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Relevance of HLA gene polymorphisms in Romanian patients with chronic renal insufficiency undergoing renal transplantation

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Abstract

Background: Chronic renal insufficiency (CRI) is a global public health problem with a high incidence in the Romanian population. In this study, we aimed to investigate genomic HLA polymorphisms in Romanian patients with CRI waiting for kidney transplantation. To determine the existence of a potential strong link between certain HLA polymorphisms and CRI, we also looked at HLA specificity combinations within the same locus or even different loci, referring to randomly inherited allelic combinations rather than potential haplotypes.

Methods: A total of 2199 patients with CRI on the kidney transplantation waiting list were included. A total of 2786 healthy individuals were included as controls. Both patients and controls were assessed for both HLA I and class II genes. HLA genes were typed using the low-resolution method polymerase chain reaction sequence-specific primer.

Results: Certain class I and class II HLA allele groups, genotypes and haplotypes were significantly more frequent in patients with CRI than in the control individuals (eg B* 40 ($p \leq .001$, $pc \leq .001$), C* 12 ($p \leq .001$, $pc \leq .001$), DRB1*14 ($p = .0022$, $pc = .04$), *C*12,-* ($p < .001$, $pc < .001$), A*01-C*15 ($p = .0003$, $pc = .03$) and A*02-C*12 ($p = .0005$, $pc = .0486$)).

Conclusions: HLA gene polymorphisms could be clinically relevant CRI-associated genetic profiles in Romanian patients with CRI.

KEYWORDS
combined HLA types, CRI, disease-associated HLA genes, haplotypes, polymorphisms

1 | INTRODUCTION

Over the last few decades, an impressive number of studies have established strong associations between certain diseases and individuals carrying particular HLA alleles.[1] Although these studies have proven a strong association between HLA and certain diseases (eg ankylosing spondylitis, type 1 diabetes and narcolepsy), the effector mechanisms underlying HLA-disease associations remain

unclear.[1] HLA associations with certain diseases can be determined by the linkage disequilibrium between genes within the major histocompatibility complex (MHC; eg in the case of hereditary haemochromatosis or congenital adrenal hyperplasia) or by the presence of anomalies in the MHC and non-MHC receptor interaction-activated pathways.[1]

HLA polymorphisms in the healthy Romanian population are well known.[2] Moreover, certain HLA genes have been associated with susceptibility to infections, such as hepatitis C in Romania.[3] Finally, the immune system (eg HLA) reportedly plays a role in the occurrence and progression of renal disease.[4-8]

Chronic renal insufficiency (CRI) is a complex and multifactorial disease that represents the final stage of chronic renal failure progression, revealed by reduced glomerular filtration below 15 mL/min/1.73 m^2 with a duration of more than 3 months, leading to permanent dialysis or a need for kidney transplantation.[9].

CRI incidence has increased markedly over the past few decades.[9] Kidney transplantation is the most efficient treatment for patients with CRI.[10] The global number of patients with CRI exceeds the number of renal transplantation procedures per year. Therefore, CRI incidence is almost 400 persons per million in the USA and other countries.[11] In the Romanian population, CRI is a serious public health problem. According to the National Transplant Agency,[12] 4792 Romanian patients with CRI were registered on the waiting list for kidney transplantation procedures at the end of 2020. Therefore, we aimed to investigate certain HLA genomic polymorphisms that might be associated with the development of CRI in Romanian patients waiting for kidney transplantation. We also looked at HLA specificity combinations within the same locus or even different loci, referring to randomly inherited allelic combinations.

2 | MATERIALS AND METHODS

2.1 | Patients

A total of 2199 patients with CRI, admitted between 2012 and 2019 to the Fundeni Clinical Institute, Romania, and who underwent kidney transplantation, were included in this study. All patients had a glomerular filtration rate below 15 mL/min at the time of inclusion in the study. At the same time, 2786 healthy donors from the Romanian Marrow Donor Registry were included as controls. To avoid bias, only one member from each family was included in the study.

Our research was undertaken in compliance with the approval of the Ethics Committee of the Fundeni Clinical Institute. Informed consent was obtained from all participants included in the study.

2.2 | HLA genotyping

Genomic DNA was extracted from the peripheral blood. DNA was isolated using the QIAamp® DNA Blood Mini Kit (Qiagen), according to the manufacturer's instructions.

HLA class I (HLA-A, -B, and -C) and HLA class II (HLA-DRB1, -DQB1, and -DPB1) genotyping were performed by the PCR sequence-specific primer low-resolution method using HLA-Ready Gene kits (Innotrain Diagnostik GmbH).

2.3 | Statistical analysis

The HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 allele and genotype frequencies were determined in patients with CRI and controls by direct counting using the Microsoft Excel software from the Office 365 package (Microsoft). The estimation-maximisation algorithm of the Arlequin software 3.5 (Swiss Institute of Bioinformatics) was used to estimate the HLA haplotype frequencies.

We used cross-tabulation (using χ^2 test) or Fisher's test in SPSS version 21.0 (IBM) to calculate the differences in allele, genotype and haplotype percentages between patients with CRI and controls. The χ^2 test was used when the expected value was higher than 5, and Fisher's test was used when the expected value was less than 5.

Odds ratios with 95% confidence intervals (95% CI) were calculated to establish the strength of each studied allele, genotype or haplotype association with CRI. The statistical significance was set at $p < .05$. To avoid the risk of false-positive allele, genotype or haplotype association identifications, all the obtained significant probability values were corrected for multiple testing using the Bonferroni correction formula.

3 | RESULTS

The HLA results for both patients and controls were obtained from our HLA tissue typing database at the Fundeni Centre for Immunogenetics and Virology. Data were available as per the typed HLA loci: 2199/2786, 2181/2689, 1062/1710, 2188/2625, 1283/1024 and 516/227 for HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1 and HLA-DPB1, respectively. Of all the patients enrolled in the study, 59.07% and 40.93% were 4–85-year-old men and women, respectively. The distributions of donors and patients by age groups and sex are shown in Table 1. No significant difference could be observed between the patients and controls when analysing age distribution and sex.

The frequencies of HLA allele groups, genotypes and haplotypes in both CRI patients and healthy controls were investigated to detect strong HLA gene polymorphisms that could be associated with CRI in the Romanian population.

3.1 | Frequency of HLA allele groups in Romanian patients with CRI

Table 2 presents the allele groups in patients with CRI compared with the control. In each group, we identified 19, 29, 13, 15, 5 and 12 alleles from loci A, B, C, DRB1, DQB1 and DPB1, respectively.

TABLE 1 Characteristics of patients and control individuals

		Patients	Controls
Category	**Subcategory**	**2199**	**2786**
Gender	Female	900	1119
		40.93%	40.17%
	Male	1402	1667
		59.07%	59.83%
Age	04–17	16	12
		0.73%	0.44%
	18–25	288	410
		13.10%	14.71%
	26–35	817	1105
		37.14%	39.67%
	36–45	754	899
		34.62%	32.26%
	46–55	306	352
		13.96%	12.62%
	>55	10	8
		0.45%	0.3%

After applying the Bonferroni correction, we found that certain HLA allele groups were associated with CRI in our group of patients (see Table 2): HLA-B*40 (OR = 1.4661, $p \leq .001$, $pc \leq 001$), HLA-C*12 (OR = 1.6966, $p \leq .001$, $pc \leq .001$), HLA-C*15 (OR = 1.8005, $p \leq .001$, $pc \leq .001$), HLA-DRB1*14 (OR = 1.2868, $p = .002$, $pc = .04$) and HLA-DPB1*02 (OR = 1.498, $p = .004$, $pc = .048$).

