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Full Length Research Paper

HLA-DQA1 and –DQB1 genotyping in individuals with family history of gastritis

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The objective was to study HLA-DQA1 and HLA-DQB1 genotyping in individuals (patients and controls) with family history of gastritis. This study was carried out in College of Medicine, University of Basrah. HLA-DQA1 and HLA-DQB1 genotyping was done in College of Medicine, University of Manitoba, and Winnpeg, Canada during the period from 17th of April 2009 to 15th of July 2010. A total of 100 patients (41 males and 59 females) and a total of 30 controls (18 males and 12 females) were included in this study. A significant decreased frequency of DQA1*0201 allele was found in individuals (patients + controls) with family history of gastritis with a strong association (odds ratio = 4.57), as compared with individuals without family history of gastritis. Significant increased alleles frequencies of DQA1*0402 and DQB1*0402 were found in individuals with family history of gastritis, but with weak association (odds ratios, 0.16 and 0.20 respectively), as compared with individuals without family history of gastritis.

Key words: HLA-DQA1, HLA-DQB1, genotyping and gastritis.

INTRODUCTION

Human leukocyte antigens (HLA) are an inherent system of alloantigens, which are the products of genes of the major histocompatibility complex (MHC). These genes span a region of approximately 4 centimorgans on the short arm of human chromosome 6 at band p21.3 and encode the HLA class I and class II antigens, which play a central role in cell-to-cell-interaction in the immune system (Conrad et al., 2006). They encode peptides involved in host immune response, also they are important in tissue transplantation and are associated with a variety of infectious, autoimmune, and inflammatory diseases (Gregersen et al., 2006; Nair et al., 2006). Moreover, the HLA loci display an unprecedented degree of diversity and the distribution of HLA alleles and haplotypes among different populations is considerably variable (Shao et al., 2004; Blomhoff et al., 2006). The expression of particular HLA alleles may be associated with the susceptibility or resistance to some diseases (Wang et al., 2006). Heterozygosity within the MHC genomic region provides the immune system with a selective advantage of pathogens (Fu et al., 2003; Kumar et al., 2007). *Helicobacter pylori* infection is in addition to being the main etiologic agent for chronic gastritis, a major cause of peptic ulcer and gastric cancer (Suerbaum and Michetti, 2002). Many studies performed in Iraq about bacteriological and immunological aspects of *H. pylori* (Al-Janabi, 1992; Al-Jalili, 1996; Al-Baldawi, 2001; Al-Dhaher, 2001; Al-Saimary, 2008), but no study was performed yet on HLA genotyping, hence, the results of the present study is compared with studies done in other countries. In developing countries, prevalence of *H. pylori* infection is > 80% among middle-aged adults, whereas in developed countries prevalence ranges from 20 to 50%. Approximately 10 to 15% of infected individuals will develop peptic disease and 3% a gastric neoplasm (Torres et al., 2005). Therefore, *H. pylori* infection is a necessary but not a sufficient cause of severe forms of gastric disease. *H. pylori* induce a host

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Table 1. Frequencies of males and females (Patients + controls) with and without family history of gastritis.

Gender	With family history of gastritis {N= 15 (%)}	Without family history of gastritis {N=85 (%)}	Total N = 100
Male	5 (10.64)	42 (89.36)	47
Female	10 (18.87)	43 (81.13)	53

(χ^2 = 1.32; P = NS; OR= 0.51; 95% CI = 0.16 to 1.62).

immune response, but the persistence of the infection suggests that the response is not effective in eliminating the infection. Furthermore, multiple lines of evidence suggest that the immune response contributes to the pathogenesis associated with the infection. As a result, the immune response induced by *H. pylori* is a subject of continuous study that has encouraged numerous questions (Azem et al., 2006). The inability of the host response to clear infections with *H. pylori* could reflect down-regulatory mechanisms that limit the resulting immune responses to prevent harmful inflammation as a means to protect the host (Yoshikawa and Naito, 2000).

