Possible Association of HLA-DR and DQ Molecules with Colorectal Cancer in Iraqi Patients

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Fac Med Baghdad
2007; Vol. 49, No.3
ReceivedSep. 2006
Accepted Jan. 2007

Summary:

Background: *Human leukocyte antigen (HLA) is the most polymorphic genetic system in man. The genes of this region influence susceptibility to certain diseases.*
Objectives: *This study was established to shed light on the possible association of HLA class-II antigens and CRC patients, and to correlate the findings with both family history and tumor location.*
Patients and Methodes: *Microlymphocytotxicity assay has been used to assess HLA-typing of 150 blood samples of 100 CRC patients and 50 healthy normal control.*
Results: *An increased frequency of HLA-DR7 was observed for patients' group versus control group with P-value (<0.005), moreover, statistical analysis showed non significant correlation of HLA-DR7 with both family history of CRC and tumor location.*
Conclusion: *This finding demonstrate that HLA-DR7 might play a role in CRC susceptibility.*
Key words: *Colorectal cancer, HLA, Family history of CRC, Tumor location.*

Introduction:

The specific causes of CRC are still mysterious, nevertheless; environmental, genetic, familial factors found to play a crucial role in the development of this cancer (1). Cancer of the large bowel occurs three to four times more commonly in relatives of patients who have this cancer than in the general population, and this excess persists even if the clearly hereditary forms are excluded (2, 3).

Chatzipetrou and colleagues noted that the HLA-Ags play an important role in the immune response and in the predisposition mechanisms for different disease, including cancer (4). Recently Gainullina and colleagues denoted that determination of the HLA alleles may be one method for early diagnosis and prognosis of the colon and rectum carcinogenesis (5).

Few studies were available about the association of this cancer with class II HLA-Ags. However; Bidwell and Soong, who studied 61 Chinese patients with primary CRC, had noted an increased frequency of DR52 in both whites and blacks (6). Chatzipetrou and co-worker observed that in Greece patients with established CRC the frequency of HLA-DQ5 was significantly increased (3).

Patients and Methods:

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Patients:

The present study included 100 Arab, Iraqi CRC patients (42 females and 58 males; mean age 51.4 years, ranged between 21-81). Duke's classification and degree of differentiation are presented in Table-1, compared with 50 healthy age and sex were matched control group.

HLA-Typing:

Microlymphoctotoxicity assay has been applied for HLA-typing as described by Terasaki and McClelland (7) and modified by Dick, et al., and Bender (8, 9).

Statistical Analysis:

Univariate analysis has been applied for the data depending on logistic regression and the results were reported as odds ratio (ORs), which represented the increased or decreased risk for CRC.

Table-1: Degree of differentiation and stage

	Well Differentiated N=8	*Moderately Differentiated N=74*	*Poorly Differentiated N=18*
Duke's A	2	4	0
Duke's B	3	43	8
Duke's C	1	15	3
Duke's D	2	12	7

classification (Duke's A-D) of the tumor.

Results:

Tumors of the colon and rectum of 100 patients were localized according to Table-2, where 25

patients had the tumors in ascending colon, 6 in the transverse colon, 32 in the descending and sigmoid colon and 37 in the rectum.

Table-2:Localization of the CRC

Location	*NO*	*Female*	*Male*
Cecum, ascending colon	25	11	14
Transverse colon	6	1	5
Descending colon, sigmoid colon	32	13	19
Rectum	37	16	21

The frequencies of the distribution of class II HLA-Ags (%, OR, inverse OR, P, EF, PF) were shown in Tables (3 & 4) for CRC patients as compared with health control groups. A survey of the distribution of HLA-DR and HLA-DQ frequencies yielded no evident association between class II antigens and CRC patients, except for DR7 which presented higher frequency in CRC patients than control groups, with P-value (0.005).

Table-3: Antigens frequency of the HLA-DR (%, OR, inverse OR, P, EF, PF) of the CRC patients and healthy control.

