

Genetic Variations in *TP53*, *RB1*, and *PTEN* in a Selected Sample of Slovak Patients With Metastatic Castration-resistant Prostate Cancer

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Abstract. *Background/Aim:* This report aimed to present identified variants with pathogenic potential in three genes — *TP53*, *PTEN*, and *RB1* — in a selected sample of patients with metastatic castration-resistant prostate cancer (mCRPC) with or without the presence of circulating tumor cells (CTCs) and splice variant AR-V7. *Materials and Methods:* Next generation sequencing was performed on an Illumina platform to analyse the genetic profiles of 50 patients with mCRPC. Identified variants were validated using the Integrative Genomic Viewer, and the correlation between these variants and the presence of CTC/AR-V7 was subjected to statistical analysis. *Results:* The study revealed a total of 15 genetic alterations in the three examined genes. The presence of rs1042522 (*TP53*) in mCRPC patients was associated with a significantly reduced likelihood of AR-V7 occurrence ($p < 0.001$), indicating a protective effect. Additionally, patients with AR-V7 showed a marked increase in prostate-specific antigen (PSA) levels. Higher PSA levels were correlated with

an increased risk of AR-V7 presence. *Conclusion:* The identified genetic mutations and PSA levels have a moderate predictive ability for determining AR-V7 status.

Prostate cancer (PC) is the most frequent oncological disease and the second most common cause of cancer-related deaths in Slovak men. With an estimated nearly 1.5 million new cases and 400 thousand deaths worldwide, PC is the third most common cancer and the fifth leading cause of death in men (1). According to the International Agency of Cancer Research, 3,606 new cases of PC were diagnosed in Slovakia in 2022, which represents 11.7% of the total types of detected malignancies; up to 944 patients succumbed to this disease this year. The etiology of PC oncogenesis is multifactorial, representing a complex of interactions between hereditary germline mutations, somatic gene alterations acquired after birth and a wide spectrum of environmental factors (2).

Hereditary prostate cancer (hPC) has the highest heritability among major cancers in men, with an estimated proportion of 5-15% of all PC cases. A significant shift in research focuses on the mutual interaction of multiple genes that may impact the development and progression of PC (2, 3). Literature suggests that genes consistently associated with hPC susceptibility include mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), homologous recombination genes (*BRCA1/2*, *ATM*, *PALB2*, *CHEK2*), and additional genes recommended for specific research, such as *HOXB13*, *BRP1* and *NSB1*. Potential therapeutic biomarkers may include tumour-suppressor genes like *TP53*, *RB1*, *PTEN*, and *CDKN1B*. The heterogeneity of PC affects further tumour behaviour, patient response to treatment, and overall survival. Androgen receptor signalling pathway (ARsp) plays an important role in the evolution of PC, affects cell proliferation and survival, and tumour invasion; its

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alterations lead to resistance to androgen deprivation therapy (ADT) (3). Although ADT is a standard treatment against hormone-sensitive metastatic PC, causes tumour cell apoptosis or cell cycle interruption with subsequent tumour regression, ultimately, there is ARsp reactivation because of the expression androgen receptor transcript splice variants (AR-V), which is also known as an important mediator of acquired resistance to AR targeting agents occurring in 15-20% of advanced, treatment resistant PCs and mostly progresses to mCRPC (4-6). This understanding prompted the development of novel AR targeting agents, such as enzalutamide and abiraterone acetate (ARTA). Despite improvements in overall survival and optimistic results, resistance eventually develops to these drugs. Resistance is invariably associated with multiple mechanisms, such as activation of the phosphatidylinositol 3-kinase (PI3K) pathway and dysregulation of additional genes implicated in growth control and genetic stability. Such genes undoubtedly include the tumour-suppressor genes *TP53*, *RBI*, *PTEN*, and *CDKN1B* (2).

Changes in protein coding regions of the mentioned genes are very common in PC. Alterations in *TP53* and *RBI* are detected in 20-50% of all mCRPC cases, while those in *PTEN* and *CDKN1B* reaches up to 62% (7). All these changes, whether deletions, loss of function mutations or polymorphisms, can disrupt the function of important signalling pathways and thus cause carcinogenesis, more aggressive course of disease, and progression to mCRPC that is AR-indifferent (8).

In this study, we analysed genomic profile of 50 patients with mCRPCa and examined their blood samples for germline mutations in three tumour-suppressors genes in combination with their AR-V7+/- status.

