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Original scientific article

THE IMPACT OF GAS5 rs145204276 ON DEVELOPMENT AND PROGNOSIS OF PROSTATE CANCER

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The long non-coding RNA (lncRNA) *GAS5* can be a marker for early diagnosis and postoperative follow-up in the patients with prostate cancer, whereby lower levels of *GAS5* correlate with tumorigenesis and unfavourable clinical course. Expression of the *GAS5* can be affected by rs145204276 polymorphism, a 5 base pairs insertion-deletion polymorphism shown as „AGGCA/-“. The aim of this study was to analyse the association between rs145204276 and prostate cancer susceptibility and prognosis.

This study was included 121 healthy subjects and 70 patients with prostate cancer. Diagnosis of prostate cancer was established by histopathology after the surgery. Genotyping was performed by allelic discrimination method using the TaqMan® assay.

In the healthy subjects, the obtained frequencies of *GAS5* rs145204276 genotypes were 80.2% of ins/ins, 16.5% of ins/del and 3.3% of del/del. The allele frequencies were 88.5% of ins and 11.5% of del, respectively. In the patient group, the frequencies of ins/ins, ins/del and del/del genotypes were 70%, 20% and 10%, respectively; the frequency of ins allele was 80% and the frequency of del allele was 20%. Observed frequencies of *GAS5* rs145204276 genotypes were not significantly different between healthy subjects and patients with prostate cancer, and also between prognostic groups of prostate cancer.

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This study demonstrate no significant association between *GAS5* rs145204276 and sussceptibility/prognosis of prostate cancer.

Key words: GAS5, long non-coding RNA (lncRNA), prostate cancer, rs145204276, single nucleotide polymorphism

INTRODUCTION

Prostate cancer is the forth most common malignancy overall and the second most common in male population worldwide (RAWLA 2019). According to data from 2018, prostate cancer accounts for 13.5% of all the newly registered carcinoma and 6.7% of all carcinoma-related deaths in male population, making prostate cancer the fifth leading cause of carcinoma deaths in male population (RAWLA *et al*., 2019; FERLAY *et al*., 2019; BRAY *et al*., 2018). Five-year survival rate in the patients with localised illness is nearly to 100%, while in the patients with metastatic disease is less than 30%, which implies the significance of disease discovery in an early stage (AMERICAN CANCER SOCIETY, 2018). Early discovery and treatment of the asymptomatic patients with prostate carcinoma significantly diminishes mortality and improves lifestyle quality (SARWAR *et al*., 2017). Therefore, identification of novel biomarkers involved in the development of prostate cancer is of great importance for the prognosis and the treatment.

Present model of prostate carcinoma screening is based on a digitorectal examination and the blood prostate specific antigen (PSA) level. At the same time, the prognosis in patients with prostate carcinoma is based on the tumor stage (Tumor, Node, Metastasis (TNM) staging system), PSA and the Gleason score of tumor grading. Several reacent papers indicated the significance of genetic features in prostate cancer prediction and prognosis (LIN *et al*., 2019).

Current molecular research show that long non-coding RNAs (lncRNAs) can be novel and significant biological markers used for early detection, diagnosis and postoperative follow up of patients with prostate cancer. LncRNAs are a group of non-coding RNA (ncRNA) molecules with length greater than 200 nucleotides with no ability to code protein, but in interaction with Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) and proteins have other important roles in cell biology, such as regulation of cell differentiation, migration, proliferation and apoptosis (LIN *et al*., 2019; MARTENS-UZUNOVA *et al*., 2014).

The *GAS5* (Growth Arrest Specific transcript 5) is a chain of long non-coding RNA 630 nucleotids long, which is transcribed from a gene located on 1q25 chromosome. *GAS5* has a role in regulation of cell proliferation and apoptosis (LIANG *et al*., 2016; PICKARD *et al*., 2013).

Previous studies have reported decreased *GAS5* expression in prostate carcinoma tissue, and lower levels of *GAS5* expresion correlate with larger tumor dimensions, lower hystological grade and higher stadiums of TNM classification. Comparative analysis of *GAS5* expresion and disease prognosis showed that patients with lower level of *GAS5* expresion have shorter survival rates and are more prone to metastasis (MISAWA *et al*., 2017; SMOLLE *et al*., 2017).

Several genetic polymorphisms have been associated with risk of prostate cancer, tumor grading and prognosis (LOEB *et al*., 2009; ZHENG *et al*., 2008). The rs145204276 variant is a 5 base pairs insertion-deletion polymorphism shown as „AGGCA/-“. Located in the promoter region of *GAS5*, rs145204276 was reported to affect the expression of *GAS5*, the most likely by influencing the binding of transcription factors or the methylation status (LU *et al*., 2019).

