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Published in:
World Journal of Gastroenterology

DOI:

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Allele and haplotype frequencies for HLA-DQ in Iranian celiac disease patients

Mohammad Rostami-Nejad, Jihane Romanos, Kamran Rostami, Azita Ganji, Mohammad Javad Ehsani-Ardakani, Ali-Reza Bakhshipour, Homayoun Zojaji, Seyed Reza Mohebbi, Mohammad-Reza Zali, Cisca Wijmenga

Mohammad Rostami-Nejad, Mohammad Javad Ehsani-Ardakani, Homayoun Zojaji, Seyed Reza Mohebbi, Mohammad-Reza Zali, Department of Celiac Disease, Gastroenterology and Liver Diseases Research Centers, Shahid Beheshti University of Medical Sciences, Tehran 1985717411, Iran
Jihane Romanos, Cisca Wijmenga, Department of Genetics, University of Groningen, University Medical Centre of Groningen, 9700 RB Groningen, The Netherlands
Kamran Rostami, Department of Gastroenterology, Worcestershire Royal Hospital, Worcester, WR5 1DD, United Kingdom
Azita Ganji, Department of Gastroenterology, Imam Reza Hospital Mashhad University of Medical Sciences, Mashhad 1351143, Iran
Ali-Reza Bakhshipour, Department of Gastroenterology, Zahedan University of Medical Sciences, Zahedan 2143453, Iran
Jihane Romanos, Department of Genetics, Institute of Human Genetics, Lebanese American University, Byblos 36, Lebanon

Author contributions: Rostami-Nejad M contributed to sample collection, article writing, final approval; Romanos J contributed to HLA typing and drafting the article; Rostami K contributed to supervisor of this project and editing the manuscript; Ganji A contributed to sample collection from Mashhad city; Mohebbi SR contributed to DNA extraction and analysis and interpretation of data; Zojaji H contributed to Sample collection from Tehran city; Bakhshipour AR contributed to sample collection from Zahedan city; Zali MR and Ehsani-Ardakani MJ contributed to concept and design of the work, final approval; Wijmenga C contributed to supervising HLA typing, article writing, final approval.

Correspondence to: Mohammad Javad Ehsani-Ardakani, MD, Department of Celiac Disease, Gastroenterology and Liver Diseases Research Centers, Shahid Beheshti University of Medical Sciences, Velenjak St., Shahid Chamran Highway, Tehran 1985717411, Iran. mjehsani@yahoo.com
Telephone: +98-21-22432518 Fax: +98-21-22432517
Received: November 2, 2013 Revised: December 31, 2013
Accepted: January 20, 2014
Published online: May 28, 2014

Abstract

AIM: To assess the distribution of human leukocyte antigen (HLA)-DQ2 and -DQ8 in Iranian celiac disease (CD) patients and compare them to healthy Iranian controls.

METHODS: To predict the HLA-DQA1 and -DQB1 genes, we used six previously reported HLA-tagging single nucleotide polymorphism to determine HLA genotypes in 59 Iranian patients with ‘biopsy-confirmed’ CD and in 151 healthy Iranian individuals. To test the transferability of the method, 50 cases and controls were also typed using a commercial kit that identifies individual carriers of DQ2, DQ7 and DQ8 alleles.

RESULTS: In this pilot study 97% of CD cases (n = 57) and 58% of controls (n = 87) were carriers of HLA-DQ2 and/or HLA-DQ8 heterodimers, either in the homozygous or heterozygous state. The HLA-DQ pattern of these 57 CD patients: heterozygous DQ2.2 (n = 14) and homozygous DQ2.2 (n = 1), heterozygous DQ2.5 (n = 2), heterozygous DQ8 (n = 13) and homozygous DQ8 (n = 2). Two CD patients were negative for both DQ2 and DQ8 (3%).

CONCLUSION: The prevalence of DQ8 in our CD population was higher than that reported in other populations (25.4%). As reported in other populations, our results underline the primary importance of HLA-DQ alleles in the Iranian population’s susceptibility to CD.