Materials and Methods

In this study, 104 patients from three Slovak urological clinics were prospectively enrolled. Out of these patients, we selected 50 based on specific criteria for genetic profiling [mean age=71.64, median age=71.5; mean prostate-specific antigen (PSA)=6.06 ng/ml, median PSA=19.29 ng/ml]. All patients were histologically confirmed to have PC, met the criteria for mCRPC and were recommended for treatment with abiraterone or enzalutamide.

DNA isolation. We purified genomic DNA (gDNA) from approx. 200 µl buffy coat (peripheral blood) by using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The quality and quantity of extracted DNA was sufficient for dilution to the required concentration of 20 ng/µl and preparation of NGS libraries.

Direct sequencing. The chosen panel (GeneSGKit[®]) contained several genes associated with the hereditary component of

carcinogenesis. Of these, we focused on mutations arising in the tumour-suppressor genes *TP53*, *RBI*, and *PTEN*. The NGS analysis was performed by external supplier (Sistemas Genómicos, Valencia, Spain) on the Illumina platform (HiSeq 2500 System, San Diego, California, USA). More details of NGS analysis and identified variations are described in more detail in Holeckova *et al.* (9).

Statistical data analysis. Data were explored and analysed using jamovi v 2.5. Contingency table of AR-V7 vs. mutation (rsID) was visualized using stacked barplot. Multivariate linear regression model of log-transformed PSA [ln(PSA)] vs. AR-V7 and mutations was fitted to the data and subjected to standard diagnostic check. Goodness of fit was quantified using the Adjusted R². Model-based estimated marginal means for AR-V7 as well as for mutations were used to quantify the net effect of each predictor. Post-hoc pairwise comparisons with Tukey adjustment of *p*-values were used to test the null hypothesis that the population mean of ln(PSA) is the same for a pair of single-nucleotide polymorphisms (SNPs). Marginal means for AR-V7 were visualized using the marginal means plot.

Predictive model of AR-V7 status (0/1) was constructed using the multivariate logistic regression with predictors PSA and mutations. Goodness-of-fit was quantified using McFadden's R². Predictive power was assessed using the ROC curve (not cross-validated). Based on the model, the probability of AR-V7 for each mutation (SNP) was obtained by the estimated marginal means.

Results

The gene profiles of 50 patients with mCRPC were analysed to determine the presence and frequency of germline mutations in three selected tumour-suppressor genes: *TP53*, *RBI*, and *PTEN*. Through next-generation sequencing (NGS) data analysis, a total of 15 variants were identified, including 2 missense variants (13.33%), 3 synonymous variants (20%), and 10 intronic variants (66.67%) (Table I).

Tumour protein p53 (TP53). *TP53* is a tumour suppressor gene localized on chromosome 17 (17p13) and also the most common mutated gene associated with human cancer. This gene encodes the p53 protein, also known as a guardian of the genome. As a respond to diverse cellular stress, p53 regulates cell function through multiple different mechanisms, including cell cycle arrest, apoptosis, senescence, DNA repairing, metabolic changes and autophagy. The gene spans 20 kb, with a non-coding exon 1 and 10kb long intron 1. p53 is 393 amino acid (aa) transcription factor that contains multiple domains: the N-terminal activation domain (aa 1-61), the proline-rich domain (aa 64-92), the DNA-binding domain (DBD, aa 100-300), the oligomerization domain (aa

Table I. All detected mutations in genes *TP53*, *RB1*, and *PTEN*.

HGMD	Mutation	Amino acid change	rsID	Type of mutation	No. of positive patients	CTC+ AR-V7+ patients	CTC+ AR-V7- patients	CTC- AR-V7- patients	
<i>TP53</i>		c.108G>A	p.P36P	rs1800370	Synonymous	1	1	–	–
	DFP	c.215C>G	p.P72R	rs1042522	Missense	48	6	17	25
		c.618G>A	p.L206L	rs142813240	Synonymous	1	–	–	1
	DP	c.639A>G	p.R213R	rs1800372	Synonymous	1	–	1	–
	DM?	c.993+12T>C		rs1800899	Intronic	1	1	–	–
<i>RB1</i>		c.1390-14A>T		rs9535023	Intronic	2	–	1	1
		c.1422-8delT		rs750651121	Intronic	12	2	3	7
		c.1499-10delT		rs768867054	Intronic	1	–	–	1
		c.2212-12G>T		rs776987458	Intronic	9	2	2	5
		c.2212-9C>T		rs765386327	Intronic	15	2	2	11
		c.2521-11G>A		rs4151624	Intronic	2	–	1	1
		c.2664-10T>A		rs3092904	Intronic	25	6	6	13
<i>PTEN</i>		c.804C>A	p.D268E	rs398123328	Missense	3	2	1	0
	DM?	c.802-3dupT		rs762344516	Intronic	12	1	4	7
		c.802-3delT		rs771859047	Intronic	13	1	5	7

HGMD: Human Gene Mutation Database; DFP: disease associated polymorphism with functional support; DP: disease-associated polymorphism; DM? – likely disease-causing mutation; rsID: number, unique label used by researchers and databases to identify a specific single nucleotide polymorphism (SNP).

