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ORIGINAL ARTICLE

HLA typing in Taiwanese patients with oral squamous cell carcinoma

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Abstract *Background/purpose:* The human leukocyte antigen (HLA) system, which plays a vital role in immunity, is the most polymorphic gene complex found in the human genome. This study investigated HLA-related alleles and haplotypes in Taiwanese patients with oral squamous cell carcinoma (OSCC).
Materials and methods: HLA class I (HLA-A and HLA-B) antigens and class II (HLA-DRB1) alleles were determined in 105 patients with OSCC and compared with those in 190 healthy controls. The antigens were measured serologically and the alleles by sequencing-based typing.
Results: Compared with the control group, patients with OSCC had higher frequencies of HLA-A24, HLA-B54, HLA-DRB1*0405, and HLA-DRB1*1201, while they had lower frequencies of HLA-B58 and HLA-DRB1*1302. Haplotype frequencies also varied significantly in individuals with OSCC, with certain haplotypes associated with lymph node metastases or a particular tumor stage.
Conclusion: These results suggest that HLA genetic factors influence susceptibility to OSCC and perhaps to lymph node metastasis and tumor progression.

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Introduction

The human leukocyte antigen (HLA) system, located on chromosome 6 and intimately involved in regulation of the immune response, is the most polymorphic gene complex found in the human genome. HLA class IA, B, and C antigens are expressed by almost all nucleated cells and platelets, and are recognized by CD^{8+} cytotoxic T cells. HLA class II DR, DQ, and DP molecules are expressed by antigen-presenting cells. Their function is to present exogenous antigens to CD^{4+} helper T cells. Obviously, quantitative changes in HLA expression may alter immune status. However, the extremely polymorphic nature of this portion of the genome also results in considerable interindividual differences. Several HLA types are associated with an increased risk of various immunologically medicated diseases.[1] There is also evidence that the HLA gene complex may mediate susceptibility to or protection from malignancies.[2,3]

Oral cancer ranks sixth in cancer incidence worldwide, but there are epidemiologic variations between different geographic regions. It is a leading form of cancer in most Asian countries and the fourth most common malignancy in men in Taiwan.[4] The frequent use of tobacco, alcohol, and betel quid among Asians likely accounts in part for regional variations in disease incidence. However, familial clustering of disease, linkage studies, and molecular findings also suggest that there may be specific genetic susceptibility among certain individuals. Alterations in immune function have been detected in patients with oral squamous cell carcinoma (OSCC),[5] along with frequent polymorphous autoimmune reactions to various tissue antigens.[6] The HLA complex has been implicated in the development of squamous cell carcinoma, particularly in head and neck tumors. Loss of heterozygosity in the HLA complex may provide tumor cells with an immune-escape phenotype. HLA class I expression in OSCC may regulate natural killer cell activity.[7–9]

We previously demonstrated an association between major histocompatibility complex class I chain-related gene A (MICA) polymorphism and OSCC. Genotyping of the HLA-A,B locus as well as MICA gene fragments in patients with OSCC may further improve our understanding of changes in immune function vis-à-vis the risk of developing this cancer. To the best of our knowledge, little is known about HLA typing in OSCC in Taiwan or Southeast Asia. Therefore, this study was designed to investigate the genotype and haplotype frequencies of HLA-A, HLA-B, and DRB1 in patients with OSCC.

Materials and methods

Study participants

Between November 2000 and December 2002, we recruited 105 consecutive patients with OSCC from the Oral and Maxillofacial Department at the Taipei Mackay Memorial Hospital. The diagnosis was made by histopathologically examining the biopsy specimens. A total of 105 patients described themselves ethnically as Min Nan (by a self-report). The control group included 190 participants identified as Min Nan, who visited our clinic for routine physical examination, minor operations for non-neoplastic disease, or who had maxillofacial trauma. In both study and control groups, individuals with autoimmune disorders, blood diseases, or a history of a previous malignancy were excluded. The participants were all unrelated to each other.

DNA extraction

Peripheral blood samples were drawn from all the participants of the study and the control groups. Genomic DNA was extracted from fresh or frozen peripheral blood leukocytes using the Pharmacia DNA isolation kit (Pharmacia Biotech, Germany).

