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Research Progress of AR Gene Family in Prostate Cancer Therapy

Maham Khan[1]

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Abstract

Prostate cancer (PCa) is a malignancy originating from the epithelial cells of the prostate gland, strongly influenced by androgens, and is one of the most common cancers in men. Androgen deprivation therapy (ADT) is the primary treatment for prostate cancer. However, after prolonged ADT treatment, nearly all patients experience an increase in prostate-specific antigen (PSA) levels and tumor regrowth. The regrowth is primarily driven by the reactivation of androgen signaling pathways within the tumor cells, leading to the development of castration-resistant prostate cancer (CRPC). The overall survival for patients with CRPC is typically less than two years. The reactivation of androgen signaling after ADT is a key mechanism leading to the progression of CRPC. In particular, abnormal expression of androgen receptor (AR) family genes, particularly *AKR1C3* and *AR-V7*, are beleived to play central roles in the emergence of CRPC. Beyond hormonal factors, various molecular mechanisms contribute to the development of castration resistance, such as genetic mutations and the role of the tumor microenvironment. Additionally, dysregulation of signaling pathways and interactions between tumor cells and the surrounding matrix furrher promote tumor survival and growth, even in the absence of androgens. Understanding these mechanisms is essential for developing more effective treatment strategies for CRPC.

Key words prostate cancer, AR family, *AKR1C3*, *AR-V7*, tumor microenvironment

1. Pharmacokinetics Department, Aston University, Birmingham B4 7ET, England, United Kingdom.
Correspondence: Maham Khan (Pharmacokinetics Department, Aston University, Birmingham B4 7ET, England, United Kingdom; Email: mahamkhan3692@gmail.com).

Introduction

Prostate cancer (PCa) is a malignant tumor originating from the epithelial cells of the prostate gland and is strongly linked to androgens. It is one of the most common cancers in men. According to a 2023 analysis of U.S. cancer statistics, prostate cancer accounts for more than a quarter of all newly diagnosed cancers in men and is projected to be the second leading cause of cancer-related deaths [1]. From 2014 to 2019, the incidence of prostate cancer in the United States rose by 3% per year with new cases expected to reach 288,300 deaths are expected to reach 34,700 by 2023 [1]. Similarly, the incidence of prostate cancer in China has been rising yearly, influenced by an aging population and changing dietary patterns [2]. In 2022, China reported 125,646 new cases of prostate cancer, and 56,239 deaths, with both figures continuing to rise [3, 4]. The high expression of *AKR1C3* and the androgen receptor splicing variant *AR-V7* are the two major drivers for the development and progression of CRPC [5-7].

AKR1C3 belongs to the aldoketone reductase superfamily and like other AKR enzymes, it is a soluble monomer enzyme that depends on NAD(P)(H) to catalyze the reduction of aldehydes and ketones. Studies have shown that *AKR1C3* is significantly expressed in metastatic and recurrent prostate xenografts and bone metastases in CRPC patients [8, 9], highlighting its role in androgen synthesis. *AKR1C3* is a key enzyme in the testosterone and dihydrotestosterone synthesis pathway [10]. *AKR1C3* is a key enzyme that promotes the production of androgens within tumor cells, an adaptive mechanism to maintain their survival after serum testosterone levels. In addition, overexpression of *AKR1C3* in prostate cancer cells is associated with enhanced intra-tumor androgen synthesis [11], even in the context of ADT. This intracellular androgen production allows tumor cells to evade systemic androgen deprivation and continue to grow and progress, leading to the development of CRPC phenotype [12]. As a result, targeting *AKR1C3* has emerged as a potential therapeutic strategy to inhibit intra-tumor androgen synthesis and combat resistance to ADT in prostate cancer.

