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GENETICS

No association of *TAP1* and *TAP2* genes polymorphism with risk of cervical cancer in north Indian population

Dor Mohammad Kordi Tamandani · Ranbir Chander Sobti · Mohammad Shekari · Seyd Ali Husseini · Vanita Suri

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Abstract

Background Transporter associated with antigen processing (TAP), a member of the ATP-binding cassette transporter super family, is composed of two integral membrane proteins, TAP-1 and TAP-2. The *TAP* gene product is involved in the processing of endogenous peptides that bind to MHC class I molecules. Mutations and/or polymorphism within these genes could alter the efficacy of the immune response which might be relevant for the development of autoimmune diseases and cancer.

Methods DNA was isolated from peripheral blood sample of 200 patients with cervical cancer and 200 healthy controls. *TAP1* and *TAP2* allele polymorphism were determined by polymerase chain reaction.

Result Significant protective OR (OR=0.22 95% CI=0.09–0.51, $P<0.001$-OR=0.47, 95% CI=0.24–0.92, $P=0.02$) was observed for *GG* and combined *AG+GG* genotypes of *TAP2* in patients with SCC respectively. Similarly, such genotypes (*GG, AG+GG)* appeared same OR for patient with cervical cancer in study group (OR=0.12, 95% CI=0.04–0.39-$P<0.001$-OR=0.5 ,95% CI=0.25–0.95-$P=0.03$). There was decrease risk of cervical cancer in user of oral contraceptive with *AG* and *GG* genotypes of *TAP2* (OR=0.55, 95% Cl=0.41–0.73, $P=0.002$, OR=0.09, 95% CI=0.02–0.36, $P<0.001$) respectively. In case of *TAP1* gene all allelic polymorphisms showed a decrease OR in patients with cervical cancer in passive smokers and user of oral contraceptives, though, no significant

Conclusion Thus, *TAP1* and *TAP2* genes polymorphism are not linked to cervical carcinoma, since no association was found between a particular genotype and the disease.

Keywords Cervical cancer · Polymorphism · TAP1 · TAP2 · Gene

D. M. Kordi Tamandani (✉)
Department of Biology,
Sistan and Baluchistan University,
Zahedan, Iran
e-mail: dor_kordi@yahoo.com

D. M. Kordi Tamandani · R. C. Sobti · M. Shekari · S. A. Husseini
Department of Biotechnology, Panjab University,
Chandigrah, India

M. Shekari
Department of Genetic,
Hormozgan University of Medical Sciences,
Bandarabbas, Iran

V. Suri
Department of Obstetrics & Gynaecology, Post Graduate Institute of Medical Education and Research,
Chandigrah, India

Introduction

Cervical cancer is the second most common cancer and an significant cause of death in women worldwide [1]. It is widely accepted that specific human papillomavirus (HPV) types are central etiologic agent of cervical carcinogenesis. Other environmental and host factors also play decisive roles in the persistence of HPV infection and further malignant conversion of cervical epithelium [2]. Because many previous reports have focused on HPV and environmental factors, the role of host susceptibility to cervical carcinogenesis is largely unknown. Epidimiological studies have proposed a range of factors, such as human leukocyte antigen type, immune suppression, sex steroid hormones, and smoking, that may be involved in the progression of cervical cancer [3]. Cotinine, a nicotine metabolite, is present

in measurable concentrations in the cervical mucus of women who smoke cigarette regularly [4]. It can also be present in the cervical mucus of nonsmoking women, which suggest that passive smoking conteributs to genotoxic and immunomodulatory effects, including carcinogenesis [5].

The transporter associated with antigen processing (TAP) is a critical component of the major histocompatibility complex (MHC) class I antigen presentation [6].

MHC class I molecules are expressed at low levels in most cells and are strongly induced by cytokines such as interferons that increased expression of MHC class I molecules correlates with increased CTL function [7].

