

HLA-A*30:01 and HLA-A*33:03 are the protective alleles while HLA-A*01:01 serves as the susceptible gene for Cervical Cancer Patients in Xinjiang, China

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Abstract

Objective: This study aims to investigate the distribution of HLA-A genes and identify alleles related to cervical cancer. **Methods:** A total of 252 cervical cancer patients (56 Han ethnic and 196 Uyghur ethnic) and 213 control subjects (103 Han ethnic and 110 Uyghur ethnic) were recruited into this study. HLA-A alleles were examined by polymerase chain reaction with sequence specific primers (PCR-SSP). The frequencies of different HLA-A alleles were compared between the two ethnic groups as well as patients and control subjects. The correlation of HLA-A frequencies with various clinical characteristics and short-term treatment efficacy was analyzed. **Results:** (1) Significantly higher frequencies of HLA-A*03:01 and HLA-A*03:02 and lower frequencies of HLA-A*11:01, HLA-A*24:02 and HLA-A*30:01 were observed in the Uyghur control groups than in Han control groups ($P \leq 0.05$). (2) The frequency of HLA-A*01:01 in patients was significantly higher than control subjects. In contrast, the frequencies of HLA-A*30:01 and HLA-A*33:03 were lower in patients ($P \leq 0.05$). (3) The frequency of HLA-A*30:01 in Han patients was lower than Han cancer group ($P \leq 0.05$). However, there was no statistically significant difference in the frequency of HLA-A between Uyghur patients and controls ($P > 0.05$). (4) There was no significant association between HLA-A alleles and HPV16 or squamous cell carcinoma.

antigen(SCC) levels($P > 0.05$).⁽⁵⁾The frequency of HLA-A*30:01 allele in CR+PR group was higher than SD+PD group ($P \leq 0.05$).Conclusions:People from two ethnic group displayed different HLA-A gene distribution.HLA-A*30:01and HLA-A*33:03alleles are the protective factors to cervical cancer patients from Xinjiang whileHLA-A*01:01 serves as the susceptible gene.

Key words: Cervical Cancer; Human Leukocyte Antigen (HLA),Clinical Characteristics, short-term treatment efficacy

Background

Cervical cancer is the third most common malignancy among women worldwide^[1]. Although American Cancer Society (ACS) has reported that mortality of cervical cancer have been continuously dropping from 1930 to 2011, largely due to the widespread uptake of screening for the prevention and early detection of cervical cancer^[2].It is still a threat to the physical and psychological wellbeing of women worldwide, especially those in the developing countries. The residents in Xinjiang, China mainly consist Uyghur and Han people. The Uyghur women displayed the highest morbidity and mortality of cervical cancer compared to other ethnicities from the same geographic areas^[3], belongs to a special high incidence of malignant tumor.The high incidence of cervical cancer among Uyghur women is partly resulted from a high percentage of human papilloma virus (HPV)infection^[3].However, most HPV infections are often transient because the host immune response can generally control viral invasion, less than 1% of HPV infections can produce cervical cancer, this indicates that HPV infection by itself is not sufficient to induce tumorigenesis^[4]. There is might additional co-factors, such as smoking and oral contraceptive use^[5], contribute to the development of cervical cancer except HPV. Human Leukocyte Antigen (HLA) is an important part of T cell immunity and a decision factor of host immune system. HLA-I alleles have the biological role of presenting endogenous antigen like tumor antigens to CD8⁺ T cells. Previous studies have linked HLA-I polymorphism with various types of cancers^[6-8].Different or even contradicting result were obtained on the relationship between cervical cancer and HLA alleles, probably due to different populations used. Besides, most of the study concentrated on HLA class II molecules^[9].Although the importance of CTL response to viral infection and tumor infection has been recognized^[10],there are few reports about the correlation between the frequency of HLA-I allele and cervical cancer.In our research, the frequencies of several HLA-A alleles were determined in the two ethnic population with or without cervical cancer. The relationship between HLA-A alleles and clinical characteristics of cervical cancer were subsequently analyzed. By doing so, we hope to understand the part of HLA-A played during the development of cervical cancer.

Materials and Methods

Subjects

The study was approved by the ethics committee of Xinjiang Medical University. The criteria of International Federation of Gynecology and Obstetrics(FIGO) in 2009^[11]

were used for the tumor staging. Standards were set to include or exclude candidates for the study. The patients (1) diagnosed with invasive cervical cancer, including squamous cell carcinoma, adenocarcinoma or other types of cancer, (2) with Karnofsky Performance Status (KPS) point ≥ 80 , and (3) showing certain indications of surgery and/or chemotherapy and radiotherapy were included into the study. The patients (1) who had a history of cancer treatment like surgery, radiotherapy, chemotherapy or immunotherapy, or (2) simultaneously diagnosed with tumors other than cervical cancer, genetic or immune-related diseases were excluded.

