The HLA DPB1*02:01:02 and DQB1*05:02:01 alleles as possible risk factors for colorectal carcinoma in the Malaysian population

[1]Nor Adzimah Johdi*, [1]Sri Noraima Othman, [1]Zuraini Abd Razak, [2]Luqman Mazlan, [2]Ismail Sagap, [1]Rahman Jamal

[1]UKM Medical Molecular Biology Institute (UMBI); [2]Department of Surgery, Faculty of Medicine; Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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ABSTRACT

Many studies have shown that the immune response highly depends on the inheritance of specific HLA genes in promoting the generation of T cells for the elimination of pathogens. Loss or alteration of HLA antigen expression in tumor cells has been observed in a variety of human malignancies leading to immune escape or immune resistance. We investigated whether the inheritance of certain alleles of HLA class II genes confers susceptibility or resistance towards the development of colorectal carcinoma (CRC). Molecular typing of HLA DRB1, DQB1 and DPB1 alleles in 42 patients diagnosed with CRC and 50 ethnically matched healthy controls using the PCR-sequence based typing (PCR-SBT) was conducted. The HLA DPB1*02:01:02 was significantly higher in CRC patients (38.1%, *p*=0.0189) compared to healthy controls (16%). Also, HLA DQB1*05:02:01 was present in 28.6% of CRC patients but only 10% of healthy controls (*p*=0.0278). The odds ratios for HLA DPB1*02:01:02 and HLA DQB1*05:02:01were 3.23 and 3.60, respectively. There were no significant association observed for the DRB1 allele with CRC. Our study suggests that the HLA DPB1*02:01:02 and HLA DQB1*05:02:01 alleles may confer a higher risk for CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide with an estimated number of 1.4 million (9.7%) cases in the year 2012 (1). In Malaysia, 2246 CRC cases (12.3%) were reported in 2011 (2). It is widely recognized that genetic factors such as inactivation of tumor suppressor genes (3-5), activation of oncogenes (6, 7), DNA–repair defects (8, 9), aberrant DNA methylation (10, 11) and chromosomal instability (12-14) play important roles in the pathogenesis of CRC.

However, avoiding immune destruction has now been recognized as an important hallmark in cancer progression (15). There is considerable evidence to suggest that the immune system plays a protective role in tumorigenesis (16-18). Although immune surveillance is responsible for the elimination of foreign antigens, the tumor cells, however, are able to manipulate and escape from host immune cell recognition. In addition, immune responses depend on the inheritance of highly polymorphic HLA genes in promoting the generation of T cells and B cells. The genetic polymorphisms, in turn, affect how the HLA presents the peptide and provide signals to the T cells. Theoretically, somatic alterations in tumor would not influence the expression of HLA class II gene in dendritic cells, macrophages and B lymphocytes (the antigen presenting cells) (18). However, it is argued that the HLA antigen processing pathway could be significantly altered as part of the tumorigenesis process (19, 20). Therefore, in many tumors, somatic alterations could indirectly contribute to the downregulation or upregulation of HLA gene expression (21). Furthermore, intrinsic modifications of various cellular compartments and components such as lipids and enzymes are likely to influence, either directly or indirectly, the processing, loading and presentation of antigen to T cells. Therefore the inheritance of certain allele(s) could affect the way the peptides are presented to T cells.

Consequently, individuals who inherit specific alleles of highly polymorphic HLA class II DRB, DQB and DPB genes might be susceptible or resistant to specific types of cancers (17, 18, 22, 23). In addition, loss of certain effector functions in HLA is often associated with susceptibility to particular types of cancers, suggesting that different malignancies are controlled by different immune effector mechanisms (24). Also, the peptides lodged in the antigen-binding grooves of specific HLA class II heterodimers may fail to activate the T cells and subsequently unable to produce the appropriate signals for cytokine release to activate the T cell response. It is likely that changes in the HLA

Correspondence to: adzimah@ppukm.ukm.my

class II expression may significantly influence tumor cell evasion of immune surveillance (16). In view of the association between HLA class II and CRC, changes in expression of HLA class II molecules in the CRC patients may have important implications for the presentation of tumor antigens to the T cell.