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Key words: Human leukocyte antigen typing; Validation; Susceptibility; Celiac disease; Iran

Core tip: We describe, for the first time, the distribution of human leukocyte antigen (HLA)-DQ2/DQ8 alleles in Iranian celiac disease patients compared to healthy Iranian controls. To assess this distribution we applied a single nucleotide polymorphism-based approach, which
was developed in European (Caucasian) study samples. We also demonstrate the transferability of such an approach to the Iranian population. Our results underline the primary importance of HLA-DQ alleles in the Iranian population’s susceptibility to celiac disease.


**INTRODUCTION**

Celiac disease (CD) is characterized by malabsorption of nutrients in the small intestine after ingestion of wheat gluten or related proteins from rye and barley. The disease is characterized by villous atrophy of the small intestinal mucosa. With adherence to a strict gluten-free diet, most CD patients show prompt clinical and histological improvement, with relapse of the symptoms if gluten is re-introduced[1-3]. Similar to Western studies, a high prevalence of CD has been reported in Iranian general population (about 1%)[4].

Many studies reflect the importance of genetic factors in the pathogenesis of CD[5]. A recent study by Anderson et al[6] suggested that a combination of human leukocyte antigen (HLA) typing and confirmatory serology could decrease the number of unnecessary endoscopies.

The HLA-DQ2 heterodimer, which is coded by alleles DQA1*05 and DQB1*02, is present in the vast majority of CD patients including approximately 95% of CD patients of Northern-European descent[7]. The most important risk factor for CD is the DQ2.5 haplotype[8]. Alpha and beta chains of this heterodimer are encoded together in cis (DQA1*05 and DQB1*02) on a DRB1*03 haplotype. Other DQ heterodimers that are encoded in trans on DR7 haplotypes are related to the DQ2.2 haplotype (DQA1*0201/DQB1*0202)[5-13]. Those CD patients who do not carry the DQ2 heterodimer, and are encoded by the DR4 haplotype, carry HLA-DQ8 (α*0301, β1*0302)[9]. HLA-DQ2 is common in Europeans and is expressed in 25%-30% of the healthy European population. Most of the CD patients who do not carry either DQ2.5 or DQ8, carry HLA-DQ7, with reported prevalences of 22.1% and 25%, respectively[14-17] (Figure 1). These studies were performed in healthy populations in different parts of the country and found considerable similarities in the distribution of HLA class II haplotypes with European countries. However, Iranian CD patients have never been studied for HLA.

Recently, Monsuur et al[18] described an HLA-tagging single nucleotide polymorphism (SNP) method for detecting the HLA risk alleles for CD. Using six SNPs, HLA genotyping for specific CD genotypes could be performed in a high-throughput mode. The results of Monsuur et al[18] and Koskinen et al[19] showed that the sensitivity and specificity of this test in recognizing DQ2.2, DQ2.5, DQ7, and DQ8 haplotypes was > 99% in the Dutch population, and > 98% in the United Kingdom, Spanish, Finnish, Hungarian, and Italian populations.

The main aim of this study was to provide new information on HLA-DQ associations with CD in the Iranian patients, which has never been investigated before, by using the tagging SNP method.

**MATERIALS AND METHODS**

**Patients**

A total of 59 CD patients (21 males and 38 females, median age 30.5 years, range 7-67 years) were included: 12 patients from East Iran (Zahedan Province, Baloch ethnicity), 13 from North Iran (Mashhad Province, Fars), 10 from West Iran (Lorestan and Kurdistan Provinces, Lour and Kurd ethnic groups), and 24 patients from Tehran, in the center of Iran (Fars). All patients had positive TGA and/or EMA antibodies and histology according to the Rostami-Marsh classification (Marsh I-IIIc)[20].

**Controls**

A total of 151 healthy controls (78 females and 73 males, median age 32.7 years, range 5-83 years) were selected from those who were negative for CD serological screening in the study areas (25 from Zahedan Province, 30 from Mashhad, 26 from Lorestan and Kurdistan provinces, and 70 from Tehran) and matched by age and sex. None of them had a personal or family history of cancer or autoimmune diseases. The study was approved by the ethical committees of the Gastroenterology and Liver Diseases Research Centers, Shahid Beheshti University of Medical Sciences, Tehran, and all the participants (or their parents/guardians) were informed about the study according to the study protocol and gave their written informed consent.