HLADRB1 allele typing by sequence-based typing

The group-specific primers used for amplification of exon 2 of DRB1 alleles were modified from those used at the Diagnostic DNA Laboratory (Utrecht) and Tissue Typing Laboratory (Maastricht).[7] The Utrecht 5′ primers were used for DR1, DR2, DR8/12, and DR7 and the Maastricht primers for DR3/11/6, DR4, DR9, and DR10. All 5′ primers were located near the 5′ end of exon 2 containing an M13 (−21) sequence at the 5′ end for sequencing with the M13 sequencing primer. Because of a polymorphic site at position 270, a newly designed 3′ primer located at the intron 2—exon 2 junction (GCGCTCACCTCGCCGCTG) was used. When combined with the group-specific 5′ primers, this 3′ primer should amplify DRB1 alleles but not DR9. For DR9 amplification, the 3′ primer located at position 263—283 (CTCGCCGCTGCACTGTGAAG) was used. Two supplemental 3′-end primers, a TG primer (GCTGCACTGTGAAGCTCTCCA), and a GT primer (GCTGCACTGTGAAGCTCTCAC) located at position 257—276 were used to separate alleles when initial group-specific amplification failed to show the two alleles.

The amplification reaction mixture contained 50 ng genomic DNA, 15 mM Tris—HCl (pH 8.0), 50 mM KCl, 1.5 mM $MgCl_2$, 0.01% gelatin, 0.1% Triton X-100, 0.2 mM of each deoxyribonucleotide, 5% glycerol, 0.1 mg/mL cresol red, and 0.25 U of AmpliTaq Gold polymerase (Perkin Elmer, Foster City, CA, USA).[10,11] The polymerase chain reaction (PCR) was carried out using the GeneAmp PCR system (Perkin-Elmer Corporation, Foster City, CA, USA). The reaction mixture was subjected to denaturation at 95°C for 10 minutes followed by 32 cycles at 95°C for 10 seconds, 62°C for 30 seconds, 72°C for 30 seconds, and by a final extension at 72°C for 5 minutes. The PCR products were checked by 2% agarose gel electrophoresis, using 5 μL of reaction volume, and 1/10 of the diluted PCR products underwent direct sequencing using a BigDye Primer Cycle Sequencing Ready Reaction Kit sequence primer (−21M13) (Applied Biosystems, Foster City, CA, USA). Samples were then subjected to electrophoresis in an ABI 377 DNA sequencer and the results were analyzed by Match Tools and Sequence Navigator (Applied Biosystems, Foster City, CA, USA).

HLA-A, B serologic typing

Blood samples from all the patients and the control group were collected in acid citrate dextrose tubes and

transported within 24 hours to the laboratory. Lymphocytes were isolated using Ficoll-Hypaque (Pharmacia Biotech, Uppsala, Sweden) gradient centrifugation from 10 mL of peripheral blood. Antigens were determined by a standard microlymphocytotoxicity technique in Terasaki Chinese HLA-ABC 72-well trays (lots 2, 3, 3A, and 3B) and the latest Terasaki Special Monoclonal Tray-Asian HLA class I (lot 3).

Sequence-specific primed PCR typing

Samples in which serologic typing failed to yield a result were assayed by the sequence-specific primed PCR typing. HLA-A and HLA-B typing was done using commercially available kits (GenoVision, Oslo, Norway). Genomic DNA was amplified by 24 PCRs for HLA-A and 48 PCRs for HLA-B. A group of 108 necrokidney donors were also typed for HLA-C with low resolution using 16 PCRs. Each 10-μL PCR mixture contained two to four alleles or group-specific primers and a control primer pair at a lower concentration, 10× PCR buffer (500 mM KCl, 15 mM $MgCl_2$, 100 mM Tris—HCl pH 8.3, 0.01% w/v gelatine), 200 mM each of deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxythymidine triphosphate, and deoxyguanosine triphosphate (Amersham Pharmacia Biotech, Uppsala, Sweden), cresol red (100 μg/mL), (Sigma, St. Louis, MO, USA), 5% (v/v) 99.5% glycerol (Fluka, St. Louis, MO, USA), 0.40 μM of the specific primers, and 0.10 μM of the control primers, 50—100 ng DNA, and 0.40 U of *Taq* polymerase (Amersham Pharmacia Biotech).