A total of 252 women (56 Han ethnic and 196 Uyghur ethnic) diagnosed with invasive cervical cancer were recruited as patients. All the patients and receive the initial therapy between May 2013 and June, 2014 from the Department of Gynecologic Radiotherapy, Tumor Hospital Affiliated to Xinjiang Medical University. The age median of the patients was 53 (28 to 82 years old). The general clinical characteristics of the 252 patients are shown in Table 1. Meanwhile, a total of 213 cancer-free women (103 Han ethnic and 110 Uyghur ethnic) from physical examination center of the same hospital were recruited as controls. Their median age was 50 (28 to 79 years old). All the subjects signed the informed consent.

HLA-A typing

Genomic DNA was obtained from peripheral whole blood. Completed the DNA extraction by strictly follow the instruction of whole blood genomic DNA extraction kits bought from Beijing Baitaika Biological Technology Co, Ltd. Determined its concentration and purity by using UV spectrophotometer, A₂₆₀/A₂₈₀ ratios were 1.8 to 1.9, adjust the final concentration to 0.3 ~ 0.5 $\mu\text{g}/\mu\text{L}$, placed in -20°C refrigerator before the test. HLA-A were genotyped by using the polymerase chain reaction with sequence specific primers (PCR-SSP) according to the protocol released by International HLA Workshops. A total of 35 alleles were examined.

Clinical Index

Vaginal secretions were taken from the patients to perform the expression of HPV16 state. Before the test all patients were informed that not to use of vaginal drugs or vaginal washing or should not have sexual behavior in three days. Then two gynecologic expert exposed the cervix of the uterus and took samples by using disposable cervical cell collector (Chaozhou Kaipu biochemistry Co. Ltd.) HPV subtype in samples was determined by Hybridmax HPV DNA detection method. Peripheral blood samples were taken to determine the level of squamous cell carcinoma antigen (SCC). Used the automatic chemiluminescence immunoassay analyzer (Abbott ARCHITECT i2000SR) and squamous cell carcinoma antigen ELISA kit (Abbott Trading Co. Ltd.) to test SCC. Normal reference parameter was 0~1.5 ng/mL . (Table 1)

Table 1 general clinical data of 252 cases of cervical cancer patients in Xinjiang

Factor	cases	Constituent ratio (%)
Nationality		
Uyghur	196	77.78
Han	56	22.22
Pathological types		
Squamous cell carcinoma	231	91.67
Non-squamous cell carcinoma	21	8.33
FIGO clinical stage		
I- II	106	42.06
III-IV	146	57.94
HPV16		
Positive	186	73.81
Negative	66	26.19
SCC		
Positive	210	83.33
Negative	42	16.67

Treatment

Radiotherapy and chemotherapy or surgery were given to all of the patients in our study. According to NCCN guideline 2012 of cervical cancer, early stage patients (IA~IIA) are given an operation that extensive or complete hysterectomy or radical trachelectomy \pm pelvic lymphadenectomy based on age and fertility requirements (If necessary abdominal aortic lymph node sampling operation should be performed). The patients who founded that there were high risk factors in postoperative pathological examination, refused surgical treatment, can not tolerate surgery because of the serious heart, brain, lung and kidney diseases or with stage IIb~IV were treated with radiotherapy and chemotherapy. Intracavitary irradiation (high dose rate brachytherapy with three dimensional conformal radiation therapy) and/or extracorporeal irradiation (intensity modulated radiation therapy or three dimensional conformal radiation therapy) were selected according to the patient's specific condition. PVB (cisplatin $50\text{mg}/\text{m}^2$ + bleomycin hydrochloride $30\text{mg}/\text{m}^2$ + vincristine sulfate $1.5\text{mg}/\text{m}^2$) or TP (taxol $135\text{mg}/\text{m}^2$ + cisplatin $50\text{mg}/\text{m}^2$) was applied to the patients according to their conditions, total were 3 times.