Therefore, both the TAPs are up-regulated by IFN-γ about 10-fold within 24 h, accompanied by an increased peptide transport capacity [8]. Polymorphism in the *TAP* genes has been described in various species. In some tumor tissues, a down-regulation of *TAP* mRNA by an unknown mechanism or mutation of *TAP* was observed [9]. The observed frequency of *TAP* gene deletions (86%) has been found considerably higher than the frequency of *MHC* class I gene mutations, and the majority of the *TAP* gene deletions are homozygous, where *TAP* allelic polymorphism allows this to be confirmed [10].

The suppression of *TAP* may be a mechanism for tumor cells to escape the immune response (11). The rat *TAP2* polymorphism is associated with different peptide binding specificities and functional differences in the MHC class I peptide complexes thereby also affecting T cell responses [11]. Polymorphism of the human *TAP1* gene in healthy volunteers and individuals with autoimmune disease has been systematically analyzed [12]. Also, Kim *et al.* [13] suggested that *TAP1* gene polymorphism may be an important factor contributing to the genetic susceptibility in the development of allergic rhinitis in the Korean population.

The cervical cancer seem to be under immune selection pressure, because an increased relative risk for cervical cancer in chronically immunosuppressed patients has been observed [14]. Vermeulen *et al.* [15] showed that defective TAP expression in cervical carcinoma is often associated with loss of heterozygosity (LOH) in the *TAP* region but not with mutations in the *TAP1* gene. The aim of our study was to determine whether there was an association between *TAP1* and *TAP2* genes polymorphism and susceptibility to cervical cancer in northern India women. Under this hypothesis, we tested combination of *TAP1* and *TAP2* genotypes with squamous cell carcinoma (SCC), adenocarcinoma (AC) and the interaction of these genes with smoking habit and use of oral contraceptive .

Materials and methods

Study subjects

The case-control study involved collection of peripheral blood samples (2–5 ml) of 400 North Indian subjects. 200 cases were newly diagnosed, previously untreated and histologically confirmed as cervical cancer patients. The samples were collected from the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh and Government Medical College (GMC), Chandigarh. The control peripheral blood samples (n=200) were collected from the same institute with no history of cancer or pre cancer. The control samples were collected from women visiting the gynecology OPD (out patient department) clinic for routine check up without any past medical history of gynecology disorder including cervical diseases.

Informed consent was obtained from all the cases and controls. Detailed data regarding age, use of oral contraceptives, education, menarche, and menopausal status, number of children, age at marriage and birth of first child, cigarette smoking history and spouse's smoking history were also obtained.

Methods

Genomic DNA was extracted from EDTA anti-coagulated peripheral blood samples according to a standard proteinase

Table 1 Demographic characteristics of cervix cancer cases and controls[a]

Variable	Cases (200)	Controls (200)	SCC(175)	AC(25)
Age ±	48.55±9.43	48.81±9.64	48.39±9.42	49.68±9.64
Age at menarche ±	14.87±1.14	14.02±1.09	14.90±1.16	14.68±1.00
Age at marriage ±	16.36±3.39	20.31±3.46	16.68±2.97	14.74±2.56
Age at first birth ± child	18.39±3.39	22.31±4.30	18.61±3.16	16.84±4.45
Children[b]	4.11	2.50	4.09±1.51	4.21±1.84
Age at menopause ±	48.31±3.56	48.26±2.39	48.29±3.62	48.44±3.40

Abbreviations: *AC* adenocarcinoma, *OR* odds ratio, *SCC* squamous cell carcinoma

[a] Values are given as mean ±SD or number (percentage) unless otherwise indicated

[b] Values are given as median for the cancer and control groups

Table 2 *TAP1* and *TAP2* genotypes in women with cervical cancer and healthy controls[a]