3.2 | Analysis of combined HLA types associated with CRI

We also studied the possible association of HLA allele heterozygosity or homozygosity with the disease at different loci.

Our study revealed a few allele combinations that remained or were not significantly and positively associated with CRI after the Bonferroni correction (see Table 3): *A*01,11* (OR = 1.73, $p = .004$, $pc = .2437$), *A*03,32* (OR = 2.33, $p = .003$, $pc = .2121$), *C*12,-* (OR = 2.51, $p < .001$, $pc < .001$), *DRB1*04,-* (OR = 2.242; $p = .006$, $pc = .7002$), *DRB1*04,14* (OR = 2.44; $p = .004$, $pc = .3596$) and *DRB1*14,-* (OR = 2.191; $p = .007$, $pc = .042$).

3.3 | Analysis of HLA haplotypes associated with CRI

Using the estimation-maximisation algorithm included in Arlequin software (version 3.5), we analysed all the HLA- A, -B, -C, -DRB1, -DQB1 and -DPB1 combinations of two, three, four, five and six loci haplotypes found in Romanian patients with CRI. To establish the haplotypes that were significantly positively associated with CRI in our patients, the Bonferroni correction was performed by multiplying the obtained P-value to the number of identified haplotypes for each locus combination (eg 1000 identified haplotypes for A-C loci combination): A*01-C*15 ($p = .0003$, $pc = .030$) and A*02-C*12 ($p = .0005$, $pc = .0486$).

4 | DISCUSSION

CRI is an important healthcare problem in Romania. Few studies have shown a strong association between HLA polymorphisms and CRI. Herein, to assess the association of HLA genes with CRI, patients and controls were enrolled and examined for both HLA class I and II genes. In this study, we assessed the association between HLA allele groups defined at low-resolution levels, genotypes, haplotypes and CRI using a case-control approach.

The appearance of CRI could be associated with other HLA types in different populations or different ethnicities of the same population. These findings could be due to differences in the number of patients and controls between studies, different techniques used for HLA-typing and different ethnic and genetic backgrounds of each population.[13]

A study performed by researchers in Azerbaijan found that A*11 and A*33 were associated with vulnerability to CRI.[14] In our study, the *A*01,11* and *A*03,32* genotypes were significantly more frequent in CRI patients than in controls, although the A*01, A*03, A*11 and A*32 alleles were not. In the Cantonese population in China,[7] A*24 was the most frequently identified allele in patients with CRI, whereas in Saudi Arabia, the A*26 allele was more frequently present in controls than in patients with CRI.[15]

Among different populations, several alleles at the HLA-C locus were identified to be significantly associated with CRI, although no consistent pattern could be observed. For example, C*01 was found more frequently in patients with CRI from Bosnia,[16] while C*04 was positively associated with CRI in 156 patients from Turkey.[17] C*02 and C*12 were negatively associated with CRI in Bosnia[16] and Saudi Arabia,[15] which contradicts our results (C*02 had a similar frequency in both the patient and control groups, while C*12 was significantly more frequent in the CRI than in the control group).

Concerning the HLA-B locus, B*40 was the only significantly more frequent allele in Romanian patients with CRI. The same allele group was also found to be positive in a prospective study conducted in Turkey[18] and in a retrospective study from China.[7]. Our results contradict the negative HLA B*40 association in Pakistan and Venezuela.[19] In other countries, B*15 was observed more frequently in patients with CRI.[19-21] In the present study, it had a similar frequency in both the control and patient groups.

B*40 and C*12 are known to be associated with diseases that might affect kidney function and disease progression to CRI. For instance, B*40 is linked to systemic lupus erythematosus in Argentina[22] and Pakistan.[23] Goebel et al. found a significant association between HLA C*12 and renal cell carcinoma in German patients.[24]

TABLE 2 Allele types in CRI patients in comparison with control group individuals

Allele group	Patients (%)	Controls (%)	Odds ratio	95% CI		*P*-value	*Pc*-value
				Lower Limit	Upper Limit		
A*01	12.48	12.65	0.9842	0.8735	1.1089	.8078	
A*02	29.45	29.72	0.9873	0.9054	1.0767	.7740	
A*03	10.11	10.39	0.9703	0.8516	1.1054	.6659	
A*11	9.64	8.87	1.0962	0.9566	1.2562	.1968	
A*23	2.02	2.76	0.7263	0.5578	0.9458	.0184	.3501
A*24	13.23	11.76	1.1443	1.0155	1.2894	.0276	.5249
A*25	2.34	3.16	0.7349	0.5744	0.9403	.0144	.2734
A*26	4.95	4.27	1.1683	0.9679	1.4101	.1111	
A*29	1.48	1.56	0.9453	0.6838	1.3068	.7429	
A*30	1.91	2.49	0.7607	0.5785	1.0003	.0560	
A*31	2.20	1.97	1.1193	0.8494	1.4750	.4370	
A*32	4.84	4.06	1.2034	0.9936	1.4573	.0617	
A*33	1.73	2.05	0.8415	0.6278	1.1280	.2687	
A*34	0.09	0.09	1.0131	0.2719	3.7751	1.0000	
A*36	0.07	0.29	0.2369	0.0690	0.8136	.0182	.3463
A*66	0.57	0.56	1.0214	0.6022	1.7324	1.0000	
A*68	2.70	2.37	1.1456	0.8913	1.4724	.3032	
A*69	0.16	0.75	0.2098	0.0942	0.4675	.0000	**.0003**
A*74	0.02	0.23	0.0972	0.0127	0.7434	.0052	
B*07	4.46	4.65	0.9561	0.7895	1.1579	.6611	
B*08	6.79	6.84	0.9920	0.8468	1.1622	.9357	
B*13	2.93	3.95	0.7333	0.5867	0.9164	.0065	.2030
B*14	2.06	2.39	0.8574	0.6531	1.1257	.2725	
B*15	3.29	3.26	1.0093	0.8068	1.2626	.9545	
B*18	10.06	11.55	0.8565	0.7528	0.9746	.0187	.5793
B*27	4.53	4.91	0.9177	0.7600	1.1081	.3889	
B*35	16.07	14.87	1.0965	0.9821	1.2242	.1022	
B*37	1.28	1.02	1.2589	0.8659	1.8303	.2495	
B*38	3.93	3.36	1.1789	0.9531	1.4582	.1410	
B*39	2.72	2.45	1.1149	0.8674	1.4330	.4038	
B*40	7.04	4.91	1.4661	1.2378	1.7366	.0000	**.0003**
B*41	2.56	1.91	1.3499	1.0299	1.7694	.0315	
B*42	0.05	0.07	0.6164	0.1128	3.3671	.6975	
B*44	7.54	8.45	0.8837	0.7624	1.0242	.1077	
B*45	0.32	0.33	0.9590	0.4764	1.9304	1.0000	
B*46	0.11	0.17	0.6847	0.2293	2.0447	.5964	
B*47	0.50	0.69	0.7319	0.4311	1.2425	.2937	
B*48	0.11	0.15	0.7705	0.2519	2.3569	.7832	
B*49	1.94	1.91	1.0180	0.7617	1.3606	.9410	
B*50	1.21	1.76	0.6842	0.4877	0.9597	.0301	.9333
B*51	10.04	9.40	1.0754	0.9400	1.2302	.3021	
B*52	4.44	3.78	1.1808	0.9660	1.4432	.1106	
B*53	0.21	0.46	0.4428	0.2065	0.9496	.0373	
B*54	0.09	0.09	0.9865	0.2648	3.6762	1.0000	

