Frequency of *HLA-C* Alleles in Differentiated Thyroid Carcinoma in Southeastern Spain

HLA-Cw7 as a Poor Prognosis Factor

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BACKGROUND. The development of thyroid carcinoma may be influenced genetically and has been associated with certain *HLA* alleles. *HLA-C* alleles have not been studied in depth, because available serology techniques have not been very reliable in detecting them. However, the development of molecular biology provided an efficient and reliable technique for allele detection. The aims of the current study were to determine whether there is a significant association between any *HLA-C* allele and differentiated thyroid carcinoma and to establish the possible susceptibility or protection alleles related to these tumors.

METHODS. *HLA-C* genotyping was performed in 63 patients undergoing surgery for differentiated thyroid carcinoma (57 patients with the papillary subtype and 6 patients with the follicular subtype). A representative sample of 100 nonrelated healthy Caucasians was used as a control group from the same geographic area. The polymerase chain reaction–sequence-specific primer technique was used for *HLA-C* genotyping. The clinical variables analyzed were age, gender, family history of thyroid pathology, residence in areas of endemic goiter, asymptomatic status, presence of hyperthyroidism, compressive symptoms, presence of an intrathoracic thyroid component, histologic variables of the tumor, and evolution. The chi-square test, the Mantel–Haenszel test, and the Bonferroni correction were used for the statistical analysis.

RESULTS. In the control group, a significant correlation was observed between the lower frequency of the *HLA-Cw7* allele and the development of differentiated thyroid carcinoma ($P < 0.05$). Analysis of the different clinical variables revealed a relation between *HLA-C* alleles and three clinical situations: cervical lymph node involvement with *HLA-Cw7* and *HLA-Cw2,* vascular involvement with *HLA-Cw7* and *HLA-Cw1,* and cervical carcinoma recurrence with *HLA-Cw1*. However, after application of the Bonferroni correction, only the association between *HLA-Cw7* and lymphatic ($P_c = 0.0483$) or vascular involvement ($P_c = 0.0324$) persisted.

CONCLUSIONS. The results revealed a relation between *HLA-Cw7* and differentiated thyroid carcinoma. In future investigations, *HLA-C* typing may help to identify patients with a poor prognosis. ***Cancer* 2004;100:264–9.**
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KEYWORDS: differentiated thyroid carcinoma, *HLA-C*, *HLA-Cw7*, *HLA-Cw1*, risk factors.

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Malignant degeneration is a multifactorial process influenced by genetic and environmental factors.[1–3] Human leukocyte antigens (HLA) have been found to be genetic factors in several types of malignant tumors,[2,3] although the mechanism by which they are related to the pathogenesis of malignant disease is uncertain, and the specific genes involved have not been accurately identified.[2] How-

ever, the interaction between the environment and the genes causing tumorigenesis is well documented.[3] The association between HLA and epithelial malignancy has been firmly established,[1,2] and it has been suggested that certain cofactors (virus, ultraviolet light, X-rays) may induce carcinoma.[1–3] The variability of these cofactors can influence the selective presence or absence of certain *HLA* alleles in different populations. It may be necessary for the concurrence of several HLA factors (Class I and II genes) in the same haplotype to cause tumorigenesis or disease induction.[1] The discrepancy between the *HLA* alleles encountered and tumor development is primarily due to the fact that disease susceptibility factors depend on different *HLA* haplotypes in different ethnic groups. Nonetheless, it must be remembered that genes other than *HLA* may be involved in thyroid tumor susceptibility[2-3].

In the thyroid, as it previously has been observed in autoimmune diseases, the HLA system may be associated with malignant disease.[4–7] In general, *HLA* studies did not analyze *HLA-C* alleles, because serology techniques were not very reliable for detecting them. However, in recent years, the development of molecular biology techniques has provided an efficient technique for reliably detecting these alleles.

The aims of the current study were to determine whether there is a significant association between *HLA-C* allele frequencies and differentiated thyroid carcinoma and to discover susceptibility and/or protection alleles for these neoplasms.

