.2	-1.7	-4.5	4.8	0.72	0.28	1.78	0.51
B14	0.0	0.6	-0.6	-0.8	3.5	0.00	0.00	6.11	0.45
B15	27.0	22.4	4.6	-3.6	14.6	1.20	0.84	1.66	0.30
B16	9.0	9.3	-0.3	-4.7	7.5	0.97	0.50	1.81	0.92
B17	5.6	3.1	2.5	-0.7	9.4	1.81	0.78	4.06	0.17
B18	5.6	9.5	-3.9	-7.2	3.0	0.59	0.25	1.32	0.21
B21	0.0	0.4	-0.4	-0.5	3.7	0.00	0.00	10.38	0.55
B22	4.5	4.3	0.2	-2.6	6.7	1.05	0.41	2.57	0.93
B27	13.5	14.4	-0.9	-6.6	7.7	0.94	0.55	1.54	0.81
B35	22.5	24.4	-1.9	-9.4	7.8	0.92	0.62	1.32	0.67
B37	2.3	1.6	0.7	-1.0	6.2	1.40	0.38	4.93	0.63
B40	18.0	16.2	1.8	-4.9	11.1	1.11	0.70	1.69	0.65
B41	1.1	0.9	0.2	-0.7	5.2	1.25	0.22	6.84	0.82
B47	0.0	1.4	-1.4	-1.7	2.7	0.00	0.00	2.96	0.26
DR1	25.8	29.7	-3.9	-11.9	6.1	0.87	0.60	1.21	0.43
DR2	20.2	28.0	-7.8	-14.9	1.8	0.72	0.47	1.06	0.10
DR3	29.2	17.1	12.1	3.7	22.3	1.71	1.21	2.31	0.003
DR4	25.8	22.8	3.0	-5.0	13.0	1.13	0.78	1.57	0.50
DR5	3.4	11.5	-8.1	-10.5	-2.0	0.29	0.10	0.82	0.016
DR6	19.1	23.0	-3.9	-10.8	5.5	0.83	0.53	1.24	0.38
DR7	12.4	10.7	1.7	-3.7	10.1	1.16	0.66	1.95	0.61
DR8	24.7	17.7	7.0	-0.8	16.9	1.40	0.95	1.96	0.08
DR9	2.2	5.6	-3.4	-5.1	2.2	0.40	0.11	1.40	0.17
DR10	0.0	1.7	-1.7	-2.0	2.4	0.00	0.00	2.44	0.21

Table 1C Comparison of observed HLA-A,HLA-B and HLA-DR prevalences in Finnish liver transplantation patients due primary sclerosing chloangitis (PSC) and primary biliary cirrhosis (PBC) in terms of the prevalence difference and prevalence ratio as well the associated large-sample significance probabilities (2-sided P-values) and 95% confidence intervals (lower and upper limits). Comparisons involving zero prevalences in both series are deleted.