During past 30 years, there are only a few studies on the association of HLA class II alleles with CRC. All of these studies emphasized on the frequency of HLA class II expression in CRC tissues which ranged from 21% to 55% using the immunohistochemistry method (17, 25-27). The studies yielded mixed results, mostly due to confounding factors such as tumor type, origin, source and small sample size. As such, the prognostic value of HLA Class II expression is certainly not universal. Very limited information is available on HLA class II allele in CRC. In fact, the only study on HLA typing showed that patients with HLA-DQB1*02 allele were more susceptible to early onset of CRC (mean age= 57.49±12.71) than those without (mean age 62.94±10.79)(28). Nevertheless, there are other studies on association HLA class II alleles with other types of cancer such as breast cancer, hepatocellular carcinoma, leukemia and cervical cancer (18, 22, 29-32). For example, HLA DQB*03032 and HLA DRB1*11 were suggested to represent protective alleles in early-onset breast cancer susceptibility (18). Both these alleles were significantly overexpressed in controls (7% and 16.3% respectively) as compared to breast cancer patients. In another study, a significant increase in the frequency of HLA DRB1*04 and HLA DQB1 *02 alleles and a decrease in the frequency of HLA DQB1*06 allele were reported in hepatocellular carcinoma patients (22). Therefore, we believe that a molecular analysis of HLA DRB, DQB and DPB alleles in our local patients with CRC and matched healthy controls might provide preliminary information to the potential existence of alleles that could confer susceptibility or resistance to this CRC in the local context. Such an approach may contribute an insight on the role of immune surveillance in cancer.

MATERIALS AND METHODS

SUBJECTS

Ethics approval was obtained from the UKM Research Ethics Committee and written informed consent was obtained from subjects prior to the collection of blood samples. Three milliliters of peripheral blood were collected in BD Vacutainer® EDTA Tubes (Becton Dickinson) from 42 CRC patients and 50 healthy controls who were admitted to UKM Medical Center, Kuala Lumpur (UKMMC) from 2012 – 2013. Samples from healthy volunteers were used as controls and classified as participants who went through endoscopy as part of their annual health screening and subsequently diagnosed as normal. The CRC patients were histologically confirmed, primary-diagnosed and did not receive any form of treatment prior to blood sample collection. The histological stage of the tumor was determined according to the Duke's staging system. Data including patient clinical history, age, gender, colorectal polyp classification and tumor staging are summarized in Table 1. None of the donors suffered from allergies or autoimmune diseases and all were free from acute or chronic infections. Patients who underwent neoadjuvant treatment or resection were excluded from the study.

HLA TYPING SEQUENCE BASED TYPING (SBT)

Genomic DNA was extracted from peripheral blood using a commercial kit (Qiagen DNeasy Blood & Tissue Kit). Genotyping of HLA class II loci DRB1, DQB1 and DPB1 was performed by a PCR-SBT technique using SBT typing kits (AlleSEQR®, Abbot Molecular) according to the manufacturer's protocol. Briefly, PCRs were performed in a total volume of 10µl using 40ng of genomic DNA and reaction mixture (Gene-specific PCR Amplification Mix and AmpliTaq Gold, Thermo Fisher Scientific Inc., Waltham, MA). Samples were denatured at 96°C for 10 minutes followed by 36 cycles of amplification with the annealing temperature of 72°C. PCR products were visualized on a 2% agarose gel. Following this, 2 µl of treated PCR product was added to 8 µl sequencing mix and treated to another round of PCR with an annealing temperature of 50°C, 30 seconds for 25 cycles. Samples were then treated with 15 µl HiDi Formamide and sequenced using the ABI3130XL genetic analyzer (Applied Biosystems®).