(Continues)

TABLE 2 (Continued)

Allele group	Patients (%)	Controls (%)	Odds ratio	95% CI		*P*-value	*Pc*-value
				Lower Limit	Upper Limit		
B*55	1.78	1.97	0.9058	0.6743	1.2167	.5496	
B*56	1.10	1.02	1.0771	0.7298	1.5896	.7653	
B*57	1.37	1.71	0.8015	0.5776	1.1124	.1895	
B*58	1.23	1.54	0.7998	0.5665	1.1294	.2259	
B*73	0.21	0.19	1.1101	0.4507	2.7344	.8219	
B*78	0.02	0.24	0.0947	0.0124	0.7239	.0050	.1563
C*01	5.13	5.61	0.9095	0.7143	1.1580	.4647	
C*02	7.58	8.83	0.8468	0.6937	1.0337	.1100	
C*03	5.93	7.16	0.8172	0.6545	1.0204	.0770	
C*04	16.62	17.13	0.9640	0.8340	1.1141	.6322	
C*05	2.50	3.60	0.6860	0.4948	0.9510	.0224	.2918
C*06	7.58	11.08	0.6581	0.5426	0.7981	.0000	.0002
C*07	21.89	24.15	0.8802	0.7735	1.0017	.0539	
C*08	2.73	3.04	0.8951	0.6462	1.2399	.5660	
C*12	17.33	10.99	1.6966	1.4526	1.9816	.0000	**.0000**
C*14	2.12	1.55	1.3751	0.9208	2.0535	.1418	
C*15	7.58	4.36	1.8005	1.4310	2.2655	.0000	**.0000**
C*16	1.79	1.64	1.0943	0.7222	1.6581	.6700	
C*17	1.22	0.85	1.4491	0.8511	2.4672	.2091	
DRB1*01	7.79	9.01	0.8531	0.7376	0.9866	.0329	.4275
DRB1*03	12.29	10.63	1.1781	1.0387	1.3361	.0109	.1419
DRB1*04	9.48	8.02	1.2012	1.0422	1.3843	.0121	.1576
DRB1*07	7.08	8.59	0.8109	0.6976	0.9426	.0063	.0820
DRB1*08	1.51	1.60	0.9413	0.6802	1.3027	.7415	
DRB1*09	0.69	0.53	1.2868	0.7676	2.1571	.3566	
DRB1*10	1.99	1.43	1.3990	1.0246	1.9102	.0383	.4984
DRB1*11	20.47	20.80	0.9798	0.8873	1.0819	.7045	
DRB1*12	1.76	1.83	0.9612	0.7102	1.3008	.8176	
DRB1*13	9.50	10.67	0.8794	0.7693	1.0052	.0622	
DRB1*14	7.40	5.85	1.2868	1.0949	1.5124	.0025	**.0327**
DRB1*15	9.30	8.95	1.0424	0.9069	1.1981	.5694	
DRB1*16	10.76	12.10	0.8761	0.7720	0.9944	.0432	.5610
DQB1*02	19.63	18.02	1.1111	0.9573	1.2895	.1733	
DQB1*03	33.92	34.38	0.9799	0.8669	1.1075	.7548	
DQB1*04	1.91	1.86	1.0289	0.6709	1.5781	.9138	
DQB1*05	30.06	28.52	1.0776	0.9483	1.2244	.2552	
DQB1*06	14.49	17.24	0.8134	0.6940	0.9534	.0116	
DPB1*01	8.91	7.05	1.2907	0.8495	1.9611	.2629	
DPB1*02	25.39	18.50	1.4988	1.1381	1.9737	.0041	**.0412**
DPB1*03	6.20	8.59	0.7035	0.4648	1.0648	.0973	
DPB1*04	47.29	51.98	0.8286	0.6643	1.0336	.1023	
DPB1*05	1.36	2.42	0.5538	0.2495	1.2296	.1867	
DPB1*09	1.26	1.10	1.1456	0.4060	3.2328	1.0000	
DPB1*10	2.13	3.74	0.5599	0.2944	1.0649	.0795	

(Continues)

TABLE 2 (Continued)

Allele group	Patients (%)	Controls (%)	Odds ratio	95% CI		*P*-value	*Pc*-value
				Lower Limit	Upper Limit		
DPB1*13	2.71	2.86	0.9461	0.4854	1.8438	.8645	
DPB1*14	2.52	2.64	0.9520	0.4760	1.9038	.8601	
DPB1*17	2.23	1.10	2.0470	0.7733	5.4188	.2122	

Note: All the bold values are less than .05, thus the alleles and combined HLA types with this values are significantly associated with the risk of developing the disease.