HLA locus	Prevalence, %		Prevalence difference, %	Confidence interval		Prevalence ratio	Confidence interval		P-value
	PSC patients	PBC patients		Lower limit	Upper limit		Lower limit	Upper limit	
A1	28.0	19.1	8.9	-5.3	24.1	1.45	0.79	2.68	0.23
A2	48.0	47.2	0.8	-16.1	17.9	1.02	0.69	1.44	0.93
A3	40.0	43.8	-3.8	-20.2	13.3	0.91	0.59	1.36	0.66
A9	18.0	22.5	-4.5	-17.5	10.4	0.80	0.39	1.58	0.53
A10	12.0	2.2	9.8	1.7	21.8	5.34	1.27	22.6	0.018
A11	4.0	6.7	-2.7	-10.7	7.3	0.59	0.14	2.46	0.51
A19	10.0	20.2	-10.2	-21.7	3.0	0.49	0.20	1.19	0.12
A28	14.0	18.0	-4.0	-15.9	9.9	0.78	0.34	1.70	0.54
B5	10.0	13.5	-3.5	-14.1	9.2	0.74	0.28	1.88	0.55
B7	18.0	24.7	-6.7	-19.9	8.3	0.73	0.36	1.41	0.36
B8	38.0	22.5	15.5	-0.0	31.6	1.69	1.00	2.84	0.05
B12	8.0	13.5	-5.5	-15.7	6.7	0.59	0.21	1.63	0.70
B13	6.0	4.5	1.5	-6.2	12.2	1.34	0.34	5.14	0.70
B15	26.0	27.0	-1.0	-15.5	15.0	0.96	0.53	1.69	0.90
B16	4.0	9.0	-5.0	-13.5	5.3	0.45	0.11	1.76	0.27
B17	8.0	5.6	2.4	-6.1	13.8	1.42	0.43	4.69	0.58
B18	4.0	5.6	-1.6	-9.3	8.3	0.71	0.16	3.1	0.68
B22	2.0	4.5	-2.5	-9.4	6.4	0.45	0.07	2.86	0.45
B27	18.0	13.5	4.5	-7.5	18.7	1.34	0.61	2.87	0.48
B35	34.0	22.5	11.5	-3.6	27.5	1.51	0.87	2.59	0.14
B37	0.0	2.2	-2.2	-7.8	5.0	0.00	0.00	3.35	0.29
B40	16.0	18.0	-2.0	-14.2	12.5	0.89	0.41	1.87	0.77
B41	0.0	1.1	-1.1	-6.1	6.0	0.00	0.00	2.96	0.45
DR1	42.0	25.8	16.2	0.00	32.4	1.63	1.00	2.61	0.049
DR2	20.0	20.2	-0.2	-13.4	14.7	0.99	0.49	1.93	0.97
DR3	38.0	29.2	8.8	-7.2	25.3	1.30	0.80	2.08	0.29
DR4	20.0	25.8	-5.8	-19.4	9.5	0.77	0.40	1.45	0.44
DR5	8.0	3.4	2.4	-3.0	15.8	2.37	0.61	9.2	0.23
DR6	20.0	19.1	0.9	-12.1	15.8	1.05	0.52	2.06	0.90
DR7	10.0	12.4	-2.4	-12.8	10.2	0.81	0.30	2.29	0.68
DR8	20.0	24.7	-4.7	-18.2	10.5	0.81	0.41	1.53	0.53
DR9	2.0	2.2	-0.2	-6.2	8.4	0.89	0.12	6.65	0.92

To cope with the problem of testing multiple hypotheses, we applied a recently developed method of Wacholder et al. [28]. Unlike classical "frequentist" statistical methods, this new approach is based on Bayesian statistical ideas. It integrates prior information on the hypothesis with the estimated prevalence ratio (and its confidence limits) and the power of the study (i.e., the probability of rejecting some null hypothesis when it was false). To decide whether a finding is "noteworthy", we used a derived measure termed "the false positive report probability" (F for short). The distinction between this measure and the statistical significance level α is crucial: α is the probability of a statistically

significant finding, given that the null hypothesis is true, whereas F is the probability that the null hypothesis is true, given that the finding is deemed statistically significant (typically at level $\alpha = 0.05$). F depends not only on the significance level (as does, e.g., the classical Bonferroni method), but also both on the power of the study (1 - β, where β is the probability of not rejecting some null hypothesis when it is false) and the prior probability that the hypothesis is true (π). Formally put [28, Appendix Equation 1]:

$$F = 1/\{1 + [\pi/(1 - \pi)][(1 - \beta)/\alpha]\}.$$

The interpretation of this equation is that the false positive report probability is always high when the significance level is much greater than the prior probability that the hypothesis s true, and even more so when the power of the study is low. The F value is calculated by substituting the observed P-value in place of α in the above equation and by estimating the statistical power from its relation to the prevalence ratio and its confidence interval. If this F value was less than the preset value F = 0.2, the association was deemed "noteworthy". The prior probability of a HLA antigen association with either a PSC or PBC disease was designated subjectively as high (≈ 0.1), moderate (≈ 0.01), or low (≈ 0.001) based on the existence of evidence from similar studies. An Excel spreadsheet was used to calculate the F values [28, online address and material].