AKR1C3 promotes drug resistance and metastasis of prostate cancer through both enzyme-dependent and non-enzyme-dependent mechanisms

AKR1C3 is a member of the aldehyde-ketone reductase superfamily, and its function is similar to other aldehyde-ketone reductases. As a soluble monomer enzyme dependent on NAD(P)(H), *AKR1C3* promotes the reduction of aldehydes and ketones and shows inducible oxidase activity [13]. Studies have shown that *AKR1C3* is highly expressed in both metastatic and recurrent prostate tumor xenografts, as well as in bone metastatic tumors of CRPC patients, playing a crucial role in the production of androgens [14]. After androgen deprivation therapy (ADT), prostate cancer cells can independently produce androgens, thus continuing to activate the androgen receptor signaling pathway (ARs) without relying on circulating androgens. This ability drives the progression of prostate cancer (PCa) to castration-resistant prostate cancer (CRPC). The synthesis of androgens within tumor cells primarily occurs through three pathways: (1) The "classical pathway," where androgens are synthesized de novo from cholesterol; (2) The "alternate pathway," in which low-activity androgens derived from the adrenal glands (such as androstenedione and dehydroepiandrosterone) are converted into more active androgens (such as testosterone and dihydrotestosterone); (3) The "backdoor pathway," which utilizes progesterone metabolites as substrates to produce dihydrotestosterone (DHT) directly without converting it into testosterone. Among these *AKR1C3* is a key enzyme located downstream in the pathway that synthesizes testosterone or dihydrotestosterone (DHT) [15]. Its enzyme activity promotes androgen synthesis in tumor cells and represents an adaptive response that allows tumor cells to survive after declining of serum testosterone levels [16]. As such, reducing androgen synthesis in tumor cells is an important therapeutic target for treating CRPC, which can be achieved by inhibiting the expression of key enzymes in the androgen synthesis pathways.

Moreover, prostate cancer patients with high levels of *AKR1C3* [17] expression are often resistant to radiotherapy and exhibit resistance to anti-androgen therapies such as enzalutamide (Enza). Recent studies, however, have indicated that *AKR1C3* functions as a selective coactivator of the androgen receptor (AR) and activates the ERK1/2 pathway, thereby enhancing non-enzymatic mechanisms of prostate metastasis. However, studies on how *AKR1C3* promotes malignant progression of prostate cancer through non-enzymatic pathways are still limited [18, 19]. In addition, the ability of prostate cancer cells to produce androgens within the tumor is a key mechanism by which these cells adapt to reduce systemic androgen levels after ADT. This adaptive response not only supports tumor survival, but also drives disease progression. Specifically, the upregulation of enzymes involved in the androgen synthesis pathway, such as *AKR1C3*, amplifies this process, enabling tumors to maintain a certain level of androgen receptor activation, thereby promoting their growth and metastasis [20]. Therefore, targeting these androgen synthesis pathways has become a promising area of research for developing new therapies that are effective against CRPC.

AR-V7 is a marker of resistance and poor prognosis in castration-resistant prostate cancer

As our understanding of prostate cancer progression deepens, androgen receptor splicing variants (AR-Vs) has received increasing attention, especially those lacking the C-terminal androgen binding domain. Among these variants, *AR-V7* is particularly important as is prevalent and plays a key role in metastatic castration-resistant prostate cancer (mCRPC) and tumors resistant to androgen receptor antagonists. *AR-V7* is one of the most extensively studied AR splicing variants and is often co-expressed with full-length AR (AR-FL). Notably, its expression is 20 times higher in CRPC patients compared to those with untreated prostate cancer. AR-V7 is generated through aberrant selective splicing of the third intron of the precursor mRNA (pre-mRNA) of the androgen receptor (AR) [21]. In the absence of androgens, *AR-V7* exhibits intrinsic activity that can naturally activate the androgen/androgen receptor signaling pathway. It is significantly co-expressed with full-length AR (AR-FL) in the cytoplasm of prostate cancer cells, and its expression tend to increase with the use of anti-androgen medications and AR receptor antagonists. Bryce et al. reported that approximately 55% of patients showed detectable levels of *AR-V7* following treatment with abiraterone [22, 23]. Additionally, the percentage of individuals exhibiting positive expression of *AR-V7* increased from 15% to 50% after treatment with enzalutamide. Patients with circulating tumor cells positive for *AR-V7* who receive lower doses of cabazitaxel early in their treatment have poorer prognoses compared to patients who are *AR-V7* negative [24]. This finding underscores the importance of monitoring *AR-V7* levels, as they may serve as a critical biomarker for evaluating treatment outcomes and guiding therapeutic strategies in CRPC. Therefore, whether *AR-V7* is naturally occurring or aberrantly generated after treatment, it has emerged as a significant marker of poor prognosis in prostate cancer. This highlights the potential role of *AR-V7* in clinical decision making, as the presence of *AR-V7* may indicate disease progression and treatment resistance. Monitoring the level of *AR-V7* in patients can help to develop personalized treatment