STATISTICAL ANALYSIS

Data analysis was performed using the MedCalc Statistical Software. The frequency of HLA DRB1, DQB1 and DPB1 in the sample populations was determined. Strength of the statistical association between sample populations with genetic markers was expressed by odds ratio (OR). Statistical significance was calculated by Student's t-test. A $p<0.05$ was considered statistically significant.

RESULTS

Genotyping of HLA class II loci DRB1, DQB1 and DPB1 was performed by PCR-SBT technique. A representative data of PCR-SBT is shown in Figure 1. We observed evenly spaced peaks and minimal base

Table 1: Demographic and clinical data of CRC patients and controls of this study.

Patients	**Number, n**	
	Normal (total =50)	**CRC (total =42)**
Sex		
Male	25	21
Female	25	21
Mean age (year)	60	62
Age range	35-70	37-82
Ethnicity		
Chinese	25	22
Malay	20	17
Indian	5	2
Duke's staging		
A	not related	4
B	not related	15
C	not related	9
D	not related	1
Others	not related	12

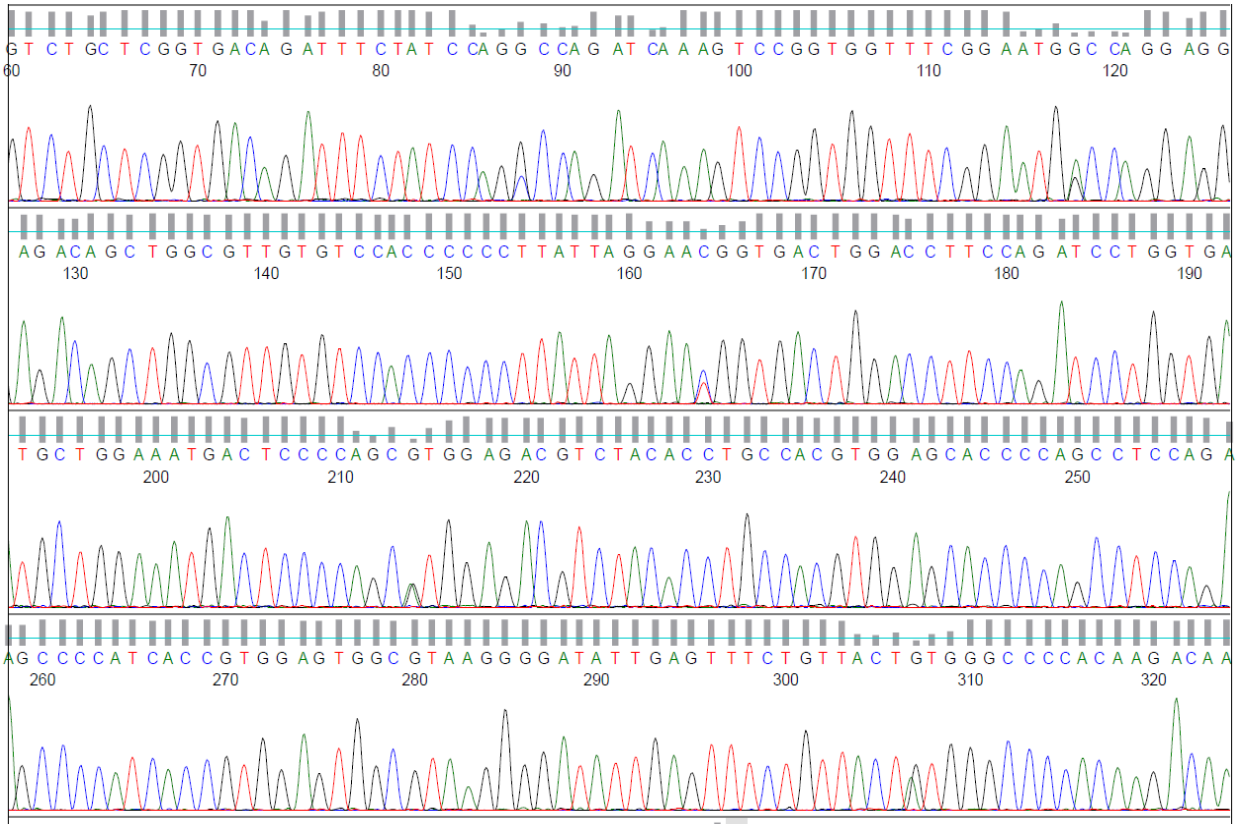

Figure 1: A representative data of PCR-sequence-based typing (SBT) showing evenly spaced peaks and minimal baseline noise in all the chromatograms, indicating good quality and strong reliability of the results.

