EFFECT OF DRD2/ANKK1 TAQIA ALLELIC POLYMORPHISM ON THE RISK AND PROGNOSIS OF CERVICAL PRECANCER AND CANCER

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ABSTRACT

Objectives: The aim of this study was to elucidate the role of dopamine receptor D2 / ankyrin repeat and protein kinase domain containing 1 (DRD2/ANKK1) TaqIA allelic polymorphism in the HPV-induced cervical carcinogenesis. Methods: 1. Effect on the risk of cervical precancer: After an 8-year follow-up, out of 214 women with persisting high-risk HPV infection, 102 developed high-grade cervical dysplasia or cervical intraepithelial neoplasia (CIN) grade III, while 112 did not. The subjects were genotyped for the DRD2/ANKK1 TaqIA polymorphism by PCR-RFLP, and the allelic distributions were compared between groups with and without high-grade dysplasia. 2. Prognostic value: Two hundred and thirty nine women with cervical precancer/cancer were followed for 5 years. Complete remission was achieved at 182 women. To assess the prognostic value of the TaqIA polymorphism, genotype frequencies were compared between patients reaching and not reaching complete remission. Results: The frequency of A1/A1+A1/A2 genotypes was higher among women who developed high-grade cervical dysplasia (OR: 1.87, 95% CI: 1.05-3.33; p=0.034) than in the other group. Occurrence of the A1 allele was more frequent among women who did not reach complete remission (OR: 2.00, 95% CI: 1.07-3.74; p=0.030) than in women with complete remission. Conclusions: This is the first report on the possible involvement of DRD2/ANKK1 TaqIA polymorphism in cervical carcinogenesis. The A1 allele seems to increase the risk of cervical precancer, and it may also be associated with a worse prognosis in women with HPV-induced cervical cancer. The results need further validation in large-scale molecular epidemiological studies.

UDC CLASSIFICATION & KEYWORDS

■ 618 ■ Cervical Cancer ■ Precancer ■ DRD2 ■ Polymorphism ■ HPV ■

INTRODUCTION

In spite of its decreasing mortality rate, cervical cancer is still an important tumor in developed countries, due to its high incidence, including precancerous lesions [1]. Human papillomavirus (HPV) infection, particularly with high-risk strains is considered to be the most important risk factor for cervical cancer [2-4]. Cancer risk has been shown to be in a strong association with certain strains of HPV (e.g. 16, 18, 31, 45), while no or weak association was found with other strains (e.g. 43, 44) [5-7]. However, even in case of a persisting infection with high-risk HPV strains not all of the affected women will develop cervical cancer or dysplasia [8]. Possibly the HPV infection exerts its carcinogenic effect in an interaction with known other risk factors like smoking, long term oral contraceptive use, immunological factors, diet, having multiple children, genetic factors [4,8-12].

Stress and other psychological risk factors have been reported to increase the risk of malignant tumors, including cervical cancer [13-15]. The effect of stress depends on its amount, type, and even more strongly on the so-called stress handling ability. Stress-handling techniques like relaxational-meditational methods have been reported to decrease the risk of psychosomatic diseases [16]. In the development of mental disorders, psychiatric diseases, personality and stress-handling problems, often disturbances in a neurotransmitter system can be demonstrated [17,18]. Dopaminergic pathways take part in important central nervous system functions like motivation, pleasure, compulsion, fine tuning motor functions [19,20]. Dopaminergic neurons are located to the substantia nigra and ventral tegmental area, with axons reaching the striatum and the frontal cortex [21]. Dopamine itself is a neurohormone, exerting its effects through membrane receptors [19].