TAP1 genotypes	Case (%)200	Control(%)200	OR(95% CI)[b]	P[c]
TT	10 (5.0)	10 (5.0)	1.0(ref)	
TC	182 (91.0)	174 (87.0)	1.05 (0.39–2.79)	
CC	8 (4.0)	16 (8.0)	0.50 (0.12–2.0)	
TC+CC	190 (95.0)	190 (95.0)	1.00 (0.37–2.67)	
TAP2 genotypes				
AA	32 (16.0)	17 (8.5)	1.0(ref)	
AG	161 (80.5)	152 (76.0)	0.56 (0.29–1.1)	
GG	7 (3.5)	31 (15.5)	0.12 (0.04–0.39)	$P<0.001$
AG+GG	168 (84.0)	183 (91.5)	0.5 (0.25–0.95)	$P=0.03$

Abbreviations: *CI* confidence interval, *NA* not applicable, *OR* odds ratio, *ref* Reference

[a] Values are given as number (percentage) unless otherwise indicated

[b] ORs were adjusted for age, smoking status, and use of oral contraceptives

[c] $p<0.05$ has been mentioned

K digestion and phenol chloroform extraction method [16]. It was amplified by polymerase chain reaction (PCR). The oligonucleotides were used as primers for *TAP1*(*C/T* intron 7), Forward:GTGCTCTCACGTTCCAAGGA, Reverse: AGGAGTAGAGATAGAAGAACC and *TAP2* (A/G exon 11), Forward:3- GGTGATTGCTCACAGGCTGCCG Reverse: CACAGCTCTAGGGAAACTC. Amplification reactions were carried out in 25-μL of reaction mixture containing 100 ng genomic DNA, 0.25 mmol/L dNTPs, 2 mmol/L $MgCl_2$, 10 mMTris-HCl (pH=8.3). 50 mM KCl, 1.5 units of Taq polymerase (MBI Fermentas, Burlington, Ontario, Canada), and 0.3 mmol/L of each primer (Sigma-Aldrich, USA). PCR was carried out at 95°C for 2.5 min, 30 cycles of 30 s at 95°C, 30 s at 55°C, and 72°C for 30 s, followed by a final 5 min at 70 C.(Amplification reactions and PCR condition were same for both genes).

Restriction digestion: RFLP assay was performed in a 15 μL reaction mixture containing PCR product (10 μL), buffer (1.6 μL), enzyme (Msp1, 3 unit per reaction) and distilled water (3 μl). The reaction mixture was incubated at 37°C for 3 h. After digestion, for *TAP1,* T allele gave a product of 183 bp and the C allele gave two fragments of 161 and 22 bp, in case of *TAP2* with same condition *AA* genotypes were identified by the presence of only 225 bp fragment, *AG* genotype by the presence of 225, 205, 20 bp fragments and *GG* genotype by 205 and 20 bp fragments.

Statistical analysis

The association between polymorphism in *TAP1* and *TAP2* genes with the risk of cervical cancer was estimated by computing odds ratio (OR) and 95% confidence intervals (95% CI), using a multivariate logistic regression analysis that included several potential confounding variables. The Statistical analysis was performed using Epi-Info software (Epi-Info, version 3.2, Center for Disease Control and Prevention, Atlanta, GA, USA) and software SPSS version 10.0 (SPSS, Chicago, IL) . Significance was set at $P<0.05$.

Table 3 Association between *TAP1* and *TAP2* genotypes and type of cervical cancer

AP1	Type of cancer	n[c]	OR (95% CI)[a]	P -value[b]
TT	No cancer	10/10	1.0(ref)	–
TC	SCC	158/174	1.01 (0.37–2.78)	
	AC	24/121	1.33 (0.20–8.97)	
CC	SCC	8/16	0.56 (0.13–2.27)	–
	AC	–		
TC+CC	SCC	166/190	0.97 (0.35–2.67)	
TAP2				
AA	No cancer	32/17	1.0(ref)	
AG	SCC	141/152	0.54 (0.27–1.08)	
	AC	2/152	0.78 (0.25–2.38)	
GG	SCC	5/31	0.22 (0.09–0.51)	$P<0.001$
	AC	2/31	0.40 (0.07–2.21)	
AG+GG	SCC	146/183	0.47 (0.24–0.92)	$P=0.02$
	AC	4/183	0.72 (0.23–2.18)	