323-355), and the C-terminal domain (aa 364-393). Mutant forms of p53 are characterized by their tumorigenic “gain-of-function” activity, which ensures increased survival and migration to tumour cells.

We identified one synonymous variant rs1800370 (c.108G>A, p.P36P) in the transactivation domain 1 (TAD1, aa 1-40), which is part of the N-terminal activation domain. TAD1 plays important role in inducing of cell cycle arrest G1 phase and apoptosis. According to databases this variant is considered as benign, yet with unknown connection to PCa.

In the proline-rich domain, which is essential for p53-mediated apoptosis, we identified a missense variant rs1042522 at codon 72 (c.215C>G, p.P72R).

With respect to all human cancers, up to 90% of all *TP53* mutations are localized in a core region of DBD, between aa residues 102-292. Approximately 10% of these are loss of function mutations and the other ones are responsible for the production of the protein with a reduced capacity to bind to a specific DNA sequence that regulates the p53 transcriptional pathway (10). In our study, we did not identify any missense or deleterious mutations in this gene. However, three polymorphisms with benign status and a frequency of 0.02% were identified: synonymous variants rs142813240 (c.618G>A) at codon 206, the rare rs1800372 (c.639A>G) at codon 213, and the common intron variant rs1800899 (c.993+12T>C). Of these variants, rs1800372 (DP, disease polymorphism) and rs1800899 (DM?, likely disease-causing mutation) often occur in patients with various types of cancer. Synonymous variants are not necessarily silent or neutral in cancer evolution. Although rs1800372 is a synonymous

variant, it is associated with unfavourable prognosis of chronic lymphocytic leukaemia (11), poor outcome in primary breast cancer and is also present in paediatric cancer survivors who subsequently developed second malignancies after exposure to radiotherapy (12). The nucleotide replacement c.993+12T>C in intron 9 was noted as polymorphism occurring in a single individual. In several cases of multiple myeloma (13), rectal and pre-menopausal breast cancer (14), it occurs simultaneously with rs1042522 and rs1800372. The mutations in *TP53* described in our study also appear in patients with different types of cancers and could be potential research targets in determining the aggressiveness of the disease, but more in-depth research of their pathogenic effect is needed.

Retinoblastoma transcriptional corepressor 1 (RB1). *RB1* is the first identified tumour suppressor gene, located on chromosome 13 (13q14.2) with a total length of approximately 180 kb. The retinoblastoma protein pRB is a key regulator of the G1/S transition of the cell cycle (CC) indicating its essential function in permanent CC arrest. Through regulation of important processes, such as gene transcription, DNA replication, DNA repair and mitosis, pRB plays a prominent role in normal development. It appears to be one of the most frequent targets for “loss of function” in human cancer (the paediatric cancer retinoblastoma, small cell cancer of the lungs) caused by the down-regulating activity of cyclin dependent kinases, which block RB1 activity leading to uncontrolled cell proliferation and growth (the paediatric cancer retinoblastoma, small cell cancer of the lungs).