METHODS

A total of 100 patients (41 males and 59 females with age groups from (15 to 66) years, with various gastritis symptoms attending endoscopy unit at Al-Sadder Teaching Hospital in Basrah and a total of 30 controls (18 males and 12 females), with age groups from (15 to 61) years, without any symptoms of gastritis were included in the present study. Blood samples were drawn from gastritis patients and subjected to HLA-DQ genotyping. The study was carried out during the period from (17th of April 2009 to 15th of July, 2010). DNA was isolated from the blood samples, using wizard genomic DNA purification Kit, Promega Corporation, USA; Protocol (Beutler et al., 1990).

HLA-DQA1 and –DQB1 genotyping

HLA-DQA1 and –DQB1 genotyping protocol was done according to Sequence-Based-Typing (SBT), which had been developed in National Microbiology Laboratories (NML), Winnipeg, Canada (Luo et al., 1999). All the steps of HLA-DQA1 and –DQB1 genotyping were done under supervision of Dr. Ma Luo in Medical Microbiology Laboratory, College of Medicine, and University of Manitoba and in Dr. Ma Luo Laboratory in National Microbiology Laboratories (NML). Agarose Gel Electrophoresis (Fisher-Biotech FBSB-710; Bio RAD).

PCR amplification of HLA-DQA1 and –DQB1 gene

The PCR amplification of HLA-DQA1 and –DQB1 gene was done in Medical Microbiology Laboratories in College of Medicine, Manitoba University, Winnipeg, Canada.

DNA purification

The purification of the amplified HLA-DQA1 and –DQB1 gene was done in National Microbiology Laboratories (NML), in Dr. Ma Luo Laboratory, College of Medicine, Manitoba University, Winnipeg, Canada.

Three methods had been used for purification of the amplified PCR DNA samples:

1. DNA purification by using vacuum.
2. DNA purification by using GenElute™ PCR clean-Up Kit (Sigma-Aldrich, Inc. USA). GenElute™ PCR Clean-Up Kit.
3. Purification in DNA core section in NML (NML, Canada).

The amplified PCR DNA was purified in DNA core laboratory in National Microbiology Laboratories (NML), Winnipeg, Canada.

Sequencing–PCR

Sequencing–PCR was done in National Microbiology Laboratories (NML), under supervision of Dr. Ma Luo.

Ethanol precipitation

Ethanol precipitation was done under supervision of Dr. Ma Luo in National Microbiology Laboratories (NML), College of Medicine, Manitoba University, Winnipeg, Canada.

Sequencing-using the (3100 Genetic Analyzer, USA)

HLA-DQA1 and –DQB1 genotyping protocol was done according to Sequence-Based-Typing (SBT), which had been developed in National Microbiology Laboratories (NML), Winnipeg, Canada (Luo et al., 1999).

Statistical analysis

For qualitative variables, frequency data were summarized as percentage. Statistical significant of the differences between two groups was tested by Pearson Chi-square (χ^2) with Yates' continuity correction. Risk was estimated using odds ratio (OR) and 95% confidence interval (95% CI). P-value was determined by Fisher's exact test, P- value of (< 0.05) was considered statistically significant. Data were analyzed using SPSS program for window (Version 10).

RESULTS

Distribution of individuals (patients+controls) with family history of gastritis according to gender

As shown in Table 1, out of 47 males, 5 (10.64%) were with family history of gastritis and 42 (89.36%) were without

Table 2. Distribution of individuals (patients + controls) with and without family history of gastritis according to age groups.

Age group	With family history of gastritis {N= 15 (%)}	Without family history of gastritis {N=85 (%)}	Total N = 100
15 > 45	11 (15.49)	60 (84.51)	71
> 45	4 (13.79)	25 (86.21)	29

(χ^2 = 0.05; P=NS; OR= 1.15; 95% CI = 0.33 to 3.94).

Table 3. HLA-DQA1 Genotype frequency in individuals with family history of gastritis and without family history of gastritis.