**HLA typing**

DNA was extracted using the phenol chloroform method[21]. The six HLA-tagging SNPs reported by Monsuur et al[18] were genotyped using 5 ng of DNA from the Iranian participants, and using TaqMan chemistry and custom assays from Applied Biosystems (ABI, Foster City, CA).
including DQ2.2 (rs2395182 and rs7775228 SNPs for DQ2.2, and rs4713586 SNP to exclude DQ4 from the DQ2.2 group), and SNPs rs2187668 (DQ2.5), rs4639334 (DQ7), and rs7454108 (DQ8). DNA was genotyped using a standard protocol provided by Applied Biosystems. The PCR assays and allelic discrimination were run using an ABI PRISM 7900HT Sequence Detection System (SDS) machine. All individuals were run on the same 384-well plate to avoid biased results due to technical issues. The data was analyzed using SDS program 2.3 (Applied Biosystems).

Validation
The HLA alleles for 20 CD cases and 30 controls were also typed using a commercial kit (BAG, Germany) which is commonly used in general diagnostic laboratories. The PCR assays and allelic discrimination were run using an ABI PRISM 7900HT Sequence Detection System (SDS) machine. All individuals were run on the same 384-well plate to avoid biased results due to technical issues. The data was analyzed using SDS program 2.3 (Applied Biosystems).

RESULTS
Testing the tag SNPs
We first evaluated the 59 CD patients and 151 controls for prediction of related HLA genotypes by TaqMan DQ7. We could thus distinguish DQ2.5-positive individuals from those who have DQ2.2.

Analysis
For the prediction of HLA alleles, we inferred the DQ types from the tag SNPs according to the method described by Monsuur et al.[13]. Only individuals with complete histology and serology data were included in this study (59 cases). The statistical analysis was performed using the $F$-test. The correlation between HLA risk alleles and Marsh classification was also investigated. A $P$-value less than 0.05 was considered statistically significant. Power calculations were performed using the Quanto program (http://hydra.usc.edu/gxe/) assuming allele frequencies of 0.15-0.30 and an odds ratio of 6.
SNPs. We observed that 83.03% of cases and 35.09% of controls were carriers of an HLA-DQ2 heterodimer, either in homozygous or heterozygous state. The patterns of the specific HLA-DQ haplotypes in the CD patients were as follows: 25.4% of CD patients were heterozygous DQ2.2 including DQ2.2/DQ2.5 compound heterozygosity, 1.7% of CD patients were homozygous DQ2.2/DQ2.2, 56% of CD patients were heterozygous DQ2.5 including DQ2.5/DQ8 compound heterozygosity, and 13.5% of CD patients were homozygous DQ2.5/DQ2.5 heterozygosity. A DQ2.2-negative genotype was seen in 66 controls and two CD cases. A DQ2.5-negative genotype was seen in 96.7% of controls. A DQ2.5/DQ8-negative genotype was seen in 71.2% of cases, 52.3% of controls; and high risk, which were homozygous for DQ2.2 and DQ8, or heterozygous for DQ8, DQ2.5 or DQ2.2 (71.2% of cases, 52.3% of controls). A DQ7/DQ7 genotype was seen in 3.4% of cases, 43.7% of controls; intermediate risk, which were homozygous for DQ2.2 and DQ8, or heterozygous for DQ8, DQ2.5 or DQ2.2 (71.2% of cases, 52.3% of controls); and high risk, which were homozygous DQ2.5/DQ2.5/DQ2.2 haplotypes are unknown (DQX).

**Risk groups**

Based on the outcome of the HLA-DQ2/DQ8 prediction using tagging SNPs, we divided the Iranian population into three risk groups: low risk, which were DQ2/DQ8-negative (3.4% of cases, 43.7% of controls); intermediate risk, which were homozygous for DQ2.2 and DQ8, or heterozygous for DQ8, DQ2.5 or DQ2.2 (71.2% of cases, 52.3% of controls); and high risk, which were homozygous DQ2.5/DQ2.5/DQ2.2 (25.4% of cases, 4% of controls) (Figure 2). The differences were statistically significant for all the risk groups when comparing cases to controls (P < 0.05). We also confirmed that CD patients carry more HLA risk alleles than healthy controls and this difference was statistically significant for the DQ2.5 haplotype distribution between cases and controls (P = 0.0001).

**Ethnic heterogeneity**

We included individuals from four areas with different ethnicities in Iran but did not find any statistical difference in the distribution of HLA-DQ2 and HLA-DQ7 genotypes in either the case or control groups (P > 0.05) (data not shown).