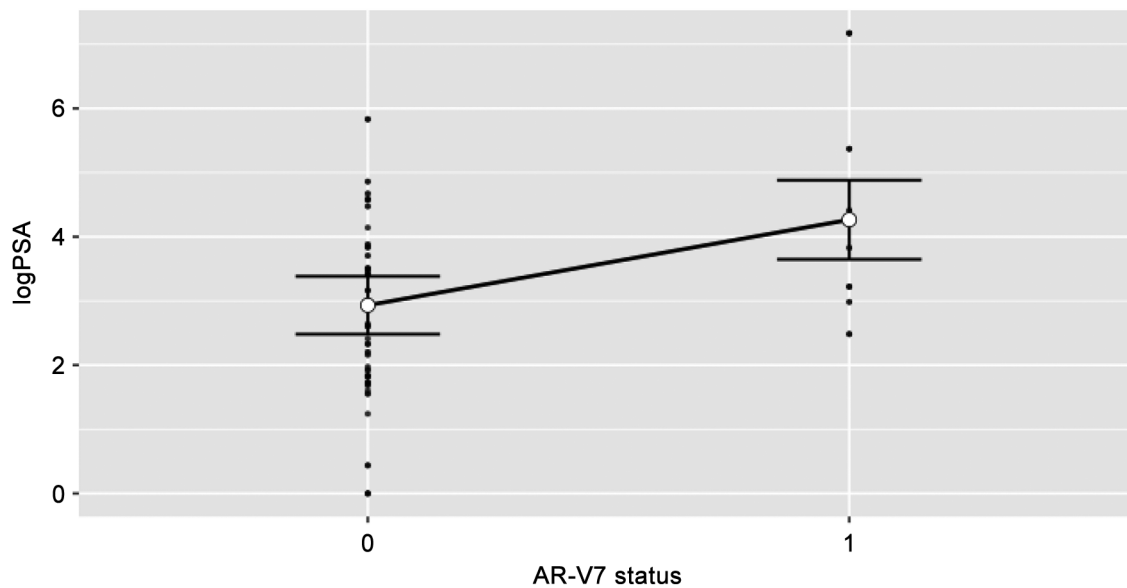


Figure 1. The association of AR-V7 presence in patients with metastatic castration-resistant prostate cancer and serum PSA levels.

pRB encompasses 928 residues and contains an N-terminal region (RB_N, aa 1-372), domain A (RB_A, aa 373-573), a spacer sequence (aa 574-644), domain B (RB_B, aa 645-766) and a C-terminal region (RB_C, 767-928). Domains RB_A and RB_B form the small AB pocket that is critical for tumour suppressor activity and highly conserved for binding viral and cellular transcription factors. Spacer is an evolutionarily conserved region of 71 aa required for the formation of the AB pocket. RB_C is responsible for blocking the G/S transition of the CC and is required for the formation of the complex with the E2F transcription factor and for mediating growth arrest and recruitment of CDK complexes. Altogether, the AB pocket and the RB_C form the large pRB pocket.

RBI consists of 27 exons and 27 introns. We managed to identify 7 intron variants – in intron 14 (rs9535023), intron 15 (rs750651121), intron 16 (rs768867054), intron 21 (rs776987458, rs765386327), intron 24 (rs4151624) and intron 25 (rs3092904).

The sequence change of rs9535023 (c.1390-14A>T) is in intron 14 of *RBI* and does not directly change the encoded aa sequence of the pRB. It is classified as benign, unlike sequence change c.1390-14A>G, which may disrupt the consensus splice side and therefore is classified as pathogenic. We identified two indel variants rs750651121 (c.1422-8delT) and rs768867054 (c.1499-10delT), which are probably rare because there is not much information about them. In databases, both of these variants have a benign status, but they lie in the splice site, which could mean that they a detrimental effect on pRB function. Similarly, the remaining intron variants have a benign status in the databases.

Phosphatase and tensin homolog (PTEN). *PTEN* is a multifunctional tumour suppressor gene located at chromosome 10 (10q23.31). This gene encodes a dual-specific protein phosphoinositide 3-phosphatase (PTEN) that antagonizes the PI3K signalling pathway and, based on protein expression levels, notably affects multiple cellular processes, such as proliferation, survival, growth, cell death, metabolism and migration. This protein consists of 403 aa. N-terminal regional contains a short PDB binding domain (aa 1-15) and a phosphatase domain (aa 16-185). The C-terminal region consists of the C2 domain (aa 186-351) and the C-terminal tail (aa 352-403).

In the C2 domain at protein position 268, a likely benign missense variant rs398123328 (c.804C>A, p.D268E) was identified. It was present in two circulating tumor cell (CTC)+/AR-V7+ patients and one CTC+/AR-V7- patient. In addition to this variant, we identified two benign variants, rs762344516 (c.802-3dupT, DM?) and rs771859047 (c.802-3delT), in intron 8. These variants were mostly found in CTC-/AR-V7- patients.

However, although mutation of *PTEN* is uncommon in many human tumour types, loss of *PTEN* expression seems to be more frequent.

Results of statistical analysis. With the aim of uncovering the relationship between serum PSA levels *versus* the occurrence of individual polymorphisms and the presence/risk of AR-V7 occurrence, we conducted a statistical analysis. From the results of this statistical analysis, several conclusions can be drawn.

Elevated levels of logarithmized PSA (logPSA) are observed in patients with the AR-V7 variant (Figure 1). This suggests that PSA could serve as a significant predictor. Furthermore, as PSA levels increase, the likelihood of AR-V7 presence also increases.

Patients with the rs1042522 polymorphism (*TP53*) are less likely to have AR-V7 presence.