HLA-DQA1 allele	Individuals with family history of gastritis		Individuals without family history of gastritis		X^2	P	OR	95% CI
	N = 14	%	N = 73	%				
010101/010102/010401/010402/0105	2	14.28	12	16.44	0.04	NS	1.18	0.23-5.96
010201/010202/010203/010204	5	35.71	21	28.77	0.27	NS	0.73	0.22-2.43
0103	3	21.42	13	17.81	0.10	NS	0.79	0.19-3.26
0201	1	7.14	19	26.03	5.37	<0.05	4.57	0.56-37.36
030101/0302/0303	3	21.42	17	23.29	0.02	NS	1.11	0.28-4.46
040101/040102/0402/0404	3	21.42	3	4.11	5.49	<0.05	0.16	0.03-0.88
050101/0503/0505/0506/0507/0508/ 0509	9	64.28	45	61.64	0.89	NS	0.89	0.27-2.94

family history of gastritis. Also Table 1 indicated that, out of 53 females, 10 (18.87%) were with family history of gastritis and 43 (81.13%) were without family history of gastritis. These results showed no significant differences between males and females with and without family history of gastritis (χ^2 = 1.32; P = NS; OR = 0.51; 95% CI = 0.16 to 1.62).

Distribution of individuals (patients+controls) with family history of gastritis according to age groups

Results shown in Table 2, indicated that out of 71 individuals from 15> 45 age group, 11 (15.49%) were with family history of gastritis and 60 (84.51%) were without family history of gastritis. Also results in Table 2 showed that, out of 29 individuals from > 45 age group, 4 (13.79%) were with family history of gastritis and 25 (86.21%) were without family history of gastritis. These results showed no significant differences between individuals with or without family history of gastritis from these two age groups (χ^2 = 0.05; P=NS; OR = 1.15; 95% CI = 0.33 to 3.94).

Genotype frequencies of HLA-DQ of individuals (patients + controls) with and without family history of gastritis

Genotyping of HLA-DQA1 was studied in individuals with family history of gastritis and compared with individuals without family history of gastritis (patients + controls). Results shown in Table 3, indicated that HLA-DQA1*0201 allele was present in 1 out of 14 individuals with family history of gastritis and in 19 out of 73 individuals without family history of gastritis, with allele frequencies of 7.14 and 26.03 respectively. The decreased frequency of HLA-DQA1*0201 allele in individual with family history of gastritis was statistically significant and showed very strong association (χ^2 = 5.37, P< 0.05, OR = 4.57, 95% CI = 0.56 to 37.46) as compared with individuals without family history of gastritis. Results shown in Table 3 also indicated that HLA-DQA1*0402 allele was present in 3 out of 14

Table 4. HLA-DQB1 Genotype frequencies of individuals with and without family history of gastritis.

HLA-DQB1 allele	Individuals with family history of gastritis		Individuals without family history of gastritis		X^2	P	OR	95% CI
	N = 14	%	N = 79	%				
020101/0202/0204	7	50.00	39	49.37	0.01	NS	0.98	0.31-3.04
030101/030104/0309/0321/0322/0324/030302	5	35.00	32	40.37	0.11	NS	1.23	0.38-3.99
030201	1	7.14	11	13.92	0.49	NS	2.10	0.30-17.72
030302	0	0.00	1	1.27	0.94	NS	1.01	0.99-1.04
0402	3	21.43	4	5.06	4.58	<0.05	0.20	0.04-0.99
050101	1	7.14	11	13.92	0.49	NS	2.10	0.30-17.72
050201	2	14.29	12	15.19	0.01	NS	1.08	0.21-5.42
050301	0	0.00	1	1.27	0.18	NS	1.01	0.99-1.04
060101/060103	1	7.14	6	7.59	0.01	NS	1.07	0.12-9.62
060201	2	14.29	3	3.80	2.57	NS	0.24	0.04-1.57
060301/060401	0	0.00	8	10.13	1.55	NS	1.11	1.03-1.20
060401/0634	1	7.14	6	7.59	0.01	NS	1.07	0.12-9.62
060801	1	7.14	0	0.00	5.70	NS	0.93	0.80-1.07
0609	0	0.00	1	0.00	0.18	NS	1.01	0.99-0.85