Statistical analysis

Allele frequencies were determined by direct counting. Agreement with Hardy—Weinberg equilibrium was tested for genotype frequencies in the controls using PyPop statistical software[12] from the International Histocompatibility Working Group, based on the method described by Guo and Thompson.[13] The odds ratio (OR) with 95% confidence intervals (CIs) for each allele family was calculated[14—16] and the frequencies of allele families and alleles were compared between patients with OSCC and healthy controls, as well in subgroups according to age, tumor site, differentiation, stage, and cervical lymph node metastasis using the Chi-square test with Yates' correction and the Fisher exact test where appropriate. The values of P were calculated using the Bonferroni inequality method.[17] A value of $P < 0.05$ (two tailed) was considered statistically significant. A power calculation was performed based on the approach of Ohashi et al.[18] SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Demographic data of all participants and clinical characteristics of those with OSCC are shown in Table 1. The alleles frequencies for HLA-A, HLA-B, and HLA-DRB1 in study patients are compared with those of the control group in Tables 2—4. The frequencies of alleles HLA-A24, HLA-B58, HLA-DRB1*0405, HLA-DRB1*1201 were significantly higher in patients with OSCC, while the frequencies of alleles HLA-B58 and HLA-DRB1*1302 were significantly lower. A number of haplotype frequencies were either higher or lower in patients with OSCC than in the control group (Tables 5 and 6). A*1101 and A*2 were the most frequently observed alleles in patients with OSCC, although the frequencies did not differ significantly from those in controls. A*24 was significantly more common in patients than in controls (23.3% vs. 16.6%; OR = 1.53, 95% CI = 1.00—2.33, P = 0.045).

Table 1 Demographic and clinical characteristics of patients with oral squamous cell carcinoma and control group.

Variable	Oral cancer (n = 105)	Control (n = 190)
Gender		
Male	100	121
Female	5	69
Age (y)		
Mean ± SEM	51.8 ± 0.9	51.3 ± 1.7
Range	30—74	23—80
Location		
Buccal mucosa	58	—
Tongue	29	—
Gingiva	12	—
Palate	3	—
Mouth floor	3	—
Stage		
I	15	—
II	25	—
III	17	—
IV	48	—
Lymph node metastases		
Absent	66	—
Present	39	—

SEM = standard error of the mean.

When patients with OSCC were stratified by age, tumor site, degree of differentiation, or tumor size, we found no particular association in the distribution of HLA alleles and haplotypes. However, patients with lymph node metastasis had higher frequencies of A2/B60, A1101/B62, A2/DR1201, and DR1101 compared with those without lymph node involvement. None of the 80 patients with nodal metastases had the A1101/B60 haplotype, compared with nine of the 130 without node involvement (Table 7). There were also several significant differences in haplotype frequencies between patients with early (Stages I and II) and late (Stages III and IV) stage OSCC (Table 8), including several that were present in one group or the other but not in both.

Discussion

In OSCC, Eura et al reported an increased frequency of HLA-A*2402 in Japan over that in controls (P = 0.030, relative risk = 3.833).[10] A similar result in our study was the significantly higher frequency of HLA-A24 is patients with OSCC (P = 0.045, OR = 1.53, 95% CI = 1.00—2.33). Tilanus et al observed significant associations between HLA-B40 antigen and HLA-B*40/DRB1*13 haplotypes in patients

Table 2 Allele frequencies of HLA-A antigens in patients with oral cancer and healthy controls.

	Oral cancer (n = 210)						Controls (n = 380)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
A1	0	0			ns		1	0.3
A1101	57	27.1			ns		119	31.3
A1102	10	4.8					18	4.7
A2	57	27.1					113	29.7
A24	49	23.3	1.53	1.00—2.33	0.045		63	16.6
A26	11	5.2					10	2.6
A29	0	0					1	0.3
A30	3	1.4					3	0.8
A31	2	1.0					10	2.6
A32	0	0					2	0.5
A33	21	10.0					39	10.3
A68	0	0					1	0.3

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio.

with OSCC in the Netherlands.[11] Different laboratory methods and sample size in addition to varying ethnicity may all contribute to reported variations in the distribution of HLA types.