Dopamine receptor D2 (DRD2) is a member of a receptor family which mediates the cellular effects of dopamine. DRD2 has several polymorphisms, but its TaqIA single nucleotide polymorphism (SNP), located in the 3' untranslated region of the gene has by far received the most attention. This polymorphism is associated with different functional changes, e.g. individuals with A1/A1 or A1/A2 genotypes had a lower level of DRD2 receptor expression in different parts of the central nervous system [22]. The TaqIA polymorphism has been identified as a risk-modifier for several psychiatric diseases, mental disorders, and different forms of addictions like smoking and alcoholism [23-28]. It has also been suspected to have an influence on the risk of certain tumors (e.g. lung, colorectal, breast) [29-31]. Recently, this polymorphism was identified to actually belong to an exon in the ankyrin repeat and kinase domain containing 1 (ANKK1) gene, neighboring to the DRD2 [32]. The ANKK1, as a member of receptor interacting protein kinases, may also play a role in the dopaminergic neurotransmission [32]. Since the TaqIA polymorphism is in strong linkage disequilibrium with other DRD2 polymorphisms, its described impact on the risk of mental disorders is most probably a joint effect of DRD2 and ANKK1 mediated mechanisms.

Since, to our best knowledge, no studies have been conducted yet on the association between DRD2 polymorphisms and cervical cancer or high-grade dysplasia; in the present study we investigated the possible effect of the most frequently studied DRD2 polymorphism (DRD2/ANKK1 TaqIA) on the risk of cervical precancer. In addition, in a separate group of patients, we also examined the possible prognostic role of this allelic polymorphism in cervical cancer.

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Materials and methods

Study subjects

Role of the DRD2/ANKK1 TaqIA allelic polymorphism as a possible risk factor. Two hundred fourteen women, free from cervical cancer or dysplasia, but with a persistent high-risk HPV positivity in their anamnesis were involved in the first part of the study (HPV positivity was verified retrospectively from archived material). The participants were selected from women attending gynecological screening at the Fejér County "Szent György" Hospital or at the Diósgyőr Hospital, Hungary. The participants were followed for an 8-year period, which involved annual gynecological control and cervix cytology, or biopsy if needed. Development of a high-grade dysplasia or cervical intraepithelial neoplasia (CIN) was registered during the observational period. Occurrence of A1/A2 alleles was compared between participants with and without the development of dysplasia. The main characteristics of the participants are summarized in Table 1.

Prognostic value of the DRD2/ANKK1 TaqIA polymorphism. In this part of the study 239 women from the same hospitals were involved, with a diagnosis of CIN grade III or cervical cancer stage I. The presence of a high-risk HPV infection was also verified. All the participants received an appropriate treatment, according to their histopathological findings, based on the current guidelines. At the end of a 5-year observation period the participants were divided into the following 2 categories: 1. Progression, eventual death, necessity of treatment at the end of the observation period. 2. Tumor free status without any signs of recurrence or metastasis. DRD2/ANKK1 A1/A2 genotype frequencies were compared between patients with and without disease progression, in order to assess the prognostic role of the DRD2 allelic polymorphism. Characteristics of the patients are shown in Table 2.

At the beginning of the follow-up, a detailed explanation was given to the participants on the goals of our study, and an informed consent was collected from them.

DRD2/ANKK1 genotyping

For the DRD2/ANKK1 TaqIA genotyping [33], DNA was isolated with the phenol-chloroform method from peripheral white blood cells. A PCR amplification was performed in a total volume of 15 µl, with 0.5-0.5 µM primers (5'CACGGCTGGCCAAGTTGTCTA3', 5'CACCTTCCTGAGTGTCATCAA3'), 0.5 U Taq DNA polymerase (Go Taq, Promega), 1X Buffer (Promega), 2 µl DNA template, 200 µM dNTP and 2.5 mM MgCl2. The parameters of the PCR reaction were as follows: 5 min denaturation at 95°C, 40 cycles of 30 s at 94°, 30 s at 55°, 1 min at 72°, followed by a final extension step of 7 minutes at 72°. The PCR product was digested with TaqI restriction endonuclease, and the DNA fragments were separated by electrophoresis in a 1.4% agarose gel. In case of the A1 allele, a 300 bp product indicated the lack of digestion, while the presence of the A2 allele resulted in two fragments (125 and 175 bp).