individuals with family history of gastritis and in 3 out of 73 individuals without family history of gastritis with frequencies of 21.42 and 4.11 respectively. The increased allele frequency of HLA-DQA1*0402 allele in individuals with family history of gastritis was statistically significant but with week association ($\chi^2 = 5.49$, $P < 0.05$, OR = 0.16, 95% CI = 0.03 to 0.88) when compared with individuals without family history of gastritis. Genotype of HLA-DQB1 was studied in 14 individuals with family history of gastritis and in 79 individuals without family history of gastritis. Results shown in Table 4 indicated that HLA-DQB1*0402 allele was present in 3 out of 14 individuals with family history of gastritis and in 4 out of 79 individuals without family history of gastritis with frequencies of 21.43 and 5.06 respectively. The increased frequency of HLA-DQB1*0402 allele in individuals with family history of gastritis was statistically significant but with week association ($\chi^2 = 4.58$, $P < 0.05$, OR = 0.20, 95% CI = 0.04 to 0.99) when compared with individuals without family history of gastritis.

Homozygosity of HLA-DQ in individuals (patients + controls) with and without family history of gastritis

HLA-DQ homozygosity was studied in individuals with and without family history of gastritis. Results shown in Table 5, indicated that for HLA-DQA1, out of 14 individuals with family history of gastritis, 2 were homozygous in one or both loci and 16 out of 73 individuals without family history of gastritis, were homozygous in one or both loci, with frequencies of 14.29 and 21.92 respectively. No significant differences were observed in frequencies of homozygous HLA-DQA1 genotype between individuals with and without family history of gastritis ($\chi^2 = 0.42$, P = NS, OR = 1.68, 95% CI = 0.34 to 8.31) (Table 5). For HLA-DQB1, 4 out of 14 individuals with family history of gastritis were homozygous in one or both loci, and 18 out of 79 individuals without family history of gastritis, were homozygous in one or both loci, with frequencies of 28.57 and 22.78 respectively. No significant differences were observed in frequencies of homozygous HLA-DQB1 genotype between individuals with and without family history of gastritis ($\chi^2 = 0.22$, P = NS, OR = 0.47, 95% CI = 0.21 to 2.64) (Table 5). For HLA- (DQA1 + DQB1), 3 out of 13 individuals with family history of gastritis were homozygous in one or both loci, and 22 out of 69 individuals without family history of gastritis, were homozygous in one or both loci, with frequencies of 23.08 and 31.88 respectively. No significant differences were observed in frequencies of homozygous HLA-(DQA1+DQB1) genotypes between individuals with and without family history of gastritis ($\chi^2 = 0.40$, P = NS, OR = 1.56, 95% CI = 0.39 to 6.24) (Table 5).

DISCUSSION

Many studies reported that there is correlation between gastritis and family history of gastritis (Peterson and Graham, 1998; Brown, 2000; Al-Baldawi, 2001). In the present study, HLA-DQA1 and –DQB1 distribution was studied in individuals with family history of gastritis.

Table 5. Homozygousity of HLA-DQ in individuals with and without family history of gastritis.

HLA-DQ Homozygousity*		Cases			
		With family history of gastritis		Without family history of gastritis	
		No	%	No	%
DQA1**	Homozygous	2	14.29	16	21.92
	Heterozygous	12	85.71	57	70.08
	Total	14	100	73	100
DQB1***	Homozygous	4	28.57	18	22.78
	Heterozygous	10	71.43	61	77.22
	Total	14	100	79	100
**** DQA1+DQB1	Homozygous	3	23.08	22	31.88
	Heterozygous	10	76.92	47	68.12
	Total	13	100	69	100

* Homozygous at one or both loci, ** $\chi^2 = 0.42$, P = NS, OR= 1.68, 95% CI = 0.34-8.31, *** $\chi^2 = 0.22$, P =NS, OR= 0.74, 95% CI = 0.21-2.64, **** $\chi^2 = 0.40$, P =NS, OR = 1.56, 95% CI = 0.39-6.24.

