

Research Article

Association of TAP Gene Polymorphisms and Risk of Cervical Intraepithelial Neoplasia

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Background. Transporter associated with antigen processing (TAP) is responsible for peptide loading onto class I major histocompatibility complex (MHC-I) molecules. TAP seems to facilitate the detection of HPV by MHC-I molecules and contributes to successful eradication of HPV. TAP polymorphisms could have an important impact on the course of HPV infection. **Objective.** The aim of this study is to evaluate the association between five TAP gene polymorphisms and the risk of CIN. **Methods.** This case-control study investigated five common TAP polymorphisms in TAP1 (1341 and 2254) and TAP2 (1135, 1693, and 1993) in 616 women with CIN and 206 controls. Associations between gene polymorphisms and risk of CIN were analysed by univariate and multivariable models. The combined effect of the five TAP gene polymorphisms on the risk for CIN was investigated by haplotype analysis. **Results.** No significant difference in genotype distribution of the five TAP polymorphisms was observed in women with CIN and controls. Haplotype analysis revealed that women with haplotype mut-wt-wt-wt-wt (TAP polymorphisms t1135-t1341-t1693-t1993-t2254) had a significantly lower risk for CIN, compared to women with the haplotype wt-wt-wt-wt-wt ($P = 0.006$; OR 0.5 [0.35–0.84]). **Conclusion.** Identification of this haplotype combination could be used to identify women, less susceptible for development of CIN following HPV infection.

1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant disease, often leading to invasive cervical cancer [1]. Cervical cancer is the second most common cancer in women [2]. It is widely known that CIN is caused by an infection with high-risk human papillomavirus (HPV) types [3, 4]. Interestingly, most HPV infections are transient and do not lead to CIN [5].

Genetic, immunologic, and socioeconomic factors play a role in the natural history of HPV infection and development of cervical intraepithelial neoplasia. Lifestyle factors, such as cigarette smoking, are well known to be a risk factor for HPV persistence and development of cervical intraepithelial neoplasia, the precursor lesion of cervical cancer [6]. Compared to women who have never smoked, current cigarette

smokers have a significantly increased risk of high-grade cervical intraepithelial neoplasia and cervical cancer [7].

Host factors such as the immune systems and genetic factors also seem to be important factors in HPV persistence and subsequent cervical cancer carcinogenesis [8, 9].

The transporter associated with antigen processing (TAP) belongs to the superfamily of ATP-binding cassette (ABC) transporter that is essential for peptide loading onto class I major histocompatibility complex (MHC-I) molecules [10, 11]. TAP genes are encoded in the MHC class II region of chromosome 6. Transporter associated with antigen processing is composed of two integral membrane proteins, TAP1 and TAP2, which have one hydrophobic region and one ATP-binding region each. They assemble into a heterodimer, which results in a four-domain transporter. TAP 1 functions

by providing a supply of candidate peptides to the MHC I molecules within the peptide loading complex and by transporting antigen peptides from the cytoplasm into the endoplasmic reticulum (ER) [12, 13].

MHC-I molecules play a major role in the immune response against viral infections and transformed cells by presenting peptide antigens to cytotoxic T lymphocytes (CTL) [14, 15]. The loss of MHC class I expression is observed commonly in various tumours and is possibly the mechanism underlying the ability of neoplastic cells to evade the immune system [16]. Regarding cervical cancer, MHC-I antigen has been reported to be downregulated in HPV-16 and -18 positive cervical malignancies [17]. TAP facilitates the detection of HPV by MHC-I molecules and contributes to successful detection and eradication of HPV despite various immunoevasion mechanisms of the virus [18]. Therefore TAP gene polymorphisms have been investigated in women with cervical cancer precursor lesions and in women with cervical cancer [19–22]. Einstein et al. ascertained a reduced risk for high-grade CIN at the presence of TAP1 I333V and TAP1 D637G.