Correspondence to: adzimah@ppukm.ukm.my

Table 2: The distribution of DPB1 alleles in controls and CRC patients.

HLA allele		Normal (n =50)	CRC (n =42)	p value	95% CI		OR
DPB1	*01:01:01	4 (8%)	1 (2.4%)	0.2642	0.0301	2.6122	0.28
	*02:01:02	8 (16%)	16 (38.1%)	**0.0189***	1.2131	8.6044	3.23
	*02:02:00	5 (10%)	9 (21.4%)	0.1365	0.7528	8.0034	2.45
	*03:01:01	5 (10%)	5 (11.9%)	0.7703	0.3269	4.5243	1.22
	*04:01:01:01	18 (36%)	17 (40.5%)	0.6597	0.5196	2.8127	1.21
	*04:02:01:01	2 (4%)	2 (4.8%)	0.8585	0.1617	8.9061	1.2
	*05:01:01	29 (58%)	18 (42.9%)	0.1494	0.2368	1.2455	0.54
	*09:01:00	1 (2%)	1 (2.4%)	0.9008	0.0725	19.7071	1.2
	*13:01:00	12 (24%)	6 (14.3%)	0.2465	0.1791	1.5554	0.53
	*14:01:00	4 (8%)	3 (7.1%)	0.8773	0.1865	4.1954	0.88
	*17:01:00	2 (4%)	1 (2.4%)	0.6666	0.0512	6.6919	0.59
	*21:01:00	1 (2%)	3 (7.1%)	0.2586	0.3772	37.6689	3.77
	*28:01:00	3 (6%)	1 (2.4%)	0.4127	0.0382	3.8175	0.38

CRC=colorectal cancer; CI=confidence interval, OR=odds ratio, *Significant difference (p <0.05)

Table 3: The distribution of DQB1 alleles in controls and CRC patients.

HLA allele		Normal (n =50)	CRC (n =42)	p value	95% CI		OR
DQB1	*02:01:01	5 (10%)	6 (14.3%)	0.5299	0.4233	5.3156	1.5
	*02:02	6 (12%)	2 (4.8%)	0.2352	0.07	1.9219	0.37
	*03:01:01:01	24 (48%)	16 (38.1%)	0.3407	0.2895	1.5351	0.67
	*03:01:02	1 (2%)	4 (9.5%)	0.1497	0.5536	48.0602	5.16
	*03:02:01	2 (4%)	6 (14.3%)	0.1012	0.7623	20.9879	4
	*03:03:02:01	8 (16%)	8 (19.0%)	0.7012	0.4198	3.6349	1.24
	*04:01:01	1 (2%)	3 (7.1%)	0.2586	0.3772	37.6689	3.77
	*04:02:01	4 (8%)	1 (2.38%)	0.2642	0.0301	2.6122	0.28
	*05:01:01:01	10 (20%)	4 (9.5%)	0.1721	0.1216	1.4574	0.42
	*05:02:01	5 (10%)	12 (28.6%)	**0.0278***	1.1502	11.2676	3.6
	*05:03:01:01	5 (10%)	3 (7.1%)	0.6296	0.1554	3.0849	0.69
	*06:01:01	8 (16%0	7 (16.7%)	0.9313	0.3463	3.1834	1.05
	*06:02:01	5 (10%)	1 (2.4%)	0.1744	0.0246	1.9582	0.22
	*06:03:01	2 (4%)	1 (2.4%)	0.6666	0.0512	6.6919	0.59
	*06:09	1 (2%)	1 (2.4%)	0.9008	0.0725	19.7071	1.2
	*06:10	1 (2%)	1 (2.4%)	0.9008	0.0725	19.7071	1.2
	*06:35	1 (2%)	1 (2.4%)	0.9008	0.0725	19.7071	1.2

CRC=colorectal cancer; CI=confidence interval, OR=odds ratio, *Significant difference (p <0.05)

Table 4: The distribution of DRB1 alleles in controls and CRC patients.