Short-term treatment efficacy assessment

Short-term treatment efficacy was assessed on the basis of World Health Organization (WHO) evaluation standard for solid tumors^[12-13]. Briefly, complete response (CR): referred to the situation when the tumors completely disappeared; Partial response (PR): the product of the maximum diameter narrow downed more than 50%, other lesions had no increase and no new lesions appeared; Stable disease (SD): the decrease of the product above mentioned is less than 50% or the increase of it no more than 25% and no new lesions

appeared;Progressivedisease(PD):the increase of the product is more than 25% or there is an emergence of new lesion. Three months after the end of the treatment, two specialist were evaluate the therapeutic effect according to tumor associated antigen, gynecological and CT examination, respectively.

Statistical Analysis

SPSS (version 17.0) was used for the statistical analyses. χ^2 test was performed to analyze the different distributions of HLA-A alleles. The relative risks were calculated by the odds ratios(ORs) and their confidence intervals(CIs) by using chi-square test.*P* values less than 0.05 were considered significant.

Results

The distribution of HLA-A alleles were different between controlsfrom Uyghur and Han

The frequencies of 28 distinct HLA-A alleles that were detected in Uyghur and Han control subjects were summarized in Table 2 and Fig 1. Of noted, the frequency of HLA-A*03:01 in Uyghur controls was 13.18%, significantly higher than Han controls' 4.85% ($P=0.003$, OR=2.976). The frequency of HLA-A*03:02 in Uyghur controls was 3.64% and this gene was not detected in Han controls, the difference was statistically significant ($P=0.008$); In contrast, the frequencies of HLA-A*11:01 (10.45% vs 16.99%, $P=0.049$, OR=0.570), HLA-A*24:02 (13.64% vs 21.84%, $P=0.026$, OR=0.565) and HLA-A*30:01 (1.36% vs 10.68%, $P=0.000$, OR=0.116) were lower in Uyghur controls than Han controls. These results indicated that ethnicity played a role in the distribution of the HLA-A alleles.

Table 2 The frequencies of HLA-A alleles in Uyghur and Han control groups

HLA-A	Alleles	Uyghur control		Han control		χ^2	<i>P</i>	OR	95% CI
		<i>n</i>	frequency (%)	<i>n</i>	frequency (%)				
*01	*01:01	17	7.73	7	3.40	3.750	0.053	2.381	0.966-5.865
*03	*03:01	29	13.18	10	4.85	8.870	0.003	2.976	1.412-6.274
	*03:02	8	3.64	0	0.00	-	0.008	-	-
*11	*11:01	23	10.45	35	16.99	3.864	0.049	0.570	0.324-1.003
*24	*24:02	30	13.64	45	21.84	4.941	0.026	0.565	0.340-0.938
*30	*30:01	3	1.36	22	10.68	15.070	0.000	0.116	0.034-0.392
*33	*33:03	15	6.82	14	6.80	0.000	0.993	1.003	0.472-2.134

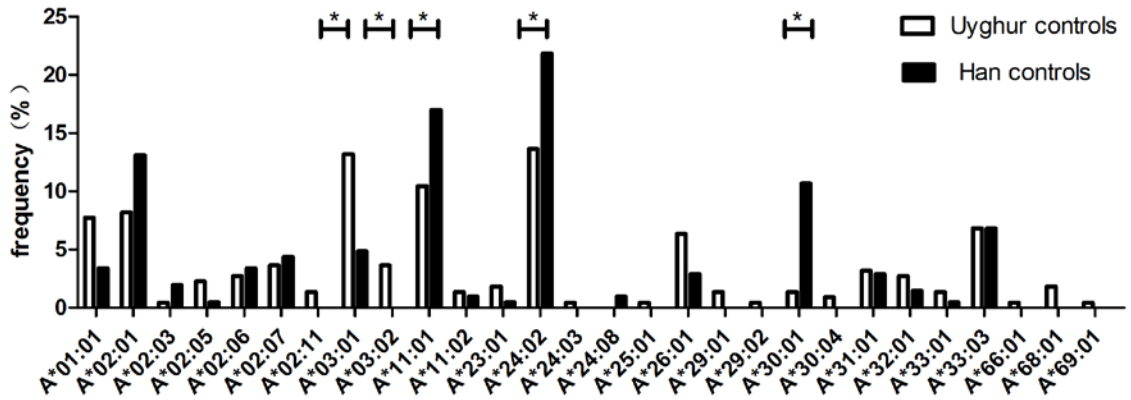


Fig1 The frequencies of HLA-A alleles in Uyghur and Han control groups

Different HLA-A allele distribution between cervical cancer patients and controls

