Gene dose effect in penetration of celiac in first degree relatives

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Background:

Celiac Disease (CD) is a multifactorial gluten sensitive enteropathy associated with genetic and environmental risk factors.

Family history is one of the risk factors for CD susceptibility.

We expect to have 7.1% of transmission in the first-degree relatives of patients with celiac, however there are some families with a high CD penetration rate among family members.
There is not any clear reason for the high family penetration rate.

Therefore, we assessed the importance of specific HLA pattern or genetic dosage effect in high penetration rate and risk stratification for screening.
Methods:

Forty-four patients from 15 families were included and categorized to three groups. Group 1 were the cases from the families with more than 70% of affected members in the first and second degree relatives (high penetration group).

Group 2 comprised of cases from the families with 50-70% of affected members (intermediate penetration group).

Group 3 was also comprised of cases belonging to the families with less than 25% affected members or families with only one affected case (low penetration group).

HLA typing was performed by Specific Primers (SSP) – PCR on blood samples using a kit with a panel of 24 alleles.
The two types of DQ2 heterodimers are:

- DQ2.5 (DQA1*0501/B1*0202)
- DQ2.2 (DQA1*0201/B1*0202).
Results:

There was significant differences in HLA pattern in three groups in which 96% of patients in group one had mainly double dose of DQ2 in homozygote and heterozygote pattern and mostly heterozygote pattern.

Homozygous (DQ2.5/DQ2.5) or heterozygous (DQ2.5/DQ2.2) genotypes are the main genetic risk factors in CD. HLA-DQB1*02 has a critical function in the interaction between class II MHC and gliadin-derived peptide to be presented to the T-lymphocytes during CD pathogenesis.

There were also significant different frequencies of DQ2.5-2.2 alleles between more than 70 % and less than 70% penetration rate (P=0.002, OR= 14.37).
HLA pattern in patients with high, intermediate, and low familial penetrations

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Penetration &gt;70%</th>
<th>Penetration 50-70</th>
<th>Penetration &lt;25%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ2.5-DQ2.2</td>
<td>22(%88)</td>
<td>5(%50)</td>
<td>3 (%33.3)</td>
<td>30(68.2%)</td>
</tr>
<tr>
<td>DQ2.5-DQ2.5</td>
<td>2(%8)</td>
<td>1(%10)</td>
<td>2 (%22.2)</td>
<td>5 (11.4%)</td>
</tr>
<tr>
<td>DQ2.5-DQ8</td>
<td>1(4%)</td>
<td>4 (%40)</td>
<td>3 (%33.3)</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>DQ8-DQ8</td>
<td>0</td>
<td>0</td>
<td>1 (%11)</td>
<td>1 (2.3%)</td>
</tr>
</tbody>
</table>
Conclusion:

HLA DQ2.5-2.2 which has double dose of HLA-DQB1*02 has a critical function and can be used as efficient predictors for the familial CD.

HLA DQ pattern can be introduced as an efficient method for the CD screening and therapeutic strategies among offspring and siblings.

**Key words**: Celiac disease, Genetic, familial, HLA pattern, gene dose, penetration
Ethics approval and consent to participate

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences. All participants gave written informed consent to participate.

Competing interests

The authors declare that they have no competing interests.