MATERIALS AND METHODS

Patients

HLA-C allele typing was performed for 63 consecutive patients undergoing surgery for differentiated thyroid carcinoma (57 patients with the papillary subtype and 6 patients with the follicular subtype) between 1995 and 2000. The mean age of patients was 40 ± 13 years, and females accounted for 84% ($n = 53$) of the study population. Eight patients had a family history of thyroid pathology (6 multinodular goiters and 2 papillary carcinomas), and 5 patients lived in areas of endemic goiter. In 51 patients (81%), there were no symptoms associated with carcinoma, whereas compressive symptoms ($n = 7$ [11%]) and hyperthyroidism ($n = 5$ [8%]) were observed in the remaining patients. The most common reason for consultation was the presence of a cervical tumor ($n = 53$ [84%]). A thyroid nodule was palpable in all patients, and an intrathoracic thyroid component was present in 6 patients (10%). A fine-needle aspiration biopsy (FNAB) was performed for all patients. The FNAB specimens indicated suspected malignancy in 20 patients (32%), follicular or Hürthle proliferation in 38 patients (60%), and colloid disease in 4 patients (6%). The remaining case was found to be hematic. All patients received total thyroidectomy, 22 of them (35%) undergoing jugular lymph node emptying. In the histologic study, 57 patients were classified as having papillary carcinomas (91%), and the remaining patients were classified as having follicular carcinomas. The mean tumor size was 1.4 ± 0.5 cm (including 5 microcarcinomas [8%]), and 2 patients had multifocal carcinoma (3%). Lymph node involvement was observed in 17 patients (27%), capsular involvement was observed in 10 patients (16%), and vascular involvement was observed in 6 patients (10%). After a mean follow-up of 36 ± 11 months, cervical recurrence of the carcinoma was observed in 10 patients (16%), and distant metastasis was noted in 1 patient.

HLA-C Typing

The polymerase chain reaction–sequence-specific primer (PCR-SSP) molecular biology technique was used for *HLA-C* genotyping.[8,9] In brief, peripheral blood was collected in a tube with ethylenediaminetetraacetic acid anticoagulant. This technique includes the Higuchi method of rapid nucleic acid extraction and DNA quantification with a spectrophotometer (Pharmacia Biotech, Gaithersburg, MD). Subsequently, the commercial kit FASTYPETM Bio-Synthesis System (Diagnostica Longwood S:L) was used following the manufacturer's recommendations. When the amplification reaction was complete, the tubes were left to cool at room temperature. The amplification was viewed in agarose gel using an ultraviolet light transilluminator. The presence of amplification was recorded using a Polaroid 440 camera (Polaroid, France).The PCR-SSP method was also used to study a control group of 100 nonrelated healthy Caucasians who were representative of the general population.

Statistical Analysis

The variables analyzed for detecting associations between certain alleles and subgroups of patients with thyroid carcinoma were age, gender, family history of thyroid pathology, residence in areas of endemic goiter, asymptomatic status, presence of hyperthyroidism, compressive symptoms, presence of an intrathoracic goiter component according to the Eschapase concept (i.e., the lower edge of the goiter is at least 3 cm below the sternal manubrium), papillary carcinoma, follicular carcinoma, tumor size (microcarcinoma [tumor ≤ 1 cm] or macrocarcinoma [tumor > 1 cm]), tumor multifocality, lymphatic involvement, vascular involvement, capsular involvement, cervical

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TABLE 1
Distribution of *HLA-C* Alleles in the Two Study Groups

HLA-C allele	No. of control patients (n = 100) (%)	No. of patients with carcinoma (n = 63) (%)	P	P_c
Cw01	4 (2)	4 (3.2)	> 0.05	—
Cw02	8 (4)	9 (7.1)	> 0.05	—
Cw03	7 (3.5)	10 (7.9)	> 0.05	—
Cw04	31 (15.5)	17 (13.5)	> 0.05	—
Cw05	15 (7.5)	8 (6.3)	> 0.05	—
Cw06	14 (7)	3 (2.4)	> 0.05	—
Cw07	49 (24.5)	18 (14.3)[a]	0.0016	0.0283
Cw08	7 (3.5)	9 (7.1)	> 0.05	—
Cw09	0	0	> 0.05	—
Cw010	0	0	> 0.05	—
Cw011	0	0	> 0.05	—
Cw012	23 (11.5)	16 (12.7)	> 0.05	—
Cw013	0	0	> 0.05	—
Cw014	2 (1)	0	> 0.05	—
Cw015	6 (3)	5 (4)	> 0.05	—
Cw016	15 (7.5)	15 (11.9)	> 0.05	—
Cw017	4 (2)	3 (2.4)	> 0.05	—
Cw018	0	0	> 0.05	—
Cw homozygotes	15 (7.5)	9 (7.1)	> 0.05	—
Total	200 (100)[a]	126 (100)[a]		

P_c: P with the Bonferroni correction.
[a] The number of alleles is twice the number of patients, as each person has two alleles—one maternal and one paternal.

recurrence, and the presence of distant metastasis in the follow-up.