Distribution of individuals (patients + controls) with family history of gastritis was studied according to gender. Results showed no significant differences between males and females with and without family history of gastritis (χ^2 = 1.32; P = NS; OR = 0.51; 95% CI = 0.16 to 1.62) (Table 1). Distribution of individuals (patients + controls) with family history of gastritis was studied according to age groups. Results showed no significant differences between individuals with or without family history of gastritis from (15 > 45) and (> 45) age groups (χ^2 = 0.05; P = NS; OR = 1.15; 95% CI = 0.33 to 3.94) (Table 2). Genotype frequency of HLA-DQ was studied in individuals (patients + controls) with and without family history of gastritis. Genotyping of HLA-DQA1 was studied in individuals with family history of gastritis and compared with individuals without family history of gastritis (patients + controls). Results shown in Table 3, indicated that HLA-DQA1*0201 allele was present in 1 out of 14 individuals with family history of gastritis and in 19 out of 73 individuals without family history of gastritis, with allele frequencies of 7.14 and 26.03 respectively. The decreased frequency of HLA-DQA1*0201 allele in individual with family history of gastritis was statistically significant and showed very strong association (χ^2 = 5.37, P< 0.05, OR = 4.57, 95% CI = 0.56 to 37.46) as compared with individuals without family history of gastritis. Results shown in Table 3 also indicated that HLA-DQA1*0402 allele was present in 3 out of 14 individuals with family history of gastritis and in 3 out of 73 individuals without family history of gastritis with frequencies of 21.42 and 4.11 respectively. The increased allele frequency of HLA-DQA1*0402 allele in individuals with family history of gastritis was statistically significant but with week association (χ^2 = 5.49, P < 0.05, OR = 0.16, 95% CI = 0.03 to 0.88) when compared with individuals without family history of gastritis. Genotype of HLA-DQB1 was studied in 14 individuals with family history of gastritis and in 79 individuals without family history of gastritis. Results shown in Table 4 indicated that HLA-DQB1*0402 allele was present in 3 out of 14 individuals with family history of gastritis and in 4 out of 79 individuals without family history of gastritis with frequencies of 21.43 and 5.06 respectively. The increased frequency of HLA-DQB1*0402 allele in individuals with family history of gastritis was statistically significant but with week association (X^2 = 4.58, P < 0.05, OR = 0.20, 95% CI = 0.04 to 0.99) when compared with individuals without family history of gastritis. These results agree with a study performed by Herrera-Goepfert et al. (2006) who found a significant increased frequency of HLA-DQB1*0401 allele in *H. pylori* -positive patients with chronic gastritis when compared with healthy subjects (19 vs 0%, P = 1 × 10-7, odds ratio (OR) = 4.96; 95% confidence interval (95% CI), 3.87 to 6.35). The HLADQB1*0401 allele was found to be associated with atrophic gastritis in *H. pylori*-infected patients. HLA-DQ homozygosity was studied in individuals with and without family history of gastritis. Results shown in Table 5 indicated that no significant differences were observed in frequencies of homozygous HLA-DQ genotype between individuals with and without family history of gastritis.

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الأهداف: لدراسة نظائر الجينات DQA1 وDQB1 في الافراد (المرضى + الاصحاء) الذين لديهم تأريخ مرضي عائلي لالتهاب المعدة.
الطريقة: اجريت هذه الدراسة في كلية الطب، جامعة البصرة . وتمت دراسة نظائر الجينات DQA1 و DQB1 في كلية الطب، جامعة مانيتوبا في مدينة وينيبغ/ كندا، خلال الفترة مابين ابريل 2009م الى يوليو 2010 م . من مجموع 100مريض (41ذكر و 59 انثى) ومن مجموع 30 من الاصحاء (18 ذكر و 12 انثى) تم شمولهم في هذه الدراسة.
النتائج و الإستنتاجات: وجدت نسبة تكرار واطئة ذات مغزى ايجابي للنظير الجيني DQA1*0201 في الافراد (المرضى + الاصحاء) الذين لديهم تأريخ مرضي عائلي لالتهاب المعدة مع وجود علاقة قوية جدا (= odds ratio) 4.57 عند مقارنتهم بالافراد بدون تأريخ مرضي عائلي لالتهاب المعدة. وجدت نسبة تكرار عالية ذات مغزى ايجابي لنظائر الجينات DQA1*0402 و DQB1*0402 في الافراد (المرضى + الاصحاء) الذين لديهم تأريخ مرضي عائلي لالتهاب المعدة مع وجود علاقة ضعيفة (odds ratios, 0.16 and 0.20), على التوالي، عند مقارنتهم بالافراد بدون تأريخ مرضي عائلي لالتهاب المعدة.