Since previous studies have brought inconsistent results about the clinical significance of *GAS5* rs145204276 in the cancer patients, this single-center study was aimed to analyze the association between rs145204276 and prostate cancer susceptibility and prognosis.

MATERIAL AND METHODS

The our study included 121 healthy subjects and 70 patients with prostate cancer who gave consent to provide blood sample for genetic testing. All patients underwent clinical examination, laboratory testing, radiologic examinations; diagnosis of prostate cancer was histologically confirmed after the surgery. Diagnostic procedures, treatment and sample collection were managed at Military Medical Academy (MMA), Belgrade, Serbia, between June 2019 and February 2021. Prostate cancer was staged considering TNM classification, Gleason score and PSA serum levels, as suggested by American Joint Committee on Cancer (AJCC) (BUYYOUNOVSKI *et al*., 2017). In the present study, patients with AJCC stage I and II were classified in the favorable prognosis group; patients with AJCC stage III and IV were considered as a group with poor prognosis. Baseline characteristics of the patients with prostate cancer are shown in Table 1.

Table 1. Baseline characteristics of patients with prostate cancer

CHARACTERISTIC		N (%)
Age (years)	≤65	26 (37)
	>65	44 (63)
PSA (ng/mL)	<10	37 (53)
	10-20	22 (31)
	>20	11 (16)
Gleason grade	1, 2, 3	63 (90)
	4, 5	7 (10)
Pathologic T stage	2	38 (54)
	3, 4	32 (46)
Pathologic N stage	N0	65 (93)
	N1	5 (7)
Invasion of seminal vesicles	Yes	11 (16)
	No	59 (84)
Perineural invasion	Yes	62 (89)
	No	8 (11)
Perivascular and perilymphatic invasion	Yes	23 (33)
	No	47 (67)

Peripheral blood was taken in ethylenediamin tetra-acetic acid (EDTA) tubes and stored at -20ºC. DNA was extracted by salting-out method as previously described (MILLER *et al*., 1988). *GAS5* rs145204276 genotyping was performed on StepOnePlus™ Real-Time PCR System (Applied Biosystems™, CA, USA) using the TaqMan® Genotyping assay C_166593916_10 (Applied Biosystems, CA, USA) according to manufacturer's instructions.

Obtained frequencies of *GAS5* rs145204276 genotypes (healthy subjects *vs.* patients with prostate cancer; favourable prognosis *vs.* poor prognosis) were compared by Pearson Chi-square test or two-tailed Fisher exact test. The p values <0.05 were considered statistically significant. Odds ratio (OR) and 95% confidence interval (CI) were used to estimate the risk of prostate cancer and poor prognosis.

The present study was approved by the Ethics committee of MMA Belgrade, Serbia (26/04/2018), in accordance with principles of Helsinki declaration.

RESULTS AND DISCUSSION

In the healthy subjects, the obtained frequencies of *GAS5* rs145204276 genotypes were as follows: 80.2% of ins/ins, 16.5% of ins/del and 3.3% of del/del. The allele frequencies were 88.5% of ins and 11.5% of del, respectively. The genotypic frequencies in the healthy participants were in Hardy-Weinberg equilibrium (Chi-square test= 1.239, p=0.538). In the patient group, the frequencies of ins/ins, ins/del and del/del genotypes were 70%, 20% and 10%, respectively; the frequency of ins allele was 80% and the frequency of del allele was 20% (Figure 1). Observed frequencies of *GAS5* rs145204276 genotypes were not significantly different between healthy subjects and patients with prostate cancer (Table 2).

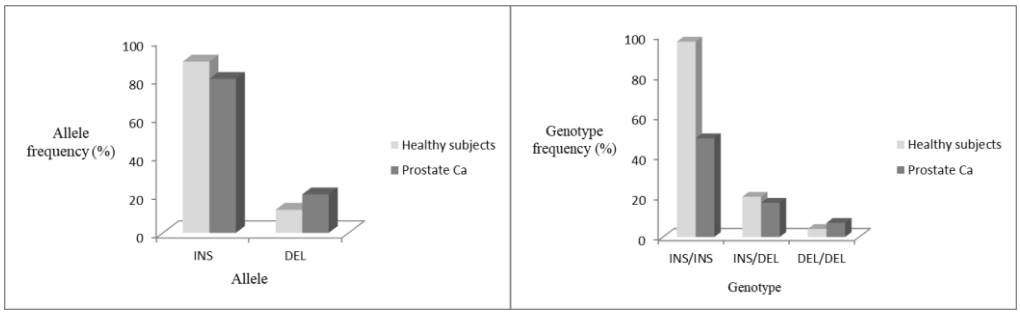

Figure 1.The frequencies of *GAS5* rs145204276 alleles and genotypes in patients with prostate cancer and healthy subjects