Statistics

The demographical characteristics of the study populations were compared by Student's t test for independent samples (for continuous variables) and Pearson's chi-square test (for binary variables). Occurrence of DRD2 allelic frequencies were compared by multivariate logistic regression analysis. A chi-square analysis was performed, and odds ratios with 95% confidence intervals were calculated to describe the effect of DRD2 genotypes. Because of the relatively low number of A1 homozygotes, this group was treated together with the heterozygous individuals. In the multivariate model the ORs were adjusted for age, age at menarche, age at first intercourse, parity, number of abortions. The first three variables were entered as continuous variables, while for parity and number of abortions two categories (0-1 or ≥2) were formed. At the analysis of prognostic significance, status of the patients at the end of the 5-year observation period was chosen as the simplest possible outcome variable. $P<0.05$ was chosen as a level of statistical significance throughout the whole analysis. The statistical analysis was performed using the IBM SPSS Statistics software package version 19.

Results

In the first part of the study, over the 8-year follow-up, 102 women showed a high-grade dysplasia or CIN grade III (group 1), while 112 had no cytological abnormalities (group 2). There was no statistically significant difference between the studied demographical characteristics (age, age at menarche, age at first intercourse, parity, number of abortions) of the two groups. The distribution of DRD2/ANKK1 TaqIA alleles in the two groups was as follows: Women with dysplasia or CIN III: 7 (6.9%) A1 homozygotes, 39 (38.2%) heterozygotes and 56 (54.9%) A2 homozygotes; women without dysplasia: 4 (3.6%) A1 homozygous, 30 (26.8%) heterozygous and 78 (69.6%) A2 heterozygous individuals. The genotype frequencies are shown in Table 3. Presence of the A1 allele, including A1 homozygous and heterozygous individuals, was statistically significantly more frequent among women with dysplasia than in the other group (OR: 1.87, 95% CI: 1.05-3.33; p=0.034). These results mean that HPV-infected women with at least one copy of the A1 allele have somewhat higher risk for the development of cervical precancer than A2 homozygous individuals.

In the second part of the study, 25 patients died during the 5-year follow-up, 32 showed progression or still received treatment at the end of the observation period (group 3), while 182 women had no sign of the tumor or a metastasis (group 4). No statistically significant difference was found between the demographical characteristics of group 3 and group 4. In group 3 there were 5 DRD2/ANKK1 TaqIA A1 homozygotes (8.8%), 25 heterozygotes (43.8%), and 27 A2 homozygotes (47.4%) (Table 4). The genotype frequencies in group 4 were as follows: A1/A1: 9 (5.0%), A1/A2: 55 (30.2%), A2/A2: 118 (64.8%). In the group with worse prognosis the occurrence of the A1 allele was statistically significantly more frequent (OR: 2.00, 95% CI: 1.07-3.74; p=0.030) than among women reacting well to the treatment. According to the results, cervical precancer and cancer patients carrying at least one copy of the A1 allele had a worse prognosis than patients homozygous for the A2 allele.

Conclusion

Cervical cancer is a special tumor type, since its major risk factor is the infection with human papillomavirus. However, HPV infection cannot be considered as the only carcinogenic factor in cervical carcinogenesis. For example, smoking has also been demonstrated to increase the risk of cervical cancer [10,11,34], and several other risk factors have been identified as well [9,12]. In the light of the strong association between HPV infection and cervical carcinogenesis, we should rather consider the other, "traditional" risk factors as modifiers of the HPV-induced cervical carcinogenesis.

Table 1. Characteristics of study subjects for the risk-analysis.