Different distribution of HLA-A alleles also existed between patients and controls. As was shown in Fig 2 and Table 3, there were different frequencies of HLA-A alleles between cervical cancer patients and controls. Of the 35 alleles genotyped, the patients were found to be overrepresentative with HLA-A*01:01 when compared to the controls (11.51% vs 5.63%, $P=0.002$, $OR=2.178$). On the other hand, HLA-A*30:01 and HLA-A*33:01 were underrepresentative in patients than in controls (3.17% vs 5.87%, $P=0.046$, $OR=0.526$ and 3.77% vs 6.81%, $P=0.037$, $OR=0.536$). When subjects from Uyghur and Han were compared separately, it was found that the only allele of the 22 allele detected at the HLA-A locus that displayed significantly difference between Han patients and Han controls was HLA-A*30:01, which was significantly lower in Han patients (1.79% vs 10.68%, $P=0.008$, $OR=0.152$) (Fig. 3, Table 4). However, when comparing the allele distribution between Uyghur patients and controls, there was no statistically significant in the frequency of HLA-A (Fig. 4, Table 5). The result revealed the fact that in different ethnic groups, different HLA-A alleles contribute to the susceptibility to cervical cancer.

Table 3 The frequencies of HLA-A alleles in patients and controls

HLA-A	Alleles	Patients		Controls		χ^2	P	OR	95% CI
		n	frequency (%)	n	frequency (%)				
*01	*01:01	58	11.51	24	5.63	9.908	0.002	2.178	1.329-3.571
*03	*03:01	46	9.13	39	9.15	0.000	0.988	0.997	0.637-1.559
	*03:02	7	1.39	8	1.88	0.348	0.555	0.736	0.265-2.046
*11	*11:01	58	11.51	58	13.62	0.939	0.333	0.825	0.559-1.218
*24	*24:02	72	14.29	75	17.61	1.912	0.167	0.780	0.548-1.110
*30	*30:01	16	3.17	25	5.87	3.976	0.046	0.526	0.277-0.999
*33	*33:03	19	3.77	29	6.81	4.352	0.037	0.536	0.296-0.971

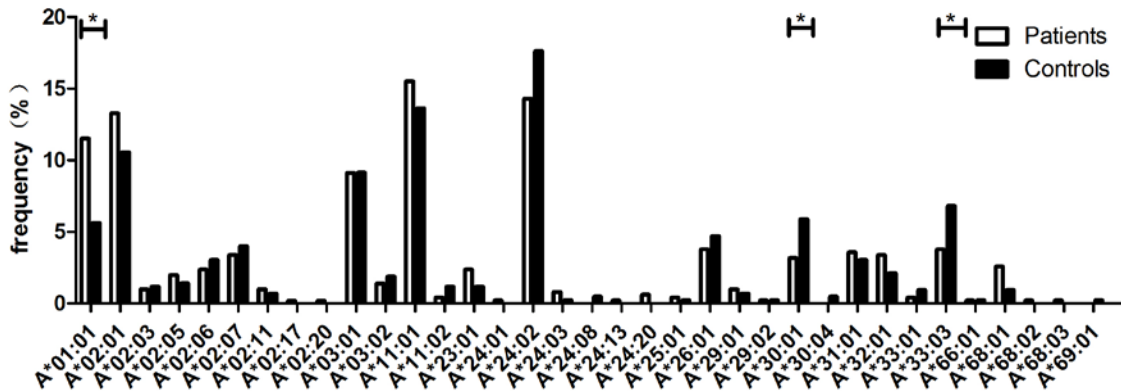


Fig 2 The frequencies of HLA-A alleles in patients and controls

Table4 The frequencies of HLA-A alleles in Han patients and Han controls

HLA-A	Alleles	Han Patients		Han Controls		χ^2	<i>P</i>	<i>OR</i>	95% <i>CI</i>
		<i>n</i>	frequency (%)	<i>n</i>	frequency (%)				
*01	*01:01	8	7.14	7	3.40	2.264	0.132	2.187	0.772-6.198
*03	*03:01	3	2.68	10	4.85	0.876	0.349	0.539	0.145-2.002
	*03:02	0	0	0	0	-	-	-	-
*11	*11:01	18	16.07	35	16.99	0.044	0.834	0.936	0.502-1.742
*24	*24:02	19	16.96	45	21.84	1.075	0.300	0.731	0.404-1.324
*30	*30:01	2	1.79	22	10.68	7.000	0.008	0.152	0.035-0.659
*33	*33:03	5	4.46	14	6.80	0.702	0.402	0.641	0.225-1.828