TABLE 3 Combined HLA types in both CRI patients and control individuals

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
A*01,-	1.64	2.37	0.6859	0.4552	1.0336	.0863	
A*01,02	7.14	7.50	0.9480	0.7646	1.1754	.6618	
A*01,03	2.18	2.66	0.8178	0.5662	1.1812	.3103	
A*01,11	3.14	1.79	1.7266	1.2264	2.5622	.0026	.2437
A*01,23	0.50	0.43	1.1622	0.5118	2.6389	.8340	
A*01,24	3.05	2.58	1.1846	0.8453	1.6601	.3412	
A*01,25	0.64	0.83	0.7697	0.3951	1.4993	.5080	
A*01,26	1.14	1.01	1.1327	0.6586	1.9481	.6781	
A*01,29	0.27	0.50	0.5417	0.2078	1.4120	.2609	
A*01,30	0.82	0.54	1.5246	0.7666	3.0321	.2911	
A*01,31	0.55	0.54	1.0136	0.4735	2.1700	1.0000	
A*01,32	0.95	1.04	0.9166	0.5213	1.6118	.8864	
A*01,33	0.45	0.43	1.0560	0.4554	2.4488	1.0000	
A*01,66	0.23	0.14	1.5850	0.4251	5.9096	.5198	
A*01,68	0.59	0.57	1.0296	0.4942	2.1450	1.0000	
A*02,-	8.96	9.30	0.9601	0.7905	1.1660	.6925	
A*02,03	5.68	5.49	1.0372	0.8133	1.3228	.8037	
A*02,11	5.41	5.78	0.9328	0.7310	1.1904	.6203	
A*02,23	1.41	1.83	0.7668	0.4890	1.2025	.2636	
A*02,24	7.59	6.68	1.1488	0.9249	1.4270	.2213	
A*02,25	1.59	1.44	1.1103	0.7029	1.7538	.7255	
A*02,26	3.18	2.37	1.3550	0.9635	1.9057	.0807	
A*02,29	1.09	0.90	1.2186	0.6941	2.1397	.5636	
A*02,30	1.14	1.40	0.8100	0.4887	1.3425	.4488	
A*02,31	1.32	1.40	0.9413	0.5802	1.5271	.9023	
A*02,32	2.50	2.84	0.8790	0.6202	1.2459	.4819	
A*02,33	0.91	1.01	0.9041	0.5079	1.6092	.7719	
A*02,66	0.18	0.39	0.4597	0.1462	1.4458	.2014	
A*02,68	1.59	1.11	1.4374	0.8835	2.3385	.1695	
A*02,69	0.18	0.39	0.4597	0.1462	1.4458	.2014	
A*03,-	1.27	1.08	1.1848	0.7058	1.9891	.5951	
A*03,11	1.36	2.12	0.6393	0.4104	0.9957	.0522	
A*03,23	0.41	0.54	0.7592	0.3316	1.7381	.5446	
A*03,24	2.86	2.58	1.1118	0.7891	1.5664	.5982	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
A*03,25	0.27	0.83	0.3287	0.1336	0.8086	.0134	
A*03,26	1.27	1.04	1.2261	0.7273	2.0672	.5028	
A*03,29	0.32	0.25	1.2678	0.4440	3.6199	.7891	
A*03,30	0.27	0.72	0.3784	0.1517	0.9438	.0306	
A*03,31	0.50	0.25	1.9959	0.7724	5.1572	.1599	
A*03,32	1.59	0.68	2.3254	1.3436	4.1291	.0023	.2121
A*03,33	0.27	0.54	0.5054	0.1958	1.3048	.1880	
A*03,68	0.41	0.50	0.8137	0.3515	1.8835	.6792	
A*11,-	1.05	0.93	1.1220	0.6384	1.9719	.7728	
A*11,23	0.36	0.32	1.1266	0.4340	2.9249	.8118	
A*11,24	2.59	2.15	1.2090	0.8377	1.7449	.3462	
A*11,25	0.32	0.57	0.5529	0.2270	1.3462	.2116	
A*11,26	0.82	0.75	1.0867	0.5776	2.0445	.8718	
A*11,29	0.27	0.18	1.5218	0.4638	4.9929	.5516	
A*11,30	0.32	0.22	1.4796	0.4965	4.4091	.5796	
A*11,31	0.55	0.29	1.9053	0.7775	4.6694	.1782	
A*11,32	1.00	0.61	1.6460	0.8719	3.1074	.1449	
A*11,33	0.36	0.22	1.6918	0.5861	4.8831	.4209	
A*11,66	0.23	0.11	2.1141	0.5047	8.8561	.3130	
A*11,68	0.36	0.39	0.9211	0.3699	2.2940	1.0000	
A*23,24	0.64	0.86	0.7374	0.3805	1.4288	.4146	
A*23,26	0.05	0.18	0.2530	0.0295	2.1676	.2379	
A*23,32	0.05	0.18	0.2530	0.0295	2.1676	.2379	
A*23,68	0.09	0.25	0.3614	0.0750	1.7415	.3144	
A*24,-	1.82	1.62	1.1285	0.7344	1.7342	.5838	
A*24,25	0.50	0.72	0.6953	0.3324	1.4542	.3688	
A*24,26	1.64	1.15	1.4324	0.8868	2.3137	.1423	
A*24,29	0.09	0.39	0.2297	0.0508	1.0372	.0481	
A*24,30	0.64	0.50	1.2686	0.6035	2.6668	.5702	
A*24,31	0.36	0.29	1.2679	0.4751	3.3837	.8019	
A*24,32	1.18	0.97	1.2226	0.7114	2.1012	.4890	
A*24,33	0.59	0.47	1.2685	0.5869	2.7420	.5586	
A*24,66	0.27	0.14	1.9029	0.5363	6.7516	.3523	
A*24,68	0.77	0.57	1.3488	0.6799	2.6757	.4823	
A*25,-	0.14	0.18	0.7598	0.1814	3.1830	1.0000	
A*25,26	0.23	0.22	1.0559	0.3218	3.4645	1.0000	
A*25,30	0.05	0.22	0.2108	0.0254	1.7523	.1429	
A*25,31	0.23	0.04	6.3469	0.7409	54.3672	.0937	
A*25,32	0.23	0.32	0.7032	0.2353	2.1012	.5989	
A*25,33	0.05	0.22	0.2108	0.0254	1.7523	.1429	
A*25,68	0.14	0.22	0.6330	0.1581	2.5338	.7396	
A*26,-	0.23	0.22	1.0559	0.3218	3.4645	1.0000	
A*26,29	0.14	0.22	0.6330	0.1581	2.5338	.7396	
A*26,31	0.23	0.14	1.5850	0.4251	5.9096	.5198	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
A*26,32	0.41	0.43	0.9500	0.3996	2.2587	1.0000	
A*26,33	0.05	0.18	0.2530	0.0295	2.1676	.2379	
A*30,-	0.05	0.18	0.2530	0.0295	2.1676	.2379	
A*30,32	0.18	0.18	1.0136	0.2718	3.7791	1.0000	
A*30,68	0.05	0.22	0.2108	0.0254	1.7523	.1429	
A*31,-	0.05	0.22	0.2108	0.0254	1.7523	.1429	
A*31,32	0.32	0.07	4.4453	0.9225	21.4201	.0495	
A*32,-	0.27	0.14	1.9029	0.5363	6.7516	.3523	
A*32,33	0.18	0.18	1.0136	0.2718	3.7791	1.0000	
A*32,68	0.32	0.14	2.2210	0.6493	7.5969	.2312	
A*33,68	0.23	0.22	1.0559	0.3218	3.4645	1.0000	
B*07,-	0.27	0.56	0.4923	0.1907	1.2710	.1864	
B*07,08	0.69	0.48	1.4270	0.6776	3.0055	.3493	
B*07,13	0.18	0.30	0.6164	0.1854	2.0498	.5651	
B*07,14	0.18	0.26	0.7047	0.2060	2.4105	.7639	
B*07,15	0.32	0.33	0.9598	0.3569	2.5814	1.0000	
B*07,18	0.82	0.96	0.8533	0.4666	1.5604	.6502	
B*07,27	0.23	0.22	1.0286	0.3135	3.3749	1.0000	
B*07,35	1.33	1.56	0.8502	0.5279	1.3694	.5489	
B*07,38	0.32	0.30	1.0802	0.3911	2.9835	1.0000	
B*07,39	0.27	0.26	1.0581	0.3551	3.1530	1.0000	
B*07,40	0.59	0.26	2.2998	0.9160	5.7744	.0748	
B*07,41	0.32	0.26	1.2350	0.4325	3.5262	.7903	
B*07,44	0.59	1.07	0.5506	0.2855	1.0617	.0859	
B*07,49	0.14	0.26	0.5283	0.1365	2.0455	.5272	
B*07,50	0.23	0.04	6.1829	0.7218	52.9638	.0958	
B*07,51	0.73	0.67	1.0978	0.5585	2.1579	.8631	
B*07,52	0.27	0.26	1.0581	0.3551	3.1530	1.0000	
B*07,55	0.23	0.19	1.2348	0.3570	4.2707	.7603	
B*07,56	0.23	0.15	1.5440	0.4141	5.7569	.5255	
B*07,57	0.09	0.19	0.4932	0.0956	2.5447	.4706	
B*08,-	0.37	0.41	0.8972	0.3603	2.2346	1.0000	
B*08,13	0.41	0.48	0.8539	0.3643	2.0013	.8311	
B*08,14	0.14	0.37	0.3694	0.1015	1.3439	.1628	
B*08,15	0.59	0.56	1.0701	0.5081	2.2537	.8517	
B*08,18	1.33	1.78	0.7423	0.4665	1.1811	.2479	
B*08,27	0.64	1.04	0.6146	0.3228	1.1704	.1609	
B*08,35	1.92	2.22	0.8613	0.5782	1.2829	.4827	
B*08,37	0.32	0.26	1.2350	0.4325	3.5262	.7903	
B*08,38	0.32	0.30	1.0802	0.3911	2.9835	1.0000	
B*08,39	0.69	0.33	2.0643	0.9016	4.7263	.0993	
B*08,40	0.69	0.52	1.3246	0.6380	2.7502	.4603	
B*08,41	0.64	0.11	5.7904	1.6619	20.1750	.0023	.3838
B*08,44	0.73	1.07	0.6786	0.3676	1.2527	.2310	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
B*08,47	0.14	0.19	0.7402	0.1767	3.1007	.7382	
B*08,49	0.37	0.22	1.6480	0.5709	4.7569	.4238	
B*08,50	0.27	0.33	0.8223	0.2922	2.3139	.7989	
B*08,51	1.28	1.33	0.9594	0.5836	1.5773	.9000	
B*08,52	0.50	0.41	1.2354	0.5346	2.8549	.6708	
B*08,55	0.41	0.22	1.8548	0.6592	5.2193	.3002	
B*08,57	0.18	0.19	0.9874	0.2648	3.6814	1.0000	
B*08,58	0.27	0.30	0.9255	0.3206	2.6713	1.0000	
B*13,-	0.14	0.33	0.4106	0.1110	1.5185	.2461	
B*13,15	0.27	0.04	7.4229	0.8930	61.7053	.0502	
B*13,18	0.55	1.00	0.5460	0.2760	1.0804	.1048	
B*13,27	0.18	0.26	0.7047	0.2060	2.4105	.7639	
B*13,35	1.01	1.00	1.0057	0.5712	1.7709	1.0000	
B*13,38	0.05	0.41	0.1118	0.0144	0.8666	.0161	
B*13,39	0.27	0.11	2.4725	0.6176	9.8977	.3146	
B*13,40	0.32	0.22	1.4413	0.4837	4.2951	.5824	
B*13,44	0.55	0.89	0.6150	0.3068	1.2326	.1817	
B*13,49	0.14	0.30	0.4621	0.1224	1.7439	.3646	
B*13,51	0.59	0.70	0.8435	0.4157	1.7119	.7228	
B*13,52	0.23	0.26	0.8813	0.2793	2.7807	1.0000	
B*14,15	0.14	0.22	0.6166	0.1540	2.4683	.7396	
B*14,18	0.50	0.70	0.7131	0.3386	1.5017	.4623	
B*14,27	0.18	0.26	0.7047	0.2060	2.4105	.7639	
B*14,35	0.69	0.70	0.9742	0.4939	1.9217	1.0000	
B*14,38	0.09	0.19	0.4932	0.0956	2.5447	.4706	
B*14,40	0.32	0.19	1.7302	0.5484	5.4592	.3927	
B*14,44	0.23	0.19	1.2348	0.3570	4.2707	.7603	
B*14,51	0.18	0.41	0.4478	0.1424	1.4083	.1977	
B*14,52	0.23	0.19	1.2348	0.3570	4.2707	.7603	
B*14,55	0.23	0.07	3.0903	0.5990	15.9443	.2542	
B*15,-	0.09	0.19	0.4932	0.0956	2.5447	.4706	
B*15,18	0.46	0.93	0.4914	0.2355	1.0253	.0606	
B*15,27	0.32	0.33	0.9598	0.3569	2.5814	1.0000	
B*15,35	1.01	0.82	1.2366	0.6830	2.2390	.5433	
B*15,38	0.41	0.11	3.7138	1.0042	13.7350	.0427	
B*15,40	0.23	0.37	0.6162	0.2103	1.8056	.4430	
B*15,41	0.23	0.11	2.0595	0.4916	8.6273	.4797	
B*15,44	0.64	0.41	1.5745	0.7133	3.4753	.3143	
B*15,49	0.18	0.15	1.2346	0.3084	4.9425	1.0000	
B*15,50	0.05	0.30	0.1539	0.0192	1.2314	.0483	
B*15,51	0.73	0.59	1.2359	0.6167	2.4771	.5951	
B*15,52	0.23	0.15	1.5440	0.4141	5.7569	.5255	
B*18,-	1.19	1.45	0.8207	0.4980	1.3524	.4543	
B*18,27	1.05	1.04	1.0140	0.5824	1.7653	1.0000	