Table 2. The frequencies of GAS5 rs145204276 genotypes in healthy subjects (n=121) and patients with prostate cancer (n=70)

GENETIC MODEL		PATIENTS N (%)	HEALTHY SUBJECT SN (%)	OR (95% CI); p[a]
Dominant	INS/INS	49 (70)	97 (80.2)	0.58 (0.29-1.14); 0.12
	INS/DEL+DEL/DEL	21 (30)	24 (19.8)	
Recessive	INS/INS+INS/DEL	63 (90)	117 (96.7)	0.3 (0.1-1.09); 0.1
	DEL/DEL	7 (10)	4 (3.3)	

[a]p values were obtained by Pearson Chi-square test or Fisher exact two-tailed test; OR demonstrates the association between ins/ins or ins/ins + ins/del genotypes and prostate cancer; OR- odds ratio; 95% CI- 95% confidence interval

In adition, genotype frequencies were not significantly different between prognostic groups (Table 3).

Table 3. The frequencies of GAS5 rs145204276 genotypes in patients with different prognosis

GENETIC MODEL		STAGE III or IV N (%)	STAGE I or II N (%)	OR (95% CI); p[a]
Dominant	INS/INS	24 (68.6)	25 (71.4)	0.87 (0.31-2.43); 0.79
	INS/DEL+DEL/DEL	11 (31.4)	10 (28.6)	
Recessive	INS/INS+INS/DEL	33 (94.3)	30 (85.7)	2.75 (0.5-15.25); 0.43
	DEL/DEL	2 (5.7)	5 (14.3)	

[a]P values were obtained by Pearson chi-square test or Fisher exact two tailed test; OR demonstrates the association between ins/ins or ins/ins + ins/del genotypes and unfavorable stage III or IV; OR- odds ratio; 95% CI- 95% confidence interval

The impact of rs145204276 on *GAS5* expression and cancer susceptibility has been investigated in several recent studies that brought inconclusive results. This study was demonstrated lack of association between *GAS5* rs145204276 and susceptibility to prostate cancer.

Since reported frequencies of *GAS5* rs145204276 alleles vary between populations, the first aim of our study was to analyze genotype and allele frequencies in Serbian population. As expected, observed frequencies of *GAS5* rs145204276 alleles in healthy subjects (11.5% of del and 88.5% of ins) were similar as those reported across the Europe, where the frequency of del allele is about 10% and the ins frequency is about 90%. The highest frequency of del variant was reported in Asian population (about 30%), while the lowest were found in Africans (about 4%) and South Americans (about 5%) (https://www.ncbi.nlm.nih.gov/snp/rs145204276?vertical_tab=true#frequency_tab; accessed 15 September 2021).

Subsequently, we analyzed the frequency of *GAS5 rs145204276* alleles and genotypes in the patients with prostate cancer. Surprisingly, ins/del and del/del genotypes were more frequent in the patients with prostate cancer than in healthy participants. However, differences in genotype frequences between the groups were not statisticaly significant. Similar to our results, Lin et al. did not find significant statistical difference in genotype/allele frequencies between patients with prostate cancer and healthy controls (LIN *et al*., 2019). Regarding the impact of *GAS5* rs145204276 genotypes in other cancers, previous studies have brought different results. The majority of reports demonstrated decreased susceptibility for cancer (particularly lung and gastric cancer) in the carriers of del allele and both ins/del and del/del genotypes (LU *et al.*, 2019; LI *et al.*, 2018; LI *et al*., 2017). However, Hsieh et al. didn't find significantly different frequencies of *GAS5* rs145204276 genotypes between patients with oral cancer and healthy individuals (HSIEH *et al*., 2021). In addition, the del allele of rs145204276 was reported to

significantly increase the risk of hepatocellular carcinoma (TAO *et al*., 2015). These differences possibly imply the different role of *GAS5* rs145204276 in carcinogenesis of different tissues.