**Marsh classification**

Fourteen patients with Marsh I histology and 12 with Marsh II were compared to 33 patients with Marsh III (including 14 Marsh IIIa, 7 Marsh IIIb and 13 Marsh IIIc) in relation to their HLA-DQ haplotypes. Table 3 shows the distribution of HLA haplotypes according to the Rostami-Marsh classification. Of the 25 patients demonstrating only minor small bowel mucosal changes (i.e.,

Table 1  Frequency of human leukocyte antigen haplotypes in Iranian cases and controls n (%)

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ2.2/DQ2.2</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>0.28</td>
</tr>
<tr>
<td>DQ2.2/DQ7</td>
<td>4 (6.8)</td>
<td>8 (5.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>DQ2.2/DQX</td>
<td>3 (5.08)</td>
<td>22 (14.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>DQ2.5/DQ2.2</td>
<td>7 (11.9)</td>
<td>5 (3.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>DQ2.5/DQ2.5</td>
<td>8 (13.6)</td>
<td>1 (0.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DQ2.5/DQ7</td>
<td>3 (5.08)</td>
<td>5 (3.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>DQ2.5/DQ8</td>
<td>7 (11.9)</td>
<td>5 (3.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>DQ2.5/DQX</td>
<td>16 (27.1)</td>
<td>10 (6.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DQ7/DQ7</td>
<td>0 (0)</td>
<td>17 (11.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>DQ7/DQX</td>
<td>0 (0)</td>
<td>17 (11.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>DQ8/DQ2.2</td>
<td>0 (0)</td>
<td>8 (5.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>DQ8/DQ7</td>
<td>1 (1.7)</td>
<td>9 (6)</td>
<td>0.29</td>
</tr>
<tr>
<td>DQ8/DQ8</td>
<td>2 (3.3)</td>
<td>4 (2.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>DQ8/DQX</td>
<td>5 (8.5)</td>
<td>8 (5.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>DX2/DQX</td>
<td>2 (3.3)</td>
<td>32 (21.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>59 (100)</td>
<td>151 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Validation results in the Iranian population using the BAG kit compared to the tag-SNP method

<table>
<thead>
<tr>
<th>Tag SNP</th>
<th>Celiac patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>59</td>
<td>151</td>
</tr>
<tr>
<td>DQ2.2 Sensitivity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>DQ2.5 Sensitivity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.8%</td>
<td>96.7%</td>
</tr>
<tr>
<td>DQ8 Sensitivity</td>
<td>86.4%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>86.4%</td>
<td>97.1%</td>
</tr>
</tbody>
</table>
Marsh I and II histology), two (3.4%) were negative for DQ2 and DQ8. Our result thus confirmed that patients with Marsh I or II histology carry low HLA risk alleles, such as HLA-DQ8. No statistically significant correlations were detected between the corresponded haplotypes and the different Marsh classifications.

**DISCUSSION**

Several epidemiological studies indicated that CD is a common disorder in the Iranian population with a prevalence of 1%[20-22], but there are no data on the frequency of HLA-related CD-predisposing alleles. We examined the frequency of the HLA-DQA1 and HLA-DQB1 haplotypes in Iranian CD patients and compared them to a matched, healthy control group.

A simple PCR-based SNP approach has been developed for large-scale population screening[13] and this method can be applied to different Caucasian populations[23]. A major advantage of this PCR-based SNP method is its ability to distinguish HLA-DQ2 and HLA-DQ8 homozygotes and heterozygotes which, in turn, translates into differences in the risk carried for CD. We tested the transferability of this method to the Iranian population and found that the sensitivity and specificity to detect the CD risk alleles was 100% and 97% for HLA-DQ2 and HLA-DQ7, respectively, but slightly lower for HLA-DQ8 (86.4%).

The lower sensitivity and specificity for HLA-DQ8 in the Iranian population might be attributable to differences in the patterns of linkage disequilibrium blocks in Iranians and Europeans. The frequency of the HLA haplotypes in Iran is not necessarily different from Europeans, but the tagging SNP method might not be the ideal test to establish the frequency of CD-associated HLA-DQ8 haplotypes in this population.

The false positives or false negatives observed with the tagging SNP method may be due to the presence of rare alleles (DQX) either in heterozygous or homozygous state that cannot be detected by the BAG kit.