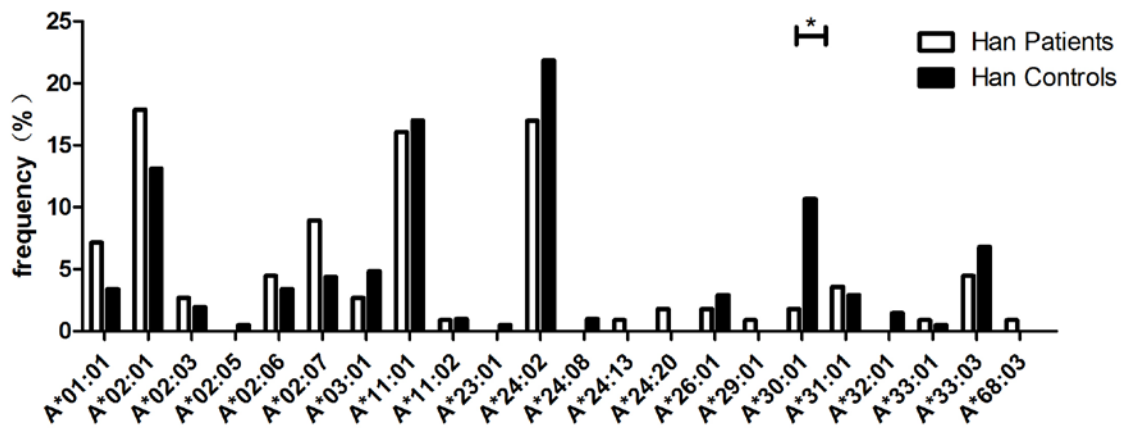


Fig 3 The frequencies of HLA-A alleles in Han patients and Han controls

Table5 The frequencies of HLA-A alleles in Uyghur patients and Uyghur controls

HLA-A	Alleles	Uyghur Patients		Uyghur Controls		χ^2	P	OR	95%CI
		n	frequency (%)	n	frequency (%)				
*01	*01:01	50	12.76	17	7.73	3.654	0.056	1.746	0.980-3.109
*03	*03:01	43	10.97	29	13.18	0.664	0.415	0.811	0.491-1.342
	*03:02	7	1.79	8	3.64	2.019	0.155	0.482	0.172-1.347
*11	*11:01	40	10.20	23	10.45	0.010	0.922	0.973	0.566-1.673
*24	*24:02	53	13.52	30	13.64	0.002	0.968	0.990	0.612-1.603
*30	*30:01	14	3.57	3	1.36	1.792	0.181	2.679	0.761-9.426
*33	*33:03	14	3.57	15	6.82	3.291	0.070	0.506	0.240-1.069

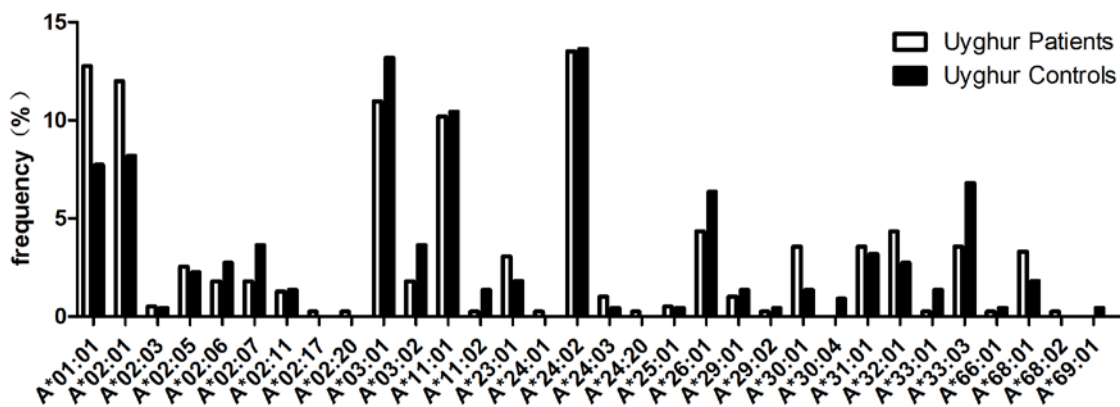


Fig 4 The frequencies of HLA-A alleles in Uyghur patients and Uyghur controls

Association of HLA-A allele frequencies with clinical characteristics and short-term treatment efficacy

We also analyze the association of HLA-A alleles with the clinical characteristics and short-term treatment efficacy. Among 252 cervical cancer patients, 186 are HPV16 positive (73.81%) and 66 are negative (26.19%); 210 are SCC positive (83.33%) and 42 are negative (16.67%). But no significant association was found between HLA-A alleles and HPV16 status (Table 6, Fig 5) or SCC level (Table 7, Fig 6).

