Associations between HLA-C alleles and papillary thyroid carcinoma

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Abstract. Objective: Papillary thyroid carcinoma (PTC) is the most frequent types of thyroid malignancies. Several genes may be involved in susceptibility of thyroid cancer including Human Leukocyte Antigens (HLA). The association of thyroid carcinoma with HLA alleles has been previously studied in other populations and certain HLA alleles were shown to be either predisposing or protective. The aim of this study was to determine the association between HLA-C allele frequencies and papillary thyroid carcinoma in an Iranian population.

Design: HLA-C\textsuperscript{w} allele frequencies were determined in patients with papillary thyroid carcinoma (N = 54) and non-related healthy controls (N = 91) using PCR -SSP.

Main Outcome: We found that HLA-C\textsuperscript{w}*4 and HLA-C\textsuperscript{w}*15 allele frequencies were significantly higher in our patients compared to the controls [\(P = 10^{-4}\), OR; 12.5, 95% CI 2.6–116.9] and [\(P = 10^{-4}\), OR; 24.7, 95% CI (3.6–1058)] respectively.

Conclusions: Our results revealed certain HLA-C alleles are predisposing factors in papillary thyroid carcinoma in an Iranian population. This confirms the previous findings for association between HLA-C alleles and differentiated carcinomas in other populations.

Keywords: Genetics, HLA, papillary carcinoma, thyroid, epidemiology

1. Introduction

Thyroid carcinoma is the most common malignancy of the endocrine system and papillary carcinoma is the most frequent type (80%) of thyroid cancers [1].

Several genes including Human Leukocyte Antigens (HLA) may be involved in susceptibility of malignant tumors [2]. The contribution of HLA molecules in immunological recognition of tumor cells might be responsible for both tumor development and immunity [3].

Several lines of evidence describe the contribution of HLA class I proteins in various types of cancers, including epithelial cancers, which could be due to a selective immunogenic T cell response in these conditions [4, 5]. T cell based immunotherapy procedures are potentially effective in cancer treatment [4]. A better understanding of the immune system mechanism in thyroid carcinoma may enhance future treatment options [6].

The association of thyroid carcinoma with HLA alleles has been studied by several investigators [7–17]. HLA antigens have been associated with well differentiated thyroid carcinoma [7,9,11,13,16]. However no associations were found in some earlier studies [12,14,
More recently Rios et al have examined the HLA-C allele frequencies in differentiated thyroid carcinoma in a population from Southeast Spain and reported HLA-Cw7 having a protective effect and simultaneously a poor prognosis factor [17].

The aim of the current study was to determine the association between HLA-C allele frequencies and papillary thyroid carcinoma in an Iranian population.

2. Materials and methods

2.1. Patients

Cases group consisted of (N = 54) consecutive patients underwent surgery for differentiated thyroid carcinoma in Shariati Hospital and Amir-Aalam Hospital, Tehran, Iran. In histologic study the patients were diagnosed as having papillary carcinomas which based on the nuclear feature of the cells on pathological examination all were sub-classified as classic papillary carcinoma. The mean age of patients was 43±13 years, and females accounted for 76% and males 23% of the study population. Controls group were comprised of (N = 91) un-related healthy people. Controls population were from the same area as cases. The study was approved by the Ethics committee of Tehran University. Informed consents were obtained from all of the patients attending the study.

2.2. HLA-Cw typing

DNA from cases and controls were extracted from anti-coagulated blood collected in EDTA using salting out method. HLA-Cw typing was performed using Dynal AllSet™ SSP kit.

2.3. Statistical analysis

HLA-Cw allele frequencies were estimated by direct count. To compare the differences between the allele frequencies in the control and carcinoma groups, a 2x2 contingency table analysis was performed using the Pearson chi-square tests, with Fisher exact test when the expected value for an HLA-Cw allele was <5.

The strength of association between HLA-Cw allele and papillary thyroid carcinoma was estimated by odds ratios (OR) and 95% confidence intervals (95% CI) using the STATA v8 program. The P values were corrected by multiplying with the number of alleles tested. Only P < 0.05 was considered to be statistically significant.

The Haldane correction was used when any of the cells in the 2x2 tables contained the value 0. The Haldane correction is used to avoid zero error in the calculation of some of the chi-square tests. It involves adding 0.5 to all of the cells of a contingency table if any of the cell expectations would cause a division by zero error.

3. Results

HLA-Cw allele frequencies were determined in patients with papillary thyroid carcinoma and controls (Table 1).

The difference in HLA-Cw allele frequencies between cases and controls was statistically different. The allele frequency of HLA-Cw*04 was 11% in the carcinoma group, whereas it was only 1% in the control group [P = 10^{-4}, OR; 12.5, 95% CI 2.6–116.9].

None of the patients in the control group were carrying HLA-Cw*15 allele. HLA-Cw*15 allele frequency was significantly higher in patients compared to the controls [P = 10^{-4}, OR; 24.7, 95% CI (3.6–1058) (Table 1).]