Traditionally, HLA polymorphisms were typed by serologic responses to HLAs, but this may result in mistyping about 20% of the time.[19,20] As pointed out by Schaffer and Olerup, this is probably because allelic variations in the HLA

Table 3 Allele frequencies of HLA-B antigens in patients with oral cancer and health controls.

	Oral cancer (n = 210)						Controls (n = 380)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
B13	16	7.6					34	8.9
B15	0	0					2	0.5
B18	0	0					1	0.3
B27	10	4.8					15	3.9
B35	10	4.8					10	2.6
B37	0	0					1	0.3
B38	4	1.9					16	4.2
B39	3	1.4					8	2.1
B44	2	1.0					2	0.5
B46	20	9.5					52	13.7
B48	4	1.9					5	1.3
B51	17	8.1					20	5.3
B52	0	0					2	0.5
B53	0	0					1	0.3
B54	19	9.0	2.42	1.20—4.87	0.010		15	3.9
B55	4	1.9					13	3.4
B56	1	0.5					2	0.5
B5603	0	0					1	0.3
B58	11	5.2	0.43	0.22—0.86	0.014		43	11.3
B60	55	26.2					84	22.1
B61	3	1.4					9	2.4
B62	12	5.7					19	5.0
B67	2	1.0					1	0.3
B7	4	1.9					2	0.5
B70	1	0.5					0	0
B71	0	0					1	0.3
B75	12	5.7					20	5.3
B76	0	0					1	0.3

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio.

Table 4 Allele frequencies of HLA-DRB1 antigens in patients with oral cancer and healthy controls.

	OSCC (n = 210)						Control (n = 380)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
DRB1*0101	2	1.0					3	0.8
DRB1*0301	10	4.8					31	8.2
DRB1*0401	1	0.5					1	0.3
DRB1*0403	8	3.8					15	3.9
DRB1*0404	1	0.5					4	1.1
DRB1*0405	32	15.2	1.89	1.13—3.18	0.014		33	8.7
DRB1*0406	6	2.9					5	1.3
DRB1*0410	2	1.0					2	0.5
DRB1*0701	3	1.4					5	1.3
DRB1*0802	0	0					3	0.8
DRB1*0803	15	7.1					34	8.9
DRB1*0809	1	0.5					1	0.3
DRB1*0901	23	11.0					59	15.5
DRB1*0903	1	0.5					0	0
DRB1*1001	1	0.5					4	1.1
DRB1*1101	19	9.0					22	5.8
DRB1*1145	1	0.5					0	0
DRB1*1201	16	7.6	2.33	1.10—4.94	0.023		13	3.4
DRB1*1202	23	11.0					36	9.5
DRB1*1301	1	0.5					1	0.3
DRB1*1302	2	1.0	0.25	0.06—1.12	0.039		14	3.7
DRB1*1312	1	0.5					3	0.8
DRB1*1401	3	1.4					15	3.9
DRB1*1403	2	1.0					2	0.5
DRB1*1404	0	0					1	0.3
DRB1*1405	4	1.9					6	1.6
DRB1*1407	0	0					1	0.3
DRB1*1443	0	0					1	0.3
DRB1*1501	15	7.1					33	8.7
DRB1*1502	4	1.9					5	1.3
DRB1*1602	13	6.2					27	7.1

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio; OSCC = oral squamous cell carcinoma.

molecule are mainly located in the peptide-binding cleft and are thus inaccessible to antibodies. Fortunately, advances in molecular HLA typing methods allow better definition and characterization of specific HLAs and alleles.[21] Typing is usually performed either by hybridizing labeled, sequence-specific oligonucleotide probes to HLA loci amplified by PCR or using PCR to amplify the HLA DNA directly with various primers for extension. We used PCR-based typing for any samples in which the type could not be identified serologically.

Previous studies of head and neck cancer have reported an association between HLA class I expression and tumor size, degree of differentiation, and the presence and extent of regional lymph node metastasis.[22—26] Of those

Table 5 Haplotype frequencies of HLA-A24, HLA-B54, HLA-B58, HLA-DRB1*0405, HLA-DRB1*1201, and HLA-DRB1*1302 antigens in patients with oral cancer and healthy controls.