Table 6 The frequencies of HLA-A alleles in HPV16 status

HLA-A	Alleles	HPV Positive group		HPV Negative group		χ^2	P	OR	95%CI
		n	frequency (%)	n	frequency (%)				
*01	*01:01	44	11.83	14	10.60	0.143	0.705	1.131	0.598-2.138
*03	*03:01	34	9.14	12	9.09	0.000	0.987	1.006	0.504-2.006
	*03:02	6	1.61	1	0.76	0.083	0.773	2.148	0.256-18.006
*11	*11:01	45	12.10	13	9.85	0.484	0.487	1.260	0.656-2.417
*24	*24:02	50	13.44	22	16.67	0.828	0.363	0.776	0.450-1.341
*30	*30:01	13	3.49	3	2.27	0.159	0.690	1.557	0.437-5.552
*33	*33:03	15	4.03	4	3.03	0.064	0.800	1.345	0.438-4.126

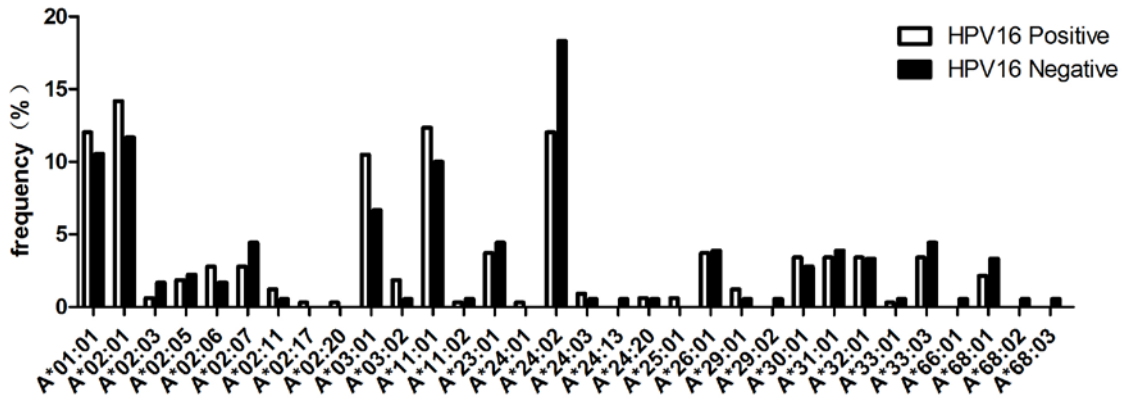


Fig 5 The frequencies of HLA-A alleles in HPV16 status

Table 7 The frequencies of HLA-A alleles in SCC level

HLA-A	Alleles	SCC Positive group		SCC Negative group		χ^2	<i>P</i>	<i>OR</i>	95% <i>CI</i>
		<i>n</i>	frequency (%)	<i>n</i>	frequency (%)				
*01	*01:01	48	11.43	10	11.90	0.016	0.901	0.955	0.462-1.973
*03	*03:01	37	8.81	9	10.71	0.306	0.580	0.805	0.373-1.738
	*03:02	5	1.19	2	2.38	0.116	0.734	0.494	0.094-2.590
*11	*11:01	49	11.67	9	10.71	0.062	0.803	1.101	0.518-2.337
*24	*24:02	62	14.76	10	11.90	0.467	0.495	1.282	0.628-2.615
*30	*30:01	14	3.33	2	2.38	0.013	0.910	1.414	0.315-6.339
*33	*33:03	17	4.05	2	2.38	0.175	0.676	1.730	0.392-7.630