Variable	Group 1 with high-grade dysplasia	Group 2 without high-grade dysplasia
Age at the beginning of the follow-up, (SD)	40.05 (13.71)	41.16 (13.05)
Age at menarche, (SD)	13.21 (1.06)	13.10 (1.00)
Age at first intercourse, (SD)	17.86 (1.67)	17.66 (1.83)
Parity 0-1	66 (64.6%)	68 (60.7%)
≥2	36 (35.3%)	44 (39.3%)
Number of abortions 0-1	91 (89.2%)	99 (88.4%)
≥ 2	11 (10.8%)	13 (11.6%)

Source: Authors

Table 2. Characteristics of patients at the analysis of the prognostic significance of DRD2/ANKK1 TaqIA polymorphism.

Variable	Group 3 - worse prognosis	Group 4 - better prognosis
Age at the beginning of the follow-up, (SD)	42.18 (12.92)	42.92 (12.53)
Age at menarche, (SD)	13.04 (1.03)	13.17 (1.15)
Age at first intercourse, (SD)	17.37 (1.70)	17.77 (1.89)
Parity 0-1	29 (50.9%)	101 (55.5%)
≥2	28 (49.1%)	81 (44.5%)
Number of abortions 0-1	52 (91.2%)	158 (86.8%)
≥2	5 (8.8%)	24 (13.2%)

Source: Authors

Table 3. Distribution of DRD2 TaqI allelic frequencies in different groups of women with persistent high-risk HPV infection.

Variable	Group 1 with dysplasia	Group 2 without dysplasia	OR (95% CI)	p-value
A2/A2	56 (54.9%)	78 (69.6%)	1.00 (reference)	-
A1/A2	39 (38.2%)	30 (26.8%)	1.87 (1.05-3.33)	p=0.034
A1/A1	7 (6.9%)	4 (3.6%)		
Total	102 (100.0%)	112 (100.0%)	0	

Source: Authors

Table 4. Distribution of DRD2 TaqI allelic frequencies in women with HPV-induced cervical precancer and cancer.

Variable	Group 3 - worse prognosis	Group 4 - better prognosis	OR (95% CI)	p-value
A2/A2	27 (47.4%)	118 (64.8%)	1.00 (reference)	-
A1/A2	25 (43.8%)	55 (30.2%)	2.00 (1.07-3.74)	p=0.030
A1/A1	5 (8.8%)	9 (5.0%)		
Total	57 (100.0%)	182 (100.0%)	0	

Source: Authors

Even persisting HPV infections do not necessarily lead to a high-grade dysplasia, e.g. a persistent HPV 16 infection may lead to a cervical precancer after 3-5 years in approximately 40% of the affected women [35-37]. In our study the incidence of precancer was somewhat higher (102 out of 214, i.e. 47.7%), which can be explained by the longer (8-year) observation period, and by the possibility that the persistence of the HPV infection was even longer than the follow-up period, because some participants had probably acquired the HPV infection long before their first HPV test. Identification of HPV carriers at a particularly high risk of cervical precancer formation would be an important step in the development of a more efficient and accurate management procedure for HPV-positive women. In order to be able to develop such a solid and well-working risk assessment structure, all the possible factors modulating the mentioned processes should be incorporated into the risk assessment framework.

Such factors might be the allelic polymorphisms of cancer-related genes. Polymorphism of several carcinogen-metabolizing enzymes can lead to an altered concentration of active carcinogenic compounds, which could easily modulate the cancer risk [38-40]. Certain allelic variants of DNA repair enzymes may be in an association with a less efficient DNA repair capacity, thus increasing the risk of cervical cancer [41-42]. The codon 72 Arg/Pro polymorphism of the p53 gene could also be important, on one side through modulation of cell cycle and apoptotic ability, and on the other side, through its specific interaction with HPV E6 protein [43-45].