	OSCC (n = 210)						Control (n = 380)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
A24	49	23.3	1.53	1.00—2.33	0.045		63	16.6
B54	19	9.0	2.42	1.20—4.87	0.010		15	3.9
B58	11	5.2	0.43	0.22—0.86	0.014		43	11.3
DRB1*0405	32	15.2	1.89	1.13—3.18	0.014		33	8.7
DRB1*1201	16	7.6	2.33	1.10—4.94	0.023		13	3.4
DRB1*1302	2	1.0	0.25	0.06—1.12	0.039		14	3.7

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio; OSCC = oral squamous cell carcinoma.

Table 6 Haplotype frequencies of HLA-A/B/DR, HLA-A/B, HLA-A/DR, and HLA-B/DR antigens in patients with oral cancer and healthy controls.

	OSCC (n = 210)						Control (n = 380)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
A33/B58/DR1302	1	0.5	0.16	0.02—1.25	0.037		11	2.9
A2/B54/DR0405	3	1.4	12.84	1.43—115.60	0.045		0	0
A24/B51/DR0405	3	1.4	12.84	1.43—115.60	0.045		0	0
A24/B54/DR0403	3	1.4	12.84	1.43—115.60	0.045		0	0
A24/B60/DR1201	4	1.9	16.58	1.92—142.90	0.016		0	0
A24/B62/DR0406	3	1.4	12.84	1.43—115.60	0.045		0	0
A26/B54/DR0405	4	1.9	16.58	1.92—142.90	0.016		0	0
A1101/B60/DR1202	0	0	0.09	0.01—0.73	0.018		9	2.4
A1101/B46	2	1.0	0.23	0.05—1.00	0.028		15	3.9
A24/B62	6	2.9	5.56	1.11—27.79	0.027		2	0.5
A33/B58	10	4.8	0.46	0.23—1.00	0.032		37	9.7
A1101/B7	3	1.4	12.80	1.42—115.29	0.045		0	0
A2/B54	3	1.4	12.84	1.43—115.60	0.045		0	0
A24/B39	3	1.4	12.84	1.43—115.60	0.045		0	0
A26/B54	3	1.4	12.84	1.43—115.60	0.045		0	0
A33/B46	3	1.4	12.84	1.43—115.60	0.045		0	0
A33/B60	3	1.4	12.84	1.43—115.60	0.045		0	0
A24/B61	0	0	0.12	0.01—1.00	0.045		7	1.8
A1101/DR0901	7	3.3	0.43	0.19—1.00	0.047		28	7.4
A1101/DR1202	14	6.7	2.64	1.15—6.06	0.017		10	2.6
A2/DR0803	3	1.4	0.28	0.08—1.00	0.020		19	5.0
A33/DR1302	1	0.5	0.15	0.02—1.14	0.026		12	3.2
A2/DR0405	8	3.8	31.94	4.02—253.91	0.001		0	0
A24/DR0803	8	3.8	31.94	4.02—253.91	0.001		0	0
A24/DR1602	3	1.4	12.84	1.43—115.60	0.045		0	0
A26/DR0405	7	3.3	28.05	3.48—225.81	0.001		0	0
A33/DR1201	4	1.9	16.58	1.92—142.90	0.016		0	0
B58/DR1302	1	0.5	0.16	0.02—1.25	0.037		11	2.9
B60/DR1201	5	2.4	9.24	1.07—79.66	0.024		1	0.3
B27/DR0405	4	1.9	16.58	1.92—142.90	0.016		0	0
B35/DR1201	3	1.4	12.84	1.43—115.60	0.045		0	0
B51/DR0405	4	1.9	16.58	1.92—142.90	0.016		0	0
B54/DR0403	5	2.4	20.37	2.44—170.33	0.006		0	0
B54/DR1405	3	1.4	12.84	1.43—115.60	0.045		0	0
B62/DR1202	3	1.4	12.84	1.43—115.60	0.045		0	0
B75/DR1501	4	1.9	16.58	1.92—142.90	0.016		0	0
B60/DR1401	0	0	0.12	0.01—1.00	0.045		7	1.8

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio; OSCC = oral squamous cell carcinoma.