In the present study, we evaluated the association between five common TAP gene polymorphisms in TAP1 and TAP2: TAP1 1341 (rs1057141), TAP1 2254 (rs1135216), TAP2 I135 (rs1800454), TAP2 1693 (rs2228396), and TAP2 1993 (rs241447) and the risk of CIN in a total number of 822 women.

2. Materials and Methods

Women, who were referred to the Department's outpatient clinic for genital dysplasia between 2004 and 2009 because of a cytological result "atypical cells of undetermined significance (ASC-UCS)" or higher, were asked to participate at the present study. In total, 616 Caucasian women with histologically proven CIN 1-3, treated at the Department of Gynaecology and Gynaecological Oncology, Medical University of Vienna, Comprehensive Cancer Centre, Vienna, Austria, were included in this study.

The examination in our outpatient clinic comprised ecto- and endocervical cytology, human papilloma virus (HPV) DNA testing (Hybrid Capture 2-test, Digene Corporation, Gaithersburg, MD, USA), application of 3% acetic acid, colposcopy, and colposcopically guided biopsy. An additional cervical smear was taken to collect the DNA sample. After the women agreed to participate at the study by signing informed consent, they were asked about their smoking status (yes including previous smokers versus no), and the clinical examination was performed. The patients, in whom no CIN 1-3 was diagnosed after colposcopically guided biopsy, were excluded of further analysis ($n = 60$ patients).

As a control group, we included 206 consecutive Caucasian women, who presented at the Department's gynaecologic outpatient clinic between 2004 and 2009 with vaginal infection, pelvic pain or similar symptoms, and without a history of conization or histologically proven CIN 1-3. Patients, who agreed to participate, signed informed consent and had in addition to their particular examination,

ecto- and endocervical cytology and one cervical smear to collect the DNA samples. Only patients with normal cytology were included in the control group. No HPV-testing was done for patients in the control group.

Patients with known HIV, hepatitis B or C infection, or a history of gynaecologic malignancy were excluded from the study. The collected PAP smears and histological samples were analyzed by a board certified pathologist specialized in Gynaecological Oncology. The study was conducted according to the Declaration of Helsinki.

The Institutional Review Board at the Medical University of Vienna approved this study (Reference: EK number 017/2004).

2.1. DNA Isolation. DNA was extracted from patients' cervical smear using QIAamp DNA Blood Mini Kit (QIAGEN, Germany) according to the instruction of manufacturer. DNA was stored at 4°C until the samples were further processed.

DNA was amplified with polymerase chain reaction (PCR) and DNA pyrosequencing was performed according to established protocols as described previously [23]. After researching *dbSNP*, the SNP database from National Center for Biotechnology Information, and PubMed, the five most common and clinically relevant TAP gene polymorphisms (i.e., TAP 1341, TAP 2254, TAP I135, TAP 1693, and TAP 1993) were chosen for investigation.

2.2. TAP Genotyping. Genotyping the five polymorphisms was carried out using pyrosequencing. Primers used for the amplification of the fragments including the polymorphic sites, the length of the PCR products, and the sequencing primers were shown in Table 1. PCR was carried out in a total volume of 25 μ L including 25 ng total DNA, 5 pmol of each sense and antisense primers and 12.5 μ L JumpStart REDTaq ReadyMix Reaction Mix (SIGMA, Missouri, USA), which contains 20 mM Tris-HCl, pH 8.3, 100 mM KCl, 4 mM MgCl₂, 0.002% gelatin, 0.4 mM each dNTP, inert dye, stabilizers, 0.06 unit/ μ L Taq DNA Polymerase, JumpStart Taq antibody. The reaction was performed on a Perkin-Elmer GeneAmp PCR system 9600 with 40 cycles at 94°C for 30 seconds, at the corresponding annealing temperature (see Table 1) for 30 seconds and 72°C for 30 seconds. The reaction was preceded by a primary denaturation step at 94°C for 1 minute and incubated at 72°C for 7 min at last.