3 Results

The phenotype frequencies of HLA antigens in patients with PSC and PBC were compared with healthy persons. In PSC patients, there was a statistically significant increase in the frequency of HLA-A1, HLA-B8, HLA-B17 and HLA-DR3 (Table 1A). The F-statistic was zero for HLA-B8 and HLA-DR3 even with a very low prior probability that there is an association (Table 2A). For the other HLA antigens the F-statistic-based analysis did not produce "noteworthy" results, except for HLA-A1 when the prior probability was high. In PBC patients, HLA antigens HLA-A28 and HLA-DR3 were positively and HLA-DR5 negatively associated with the disease (Table 1B). In case of HLA-DR3 and HLA-DR5 the F-statistic-based analysis yielded a "noteworthy" result with a high prior probability of an association (Table 2B).

The significant prevalence differences and observed prevalence ratios between patients with PSC or PBC are shown in Table 1C. When the frequencies of HLA antigens in patients with PSC and PBC were compared with each other it was found that the frequencies of HLA-A10, HLA-B8 and HLA-DR1 were higher in patients with PSC compared to patients with PBC. According to the F-statistic-based analysis, only the HLA-A10 finding was deemed "noteworthy" when the prior probability was high (Table 2C).

Table 2A False positive report probability (F*) values to test the observed statistically significant differences/ratios in the phenotype prevalences of HLA antigens between PSC patients and healthy donors (reported in Table 1A).

HLA antigen Observed prevalence difference / ratio Power**	Prior probability of association 0.1	0.01	0.001
A1 11.8% / 1.73 0.89	*0.17*	0.66	0.96
B8 21.5% / 2.30 0.58	*0.00*	*0.00*	*0.00*
B17 4.9% / 2.58 1.00	0.30	0.82	0.98
DR3 20.9% / 2.33 0.50	*0.00*	*0.00*	*0.00*

* Probability that the null hypothesis is true, given a statistically significant finding.
The italicized figures indicate probabilities that fall below the preset value of F = 0.2 for "noteworthiness".
** Probability of the study to reject the null hypothesis for the estimated prevalence ratio.

Table 2B False positive report probability (F) values to test the observed statistically significant differences/ratios in the phenotype prevalences of HLA antigens between PBC patients and healthy donors (reported in Table 1B).*

HLA antigen Observed prevalence difference / ratio Power**	Prior probability of association 0.1	0.01	0.001
A28 6.7% / 1.59 0.85	0.34	0.85	0.98
DR3 12.1% / 1.71 0.70	*0.037*	0.30	0.81
DR5 -8.1% / 0.29 1.00	*0.13*	0.61	0.94

* See footnotes of Table 2A.

Table 2C False positive report probability (F) values to test the observed statistically significant differences/ratios in the phenotype prevalences of HLA antigens between PSC and PBC patients (reported in Table 1C).*

HLA antigen Observed prevalence difference / ratio Power**	Prior probability of association 0.1	0.01	0.001
A10 9.8% / 5.34 1.00	*0.14*	0.64	0.95
B8 15.5% / 1.69 0.93	0.33	0.84	0.98
DR1 16.2% / 1.63 0.89	0.33	0.85	0.98

* See footnotes of Table 2A.

4 Discussion

In our PSC patients, a significant increase of HLA haplotype HLA- B8, HLA-DR3 was found, which is in accordance with a previous report of Norwegian PSC patients [29]. The association between PSC and HLA-DR3 is well established in other studies, too [11, 12, 15]. The weak association of HLA-B17 with PSC has not been observed by others and the association no longer existed after correcting for multiple testing. The prevalence of HLA-B12 was similar in our PSC patients (8%) compared to that of PSC patients in an early study of Chapman et al. [9], and it was decreased compared to the prevalence of HLA-B12 in referent persons (14%) in our study, but the difference did not reach the customary 5% statistical significance level. Therefore, negative association of HLA-B12 and PSC could not be seen, which differs from the study of Chapman et al. in which the number of PSC patients was rather small, 25 only.

In a recent study of PSC patients from five European populations, a significant increase of the alleles DRB1*03 (DR3), DRB1*15 (DR2) and DRB1*13 (DR6), and a significant decrease of the allele DRB1*04 (DR4) were also found [11]. We did not find any significant association between HLA-DR2, HLA-DR6 or HLA-DR4 and PSC, which differs from that study. The prevalence of HLA DR4 in PSC patients (20%) in this study was not increased compared with that of healthy donors (22.8%), although rapid disease progression has been identified in HLA DR4 positive PSC patients in another study [14]. A further study comparing HLA frequencies in mild and severe forms of PSC is needed to evaluate whether discrepancies between our study and other studies could be explained on that grounds.