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
B*18,35	3.11	3.56	0.8702	0.6345	1.1935	.4246	
B*18,37	0.23	0.22	1.0286	0.3135	3.3749	1.0000	
B*18,38	0.91	0.93	0.9873	0.5469	1.7823	1.0000	
B*18,39	0.46	0.41	1.1226	0.4759	2.6482	.8285	
B*18,40	1.33	0.93	1.4375	0.8394	2.4616	.2155	
B*18,41	0.41	0.41	1.0099	0.4177	2.4414	1.0000	
B*18,44	1.65	1.74	0.9444	0.6096	1.4632	.8246	
B*18,49	0.55	0.33	1.6492	0.6936	3.9212	.2773	
B*18,50	0.18	0.19	0.9874	0.2648	3.6814	1.0000	
B*18,51	2.10	2.45	0.8572	0.5858	1.2544	.4434	
B*18,52	0.64	0.67	0.9597	0.4762	1.9340	1.0000	
B*18,55	0.37	0.70	0.5179	0.2263	1.1854	.1240	
B*18,56	0.27	0.07	3.7101	0.7481	18.4006	.1508	
B*18,57	0.37	0.41	0.8972	0.3603	2.2346	1.0000	
B*18,58	0.18	0.30	0.6164	0.1854	2.0498	.5651	
B*27,-	0.14	0.37	0.3694	0.1015	1.3439	.1628	
B*27,35	1.60	1.56	1.0290	0.6547	1.6173	.9085	
B*27,38	0.41	0.52	0.7926	0.3424	1.8346	.6769	
B*27,39	0.32	0.19	1.7302	0.5484	5.4592	.3927	
B*27,40	0.73	0.33	2.2030	0.9716	4.9950	.0682	
B*27,41	0.18	0.19	0.9874	0.2648	3.6814	1.0000	
B*27,44	0.50	0.74	0.6772	0.3238	1.4164	.3661	
B*27,49	0.27	0.11	2.4725	0.6176	9.8977	.3146	
B*27,51	1.10	1.11	0.9872	0.5754	1.6937	1.0000	
B*27,52	0.46	0.33	1.3731	0.5569	3.3851	.4986	
B*27,55	0.09	0.26	0.3520	0.0731	1.6964	.2008	
B*35,-	2.84	2.45	1.1641	0.8192	1.6541	.4182	
B*35,37	0.55	0.15	3.7176	1.1973	11.5431	.0210	
B*35,38	1.42	1.11	1.2793	0.7719	2.1202	.3657	
B*35,39	1.01	0.74	1.3613	0.7410	2.5008	.3515	
B*35,40	2.42	1.67	1.4649	0.9806	2.1884	.0650	
B*35,41	0.91	0.44	2.0668	1.0081	4.2373	.0497	
B*35,44	2.29	2.15	1.0655	0.7268	1.5620	.7696	
B*35,49	0.55	0.56	0.9873	0.4612	2.1137	1.0000	
B*35,50	0.37	0.70	0.5179	0.2263	1.1854	.1240	
B*35,51	2.74	2.19	1.2623	0.8773	1.8164	.2254	
B*35,52	1.42	1.11	1.2793	0.7719	2.1202	.3657	
B*35,53	0.09	0.19	0.4932	0.0956	2.5447	.4706	
B*35,55	0.50	0.63	0.7976	0.3728	1.7064	.7038	
B*35,56	0.41	0.41	1.0099	0.4177	2.4414	1.0000	
B*35,57	0.41	0.56	0.7395	0.3230	1.6930	.5411	
B*35,58	0.41	0.48	0.8539	0.3643	2.0013	.8311	
B*37,40	0.23	0.15	1.5440	0.4141	5.7569	.5255	
B*37,44	0.23	0.33	0.6850	0.2292	2.0468	.5962	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
B*37,51	0.27	0.41	0.6723	0.2482	1.8209	.4745	
B*38,-	0.32	0.19	1.7302	0.5484	5.4592	.3927	
B*38,39	0.23	0.11	2.0595	0.4916	8.6273	.4797	
B*38,40	0.59	0.33	1.7874	0.7626	4.1895	.2005	
B*38,41	0.09	0.37	0.2462	0.0539	1.1246	.0775	
B*38,44	0.78	0.56	1.4019	0.6985	2.8136	.3752	
B*38,51	0.64	0.30	2.1674	0.9075	5.1760	.0867	
B*38,58	0.09	0.22	0.4109	0.0828	2.0377	.3101	
B*39,40	0.09	0.37	0.2462	0.0539	1.1246	.0775	
B*39,44	0.50	0.41	1.2354	0.5346	2.8549	.6708	
B*39,51	0.55	0.44	1.2355	0.5540	2.7556	.6825	
B*39,52	0.14	0.26	0.5283	0.1365	2.0455	.5272	
B*40,-	0.91	0.37	2.4820	1.1593	5.3136	.0169	
B*40,41	0.41	0.30	1.3901	0.5354	3.6090	.6266	
B*40,44	0.87	0.70	1.2363	0.6529	2.3409	.5177	
B*40,50	0.09	0.22	0.4109	0.0828	2.0377	.3101	
B*40,51	1.28	0.93	1.3873	0.8066	2.3861	.2670	
B*40,52	1.05	0.82	1.2934	0.7189	2.3269	.4520	
B*40,57	0.23	0.07	3.0903	0.5990	15.9443	.2542	
B*40,58	0.09	0.22	0.4109	0.0828	2.0377	.3101	
B*41,44	0.32	0.30	1.0802	0.3911	2.9835	1.0000	
B*41,51	0.46	0.15	3.0951	0.9694	9.8824	.0584	
B*41,52	0.32	0.15	2.1636	0.6325	7.4007	.2364	
B*44,-	0.55	1.00	0.5460	0.2760	1.0804	.1048	
B*44,49	0.55	0.52	1.0582	0.4884	2.2927	1.0000	
B*44,50	0.14	0.30	0.4621	0.1224	1.7439	.3646	
B*44,51	2.20	1.63	1.3542	0.8960	2.0467	.1688	
B*44,52	0.32	0.44	0.7191	0.2826	1.8295	.6451	
B*44,55	0.18	0.30	0.6164	0.1854	2.0498	.5651	
B*44,57	0.09	0.22	0.4109	0.0828	2.0377	.3101	
B*44,58	0.32	0.30	1.0802	0.3911	2.9835	1.0000	
B*49,51	0.46	0.30	1.5453	0.6088	3.9221	.4773	
B*49,52	0.14	0.26	0.5283	0.1365	2.0455	.5272	
B*50,51	0.18	0.30	0.6164	0.1854	2.0498	.5651	
B*50,52	0.23	0.07	3.0903	0.5990	15.9443	.2542	
B*51,-	1.24	1.26	0.9799	0.5893	1.6292	1.0000	
B*51,52	0.64	0.56	1.1529	0.5553	2.3937	.7122	
B*51,55	0.27	0.26	1.0581	0.3551	3.1530	1.0000	
B*51,56	0.23	0.15	1.5440	0.4141	5.7569	.5255	
B*51,57	0.18	0.44	0.4103	0.1322	1.2741	.1344	
B*51,58	0.23	0.26	0.8813	0.2793	2.7807	1.0000	
B*51,78	0.05	0.19	0.2465	0.0288	2.1115	.2339	
B*52,-	0.69	0.48	1.4270	0.6776	3.0055	.3493	
B*57,-	0.23	0.22	1.0286	0.3135	3.3749	1.0000	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