Abbreviations: *AC* adenocarcinoma, *CI* confidence interval, *NA* not applicable, *n*[c] number of case and control, *OR* odds ratio, *ref* Reference, *SCC* squamous cell carcinoma

[a] ORs were adjusted for age, smoking status, and use of oral contraceptives

[b] $p<0.05$ has been mentioned

Table 4 Association between *TAP1* and *TAP2* genotypes and smoking habits in women with cervical cancer and healthy controls

*TAP1*genotype	Statue of smoking	Case %	Control %	OR(95% CI)[a]
TT	Never smoking	5 (4.5)	5 (4.2)	1.0(ref)
TT	Passive smoking	5 (5.7)	1 (6.6)	
TC	Passive smoking	80 (90.9)	53 (80.3)	1.20 (0.64–2.3)
CC	Passive smoking	3 (3.4)	2 (13.2)	1.20 (0.47–3.09)
TC+CC	Passive smoking	83(94.3)	55(98.2)	1.08(0.59–1.97)
*TAP2*genotype				
AA	Never smoking	16 (14.5)	8 (5.8)	1.0(ref)
AA	Passive smoking	16 (18.2)	5 (8.9)	
AG	Passive smoking	68 (77.3)	49 (78.5)	0.69 (0.25–1.90)
GG	Passive smoking	4 (4.5)	2 (3.5)	1.00 (0.53–1.88)
AG+GG	Passive smoking	72(81.8)	51(91.07)	0.71(0.25–1.92)

Abbreviations: *CI* confidence interval, *OR* odds ratio, *ref* Reference

[a] ORs were adjusted for age and use of oral contraceptives

Results

The genotype of the *TAP1* and *TAP2* genes in cervical cases and healthy controls derived from north India population was analyzed.

Demographic variables for cases and controls have been summarized in Table 1. The variables have also been categorized for squamous cell carcinoma (SCC) and adenocarcinoma (AC) cervical cancer; 175 were identified as SCC and 25 as AC.

The mean±SD age was 48.55±9.43 years in the study group and 48.81±9.64 years in the control group. Compared with the controls, the study group had younger age at the time of the marriage (16.36±3.39) and of the birth of first child (18.39±3.39) and had a greater median number of children (4.11 vs 2.50). Ages at menarche and menopause were found to be comparable between cases and controls.

As shown in Table 2, the distribution of *TAP1* genotypes among cervical cancer cases and controls. The frequency of *TC* genotype was greater in cases (91.0%) than controls (87.0%), while those of *CC* genotype was higher in controls (8.0%) than cases (4.0%). In case of *TAP2* , the frequency of *AA* (16%) and *AG* (80.5%) genotypes was greater in cases than controls (8.5%,76% respectively). On the other hand, *GG* genotype of *TAP2* was more frequent in control (15.5%) than cases (3.5%).

The association between the *TAP* genes and cervical cancer is summarized in Table 2. In case of *TAP1*, marginal risk of cervical cancer was found in individuals with *TC* and combined *TT* + *CC* (OR=1.05, 95% CI=0.39–2.79–OR= 1.0, 95% CI=0.37–2.67) genotypes respectively. There was a decrease in OR (OR=0.50, 95% CI=0.12–2.0) for *CC* genotype as well. A highly significant decrease was observed in the OR of patients carrying *GG* and combined *AA+GG* genotypes of *TAP2* (OR=0.12, 95% CI, 0.04–0.39, $P<0.001$ and OR=0.50, 95% CI=0.25–0.95, $P=0.03$ respectively).

When the genotypes of *TAP1* were stratified according to histological subtypes (Table 3), there was no association between *TAP1* genotypes and type of cervix cancer. A significant decrease in OR was observed for patients with *GG* and combined *AA* + *GG* genotypes of *TAP2* for SCC (OR=0.22, 95% CI=0.09–0.51, $P<0.001$ and OR=0.47, 95% CI=0.24–0.92, $P=0.02$ respectively).