Polymorphisms were detected using Pyrosequencer PSQ 96 and PSQ 96 SNP Reagent Kit. 25 μ L PCR product was used for pyrosequencing according to the instruction of the manufactory. 5 pmol of the sequencing primer was applied to detect the polymorphisms.

2.3. Statistical Analysis. Hardy-Weinberg equilibrium was tested by chi-square tests comparing observed and expected genotype frequencies. Differences in gene polymorphism frequencies and smoking between women with CIN and controls were assessed by chi-square tests; results are given as *P* value and odds ratio (OR) (95% confidence interval (95% CI)). In a multivariate logistic regression model, we

TABLE 1: Analysis of the five TAP gene polymorphisms.

SNP	Allele specific probes	PCR product	Sequencing primer	Annealing temperature
TAP1 1341	biotin-5'-TACCTGGTGCAGGCCTATGTC 5'-AGCGGGCCAACTCCATGAAC	150 bp	5'-AAAAGCAGAGGCAGG	64°C
TAP1 2254	5'-CATGTGGCTATAACCGTTC biotin-5'-GGATAAGTACACACGGTTTC	135 bp	5'-TTGCTCTGCAGAGGTAG-3'	52°C
TAP2 1135	5'-GAAGTCTGTGCTATAAAGAG biotin-5'-GGCTCCTTTCACAACCAC	124 bp	5'-CGCCTTGACCTGCT-3'	52°C
TAP2 1693	biotin-5'-GCACAGGTGGTTTCAGTTGG 5'-CTTATCATCTTCGCAGCTCTGC	96 bp	5'-GCTCTGCAGCCCATA-3'	58°C
TAP2 1993	5'-TCTTTCTGAGGCACTGTGATC biotin-5'-GGAAACTCAAAGCAGGAAC	283 bp	5'-TGATTGCTCACAGGCT-3'	54°C

SNP: single nucleotide polymorphism.

PCR: polymerase chain reaction.

TAP: transporter associated with antigen processing.

TABLE 2: Patients' characteristics broken down by women with cervical intraepithelial neoplasia (CIN) and controls.

Characteristics	Controls	CIN	<i>P</i>	OR (95% CI)
Total number	206	616	—	
Histology			—	
CIN 1	—	206 (33.4%)		
CIN 2	—	205 (33.3%)		
CIN 3	—	205 (33.3%)		
Smoking			0.0001 ^a	2.6 (1.7–3.9)
No	70 (64.2%)	225 (41.2%)		
Yes	39 (35.8%)	321 (58.8%)		
HPV high-risk infection			—	
Negative	—	61 (14.5%)		
Positive	—	361 (85.5%)		

^aStatistical analysis by chi-square test.

CIN: cervical intraepithelial neoplasia.

HPV: human papillomavirus.

OR (95% CI): odds ratio (95% confidence interval).

assessed the independent association between TAP gene polymorphisms, smoking, and risk of CIN. Differences in gene polymorphism frequencies between women with CIN I and CIN 2/3 were assessed by chi-square tests; results are given as *P* value and odds ratio (OR) (95% confidence interval (95% CI)).

We used the software SAS System (Version 9.1 SAS Institute Inc., Cary, NC, USA) and SPSS (SPSS 19.0, SPSS Inc. Chicago, IL, USA) for statistical analysis. Two-sided *P* values ≤ 0.05 were considered statistically significant.

Haplotypes can only be estimated and then probability values between 0 and 1 are assigned, expressing the likelihood for each haplotype to be present in one allele of a patient. These probabilities sum up to 2 in each patient (for the two alleles) and were included as continuous covariates (one for each haplotype) in the logistic regression model. Haplotypes occurring with a frequency $<5.0\%$ were pooled. A logistic regression model was estimated to evaluate whether the presence of one or more copies of each particular haplotype

in a patient is associated with a higher or lower risk of CIN, compared to a patient with two copies of the wild-type haplotype. Haplotype analysis was performed by using SAS/Genetics software.