C*01,-	0.47	0.88	0.5345	0.1937	1.4750	.2556	
C*01,02	0.47	0.64	0.7306	0.2531	2.1087	.6176	
C*01,03	0.85	0.53	1.6154	0.6392	4.0825	.3359	
C*01,04	1.60	1.87	0.8531	0.4713	1.5440	.6584	
C*01,06	0.75	0.70	1.0740	0.4376	2.6361	1.0000	
C*01,07	2.17	3.33	0.6420	0.3931	1.0483	.0804	
C*01,08	0.56	0.18	3.2330	0.8068	12.9546	.0942	
C*01,12	1.32	0.88	1.5095	0.7257	3.1400	.3369	
C*01,14	0.19	0.29	0.6434	0.1246	3.3223	.7146	
C*01,15	0.85	0.58	1.4530	0.5885	3.5875	.4797	
C*02,-	0.56	2.22	0.2500	0.1053	0.5934	.0005	
C*02,03	0.85	0.76	1.1157	0.4753	2.6192	.8278	
C*02,04	2.54	2.69	0.9437	0.5831	1.5273	.9030	
C*02,05	0.38	0.70	0.5350	0.1721	1.6631	.3145	
C*02,06	1.32	1.70	0.7743	0.4073	1.4722	.5278	
C*02,07	2.82	3.16	0.8915	0.5667	1.4024	.6502	
C*02,08	0.28	0.58	0.4816	0.1322	1.7539	.3924	
C*02,12	3.39	1.93	1.7831	1.1048	2.8779	.0233	
C*02,14	0.56	0.23	2.4233	0.6822	8.6075	.1962	
C*02,15	1.04	0.29	3.5690	1.2366	10.3007	.0179	
C*02,16	0.19	0.29	0.6434	0.1246	3.3223	.7146	
C*02,17	0.19	0.23	0.8047	0.1471	4.4012	1.0000	
C*03,-	0.28	1.75	0.1586	0.0483	0.5211	.0002	**.0153**
C*03,04	2.35	2.28	1.0329	0.6214	1.7169	.8972	
C*03,05	0.19	0.41	0.4590	0.0952	2.2138	.4965	
C*03,06	0.94	0.94	1.0064	0.4550	2.2261	1.0000	
C*03,07	2.45	2.92	0.8332	0.5155	1.3468	.4759	
C*03,08	0.47	0.41	1.1508	0.3643	3.6354	.7760	
C*03,12	1.60	1.58	1.0140	0.5500	1.8695	1.0000	
C*03,15	0.66	0.58	1.1280	0.4280	2.9724	.8068	
C*03,16	0.47	0.18	2.6916	0.6419	11.2860	.2731	
C*04,-	3.30	5.20	0.6207	0.4166	0.9249	.0181	
C*04,05	0.47	0.94	0.5008	0.1829	1.3711	.2591	
C*04,06	2.45	3.10	0.7846	0.4876	1.2625	.3489	
C*04,07	6.21	7.19	0.8550	0.6275	1.1650	.3525	
C*04,08	0.66	0.88	0.7498	0.3047	1.8450	.6615	
C*04,12	6.50	2.98	2.2604	1.5607	3.2737	.0000	**.0013**
C*04,14	0.47	0.12	4.0397	0.7823	20.8598	.1144	
C*04,15	2.35	0.94	2.5524	1.3564	4.8033	.0034	.2248
C*04,16	0.56	0.64	0.8776	0.3236	2.3800	1.0000	
C*05,06	0.66	0.88	0.7498	0.3047	1.8450	.6615	
C*05,07	1.04	1.93	0.5319	0.2676	1.0569	.0846	
C*05,08	0.47	0.12	4.0397	0.7823	20.8598	.1144	
C*05,12	0.38	0.64	0.5839	0.1855	1.8386	.4327	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
C*05,15	0.56	0.47	1.2088	0.4183	3.4936	.7857	
C*06,-	0.66	2.98	0.2158	0.0976	0.4774	.0000	**.0009**
C*06,07	3.30	4.68	0.6944	0.4632	1.0409	.0785	
C*06,08	0.47	0.35	1.3434	0.4090	4.4129	.7578	
C*06,12	2.17	1.93	1.1249	0.6569	1.9265	.6787	
C*06,14	0.28	0.29	0.9660	0.2304	4.0505	1.0000	
C*06,15	1.22	1.05	1.1649	0.5684	2.3874	.7121	
C*06,16	0.19	0.41	0.4590	0.0952	2.2138	.4965	
C*07,-	5.93	7.54	0.7729	0.5660	1.0554	.1068	
C*07,08	1.13	1.64	0.6865	0.3476	1.3560	.3272	
C*07,12	7.16	5.44	1.3402	0.9798	1.8332	.0724	
C*07,14	0.56	0.53	1.0739	0.3811	3.0256	1.0000	
C*07,15	3.39	1.23	2.8221	1.6384	4.8609	.0002	**.0104**
C*07,16	0.85	0.76	1.1157	0.4753	2.6192	.8278	
C*07,17	0.85	0.41	2.0794	0.7721	5.6002	.1955	
C*08,12	0.75	0.82	0.9195	0.3844	2.1993	1.0000	
C*12,-	3.95	1.81	2.5102	1.3931	3.5703	.0006	**.0414**
C*12,14	0.56	0.35	1.6136	0.5191	5.0163	.5533	
C*12,15	1.98	1.46	1.3597	0.7572	2.4413	.3589	
C*12,16	0.56	0.12	4.8523	0.9775	24.0857	.0608	
C*14,15	0.19	0.35	0.5358	0.1080	2.6598	.7183	
C*15,-	1.13	0.64	1.7652	0.7761	4.0149	.1976	
DRB1*01,-	1.01	1.37	0.7305	0.4285	1.2453	.2889	
DRB1*01,03	1.74	1.71	1.0133	0.6555	1.5665	1.0000	
DRB1*01,04	1.42	1.49	0.9530	0.5926	1.5325	.9040	
DRB1*01,07	1.33	1.75	0.7531	0.4715	1.2028	.2447	
DRB1*01,08	0.14	0.38	0.3590	0.0987	1.3062	.1615	
DRB1*01,10	0.18	0.27	0.6850	0.2003	2.3430	.7636	
DRB1*01,11	3.02	3.43	0.8761	0.6344	1.2099	.4622	
DRB1*01,12	0.27	0.30	0.8995	0.3116	2.5965	1.0000	
DRB1*01,13	1.69	1.45	1.1710	0.7420	1.8481	.5593	
DRB1*01,14	1.01	0.61	1.6562	0.8677	3.1615	.1415	
DRB1*01,15	1.28	1.60	0.7972	0.4925	1.2904	.3981	
DRB1*01,16	1.42	2.17	0.6475	0.4165	1.0065	.0525	
DRB1*03,-	2.47	1.56	1.5948	1.0584	2.4032	.0285	
DRB1*03,04	2.06	1.49	1.3924	0.9034	2.1460	.1506	
DRB1*03,07	1.46	1.52	0.9592	0.6005	1.5322	.9055	
DRB1*03,08	0.32	0.34	0.9329	0.3469	2.5091	1.0000	
DRB1*03,10	0.41	0.30	1.3511	0.5204	3.5079	.6283	
DRB1*03,11	4.25	3.92	1.0869	0.8163	1.4472	.6083	
DRB1*03,12	0.37	0.38	0.9596	0.3781	2.4357	.0000	
DRB1*03,13	2.06	2.97	0.6857	0.4730	0.9941	.0537	
DRB1*03,14	1.60	1.22	1.3173	0.8128	2.1347	.2688	
DRB1*03,15	2.10	1.94	1.0839	0.7246	1.6212	.7575	