Discussion

In this study, we analysed the distribution of exonic and intronic polymorphisms/genetic changes in three tumour suppressor genes in mCRPCa patients.

TP53 (p53) represents a vital tumour suppressor protein and a key regulator of apoptosis, tumour cell proliferation, migration, and cell cycle arrest, thereby ensuring genomic stability and preventing the development of malignant tumours (15). In contrast to numerous other tumour suppressor genes that typically exhibit deletions or substitutions in cancer cells, mutations in the *TP53* primarily consist of missense mutations located in the central DBD region of the protein (16). However, in this region, we did not identify any missense variants. The only missense variant localized in *TP53* was rs1042522 in the proline-rich domain, crucial for p53-induced apoptosis. Some studies indicate that rs1042522 polymorphism has a significant impact on the regulation of the binding between mutant p53 and PGC-1 α , representing a novel “gain-of-function” partner of mutant p53. This interaction is negatively correlated with metastasis in prostate cancer. This interaction is believed to enhance migration and metastasis, and to influence metabolism (17). Also, rs1042522 has been associated with several cancers including breast, ovarian, cervical, lung, colon and prostate cancer (17-19). In our study, this variant was present in heterozygosity and in 96% of patients, of which 52% were CTC-. Nevertheless, this polymorphism at codon 72 has yielded conflicting findings regarding its association with cancer risk (18). VarSome and ClinVar classify it as benign, while the HGMD database places it in the DFP (disease associated polymorphism with functional support) category. Additionally, in-silico tools such as SIFT and PolyPhen-2 have also predicted its benign impact. Statistical analysis of our data showed that individuals carrying the rs1042522 polymorphism exhibit a reduced likelihood of expressing AR-V7. This result suggests a protective effect of this variant. The findings of our study do not align with the recent research conducted by Toscano-Guerra *et al.* (17), who established a significant association ($p < 0.0001$) between the presence of the rs1042522 variant and the susceptibility to/risk of prostate cancer. Based on an earlier meta-analysis (20), it appears that there was no significant association between rs1042522 and PCa susceptibility in the overall population under five genetic models. These results suggest that rs1042522 is not a risk factor for PC.

Generally, CTC and AR-V7 show promise as valuable biomarkers in clinical settings, particularly for treatment selection and predicting the clinical outcomes of patients with mCRPC. Research on CTC has enhanced our understanding of tumour cell dissemination and the prognostic threshold in PCa (21, 22). Multiple studies have linked AR-V7 expression to poor responses to ARTA treatment (23-27). Furthermore, AR-V7+ patients typically exhibit advanced disease stages, elevated serum PSA levels, and alkaline phosphatase levels. While the Schlack *et al.* study (28) suggests a reduced PSA response in AR-V7+ patients compared to AR-V7- individuals, significant PSA responses have also been observed in AR-V7+ patients. These findings question the predictive value of AR-V7 as a biomarker for ARTA treatment. Our study found higher PSA levels in AR-V7+ patients ($p < 0.001$).

Our primary analysis results indicate that the response rate, *i.e.*, a decrease in PSA values by more than 50% (after 3 months of ARTA treatment), was reduced by over half in mCRPC patients with AR-V7. We noted a statistically significant difference ($p < 0.001$) comparing the number of CTC- patients showing a decrease in PSA values by more than 50% compared to AR-V7+ patients. The presence of CTC and AR-V7 in our patient group also adversely affected the overall survival of patients with mCRPC treated with ARTA. A decrease in PSA values by more than 50% after 12 weeks of ARTA treatment correlates with extended survival and vice versa. However, stable or increasing PSA values predict a poor prognosis (29, 30).

Prostate cancer belongs to multifactorial diseases, involving multiple factors in its onset and progression. Similarly, in the realm of biomarkers, it is not possible to focus solely on one specific biomarker. Germline variants, also known as SNPs, are present in more than 1% of the population, occurring naturally and generally considered to have a minimal impact on overall health. Nevertheless, it is important to note that some of these variants may affect the structure or function of genes or proteins. Genetic changes, analysis of the presence of CTC and AR-V7 may have therapeutic and prognostic potential.

Conflicts of Interest

The Authors confirm that there are no conflicts of interest in regard to this study.

Authors' Contributions

KH and JK conceived the study and were in charge of overall direction and planning. KH analysed the data, performed literature reviews and drafted the manuscript in consultation with MH, HBD and JK. JK provided samples from Urology Clinic. MG was responsible for the statistical analysis. All Authors discussed the results and contributed to the final manuscript.

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