HLA-C allele frequencies were estimated by direct counts. To compare the differences between the allele frequencies in the control and carcinoma groups, a 2×2 contingency table analysis was performed using the Pearson chi-square and Mantel–Haenszel tests, with Yates's correction and the Fisher exact test when the expected value for an *HLA* marker was < 5. All statitical methods were provided in the EPI-INFO-5.01 software package (Centers for Disease Control, Atlanta, GA). The relative risk (RR) was calculated according to Woolf's method. The P values were corrected by multiplying the number of alleles tested (Bonferroni's correction).[10] The association between the clinical variables and *HLA-C* alleles was made using the Pearson chi-square test, complemented with a two-tailed t test for independent samples. Only $P < 0.05$ was considered to be statistically significant. For the most significant associations, the etiology fraction (EF) using the formula, EF = P (RR − 1) / 1 + P (RR − 1), was used.

RESULTS

General Analysis

As shown in Table 1, the most common *HLA-C* alleles in patients with differentiated thyroid carcinoma were *HLA-Cw7* (14.3%), *HLA-Cw12* (12.7%), and *HLA-Cw16* (11.9%). Allelic distribution in the control and differentiated carcinoma groups had a similar order of frequency. The only statistically significant difference was found between the lower incidence of the *HLA-Cw7* allele and a diagnosis of differentiated thyroid carcinoma ($P = 0.0016$; $P_c = 0.0283$). In the control group, the frequency of the *HLA-Cw7* allele was 24.5%, whereas it was only 14.3% in the carcinoma group. Among patients with differentiated thyroid carcinoma with the *HLA-Cw7* allele, RR = 0.51.

Analysis of Clinical Variables

In the differentiated thyroid carcinoma subgroup (Table 2), no association was found between *HLA-C* alleles and the following clinical variables: age, gender, family history of thyroid pathology, residence in an area of endemic goiter, patient's clinical status (asymptomatic, compressive symptoms, or hyperthyroidism), presence of an intrathoracic goiter component, type of differentiated carcinoma (papillary or follicular), presence of multifocality, tumor size (i.e., microcarcinoma), thyroid capsular involvement, and the presence of distant metastasis. In contrast, 3 clinical situations exhibited a significant association with *HLA-C* (Table 2): 1) cervical lymphatic involvement was related to alleles *HLA-Cw7* ($P = 0.0026$; RR = 3.2) and *HLA-Cw2* ($P = 0.0370$; RR = 4.37); 2) vascular involvement was also related to *HLA-Cw7* ($P = 0.0018$; RR = 16.92) and *HLA-Cw1* (P=0.0044; RR=13.75); and 3) cervical recurrence of the carcinoma exhibited an association with *HLA-Cw1* ($P = 0.049$; RR = 6.37). When the Bonferroni correction was applied, only 2 relations persisted: lymphatic involvement and the *HLA-Cw7* allele ($P_c = 0.0483$; EF = 34,5%) and vascular involvement and the *HLA-Cw7* allele ($P_c = 0.0324$; EF = 79%).

DISCUSSION

It is well known that HLA molecules present specific antigens to lymphocytes.[11] This ability can be used for an effective tumor peptide antigen presentation and T-lymphocyte activation. Therefore, these activated cells may trigger or suppress the specific immune response developed against a particular tumor antigen.[3] The HLA system plays a role both in the presentation and recognition of neoantigens and in the subsequent level of tumoral immune response. There also is variability in the reported correlation between HLA and malignant disease; this variability may be due to the involvement of susceptibility factors other than those encoded by the *HLA* region or flanking genes or due to the fact that a single histology may be the result of different etiopathogenies, which are not always

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TABLE 2
Correlation between Clinical Variables and the Distribution of *HLA-C* Alleles