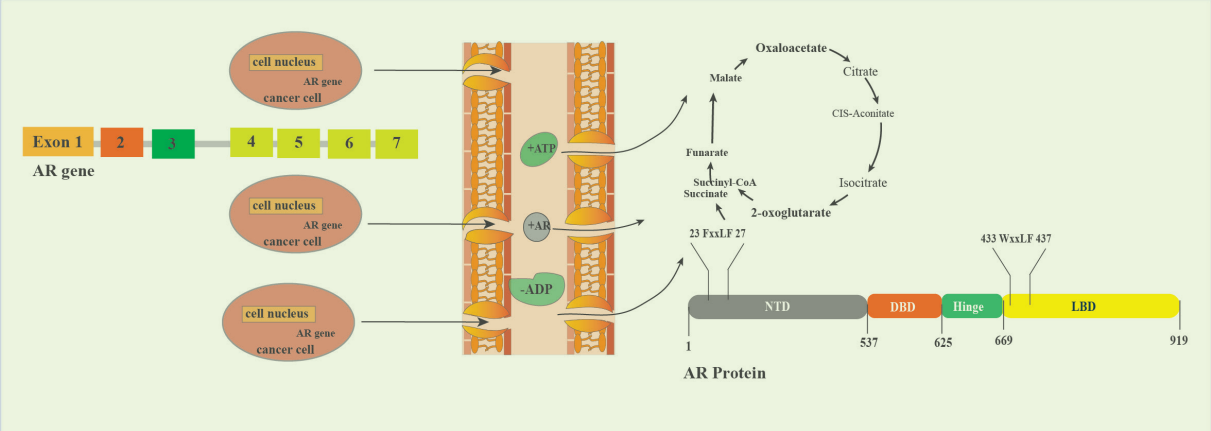

Figure 1. Schematic diagram of AR splicing variants. This diagram illustrates the structural variations of androgen receptor (AR) splice variants. These variants arise from alternative splicing of the AR gene, leading to different protein isoforms that can have distinct biological functions and implications in various conditions, particularly in prostate cancer.

strategies, predict prognosis and guide the use of targeted therapies, thereby ultimately improving the efficiency of patient management and survival [25, 26]. Further research into the mechanisms driving *AR-V7* expression and its impact on treatment resistance is critical for developing more effective treatment strategies for prostate cancer patients.

Previous studies have shown that AR variants (AR-VS) arise from structural rearrangements or selective RNA splicing of AR genes [27]. Selective RNA splicing is the mechanism through which exons are differentially spliced from precursor mRNA (pre-mRNA), leading to the creation of various combinations of exons that ultimately form translatable mRNA. *AR-V7* mRNA is selectively spliced at the 3' splice site (3'ss) of exon 3B instead of at the 3' splice site of exon 4. *AR-V7* can be regulated by various RNA splicing regulatory factors, such as U2AF65, ASF/SF2 [28], and JMJD1A [29], or through the regulation of cis-acting elements like Hoxb13 [30] and FOXA1 [31]. In addition to transcriptional regulation, the control of AR-V7 protein levels has also been studied. Liu et al. further identified that the HSP70/STUB1 complex mediates AR-V7 protein stabilization, which enhances resistance to next-generation anti-androgen drugs. STUB1 induces AR-V7 protein degradation by blocking the formation of the HSP70/AR-V7 complex [32]. Li et al. reported that PP-1 and Akt signaling regulate AR-V7 serine phosphorylation through the E3 ligase MDM2, which recognizes the phosphorylated sites on AR-V7 and induces its ubiquitination and degradation [33]. Currently, no specific chemotherapeutic agents directly target *AR-V7*, and the and the available treatments often prove ineffective or show inherent resistance in *AR-V7*-positive patients. As a result, targeting the epigenetic processes to regulate the production or stability of *AR-V7* offers a promising therapeutic strategy for treating patients with *AR-V7*-positive prostate cancer.