HLA antigen	*Healthy control*		*Colorectal cancer cases*		*OR*	*Inverse OR*	*P*	*EF*	*PF*
	N	*%*	*N*	*%*					
HLA-DR									
1	4	8.0	3	3.0	0.4	2.8	NS	**	0.052
2	6	12	11	11.0	0.9	1.1	NS	**	0.011
3	10	20	18	18.0	0.9	1.1	NS	**	0.024
4	16	32.0	24	24.0	0.7	1.5	NS	**	0.105
5	2	4.0	4	4.0	1.0	**	NS	**	**
6	1	2	0	0.0	0.2	6.1	NS	**	**
7	10	20.0	44	44.0	3.1	**	0.005	0.300	**
8	3	6.0	2	2.0	0.3	3.1	NS	**	0.041
9	1	2.0	0	0.0	0.2	6.1	NS	**	**
10	5	10.0	8	8.0	0.8	1.3	NS	**	0.022
11	0	0.0	6	6.0	6.9	**	NS	0.051	**
13	1	2.0	1	1.0	0.5	2.0	NS	**	0.010
14	2	4.0	4	4.0	1.0	**	NS	**	**
15	3	6	4.0	0.7	1.5	**	NS	**	0.021
52	5	10.0	6	6.0	0.6	1.7	NS	**	0.043
53	3	6.0	4	4.0	0.7	1.5	NS	**	0.021
Blank	28		61						
Total	100		200						

Table-4: Antigens frequency of the HLA-DQ (%, OR, inverse OR, P, EF, PF) of the CRC patients and healthy control.

HLA antigen	*Healthy control*		*Colorectal cancer cases*		*OR*	*Inverse OR*	*P*	*EF*	*PF*
	N	*%*	*N*	*%*					
HLA-DQ									
1	13	26	26	26.0	1	**	NS	**	**
2	13	26.0	26	26.0	1.0	**	NS	**	**
3	10	20.0	18	18.0	0.9	1.1	NS	**	0.024
4	8	16.0	13	13.0	0.8	1.3	NS	**	0.034
Blank	56		117						
Total	100		200						

In regarding to correlation between the HLA-DR7 and patients with positive family history, the present study revealed a strong correlation between HLA-A28 and CRC patients with positive family history (Inverse OR= 5.1) but statistically not significant, Table (5).Moreover, the present results also showed no differences in the distribution of these specific antigens between colon and rectum, Table (6).

Table-5: Antigens frequency of the specific HLA-Ags in CRC patients according to family history.

	Family history of colorectal cancer						
	Negative		Positive				
HLA antigen	N	%	N	%	OR	Inverse OR	P
HLA-DR7							
Negative	47		9				
Positive	40	46.0	4	30.8	0.5	1.9	NS
Total	87		13				

Table-6: Antigens frequency of the specific HLA-Ags in CRC patients according to tumor location.

	Tumor location						
	Rectum		Colon				
HLA antigen	No.	%	No.	%	OR	Inverse OR	P
HLA-DR7							
Negative	22		34				
Positive	15	40.5	29	46.0	1.3	**	NS
Total	37		63				

Discussion:

The role of genetic factors in the etiology of CRC was documented in many decades ago. As a result, the investigative efforts were focused on the genetic markers of susceptibility to this disease. Moreover, the high familial incidence of CRC suggests the possibility of a linkage or an association of disease with MHC. Sivak and colleagues have reported a family study compatible with the linkage of adenocarcinoma of the colon with the MHC (10).

Our finding in this study was the higher expression of DR7 in patients which account for 44% versus 20% in healthy subjects, while other reported study proposed a positive association between DR52 and CRC in the Chinese patients (6).

The frequencies of HLA-DQ Ags were shown no differences in frequency of these antigens with CRC patients as compared with control groups, this result was in contrast to that reported by Chatzipetrou et al., in which there was a positive significant association between this cancer and HLA-DQ5(4).

No significant association between DR7 and those patients with positive family history of CRC patients was observed. This might, in part, result from the limited number of investigated patients. However; other study reported a strong positive association of HLA-DQ5 with a family history of CRC in Greece population (4).

In addition to negative association between DR7 and family history, there was a negative correlation with tumor location as well, this result was correspondent with previous results reported by Chatzipetrou et al.,(4).

Shortly, the current study denoted the role of DR7 as highly significant risk factors.

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