3. Results

Women with CIN presented with the following histological results: CIN I $n = 206/616$ (33.4%), CIN II $n = 205/616$ (33.3%), and CIN III $n = 205/616$ (33.3%). Sixty-one of 422 (14.5%) women with CIN were tested negative and 361 of 422 (85.5%) positive for high-risk HPV infection. Of note, in 191 of 616 (46.0%) patients HPV tests are missing. Patients with CIN (58.8%) were smoking significantly more often than controls (35.8%) ($P = 0.0001$) (Table 2).

The TAP SNPs 1341, 2254, 1135, 1693, and 1993 were genotyped in 616 patients with CIN and 206 controls. The genotype frequencies for all the studied SNPs were in Hardy-Weinberg equilibrium in both controls and patients with

TABLE 3: Genotype and allele frequencies of the five investigated TAP gene polymorphisms in women with cervical intraepithelial neoplasia (CIN) and controls.

Gene polymorphisms	Controls (%)	CIN (%)	<i>P</i> ^a	OR (95% CI)
TAP 1341			0.08	1.4 (1.0-2.0)
wt/wt	155 (75.2%)	423 (68.7%)		
wt/mt	44 (21.4%)	172 (27.9%)		
mt/mt	7 (3.4%)	21 (3.4%)		
TAP 2254			0.3	1.3 (0.9-1.8)
wt/wt	161 (78.2%)	455 (73.9%)		
wt/mt	39 (18.9%)	148 (24.0%)		
mt/mt	6 (2.9%)	12 (1.9%)		
TAP 1135			0.8	0.9 (0.7-1.3)
wt/wt	143 (69.4%)	435 (70.6%)		
wt/mt	51 (24.8%)	165 (26.8%)		
mt/mt	12 (5.8%)	16 (2.6%)		
TAP 1693			0.3	1.3 (0.8-2.2)
wt/wt	184 (89.3%)	531 (86.2%)		
wt/mt	22 (10.7%)	84 (13.6%)		
mt/mt	0 (0%)	1 (0.2%)		
TAP 1993			0.2	0.8 (0.6-1.1)
wt/wt	90 (43.7%)	301 (48.9%)		
wt/mt	92 (44.7%)	248 (40.3%)		
mt/mt	24 (11.7%)	66 (10.7%)		

^aStatistical analysis by chi-square test are calculated wt/wt versus wt/mt and mt/mt.

TAP: transporter associated with antigen processing.

CIN: cervical intraepithelial neoplasia.

OR (95% CI): odds ratio (95% confidence interval).

TABLE 4: Multivariable regression model to determine independent risk factors for cervical intraepithelial neoplasia (CIN).

	Multivariable regression	
	<i>P</i>	OR (95% CI)
TAP 1341 (wt/wt versus wt/mt and mt/mt)	0.07	2.5 (0.9-7.0)
TAP 2254 (wt/wt versus wt/mt and mt/mt)	0.3	0.6 (0.2-1.6)
TAP 1135 (wt/wt versus wt/mt and mt/mt)	0.8	1.1 (0.6-1.8)
TAP 1693 (wt/wt versus wt/mt and mt/mt)	0.5	0.8 (0.4-1.6)
TAP 1993 (wt/wt versus wt/mt and mt/mt)	0.7	0.9 (0.6-1.4)
Smoking (no versus yes)	0.002	1.9 (1.3-2.9)

TAP: transporter associated with antigen processing.

CIN: cervical intraepithelial neoplasia.

OR (95% CI): odds ratio (95% confidence interval).

CIN. Genotype frequencies of the five investigated TAP gene polymorphisms are given in Table 4. Distribution of genotypes for the five SNPs did not differ significantly between patients with CIN and controls (Table 3). In a multivariate

model, smoking, but none of the investigated five SNPs, was independently associated with risk of CIN (Table 4).