HLA-Cw*14 and HLA-Cw*18 frequencies were significantly decreased in papillary thyroid carcinoma but after Bonferroni correction this was not statistically significant (Table 1).

4. Discussion

HLA-Cw alleles are involved in the regulation of natural killer cells and cytotoxic T-cells specificity and activity [18]. We found that HLA-Cw*04 and HLA-Cw*15 contribute risk for the development of papillary thyroid carcinoma in our study. In addition, we observed lower frequencies of the HLACw14 and HLACw18 in papillary thyroid carcinoma in our population and these alleles could be considered as protective factors. However after correcting for the multiple testing the difference was not statistically significant.

Ozaki et al found an association between the HLA-Cw*07 allele and papillary and follicular carcinomas [19]. An association between the lower frequency of the HLA-Cw*07 allele and the presence of differentiated carcinoma also has been recently reported (17). A correlation between the HLA-Cw*07 allele and other tumors already had been established as a factor in-
Table 1

<table>
<thead>
<tr>
<th>HLA-C allele</th>
<th>No. of patients with carcinoma (n=91) (%)</th>
<th>No. of controls (n=54) (%)</th>
<th>P</th>
<th>Pc = p*18</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cw*01</td>
<td>3(3%)</td>
<td>7(3%)</td>
<td>&gt;0.05</td>
<td>0.005</td>
<td>12.5 (2.6—116.9)</td>
</tr>
<tr>
<td>Cw*02</td>
<td>8(7%)</td>
<td>7(3%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*03</td>
<td>7(6%)</td>
<td>9(4%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*04</td>
<td>12(11%)</td>
<td>2(1%)</td>
<td>10^-4</td>
<td>0.0018</td>
<td></td>
</tr>
<tr>
<td>Cw*05</td>
<td>1(1%)</td>
<td>0(0%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*06</td>
<td>12(10%)</td>
<td>33(18%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*07</td>
<td>15(14%)</td>
<td>25(14%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*08</td>
<td>3(3%)</td>
<td>4(2%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*12</td>
<td>21(19%)</td>
<td>43(24%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*13</td>
<td>0(0%)</td>
<td>3(1%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*14</td>
<td>2(2%)</td>
<td>17(9%)</td>
<td>0.01</td>
<td>0.18</td>
<td>0.1(0.02—0.8)</td>
</tr>
<tr>
<td>Cw*15</td>
<td>13(12%)</td>
<td>0(0%)</td>
<td>10^-4</td>
<td>0.0018</td>
<td>24.7(3.6—1058)</td>
</tr>
<tr>
<td>Cw*16</td>
<td>5(5%)</td>
<td>9(5%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*17</td>
<td>1(1%)</td>
<td>7(4%)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*18</td>
<td>3(3%)</td>
<td>16(9%)</td>
<td>0.04</td>
<td>0.72</td>
<td>0.2 (0.05—1.07)</td>
</tr>
</tbody>
</table>

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

Involved in tumor pathogenesis [20,21]. We did not find any difference in the HLA-Cw*07 frequencies between cases and controls, suggesting that this allele may not be a risk factor for papillary thyroid carcinoma in our population.

Recent evidence from thyroid autoimmune diseases point to a primary role for class I-mediated responses in Grave’s disease and has showed that HLA-Cw has the strongest association with HLA-Cw7 as predisposing and both HLA-Cw3, HLA-Cw16 as protective alleles [22]. A significant association was reported between the lower incidence of the HLA-Cw4 allele and the appearance of multinodular goiter that suggest a protective effect for HLA-Cw4 allele against multinodular goiter [22]. Also in another study the absence of the HLA-Cw4 allele was associated with goiters presenting with an intrathoracmonic component and greater weight [23]. The HLA-Cw1 was associated with the presence of goiter-associated thyroid carcinoma [23]. In addition, associations were found between HLA-Cw1 and the presence of vascular involvement and cancer recurrence and between HLA-Cw2 and lymphatic involvement of thyroid carcinoma [17]. In our study HLA-Cw1 and Cw2 frequency was not significantly different between cases and controls.

HLA association studies will help us in better understanding of underlying mechanisms in thyroid carcinoma. Studies in different populations draw a clear picture of susceptibility markers in various ethnic groups. In this study we have found that certain HLA-Cw alleles are predisposing factors in papillary thyroid carcinoma in Iranian population. Previous data show that genetic factors are more strongly involved in the presence of multifocal PTC rather than unifocal PTC [24].

It is known that interactions between killer cell immunoglobulin-like receptors (KIRs) and human HLA-class I ligands regulate the development and response of human natural killer (NK) cells. Combinations of HLA-C allele and KIR haplotypes is driven by natural selection and varies in different populations. These haplotypes are of recent evolutionary origins since the ape/human transition and vary in composition and number [25,26].

In this study we have performed HLA-C typing in one of the largest series of patients with papillary thyroid carcinoma reported to date [15–17]. However the reproducibility of this finding needs to be investigated in larger populations. Future studies of HLA-C allele frequencies on other types of thyroid tumors such as follicular type will be useful to further examine whether these markers are valuable in predicting the prognosis of such tumors [27].

References

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