HLA allele		Normal (n =50)	CRC (n =42)	p -value	95% CI		OR
DRB1	*01:01:01	2 (4%)	1 (2.4%)	0.6666	0.0512	6.6919	0.59
	*03:01:01:01	6 (12%)	4 (9.5%)	0.7044	0.2026	2.9409	0.77
	*04:03:01	4 (8%)	2 (4.8%)	0.5353	0.1	3.3072	0.58
	*04:05:01	4 (8%)	5 (11.9%)	0.5325	0.3893	6.2033	1.55
	*07:01:01:01	9 (18%)	6 (14.3%)	0.6316	0.2463	2.3407	0.76
	*08:03:02	1 (2%)	3 (7.1%)	0.2586	0.3772	37.6689	3.77
	*09:01:02	5 (10%)	5 (11.9%)	0.7703	0.3269	4.5243	1.22
	*10:01:01	3 (6%)	1 (2.4%)	0.4127	0.0382	3.8175	0.38
	*11:01:01	4 (8%)	4 (9.5%)	0.7963	0.2837	5.1658	1.21
	*12:01:01	2 (4%)	1 (2.4%)	0.6666	0.0512	6.6919	0.59
	*12:02:01	17 (34%0	16 (38.1%)	0.6834	0.5083	2.8076	1.2
	*13:01:01	2 (4%)	1 (2.4%)	0.6666	0.0512	6.6919	0.59
	*14:01:01	3 (6%)	2 (4.8%)	0.7946	0.1246	4.9236	0.78
	*14:04	2 (4%)	1 (2.4%)	0.6666	0.0512	6.6919	0.59
	*15:01:01:01	13 (26%)	7 (16.7%)	0.2829	0.2035	1.5921	0.57
	*15:02:01	9 (18%)	8 (19%)	0.8974	0.3731	3.0795	1.07
	*16:02:01	4 (8%)	4 (9.5%)	0.7963	0.2837	5.1658	1.21

CRC=colorectal cancer; CI=confidence interval, OR=odds ratio, †Significant difference (p <0.05)

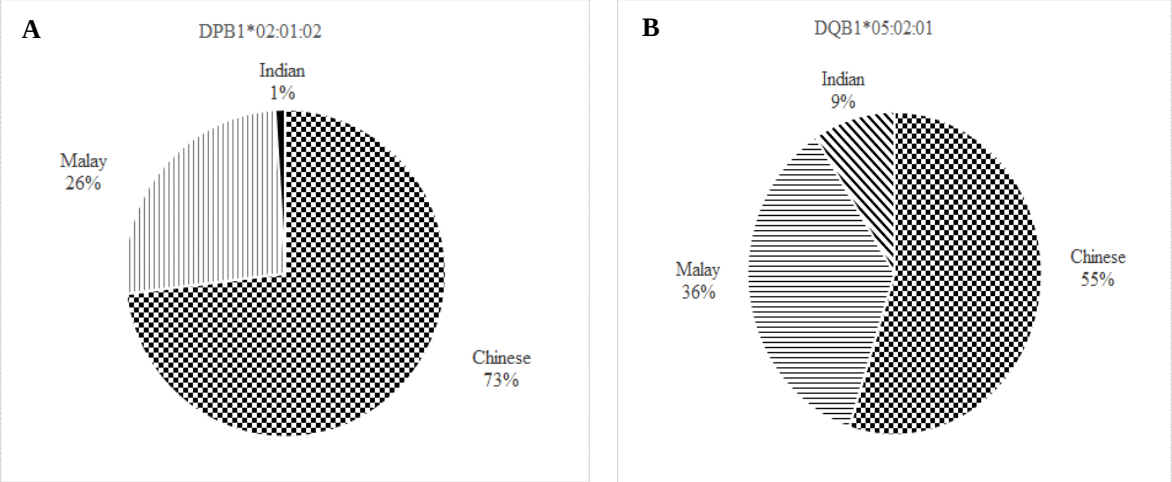

Figure 2: Percentage distribution of HLA DPB1*02:01:02 (A) and DQB1*05:02:01 (B) alleles according to ethnicity.