Variable	No. of Patients (n = 63)[a]	Associated alleles	No. of patients with positive alleles	P	P_c
Mean age ± SD	40 ± 13	—	—	—	—
Gender (F/M)	53/10	—	—	—	—
Family history of thyroid pathology	8	—	—	—	—
Residence in areas of endemic goiter	5	—	—	—	—
Asymptomatic	51	—	—	—	—
Hyperthyroidism	5	—	—	—	—
Compressive syndrome	7	—	—	—	—
Intrathoracic component	6	—	—	—	—
Papillary carcinoma	57	—	—	—	—
Follicular carcinoma	6	—	—	—	—
Microcarcinoma	5	—	—	—	—
Multifocality	2	—	—	—	—
Lymphatic involvement	17	*Cw7*	8/17	0.0026	0.0483
		Cw2	5/17	0.0370	0.6661
Vascular involvement	6	*Cw7*	5/6	0.0018	0.0324
		Cw1	2/6	0.0044	0.0792
Capsular involvement	10	—	—	—	—
Cervical recurrence	10	*Cw1*	2/10	0.0453	0.8154
Distant metastasis	1	—	—	—	—

M: male; F: female; SD: standard deviation; P_c: P with the Bonferroni correction.
[a] The number of patients presenting the analyzed variable is shown.

linked to HLA. Currently, the most accepted theory is that some cofactors may induce tumors linked to HLA via immunologic mechanisms, so far undefined, but in which HLA can have a function (e.g., viral or neoplastic antigen presentation).[1–3] However, it is not entirely clear that *HLA* contains genes directly responsible for tumor susceptibility.

Studies on *HLA* in thyroid carcinoma are rare, and those that exist generally have involved a small number of patients. The first significant association between papillary and follicular thyroid carcinoma and *HLA* alleles was reported in 1982 by Panza et al.[4] The following year, Juhasz et al.[5] reported an association between *HLA* alleles and medullary thyroid carcinoma. In subsequent publications, the results differed with regard to the individual *HLA* frequency and to the existing association between HLA and thyroid carcinomas (Table 3). The differences in results among the studies in Table 3 probably are due to the small number of cases rather than ethnic or geographic origin. However, not all studies found an association between HLA and thyroid carcinoma. For example, Larsen et al.,[7] Weissel et al.,[19] and Ahuja et al.[6] did not find an association between HLA and papillary and follicular carcinomas. In the literature, the most frequent allelic association was found between differentiated thyroid carcinoma and *HLA-DR1*.[4,15,16,18] Panza et al.[4] reported a strong association between *HLA-DR1* and thyroid carcinoma, especially the follicular type, which was confirmed by Juhasz et al.[16] in iodine-deficient areas. Since then, most authors[13,15] have reported a generally strong association with the *HLA-DR* locus, but with different alleles. However, Larsen et al.[7] did not confirm the predisposition of individuals bearing *HLA-DR1* alleles to develop thyroid carcinoma in iodine-deficient areas. Juhasz et al.[5] and Sridama et al.[13] described an association between *HLA-DR7* and differentiated or medullary thyroid carcinoma. *HLA-DR7* also has been found to be associated with other tumors, especially testicular carcinoma; based on this finding, Sridama et al.[13] concluded that *HLA-DR7* may be related to the development of carcinomas in general. Nonetheless, this hypothesis is not confirmed by the findings of other authors (Table 3). Weissel et al.[19] believed that the differences in the Sridama et al.[13] study were due to ethnic differences in the populations studied.

Rigopoulou et al.[1] examined Class I and II HLA in patients with thyroid carcinoma and found an association between papillary carcinoma and the *HLA-B35* and *HLA-DR11* alleles and between Hürthle carcinoma and the *HLA-DR4* allele. Therefore, an association could exist between both HLA Class I (B35) and Class II (DR11), especially in papillary carcinoma, but this has not been confirmed in follicular carcinoma. No significant association was found between HLA and the activity of the disease (evidence of metastasis), although the observed percentage of *HLA-DR4* in-

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TABLE 3.
***HLA* Alleles Associated with Thyroid Carcinoma as Reported in Other Studies**