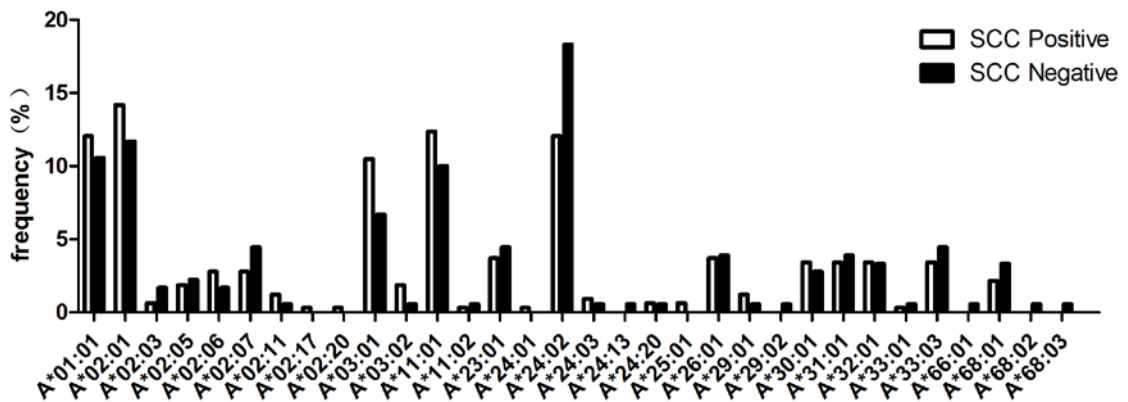


Fig6 The frequencies of HLA-A alleles in SCC level

Short-term treatment efficacy was assessed using image information. In our study, there were 196 patients grouped into CR and PR (CR+PR group) while 56 patients grouped into SD and PD (SD+PD group). Comparing these two sub-groups, we found that the frequency of HLA-A*30:01 in CR+PR group was 4.08% and this gene was not detected in SD+PD group, the difference was statistically significant ($P=0.029$) (Table 8, Fig 7).

Table 8 The frequencies of HLA-A alleles in among CR+PR group and SD+PD group in all cervical cancer patients

HLA-A	Alleles	CR+PR group		SD+PD group		χ^2	<i>P</i>	<i>OR</i>	95% <i>CI</i>
		<i>n</i>	frequency (%)	<i>n</i>	frequency (%)				
*01	*01:01	45	11.48	13	11.61	0.001	0.970	0.988	0.512-1.904
*03	*03:01	36	9.18	10	8.93	0.007	0.934	1.031	0.495-2.150
	*03:02	5	1.28	2	1.76	0.000	1.000	0.711	0.136-3.713
	*11	*11:01	47	11.99	14	12.50	0.021	0.884	0.954
*24	*24:02	53	13.52	21	18.75	1.902	0.168	0.677	0.389-1.181
*30	*30:01	16	4.08	0	0.00	-	0.029	-	-
*33	*33:03	13	3.32	5	4.46	0.333	0.564	0.734	0.256-2.105

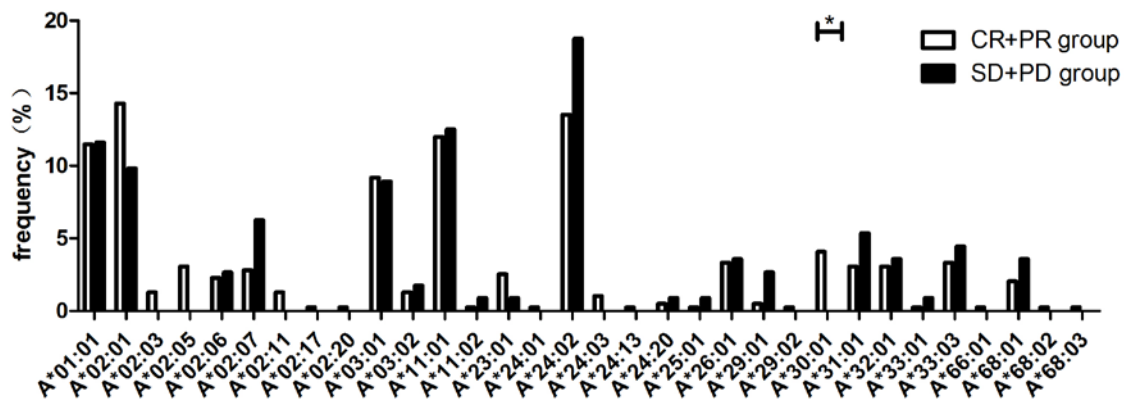


Fig 7 The frequencies of HLA-A alleles in among CR+PR group and SD+PD group in all cervical cancer patients

Discussion

The cervical cancer incidence among Uyghur people is 527/100000, much higher than the average rate of 126.94/100000 in China^[14]. A great many of researches demonstrated that some HLA-II molecules were associated with susceptibility and protectiveness to cervical cancer, but HLA-A alleles were less investigated, especially in Uyghur women from China. It were reported that there are significant differences of HLA-A allele frequencies between cervical cancer patients and healthy females in Switzerland^[15]. Two studies suggested that in cervical squamous cell carcinoma

people the presence of HLA-A*02:06 and HLA-A*03:01 potentially reduce the risk of cervical cancer^[10,16]. Chan et al^[17] demonstrated that the HLA-A*02:07 or A*24:02 can reduce the risk of cervical cancer while HLA-A*11:04 might be responsible for elevated risk of cervical cancer.