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
DRB1*03,16	2.88	2.17	1.3357	0.9292	1.9200	.1372	
DRB1*04,-	1.46	0.69	2.2419	1.2033	3.8405	.0097	.7002
DRB1*04,07	1.19	1.79	0.6596	0.4072	1.0686	.0976	
DRB1*04,08	0.55	0.27	2.0625	0.8106	5.2478	.1650	
DRB1*04,10	0.46	0.23	2.0041	0.7272	5.5231	.2110	
DRB1*04,11	3.38	3.92	0.8571	0.6323	1.1619	.3561	
DRB1*04,12	0.32	0.08	4.2093	0.8735	20.2838	.0888	
DRB1*04,13	1.51	1.64	0.9195	0.5821	1.4525	.7295	
DRB1*04,14	1.42	0.61	2.4435	1.2784	4.2960	.0050	.3596
DRB1*04,15	1.55	1.52	1.0201	0.6435	1.6171	1.0000	
DRB1*04,16	2.10	1.56	1.3535	0.8850	2.0699	.1920	
DRB1*07,-	0.73	0.95	0.7661	0.4080	1.4386	.4349	
DRB1*07,08	0.18	0.19	0.9597	0.2574	3.5784	1.0000	
DRB1*07,10	0.46	0.27	1.7172	0.6525	4.5188	.3315	
DRB1*07,11	3.11	3.24	0.9585	0.6932	1.3253	.8052	
DRB1*07,12	0.37	0.30	1.2005	0.4498	3.2038	.8037	
DRB1*07,13	1.14	1.60	0.7108	0.4318	1.1701	.2164	
DRB1*07,14	0.87	1.33	0.6482	0.3697	1.1365	.1330	
DRB1*07,15	0.96	1.52	0.6263	0.3682	1.0653	.0925	
DRB1*07,16	1.55	1.64	0.9478	0.6023	1.4916	.9083	
DRB1*08,11	0.69	0.72	0.9468	0.4800	1.8677	1.0000	
DRB1*08,13	0.18	0.30	0.5991	0.1802	1.9924	.5641	
DRB1*08,15	0.23	0.11	2.0018	0.4779	8.3861	.4812	
DRB1*08,16	0.23	0.42	0.5443	0.1888	1.5689	.3186	
DRB1*09,11	0.41	0.15	2.7064	0.8323	8.8005	.0990	
DRB1*10,11	0.73	0.38	1.9263	0.8724	4.2536	.1152	
DRB1*10,13	0.41	0.19	2.1643	0.7243	6.4676	.1845	
DRB1*10,14	0.23	0.23	0.9998	0.3047	3.2804	1.0000	
DRB1*10,15	0.50	0.30	1.6529	0.6637	4.1167	.3568	
DRB1*10,16	0.41	0.42	0.9815	0.4060	2.3729	1.0000	
DRB1*11,-	4.89	4.61	1.0640	0.8151	1.3890	.6828	
DRB1*11,12	0.82	0.72	1.1377	0.5956	2.1732	.7418	
DRB1*11,13	4.48	4.61	0.9704	0.7388	1.2745	.8354	
DRB1*11,14	2.47	2.40	1.0291	0.7122	1.4868	.9252	
DRB1*11,15	3.43	3.05	1.1292	0.8197	1.5554	.4618	
DRB1*11,16	4.39	5.83	0.7414	0.5707	0.9633	.0262	
DRB1*12,13	0.23	0.30	0.7493	0.2448	2.2936	.7823	
DRB1*12,14	0.23	0.11	2.0018	0.4779	8.3861	.4812	
DRB1*12,15	0.41	0.42	0.9815	0.4060	2.3729	1.0000	
DRB1*12,16	0.32	0.53	0.5986	0.2412	1.4857	.2825	
DRB1*13,-	1.28	1.37	0.9323	0.5670	1.5327	.8020	
DRB1*13,14	1.10	0.88	1.2547	0.7062	2.2292	.4642	
DRB1*13,15	1.42	1.90	0.7401	0.4711	1.1628	.2160	
DRB1*13,16	2.15	2.67	0.8013	0.5512	1.1647	.2603	