In an early study of Swedish PSC patients, no statistically significant association be-

tween PSC and HLA class II was found [30]. The small number of PSC patients, only 21, of which seven patients had end-stage disease, may explain their finding. However, in another study of Swedish patients, significant associations between HLA DRB1*0301 (DR3), DRB1*1301 (DR6), DRB1*1501 (DR2), but not DRB1*04 (DR4) and PSC were found [10]. Their study population consisted of 75 PSC patients of which twelve patients were transplanted and ten nontransplanted patients died during the study period, meaning 29% of patients being of severe clinical stage.

In our PBC patients, HLA-DR8 was more common than in controls but the difference did not reach the 5% statistical significance level. Our result concerning HLA-DR8 differs remarkably from several studies, in which a strong association of HLA-DR8 and PBC has been demonstrated [16, 18, 19, 21, 22]. The frequency of HLA-DR8 in our PBC patients was similar (25%) compared to that in other studies (9-36%), but HLA-DR8 was more common in our controls (18%) compared to other studies (3-9%), which may, at least partly, explain the discrepancy between our study and other studies.

HLA-DR3 was found to be strongly associated with PBC in this study but the Bayesian analysis indicated that this finding was noteworthy only when the prior probability the hypothesis was high. A similar association between HLA-DR3 and PBC was found in a Danish study [20] which, however, did not find any increase in HLA-DR8 in their study population. Furthermore, HLA-A28 was weakly positively and HLA-DR5 was weakly negatively associated with PBC in the present study.

The frequencies of HLA-A10, HLA-B8 and HLA-DR1 were significantly higher in patients with PSC than in PBC patients but, according to F-statistics, the difference was noteworthy only for HLA-A10 with a high prior probability. Furthermore, we found that both PSC and PBC were significantly associated with HLA-DR3, which has been reported to associate with a rapid progression of PSC in one study [15]. Our finding may support the role of HLA-DR3 in more aggressive disease, not only in PSC but also in PBC as all our PSC and PBC patients had severe form of these diseases and were transplanted. The association between HLA-B8 was significant in PSC but not in PBC and we could not find any significant associations between any HLA A or HLA B antigens and PBC.

The etiology of PSC and PBC is still unknown but the immune system is believed to be involved in the pathogenesis of these diseases [4, 5, 22, 23, 31], and the haplotype A1-B8-DR3 or HLA DR4 have consistently been shown to associate with autoimmune hepatitis [32, 33]. Overlapping syndromes especially between PBC and autoimmune hepatitis are well known. In our study overlapping autoimmune hepatitis patients were excluded from this study however at end stage cirrhosis histologically it is sometimes impossible to separate between PBC and autoimmune cholangitis.

Certain HLA alleles have been reported to be markers for rapid disease progression [14, 15]. In that case significant HLA associations found in our patients with end-stage liver disease should represent markers for progressive disease, and discrepancies between previous reports might be explained by different clinical stage of patients in different studies. However, in some studies, HLA markers have been speculated to be more important for the onset of the disease rather than for the progression of the disease [10, 12].

In that case, HLA associations found in our end-stage liver disease patients should be considered as true pathogenetic markers. Discrepancies between previous studies and ours may also reflect the differences in genetic background and size of the populations analyzed. Furthermore, we have applied a recently developed statistical method based on Bayesian statistical ideas which also differs from previous studies.

In conclusions, in this study of end-stage liver disease patients, the well-established positive association between PSC and HLA-B8 and HLA-DR3 was confirmed. We could not observe HLA-DR2, HLA-DR4, HLA-DR5 or HLA-DR6 association in our PSC patients. Similarly, a significant positive association of HLA-DR3 and a negative association of HLA-DR5 with PBC were found but associations between HLA-DR2, HLA-DR6 or HLA-DR8 and PBC could not be confirmed in this study. Our results suggest that HLA-B8 and HLA-DR3 in PSC and HLA-DR3 in PBC may be significant and noteworthy in disease progression. Working up with HLA associations may help to develop strategies for immune therapy, e.g. T-cell vaccination, tolerance induction or blocking of HLA-peptide interaction [34].

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