In our study, we found that the distribution of HLA-A alleles showed differences between controls from Uyghur and Han people. It suggested a difference of frequency of HLA-A allele between Uyghur and Han healthy people. The comparison between 252 patients and 213 controls led to finding that of HLA-A*01:01 was more frequently represented in cervical cancer patients (11.51% vs 5.63%, $P=0.002$, OR=2.178), might be susceptibility genes to cervical cancer. It was worth noting was that this allele was also over representative in Uyghur controls compared to Han controls ($P=0.053$), and its expression in the Uyghur patients is also higher than the Uyghur controls ($P=0.056$). Although there is no statistically differences between two groups, this might partly explain why the Uyghur women are more susceptible to cervical cancer than Han women. Takasugi et al^[18] showed that the frequency of HLA-A*01 in white cervical cancer patients is higher than control groups despite there is no statistically significant, so we believe this allele is still necessary to carry out more research to test it. The frequencies of HLA-A*30:01 and HLA-A*33:03 were lower in patients than controls (3.17% vs 5.87% and 3.77% vs 6.81%, $P=0.046$ and $P=0.037$), they might be the protective gene for cervical cancer (Fig.2). Differences of HLA-A allele distribution were more obvious and complex when ethnicity of patients was taken into consideration. We noticed that there was no statistically significant in the frequency of HLA-A between Uyghur patients and Uyghur controls. Unlike in Uyghur subjects, HLA-A*30:01 frequencies in Han patients was significant lower than in Han controls (1.79% vs 10.68%), so it is not too difficult to see that HLA-A*30:01 allele may also be the protective gene to cervical cancer. If the allele missed, it may cause the susceptibility. Uyghur controls generally lack of HLA-A*30:01 (1.36%) compared to Han controls (10.68%), The percentage in Uyghur population was only 1/7 of the Han population. So, the lack of HLA-A*30:01 in Uyghur women potentially resulted in the relatively high incidence of cervical cancer. From this piece of evidence, we can see that in women from Uyghur and Han people, different alleles were associated with the risk of cervical cancer. Previous studies have reported that HLA-A*30:01 and HLA-A*33:03 alleles should be the susceptible or protective gene to some infectious or chronic inflammatory disease^[19-20]. However, we have not found any report about the correlation between the above-mentioned alleles and the development of tumors. Therefore, it is needed to further research to prove this point and explain the reasons.

There were about 15 high-risk HPV causing around 95% of all cervical carcinomas, the type HPV16 account for about 50% of all cases respectively^[21]. So we carried out a comparison between HLA-A alleles and HPV16 status, but in our study, there was

no statistically significant of alleles between HPV16 negative and positive groups, still need to study further after expand the samples. SCC is an important biomarkers for clinical diagnosis of cervical squamous cell carcinoma^[22]. The clinical sensitivity of serum concentration of SCC antigen was 29% in stage I of primary cervical cancer, and it is increased to 89% in stage IV^[23]. The dynamic fluctuation of serum SCC level can reflect the development of cervical squamous cell carcinoma, thus it can be used to evaluate the tumor recurrence and metastasis. However, we have not found any difference on the expression of HLA-A between SCC positive and negative groups. We will continue to watch the correlation between SCC concentration of cervical cancer and the expression of HLA-A.

In our study, the association of HLA-A alleles with short-term treatment efficacy of cervical cancer patients after standard therapy was investigated. It was discovered that the frequency of HLA-A*30:01 allele in the CR+PR group (4.08%) was higher than the SD+PD group (0%), indicated that patients inheriting HLA-A*30:01 might be better treated than the rest with therapeutic strategy in our study, so that HLA-A*30:01 might be a protective gene for cervical cancer is further verified.

Our study for the first time reported the different distribution of HLA-A alleles in Uyghur and Han women living in Xinjiang, China. Also, our findings suggested that the varied frequencies of certain HLA-A alleles may potentially contribute to the development of cervical cancer in Xinjiang. Besides, the presence or absence of certain alleles might potentially affect the short-term treatment efficacy. These results may be helpful for expanding our knowledge on the HLA allele distribution in Chinese. More importantly, our study contributes to identify novel HLA alleles or allele groups associated with susceptibility of cervical cancer. Therefore, it could serve as evidence to sketch plan for individualized therapeutic strategy in the future.

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