Moreover, in 616 patients with CIN the risk of high-grade CIN was investigated. No significant association was found between the investigated TAP genotypes and risk for high-grade CIN ($P = 0.08$ for TAP 1341; $P = 0.3$ for TAP 2254; $P = 0.8$ for TAP 1135; $P = 0.3$ for TAP 1693; $P = 0.2$ for TAP 1993) (Table 3).

The combined effect of the five TAP gene polymorphisms on the risk for cervical intraepithelial neoplasia was investigated by haplotype analysis (Table 5). Haplotype analysis revealed that women with haplotype mut-wt-wt-wt (TAP polymorphisms t1135-t1341-t1693-t1993-t2254) had a significantly lower risk for CIN, compared to women with the haplotype wt-wt-wt-wt-wt ($P = 0.006$; OR 0.5 [0.35-0.84]).

4. Discussion

The aim of the present study was to evaluate the association between five common TAP gene polymorphisms and risk for CIN. The haplotype combination mut-wt-wt-wt (TAP polymorphisms t1135-t1341-t1693-t1993-t2254) was associated with a reduced risk for the presence of cervical intraepithelial neoplasia (OR 0.5 (0.4-0.8)).

This finding seems biologically plausible, as TAP facilitates the detection of HPV by MHC-I molecules and contributes to successful detection and eradication of HPV

TABLE 5: Association between TAP gene haplotype combinations and risk of cervical intraepithelial neoplasia (CIN).

Haplotypes	Haplotype frequency		P	OR (95% CI)
	Controls in %	CIN in %		
(t1135-t1341-t1693-t1993-t2254)				
wt-wt-wt-wt-wt (reference)	31.2%	28.8%	—	1.0
mut-wt-wt-wt-wt	9.7%	7.3%	0.006	0.5 (0.4–0.8)
wt-mut-wt-wt-mut	5.5%	6.5%	0.7	1.1 (0.6–1.9)
wt-wt-wt-mut-wt	20.9%	16.4%	0.2	0.8 (0.6–1.1)
Others ^a	32.7%	43.6%	0.1	2.0 (0.8–4.7)

^aHaplotypes <5% were pooled (= others).

TAP: transporter associated with antigen processing.

CIN: cervical intraepithelial neoplasia.

OR (95% CI): odds ratio (95% confidence interval).

despite various immunoevasion mechanisms of the virus [2]. Although the biological implication of the observed haplotype combination is not fully elucidated, this haplotype combination might facilitate the detection of HPV and subsequently reduce the risk for CIN development.

Our observation is in line with studies investigating the role of TAP gene polymorphisms and risk for high-grade CIN and cervical cancer [7, 13]. Einstein et al. ascertained a reduced risk for high-grade CIN at the presence of TAP1 I333V ($P = 0.02$) and TAP1 D637G ($P = 0.01$). In women with cervical cancer, a TAP2 gene polymorphism has been associated with a reduced risk for cervical cancer [13]. Of note, this study was performed in an Indian cohort although no population diversities for these gene polymorphisms are described.

Interestingly, we were not able to ascertain any association between five common TAP polymorphisms and risk of CIN in a relatively large number of women. As we did not aim to evaluate the exact biological mechanisms exerted by the five TAP gene polymorphisms or their haplotype combinations, we did not investigate MHC-I serum levels and we did not obtain tissue of the patients. Moreover, patients in the present study represent a highly selected group of women, as all patients were of Caucasian origin and have been recruited at a single tertiary care center in Vienna, Austria.

In a multivariate model, smoking, but none of the investigated five SNPs, was independently associated with risk of CIN. It is well known that women smoking cigarettes are at higher risk for development of CIN. Due to these facts patients should be advised to quit smoking to reduce the risk for high-grade CIN development and increase spontaneous regression.

In the present study the protective effect of a TAP1 and TAP2 haplotype combination for the presence of CIN has been observed in a relatively large cohort of Caucasian women. Although its further implication has to be elucidated, this haplotype combination could be used to identify women, less susceptible for development of CIN following an infection with high-risk human papillomavirus.

Conflict of Interests

The authors declare that they have no conflict of interests.

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