Table 5 Relationship between *TAP1* and *TAP2* genotypes and oral contraceptive use in women with cervical cancer and healthy controls

TAP1	Case (%)	Control (%)	OR(95% CI)	P –value[b]
TT (none used)	5 (4.0)	6 (7.5)	1.0(ref)	–
TT	5 (6.7)	1 (0.83)	1.83(0.87–3.04)	
TC	65 (86.7)	111 (89.0)	0.81 (0.41–1.60)	
CC	5 (6.7)	8 (6.6)	0.75(0.11–5.13)	
TC+CC	70(35.0)	119(59.5)	0.81(0.42–1.60)	
TAP2				
AA(none used)	20 (16.0)	6 (7.5)	1.0(ref)	–
AA	12 (16.0)	10 (8.3)	0.36(0.09–1.46)	
AG	61 (81.3)	84 (70.0)	0.55 (0.41–0.73)	$P=0.02$
GG	2 (2.7)	26 (21.6)	0.09 (0.02–0.36)	$P<0.001$
AA + GG	63(31.5)	110(55.5)	0.47(0.35–0.63)	0.0002

Abbreviations: *CI* confidence interval, *OR* odds ratio, *ref* Reference

[a] ORs were adjusted for age and smoking status

[b] $p<0.05$ has been mentioned

None of the genotypes of *TAP1* and *TAP2* were found to be significantly associated with the risk of cervical cancer in passive smokers (Table 4)

The relationship between *TAP1* and *TAP2* genotypes and use of oral contraceptives are given in Table 5. There was an decreased OR in patients using oral contraceptives having TAP_1 (*TC*) genotype (OR=0.81, 95% CI=0.41–1.60). In case of *TAP2*, statistically significant relationship was found between the use of oral contraceptives and decreased risk of cervical cancer in those having TAP_2 (*AG* and *GG*) genotypes (OR=0.55, 95% CI=0.41–0.73, P=0.002 and OR=0.09, 95% CI=0.02–0.36, P<0.001 respectively).

Discussion

To the best of our knowledge, no such study has been carried out on cervical cancer. So this is the first case-control study which has analyzed the effect of *TAP* gene polymorphism on the risk of developing cervical cancer in north Indian population. The importance of host factors, particularly immunoregulatory genes, in the pathogenesis of cervical cancer has become more evident over the past decade. Longitudinal studies have shown that most women exposed to high risk types of HPV clear the virus [17, 18]. A smaller subset has intermittent virus present in the genital mucosa, but about 11% of women have consistent detectable virus in the mucosal tissues after exposure [19]. The factors that result in persistent carriage of the virus are unknown, but one factor appears to be the absence of a cytotoxic T-cell response with which to clear the virus [20].

The present study sought to identify the possible link between *TAP* gene polymorphisms and the risk of developing cervical cancer in north Indian population. No association has been identified between risk of cervical cancer and *TAP1* and *TAP2* genes polymorphism. Fowler *et al* [21] demonstrated that *TAP2 AB* genotype, having high frequency in patients with cervical cancer, may be relevant to evolution of cervical cancer from precursor lesions. Hodson *et al* [22] did not found any association between *TAP2* gene polymorphism and renal cell carcinoma. It has been reported that a neoplastic transformation is frequently associated with impaired TAP expression [23]. In addition, lack of TAP resulted in reduction of MHC class 1 antigen in various cancers [24]. Loss of MHC class 1 antigen expression on the cell surface is assumed to allow tumors to avoid being killed by cytotoxic T lymphocytes [25].

The limitations of the present study are as follows: first the present study is hospital-based and exist in environment; therefore, it can't be free from any selection bias. Second, the current study didn't include all clustered polymorphism site of *TAP1*, *TAP2* and associated genes; the haplotypes analysis could not be done. So it would be worthwhile to perform further large scale population-based study including the analysis of various clustered polymorphisms. In conclusion, in north Indian population, *TAP1* and *TAP2* genotypes are not associated with increased risk of cervical cancer.

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