Considering the impact of *GAS5* rs145204276 on clinical characteristics and course of disease, published data also imply different role depending on cancer type. In oral cancer, the presence of del allele (ins/del and del/del genotype) is associated with moderate to poor cell differentiation. Advanced tumor stage and larger tumor size were more common in the non-alcohol-drinking patients with at least one del allele than in the patients with ins/ins genotype (HSIEH *et al*., 2021). In the patients with gastric cancer, del/del genotype was less frequent in the patients with advanced tumor stage and the Union Internationale Contre le Cancer (UICC) stage III and IV. In adition, patients with del/del genotype had lower incidence of cancer progression and metastasis, and also higher survival rate (LI *et al*., 2018). Data reported for prostate cancer suggested increased survival rates in the patients with *GAS5* rs45204276 ins allele and *HOTAIR* rs4759314 A allele (DENG *et al*., 2020). In the study of Lin et al., the *GAS5* rs145204276 did not affect susceptibility for prostate cancer, but lymph node involvement was more often in carriers of del allele, particularly those older than 65 years (LIN, *et al*., 2019; LI *et al*., 2017). In our study, patients with del/del genotype more frequently experienced stage I or II prostate cancer than ins carriers, but difference in genotype frequencies between prognostic groups did not reach statistical significance.

It should be noted that the majority of previous studies reported tumor-suppressor role of *GAS5* in cancer, whereby down-regulation of *GAS5* was associated with susceptibility to cancer, the presence of progressive disease and resistance to therapy across different types of tumors (YU and HANN 2019). In addition, the *GAS5* rs145204276 del variant was shown to increase the expression of *GAS5* mRNA (LI *et al*., 2018; LI *et al*., 2017; HSIEH *et al*., 2021). Some authors suggested that rs145204276 may be considered as marker of prognosis and prediction in cancer management. However, studies on some cancers (e.g. lung, gastric, colorectal) are consistent, but studies on hepatocellular or oral cancer brought discordant results, as already discussed in the paragraph above. These findings imply the need for further investigation of *GAS5* rs145204276 role in cancer. We should keep in mind that occurrence and progression of cancer is a complex process that involves accumulation of gene mutations, genomic instability, epigenetic modifications and aberrant gene expression. Furthermore, same genetic variation may have different role in pathologic processes of different tissues as a consequence of gene-environment interactions.

Thus, Tao et al. reported that *GAS5* overexpression have leads to anti-apoptotic effects in hepatocellular cancer cell lines and suggested that *GAS5* may act as a proto-oncogene in hepatocellular carcinoma. Analysis of genotype-phenotype association in their study demonstrated significant correlation of the del allele with higher expression of *GAS5* in hepatocellular cancer tissues (TAO *et al., 2015*). The another example that may be atributed to gene-environment interactions is presented in the study on *GAS5* expression in osteoporotic patients (VISCONTI *et al*., 2020). The authors reported correlation between rs145204276 del allele and a higher expression of *GAS5* in the patients with osteoporosis. However, they were unable to find a similar correlation in the control group (healthy subjects).

In summary, despite the majority of previous studies implied protective role of *GAS5* rs145204276 del allele in cancer development and progression, some discordant data imply need

for further evaluation. The our study demonstrated the lack of association between *GAS5* rs145204276 and sussceptibility, as well as prognosis of prostate cancer. However, further evaluation should include a larger cohort of patients, as well as *GAS5* expression analyses.

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UTICAJ GAS5 rs145204276 NA RAZVOJ I PROGNOZU KANCERA PROSTATE

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Izvod

Dugi lanci nekodirajuće RNK (long non-coding RNA- lncRNA) *GAS5* mogu biti marker za ranu dijagnozu i postoperativno praćenje pacijenata sa karcinomom prostate, pri čemu niži nivoi *GAS5* koreliraju sa tumorigenezom i nepovoljnim kliničkim tokom. Na ekspresiju *GAS5* može uticati polimorfizam rs145204276, polimorfizam od 5 parova baza koji se prikazuje kao „AGGCA/-". Ova studija ima za cilj da analizira vezu između rs145204276 i karcinoma prostate. Studija je obuhvatila 121 zdravu osobu i 70 pacijenata sa karcinomom prostate. Dijagnoza karcinoma prostate potvrđena je postoperativno, histopatološkim pregledom. Genotipizacija je izvedena metodom alelne diskriminacije korišćenjem TaqMan® testa.

Kod zdravih ispitanika dobijene učestalosti *GAS5* rs145204276 genotipova bile su 80,2% ins/ins, 16,5% ins/del i 3,3% del/del. Učestalosti alela bile su 88,5% ins i 11,5% del. U grupi pacijenata, učestalost genotipova ins/ins, ins/del i del/del iznosila je 70%, 20% i 10%; učestalost ins alela je bila 80%, a učestalost del alela 20%. Uočene učestalosti genotipova *GAS5* rs145204276 nisu se značajno razlikovale između zdravih ispitanika i pacijenata sa karcinomom prostate, kao ni između prognostičkih grupa karcinoma prostate.

Ova studija ne pokazuje značajnu povezanost između *GAS5* rs145204276 i karcinoma prostate.

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