AR-V7 genetic mutation leads to the development of prostate cancer

AR-V7 is the most abundantly expressed and functionally potent of the AR-Vs. The N-terminal domain of *AR-V7* is inherently disordered [34]. Therefore, understanding the mechanism of *AR-V7* production is crucial for adopting targeted epigenetic approaches to reduce its expression, which could be a feasible strategy to overcome resistance. Studies have shown that *AR-V7* splicing is both a dynamic and plastic process [35, 36]. The regulatory mechanisms underlying the abnormal production of AR splice variants in malignant cells remain largely unclear. The emergence of AR-Vs splice variants in prostate tumors is thought to be a result of AR gene rearrangements (AR-GSR) and the selective splicing of AR precursor mRNA.

In CRPC 22Rv1 cells, genomic editing of AR gene rearrangements revealed that the stability and high-level expression of truncated AR subtypes are associated with an intragenic rearrangement of a roughly 35 kb AR genomic fragment, which includes AR exon 3 and several 3′-terminal cryptic exons (CE) expressed in AR-Vs, [37]. Subsequently, the same research group discovered an 8579 bp deletion of AR exons 5, 6, and 7 in the LuCaP 86.2 xenograft model, which provided a reasonable explanation for the synthesis of truncated AR-V567 in this model [38]. A study by De Laere, demonstrated that the majority of AR-GSR-positive patients expressed AR-Vs, with only a few exceptions. The association between AR-GSR and AR-Vs has also been confirmed in clinical tumors. AR-GSR in individual tumors showed varying degrees of clonal enrichment, revealing that tumors with high clonal enrichment of AR-GSR were found to express unique AR-GSR-dependent AR-Vs [39]. AR gene rearrangements are an important mechanism for generating AR-Vs in cells that express AR-Vs but not full-length AR (AR-FL).

Recent studies have shown that abnormal RNA intra gene splicing is another key mechanism for AR-Vs expression. This explains why full-length androgen receptor (AR-FL) and AR-Vs can be co-expressed in the same cell in patients with (CRPC) [36]. RNA splicing facilitates mRNA translation by cutting out introns and exons, resulting in multiple transcriptional variants from a single precursor messenger RNA (pre-mRNA). This process allows eukaryotic cells with around 20,000 genes to expand into a diverse proteome containing about 95,000 proteins [40]. mRNA splicing is carried out by the splicosome, a large complex of small nuclear ribonucleoproteins (snRNPs, such as U1, U2, U4, U5, and U6) and their associated helper proteins. The splicosome sequentially binds to the transcribed RNA, recognizing specific sequence elements in the intron (such as the 5' splicing site and the 3' splicing site) to cut out the intron in the pre-mRNA and link the adjacent exons together [41]. The expression of specific splicing variants is regulated by the rate of gene transcription and the splicing factors that bind to pre-mRNA during splicing [42].