As reported for other populations[23-25], the most frequent haplotype in Iranian CD patients was HLA-DQ2.5 (69.5%) and its frequency is very similar to that seen in European CD populations.

Surprisingly, in contrast to the low prevalence of HLA-DQ8 in CD population reported in the literature (0.6% in Cameroon, 2% in Italy, 2.3% in Hungary, 4.2% in United States, 6.4% in Finland and 7.6% in Japan),[12,26] we found a higher prevalence (25.4%) of this genotype in the Iranian CD population. Our result is comparable with those presented by Catassi et al[27] in 2009 for Turks (22%), North American Indians (25.3%), Mexicans (28.3%) and Bushmen (ethnic groups in Southern Africa) (30%).

Karell et al[28] and Polvi et al[29] suggested that only a small number of CD patients (6%) carry neither DQ2 nor DQ8. Our study supports these figures, as we only found two CD patients (3.4%) who were DQ2-DQ8-negative.

Several studies have shown that individuals homozygous for HLA-DQ2.5 or heterozygous for HLA-DQ2.5/DQ2.2 genotypes have an increased risk for CD compared to those homozygous for HLA-DQ2.2 or heterozygous for HLA-DQ2.5 or HLA-DQ2.2/DQ8. Similarly, our results show that 25.4% of cases lie in the high risk group for CD compared to 3.4% in the low risk group. The frequencies of intermediate risk and high risk groups were, as expected, higher in cases than controls (Figure 2).

The frequency of DQ8/DQ2.2 in the cases was zero but this number may be less reliable. This may be due to differences in the patterns of linkage disequilibrium blocks in Iranians or may result from low concentrations of DNA samples (the concentration of the samples was reduced when they were sent to the UMCG for genetic analysis). We concluded that DQ2 worked well, but DQ8 needs to be interpreted more carefully when identified using tagging SNPs.

In conclusion, this pilot study has provided information on the genetic background of CD in Iranians. This should prove useful to other researchers and to future

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**Table 3 Distribution of human leukocyte antigen haplotypes according to the degrees of mucosal changes**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Rostami-Mash classification</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA- DQ2.2/DQ2.2</td>
<td>Marsh I</td>
<td>Marsh II</td>
<td>Marsh III</td>
</tr>
<tr>
<td>DQ2.2/DQ7</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>DQ2.2/DQX</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DQ2.5/DQ2.2</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DQ2.5/DQ2.5</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>DQ2.5/DQ8</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DQ2.5/DQX</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>DQ8/DQ2</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>DQ8/DQ7</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>DQ8/DQ8</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>DQ8/DQX</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>DQX/DQX</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>13</td>
<td>34</td>
</tr>
</tbody>
</table>
work on this disease. Despite our small cohort, the data we present offer a first step towards defining the genetic structure of HLA in the Iranian population with CD and provide information that can be used in family screening. In addition, our data suggest that the Iranian population, as a non-European Caucasian population, does share certain HLA class II genetic components with the CD populations of European ancestry. We found that Iranians are most similar to non-European Caucasian CD patients, given their increased frequency of HLA-DQ8 carriers. Further works, with larger sample sizes, on HLA polymorphisms among people living in different parts of Iran will provide more detailed information about the genetic background of the Iranian population and its relationship to other ethnic populations in the world.

ACKNOWLEDGMENTS

This work was performed within the framework of an agreement between the University Medical Center Groningen (UMCG, Groningen, the Netherlands) and the Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran (Iran). It was financed by the UMCG, by grants from the Dutch Celiac Disease Consortium (an innovative cluster approved by the Netherlands Genomics Initiative and partly funded by the Dutch Government (grant BS1K03009 to C.W.), the Netherlands Organization for Scientific Research (NWO-VICI grant 918.66.620 to C.W.), the Dutch Digestive Disease Foundation (MLDS W011-30 to C.W.), and the Iran National Science Foundation (INSF). We sincerely thank R. Booij and S. Medema-Jankipersadsing (UMCG) for their help in genotyping, Dr. M.A. Pourhosseingholi for his assistance in statistical analysis and J.L. Senior and K. Mc Intyre (UMCG) for editing the manuscript. This paper resulted from part of the PhD research of Mohammad Rostami-Nejad.

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