Study (yr)	No. of Patients	Type	HLA allele
Panza et al. (1982)[4]	20 and 37	Papillary and follicular	*DR1; Bw35*
Juhasz et al. (1983)[5]	9	Medullary	*DR7*
Lipinski (1984)[12]	29	Medullary	*B15*
Sridama et al. (1985)[13]	65	Papillary and follicular	*DR7*
Sridama et al. (1985)[13]	8	Medullary	*DR7*
Dralle et al. (1986)[14]	51	Papillary and follicular	*DR5; Bw62; DRw6*
Dralle et al. (1986)[14]	11	Medullary	*DR3*
Jushasz et al. (1986 and 1989)[15, 16]	30 and 27	Papillary and follicular	*DR1*
Jushasz et al. (1986 and 1989)[15, 16]	3	Anaplastic	—
Larsen et al. (1986)[7]	45	Papillary and follicular	—
Guillausseau et al. (1988)[17]	137	Medullary	—
Ozaki et al. (1988)[18]	23	Papillary and follicular	*B7; DR1; Cw7*
Weissel et al. (1988)[19]	61 and 44	Papillary and follicular	—
Weissel et al. (1988)[19]	22	Medullary	*DR2*
Matsubayashi et al. (1989)[20]	23	Thyroid lymphoma	—
Ahuja et al. (1992)[6]	12 and 10	Papillary and follicular	—
Ahuja et al. (1992)[6]	18	Medullary	—
Rosawoki et al. (1993)[21]	97	Papillary	*B15; B18*
Rigopoulou et al. (1994)[1]	137	Papillary	*B35; DR11*
Rigopoulou et al. (1994)[1]	16	Follicular	—
Rigopoulou et al. (1994)[1]	6	Hürthle carcinoma	*DR4*

volvement doubled in patients (n = 15 [53%]) compared with the control group (n = 176 [23%]). This result was not significant after correction. These data differ from the findings of other studies performed in the Hungarian population, in which an association was found between DR1 and metastases.[15]

Currently, there are few studies on the correlation between *HLA-C* and thyroid pathology. These studies were performed with serology,[1,6] which is an unreliable technique for accurately determining *HLA-C* alleles. The progressive development of molecular biology techniques has allowed more accurate detection of histocompatibility alleles.[8,9,22–24] In malignant thyroid pathology, the only association between the *HLA-Cw7* allele and papillary and follicular carcinomas was found by Ozaki et al.[18] Our results indicate an association between the lower frequency of the *HLA-Cw7* allele and the presence of differentiated carcinoma. In our analysis of the associations between the clinical variables of differentiated carcinoma and the various *HLA-C* alleles, the *HLA-Cw7* allele appears to be associated with the presence of lymphatic and vascular involvement of the carcinoma. A correlation between the *HLA-Cw7* allele and other tumoral diseases already had been established as a factor involved in tumor pathogenesis.[25,26] Furthermore, in patients with certain carcinomas, the *HLA-Cw7* allele is a predictor of poor response to therapy.[26] The *HLA-Cw7* allele also has been associated with benign diseases such as alopecia areata[27] and primary Sjogren syndrome[28] and represents a potentially important control mechanism for the in vivo replication of certain viruses, including the human immunodeficiency virus.[29] When the *HLA-Cw7* allele occurs in patients with differentiated thyroid carcinoma, there is a greater incidence of lymphatic and vascular involvement and, therefore, a poorer prognosis for these patients.

In addition, associations were found between *HLA-Cw1* and the presence of vascular involvement and cancer recurrence and between *HLA-Cw2* and lymphatic involvement. However, in both cases, the results were not significant after applying the Bonferroni correction. In the former case, an association also was found between the *HLA-Cw1* allele and certain human malignant cell lines.[30] In the latter case, an association was found between the *HLA-Cw2* allele and neoplasms such as multiple myeloma,[31] but generally, the allele has been associated with benign pathologies such as Type II psoriasis[32] and spondyloarthropathy.[33] The detected association between these alleles and thyroid carcinoma needs to be confirmed in further studies.

In summary, we believe that *HLA-C* genotyping can help to identify patients with differentiated thyroid carcinoma who have a poor prognosis, particularly patients with the *HLA-Cw7* allele. Therefore, the *HLA-Cw7* allele must be considered a protection factor against the development of differentiated thyroid carcinoma, even though patients suffering from this carcinoma and bearing this allele had a poorer prog-

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nosis. In the future, the development of cost-efficient *HLA* diagnostic techniques will be another decision-making tool in clinical situations.

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