In contrast to the previously mentioned factors, the effect of the DRD2 receptor polymorphism on the risk of cervical cancer is probably exerted primarily through indirect, psychological mechanisms. These mechanisms may involve higher risk for different types of addictions (alcoholism, smoking, possibly drug addictions) which can be considered as sources of chemical carcinogens [46-50]. In addition, certain behavioral patterns (e.g. having more sexual partners) possibly associated with the DRD2 genotypes may increase the risk of the infection with further HPV strains [51]. However, according to our hypothesis, the most important component of the DRD2/ANKK1-effect is its influence on the so-called stress handling ability, the way of how people cope with emotional tension and psychosocial load. Some people are more likely to develop somatic diseases or symptoms as a reaction to chronic mental stress and frustrating situations, while others have better stress-handling capability. In our present study the mode of action could not be analyzed, since no homogeneous groups could be formed due to the limited number of participants. In order to see the effect exerted through affecting the stress-handling ability, matching for alcohol consumption or smoking would have been a logical choice, but it could have reduced the overall effect of the studied polymorphism. The goal of our report was to give a rapid estimation on the overall effect, independently from how (through which intermediate variables) these effects are exerted. The different mechanisms and their interactions should be analyzed later, in separate, larger studies. Moreover, peripheral dopamine receptor

containing cells might also play a role in the DRD2 mediated risk-modification, as it was demonstrated in human colorectal carcinogenesis [52,53].

Considering the further progression of precancerous lesions, it is a well-established phenomenon that an existing cervical dysplasia does not necessarily progress toward a clinical cancer; it may even disappear (nowadays rarely seen, because – particularly high-grade atypias – are not left without treatment) [54,55]. All the factors affecting this or later stages of the tumorigenesis should be considered as prognostic factors. The fact that the DRD2/ANKK1 A1 allele proved to be a risk factor, does not necessarily confirm its role as a prognostic factor. Therefore, the prognostic value was separately analyzed in the second part of our study. These results were in accordance with the findings on its risk-increasing effect, the A1/A1 and A1/A2 genotypes were associated with a worse prognosis. Similarly to the risk evaluation, no further factors were taken into account at the prognostic analysis either, the comparison was restricted to the difference between patients with and without a complete remission.

The very few previous studies on the association of DRD2 polymorphisms with cancer were restricted to certain tumor types. The effect of single nucleotide polymorphisms within the DRD2 gene was studied on the risk of colorectal cancer [30], leiomyoma [56], breast [31,57], lung [29], and bladder [58] cancer. In case of leiomyoma, colorectal, and lung cancer the affected organs contain cells expressing the DRD2 receptor. The properties of the receptor thus modulate the direct cellular effects of dopamine, involving changes in the expression of genes responsible for cell cycle regulation and cell proliferation. Concerning breast, bladder, and also partially lung cancer, the authors explain their findings with the effect of DRD2 polymorphisms on the probability of high-risk behavior patterns. Certain DRD2 genotypes increase the risk of drug dependence, smoking, alcoholism, which leads to an elevated level of carcinogenic exposure (e.g. polycyclic aromatic hydrocarbons in the cigarette smoke). Such factors, in an interaction with each other, might be relevant in relation to the cervical carcinogenesis as well. It might also be of importance that DRD2 polymorphisms were shown to have an influence on the age at first sexual intercourse [51]. Thus, the effects of DRD2 polymorphisms on the cervical carcinogenesis are possibly exerted through a complex network of mechanisms, including smoking habits, alcohol consumption, stress-handling, and factors related to sexual behavior.

Summarizing the results, our present study demonstrated a possible risk modifying effect of the DRD2/ANKK1 TaqIA polymorphism in the HPV-induced cervical carcinogenesis. Women with the A1 allele seem to have a higher risk of cervical cancer, as it is indicated by the comparison with healthy individuals (without dysplasia). The same allele also increases the risk of tumor progression, and is associated with a worse prognosis, in HPV-induced cervical precancer and cancer. Involvement of the DRD2/ANKK1 allelic polymorphism in the risk assessment for cervical carcinogenesis seems to be a valuable tool, and deserves further molecular epidemiological studies, in order to explore this relationship and its possible molecular mechanisms.

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