(Continues)

TABLE 3 (Continued)

Combined HLA types	Patients	Controls	95% CI			*P*-value	*Pc*-value
			Odds ratio	Lower Limit	Upper Limit		
DRB1*14,-	1.51	0.72	2.1910	1.1910	3.7040	.0111	.8010
DRB1*14,15	1.60	1.22	1.3173	0.8128	2.1347	.2688	
DRB1*14,16	1.10	1.49	0.7354	0.4409	1.2267	.2538	
DRB1*15,-	1.74	1.33	1.3079	0.8234	2.0775	.2867	
DRB1*15,16	1.65	1.60	1.0288	0.6568	1.6116	.9092	
DRB1*16,-	1.65	1.83	0.8981	0.5808	1.3888	.6596	
DQB1*02,-	5.07	2.93	1.7268	1.1380	2.7473	.0112	.1561
DQB1*02,03	11.61	12.01	0.9625	0.7464	1.2412	.7951	
DQB1*02,04	0.39	0.29	1.3315	0.3175	5.5848	1.0000	
DQB1*02,05	10.83	10.06	1.0865	0.8300	1.4221	.5845	
DQB1*02,06	5.22	7.71	0.6591	0.4708	0.9227	.0159	.2227
DQB1*03,-	12.47	11.52	1.0939	0.8490	1.4095	.5200	
DQB1*03,04	1.71	1.37	1.2586	0.6407	2.4725	.6127	
DQB1*03,05	20.42	19.14	1.0841	0.8817	1.3328	.4623	
DQB1*03,06	9.04	12.01	0.7281	0.5569	0.9521	.0231	.3238
DQB1*04,05	0.62	1.27	0.4880	0.2015	1.1819	.1239	
DQB1*04,06	0.39	0.20	1.9992	0.3871	10.3261	.4729	
DQB1*05,-	9.82	9.18	1.0774	0.8137	1.4266	.6182	
DQB1*05,06	8.65	8.11	1.0738	0.7978	1.4452	.6513	
DQB1*06,-	2.81	3.22	0.8670	0.5366	1.4006	.6231	
DPB1*01,02	2.33	1.32	1.7778	0.4968	6.3617	.5719	
DPB1*01,04	2.91	4.85	0.5879	0.2657	1.3009	.1969	
DPB1*02,-	7.36	2.64	2.9282	1.2198	7.0290	.0110	.1866
DPB1*02,03	2.71	2.64	1.0272	0.3896	2.7081	1.0000	
DPB1*02,04	24.61	22.03	1.1557	0.7964	1.6772	.5129	
DPB1*02,13	0.97	0.88	1.1008	0.2120	5.7165	1.0000	
DPB1*02,14	1.16	1.32	0.8784	0.2177	3.5438	1.0000	
DPB1*02,17	1.16	0.44	2.6588	0.3182	22.2137	.6819	
DPB1*03,04	6.40	9.69	0.6366	0.3623	1.1187	.1283	
DPB1*04,-	20.74	25.11	0.7803	0.5401	1.1271	.2118	
DPB1*04,05	0.97	1.76	0.5455	0.1451	2.0506	.4669	
DPB1*04,09	1.36	0.44	3.1081	0.3802	25.4108	.4462	
DPB1*04,10	2.52	5.73	0.4254	0.1940	0.9330	.0482	.8199
DPB1*04,13	3.68	2.64	1.4081	0.5548	3.5740	.6590	
DPB1*04,14	2.13	3.52	0.5963	0.2366	1.5029	.3133	
DPB1*04,17	2.13	0.88	2.4505	0.5387	11.1465	.3634	
DPB1*01,-	6.01	3.52	1.7497	0.7914	3.8688	.2109	

Note: All the bold values are less than .05, thus the alleles and combined HLA types with this values are significantly associated with the risk of developing the disease.

Some of the HLA-DRB1 alleles were significantly different in patients with CRI compared with the controls in certain studies. For instance, HLA-DRB1*03, HLA-DRB1*04, HLA-DRB1*11 and DQB1*02 were linked to the CRI risk in China,[25] whereas DRB1*14 was observed more frequently in patients from Vietnam.[26]

The identified HLA alleles might be identified as potential haplotypes of allele groups inherited in patients with CRI. For example, C*12 and C*15 were related to certain common haplotypes within Romanian patients with CRI: A*01-C*15 and A*02-C*12. The frequency of other haplotypes carrying the C*12 or C*15 alleles did

not differ significantly between the patients with CRI and control groups. This could be explained by the fact that in different haplotypes, alleles might have different behaviours, either acting as triggers or as protective factors against the appearance of the disease.[25]

Our work has several limitations: only asymptotic tests were used, without performing any exact tests. The research focused on allele, genotype and haplotype analyses. Since CRI is still a relatively frequent condition, it is not possible to exclude that in the control population. Therefore, certain subjects would be diagnosed with CRI during their life. Considering these limitations, the results regarding certain alleles, genotypes and haplotypes could be questionable.

In conclusion, our results indicate that several HLA allele groups and genotypes are strongly associated with CRI in the Romanian population. B*40, C*12, C*15, DRB1*14, DPB1*02, C*12, -, A*01-C*15 and A*02-C*12 could be positively associated with CRI. We believe that this work could be extended to determine whether selecting kidney donors without susceptible HLA allele groups or genotypes for CRI development could lead to longer survival rates in kidney allografts in our patients. Furthermore, this study could help identify patients presenting with certain HLA profiles at risk of developing renal insufficiency. This would enable nephrologists to better manage these patients to improve their clinical state.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Ion Mărunţelu initiated the work and contributed essentially to the manuscript. Ion Mărunţelu and Ileana Constantinescu made the research design and implementation. Bogdan Mihai Cristea, Secil Omer and Carmen Monica Preda contributed to the analysis of the results and the writing of the manuscript. Ileana Constantinescu supervised the entire project.

DATA AVAILABILITY STATEMENT

Data pertaining to this study is available with the corresponding author and can be shared upon reasonable request.

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