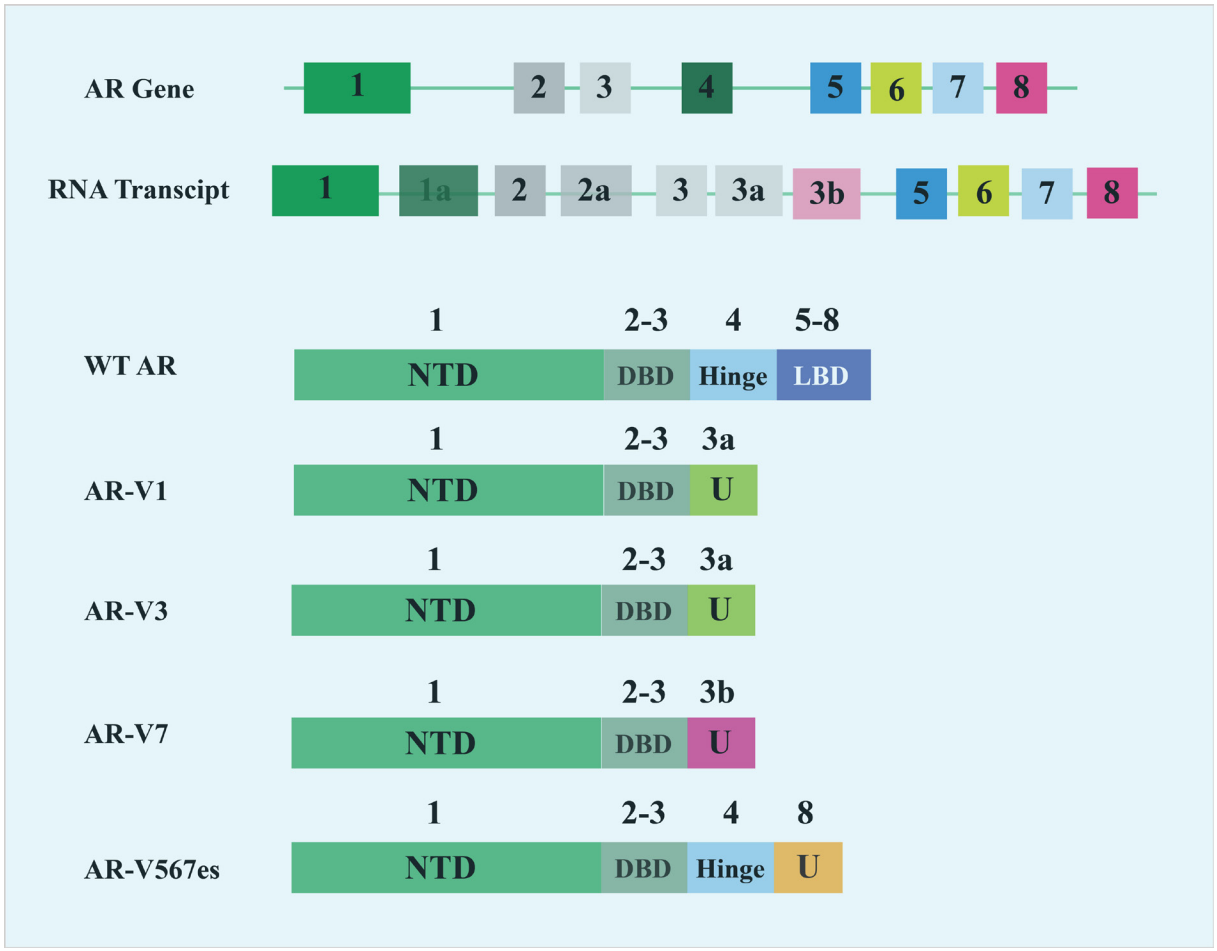

Figure 2. The process of transforming AR family genes into proteins in tumor cells.