Table 7 Haplotype frequencies of HLA-A/B, HLA-A/DR, and HLA-DR antigens in patients with oral cancer with or without cervical lymph node metastasis.

	Nodal metastasis (n = 80)						No nodal metastasis (n = 130)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
A2/B60	9	11.2	0.19	0.05—0.72	0.010		3	2.6
A1101/B60	0	0	12.88	1.61—102.80	0.011		9	6.9
A1101/B62	4	5.0	0.07	0.01—0.58	0.021		0	0
A2/DR1201	4	5.0	0.07	0.01—0.58	0.021		0	0
DR1101	11	13.8	0.36	0.13—1.00	0.040		7	5.4

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio.

Table 8 Haplotype frequencies of HLA-A/B/DR, HLA-A/B, HLA-A/DR, HLA-B/DR, HLA-B38, and HLA-DR0803 antigens in patients with oral cancer with early (Stages I and II) and late (Stages III and IV) stage disease.

	Early stage (n = 68)						Late stage (n = 142)	
Antigens	No.	%	OR	95% CI	P	Pc	No.	%
A1101/B54/DR0405	3	4.4	15.40	1.68—140.84	0.032		0	0
A1101/B60/DR0901	4	5.8	20.15	2.30—176.43	0.010		0	0
A24/B51/DR0405	3	4.4	15.40	1.68—140.84	0.032		0	0
A1101/B60/DR1202	0	0	0.12	0.01—1.00	0.041		8	5.6
A1101/B60	10	14.7	25.00	3.12—200.44	0.0001		1	0.7
A24/B51	6	8.8	13.89	1.63—118.16	0.005		1	0.7
A2/B38	3	4.4	15.40	1.68—140.84	0.032		0	0
A2/B60	0	0	0.07	0.01—0.54	0.005		13	9.1
A24/B54	0	0	0.12	0.01—1.00	0.041		8	5.6
A1101/DR0901	6	8.8	4.56	1.10—18.89	0.033		3	2.3
A24/DR0405	4	5.8	8.93	1.00—81.71	0.038		1	0.7
A1101/DR0403	3	4.4	15.40	1.68—140.84	0.032		0	0
A1101/DR1202	0	0	0.06	0.01—0.50	0.003		14	10.7
B60/DR0901	4	5.8	8.93	1.00—81.71	0.038		1	0.7
B38	3	4.4	15.28	1.67—139.73	0.033		0	0
DR0803	8	11.6	3.08	1.00—9.31	0.041		6	4.6

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio.

three variables in our study, only nodal involvement was associated with differences in haplotype frequency, patients with nodal metastases having a higher frequency of A2/B60, A1101/B62, A2/DR1201, and DR1101 and a lower frequency of A1101/B60. Ogoshi et al reported that HLA-DR4 and HLA-B52 antigens are associated with lymph node metastasis in gastric cancer.[27] We also found significant differences in haplotypes between the early and late stages of the disease. There are varied reasons that affect the patients' tumor stages. Cervical node metastasis may be an important factor in this regard. However, the exact mechanism by which these antigens are involved in cervical lymph node metastasis or how they may impact survival needs further investigation.

Some of the same HLA alleles we noted in our study have been reported in association with other cancers. HLA-A24, more common in our patients with OSCC than in controls, was identified as a predictor of bilateral breast cancer in Japanese women.[28] The lower frequency of DRB1*1302 in our patients with OSCC was also noted in patients with lung cancer.[29] These findings raise the possibility that particular alleles may contribute to or protect from carcinogenesis. If this theory is borne out by further investigation, it might eventually lead to specific anticancer immunotherapy.[30]

There is no question that environmental agents are involved in the development of OSCC, yet other factors must be at work as well. Finding specific HLA-type differences in people with and without OSCC as well as among those whose OSCC has particular clinical behaviors is the first step in trying to tease out some of these factors. The ultimate goal, of course, is to develop better prophylactic, prognostic, and therapeutic option than we currently have. Studies such as ours contribute to genetic databases needed to undergird studies of molecular mechanisms in cancer. Amassing such data should help identify targets that may be amenable to therapeutic manipulation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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