line noise in all the chromatograms, indicating good quality and strong reliability of the results.

Statistical analysis on the frequency distribution of DPB1, DQB1 and DRB1 alleles showed that DPB1*02:01:02 and DQB1*05:02:01were statistically significant in the sample populations (Table 2-4). The frequency of DPB1*02:01:02 allele was found to be 38.1% in CRC patients compared to 16% in healthy controls (p=0.0189, OR=3.23; Table 2). For the DQB1*05:02:01 allele, frequency of distribution was 28.6% in CRC patients and 10% in healthy controls (p=0.0278, OR=3.60; Table 3). No significant association was found in the samples for DRB1 alleles (Table 4).

Further analysis on DPB1*02:01:02 and DQB1*05:02:01 alleles based on frequency distribution within ethnicities showed that DPB1*02:01:02 allele was detected in 73% of the Chinese subjects, 26% in the Malays and 1% in the Indians (Figure 2a). As for the DQB1 *05:02:01 allele, it was found in 55% of Chinese subjects, 36% in the Malays and 9% in the Indians (Figure 2b). Association of these two alleles with the patients' clinical data showed that more than 80% of the patients with DPB1*02:01:02 and HLA DQB1*05:02:01 alleles had Dukes' A and Dukes' B CRC.

DISCUSSION

The inheritance of specific HLA class II genes may influence immune responses or confer immunological tolerance towards pathogens or tumor antigens. HLA class II antigens play a pivotal role in stimulating inflammatory responses. Therefore, information on polymorphisms of HLA class II alleles may provide a better understanding of the roles of these molecules in the tumor immunology. This further opens up new avenues for immunodiagnostics and strategies in immunotherapy.

In this study, CRC was chosen as a model not only because it is one of the commonest cancers in the world (1, 2), but also based on the presumption that genetic instability that occurs in many CRC cases might also affect the genetic structure and effector functions of the HLA alleles.

A significant positive association between the DPB1*02:01:02 and DQB1*05:02:01 alleles with CRC indicate that the DPB1*02:01:02 and DQB1*05:02:01 alleles confer a higher risk of developing CRC and a possible role in promoting chronic inflammation. Other studies have suggested that the HLA-DQB*03032 allele may have a protective effect for early-onset breast cancer susceptibility (18). The group also suggest that the allele could be in linkage disequilibrium with an unidentified growth-regulating gene which dominantly suppresses mammary tumorigenesis (18). Taking that into the CRC context, it could be possible that the HLA-DPB1*02:01:02 and DQB1*05:02:01 alleles are in linkage disequilibrium with a growth-regulating gene related to CRC such as the hSETD1A gene (33), PTTG gene (34, 35) or TGFBR2 (36). These polymorphic alleles may dominantly enhance the CRC tumorigenesis. However, further validation of the significance of these two HLA alleles is needed in a bigger sample size and functional analysis is crucial to support this hypothesis.

A significant association between CRC with the DRB1 allele was not observed in this study in contrary to many reports in other studies (18, 25, 29, 32). This could due to a limitation in sample size.

In conclusion, we identified the DPB1*02:01:02 and DQB1*05:02:01 alleles as possible risk factors for CRC. More studies need to be conducted to investigate the possible association and roles of these alleles with CRC. The positive association noted for DPB1*02:01:02 and DQB1*05:02:01 warrants validation in larger numbers of CRC patients.

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Correspondence to: adzimah@ppukm.ukm.my

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