Both the initiation and elongation rate of transcription can affect splicing. The transcription initiation and elongation rates can influence splicing, while splicing factors regulate the spliceosome's recognition of splicing sites by binding to regulatory proteins on the pre-mRNA [43]. Enhanced expression of splicing factors promotes their recruitment to pre-mRNA, thereby facilitating this dynamic and reversible mRNA splicing process. These factors bind to specific sequence elements on pre-mRNA, influencing exon inclusion or skipping and thereby regulating the efficiency of the spliceosome's recognition of splicesome [29]. Both *AR-V7* and AR-FL are generated through alternative splicing of AR pre-mRNA. *AR-V7* is generated by the spliceosome through aberrant splicing at a cryptic exon 3b (3'SS) located in the third intron of AR, rather than at the 3'SS of exon 4 [44]. Numerous splicing factors are involved in the splicing mechanism of *AR-V7*. Multiple splicing factors are implicated in this splicing mechanism, including PSF/SFPQ, which are rich in proline and glutamine. The expression of PSF/SFPQ has been associated with poor prognosis in prostate cancer patients, as they promote the expression of several spliceosomal genes, leading to increased production of *AR-V7*.

Current research status of the association and regulatory mechanisms between *AKR1C3* and *AR-V7*

In early stages androgen deprivation therapy (ADT) for prostate cancer, tumor cells adapt to survive under low testosterone levels by increasing the expression of *AKR1C3*, a key enzyme responsible for synthesizing androgens within tumor cells. *AKR1C3* enhances the production of androgens, contributing to tumor survival despite systemic androgen depletion. Previous studies have primarily focused on *AKR1C3* as a factor in androgen-dependent pathways and *AR-V7* as a factor in androgen-independent pathways that drive the progression of prostate cancer, examining their individual roles in activating AR signaling pathways to promote prostate cancer progression. However, their potential interaction had not been thoroughly explored. A study by Bin Wang et al., revealed a potential connection between *AKR1C3* and *AR-V7*. Among 90 patients with castration-resistant prostate cancer (CRPC), 37 were positive for *AKR1C3*, and of those, 35.1% were also positive for *AR-V7*. This finding indicates that a subset of CRPC patients may express both *AKR1C3* and *AR-V7*, suggesting a possible regulatory link between the two proteins [45]. Further research by, Fan L et al. demonstrated that *AKR1C3* may regulate AR/*AR-V7* at the protein degradation level [46]. Specifically, *AKR1C3* enhances the stability of the E3 ligase SIAH2, which in turn increases SIAH2-dependent AR activity. In prostate cancer cells resistant to enzalutamide (Enza), *AKR1C3* has been shown to stabilize *AR-V7* through the ubiquitin-mediated proteasome pathway, further promoting treatment resistance and prostate cancer progression [47].

Research status of targeting *AKR1C3* and *AR-V7* in the treatment of prostate cancer

As our understanding of the malignant progression of prostate cancer deepens, we have identified that androgen deprivation therapy (ADT) inhibits the androgen-dependent pathway, but triggers the adaptive upregulation of *AKR1C3* in tumor cells. Moreover, androgen-independent pathways like the production of *AR-V7* are activated in hidden manner. Since *AR-V7* is inherently active and can promote non-ligand-dependent AR signaling in the absence of androgens, driving the malignant progression of prostate cancer. This suggests that while potent AKR1C3 inhibitors can reduce androgen production within tumors, they may not fully block *AR-V7* from activating non-ligand-dependent AR signaling pathways, thereby promoting tumor growth. As a results, new therapeutic strategies for CRPC (Castration-Resistant Prostate Cancer) focus on suppressing tumor androgen synthesis while simultaneously targeting and eliminating AR splice variants. Currently, chemists are striving to develop selective *AKR1C3* inhibitors. In the search of small molecule compounds, such as cinnamic acid derivatives, phenolic acid derivatives, isoquinoline alkaloids, and organic ruthenium complexes, several compounds with IC50 values in the nanomolar range have been identified for *AKR1C3* inhibition [48, 49]. However, due to the structural similarities among the aldo-keto reductase family, especially among family members AKR1C1, AKR1C2, and AKR1C4, there remains a need for compounds that are highly selective for *AKR1C3* and exhibit favorable pharmacokinetic properties. Novel *AKR1C3* inhibitors demonstrating biological efficacy have been developed and are currently undergoing clinical trial [50, 51] (**Figure 1**).

Among the studied compounds, ASP9521 (3mg/kg) was shown to significantly suppress intratumoral testosterone levels in human CRPC (castration-resistant prostate cancer) xenograft mice with a single oral dose, and this effect persisted for 24 hours [52]. This compound entered phase I/II clinical trials for metastatic CRPC, where it demonstrated acceptable safety and tolerability, though it did not exhibit significant clinical activity, potentially due to suboptimal patient selection [53]. Another inhibitor, BAY1128688, a steroid-based analogue, entered phase II clinical trials for endometriosis but was discontinued due to its association with liver toxicity [54, 55]. Currently, no *AKR1C3* inhibitors are specifically approved for prostate cancer treatment. In 2023, HSK38008, a novel oral *AR-V7* degrader, was developed, effectively targeting AR-V7 protein degradation through the proteasomal pathway. However, despite these advances, no clinically proven drugs directly inhibit *AR-V7* production. Developing such therapies is crucial for overcoming the complexities of androgen receptor signaling in CRPC, offering potential new avenues for managing this challenging disease.

Discussion

Prostate cancer, a malignant tumor arising from the prostatic epithelium, is closely linked to androgen in its development and progression, making it a most common cancer among males. Based on 2023 cancer statistics in the United States, prostate cancer is projected to represent over 25% of all new cancer diagnoses in men, and it is expected to be the second leading cause of cancer-related deaths among them [56]. Between 2014 and 2019, the rate of prostate cancer in the United States rose by 3% annually. By 2023, it is forecasted that there will be 288,300 new cases and 34,700 fatalities from this disease. The incidence of prostate cancer has been rising annually, attributed to an aging population and shifts in dietary habits in China [57].

To date over 20 AR variants (AR-Vs) have been identified in human prostate cancer cell models and clinical specimens. These variates arise due to the splicing of "cryptic" exons into upstream exons encoding the AR DNA-binding domain [58]. With the exception of AR45, which is truncated in the N-terminal domain (lacking the entire region encoded by exon 1 of the AR gene) [59], all other variants contain intact N-terminal transactivation and DNA-binding domains but lack the LBD (ligand-binding domain) (**Figure 2**). Although these truncated proteins cannot bind ligands, they possess constitutive activity as transcription factors and can promote the expression of target genes [60]. As a result, these truncated receptor forms drive androgen-independent transcription of AR target genes, supporting the growth of hormone-independent prostate cancer cells. Enzalutamide which exerts its antitumor activity by interacting with the ligand-binding domain of the androgen receptor, may become less effective in the presence of AR variants, potentially contributing to enzalutamide resistance [61]. Increasing evidence suggests that prostate tumors adapt to androgen deprivation therapies, such as abiraterone and enzalutamide by activating AR target genes through AR-Vs that lack a functional ligand-binding domain.

AR-V7 has been detected in circulating tumor cells (CTCs) isolated from blood samples, whole blood mRNA, ctRNA, tumor-derived cell vesicles, plasma or serum, and even in so-called exosomes found in urine [62-64]. Patients with detectable *AR-V7* in liquid biopsies often exhibit more aggressive disease and shorter survival times [65]. Alessandro Sciarra [39] and colleagues analyzed 56 cases of PCa based on clinical risk, detecting *AR-V7* expression in 24/32 cases in the high-risk group, 4/13 in the intermediate-risk group, and only 2/11 in the low-risk group. A significant correlation was observed between *AR-V7* positivity and risk classification ($P<0.001$) as well as postoperative progression ($P<0.001$). *AR-V7* has also been identified to predict poor prognosis in mCRPC patients treated with drugs such as enzalutamide or abiraterone [66, 67]. Increasing evidence suggests that alternative splicing pathways play a crucial role in regulating *AR-V7* production. Understanding the regulatory mechanisms opens new avenues for prostate cancer treatment strategies focused on targeting *AR-V7*.

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Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Maham Khan searched academic literature, wrote the draft manuscript, supervised the review writting progress and approved the final manuscript submission.

Competing interests

Authors report no conflict of interest.

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