Pharmaceutical Sciences Asia

Pharm Sci Asia 2024; 51 (3), 233-240
DOI:10.29090/psa.2024.03.24.AP0911

Research Article

Integrated Bioinformatics Analysis of hsa-miR-4783-3p Target Genes and Functions in Prostate Cancer

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ABSTRACT

Prostate cancer (PCa) is a significant global health challenge, necessitating a deeper understanding of its complex regulatory mechanisms. This study conducted a comprehensive examination of the involvement of hsa-miR-4783-3p in PCa using integrated bioinformatics methodologies, including target gene prediction, interaction network analysis, expression validation of identified genes, pathway annotation, and analysis of miRNA-target binding and determination of shared targets with other miRNAs. The analysis identified 66 key genes regulated by hsa-miR-4783-3p and revealed a complex regulatory network, highlighting the diverse interactions mediated by this miRNA in PCa. Notably, genes such as *AKT1*, *ARFGAP1*, *ARHGDIA*, *HRH2*, and *NF2* are implicated in critical pathways associated with PCa development. Furthermore, the findings indicate potential regulatory relationships between hsa-miR-4783-3p and its target genes, as well as shared target genes with other pathogenic miRNAs, providing insights into the complex interplay among regulatory networks in PCa progression. While these findings offer a comprehensive insight into the role of hsa-miR-4783-3p in PCa, indicating new avenues for therapeutic intervention, further in-depth research and experimental validation are essential to fully understand the functional implications of these findings.

Keywords:
Prostate cancer; Hsa-miR-4783-3p; Bioinformatics analysis; Gene targeting; Regulatory networks.

1. INTRODUCTION

Prostate cancer (PCa) is a paramount global health concern, emerging as the second most commonly diagnosed cancer among men worldwide[1]. Despite advancements in detection and management, the complex molecular mechanisms underpinning PCa onset and progression remain partially understood[2]. Therefore, a deeper understanding of these mechanisms is crucial for enhancing diagnostic precision, developing innovative therapeutic strategies, and improving patient outcomes.

MicroRNAs (miRNA/miR) have emerged as promising biomarkers in cancer research because of their critical roles in gene regulation[3,4]. Although hsa-miR-4783-3p has demonstrated oncogenic potential in some cancers, such as gastric cancer, its specific functions and relevance in PCa remain largely unexplored[5]. Prior studies have not yet provided evidence of hsa-miR-4783-3p dysregulation, roles in processes such as cell cycle regulation or metastasis, or potential as a biomarker in PCa[6]. This lack of prior research highlights the need for a comprehensive investigation into the potential functions and molecular mechanisms of hsa-miR-4783-3p in PCa.

In this study, we employ integrated bioinformatics approaches to systematically examine the potential targets and regulatory networks of hsa-miR-4783-3p in PCa for the first time. Our methodology includes i) predicting target genes, ii) analyzing their interaction networks, iii) evaluating gene expression, iv) annotating pathways, and v) examining predicted binding sites using established bioinformatics tools and databases. This exploratory analysis provides initial insights into whether and how hsa-miR-4783-3p is

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involved in the molecular biology of PCa. By conducting an integrated bioinformatics investigation of hsa-miR-4783-3p in PCa, our research seeks to contribute to the foundational understanding in this area, which could inform future experimental studies and potential clinical applications.

2. MATERIALS AND METHODS

2.1. Target gene identification

We used the miRNet platform, integrating data from miRTarBase and TarBase to identify target genes regulated by hsa-miR-4783-3p[7]. miRTarBase, which is known for collecting experimentally verified miRNA-gene interactions, provides a reliable preliminary gene list[8]. TarBase complemented this with additional validated miRNA-target interactions, enhancing the robustness of our target gene identification[9].

2.2. Functional analysis and pathway annotation

We used GeneMANIA and the Reactome database for functional analysis and pathway annotation of the identified genes. GeneMANIA helped uncover gene-gene interactions and functional networks, categorizing the connections into co-expression, physical interactions, predicted interactions, and genetic interactions. The percentage breakdowns of each connection type were calculated directly from the output files generated by GeneMANIA analysis[10]. The Reactome provides insights into genes implicated in PCa pathogenesis[11]. In our pathway analysis using the Reactome database, we only focused on pathways with statistical significance, considering only those with p-values and adjusted p-values (adj. p) less than 0.05 (data not shown). This stringent criterion ensured that our analysis highlighted the most relevant and robust pathways associated with hsa-miR-4783-3p in PCa.

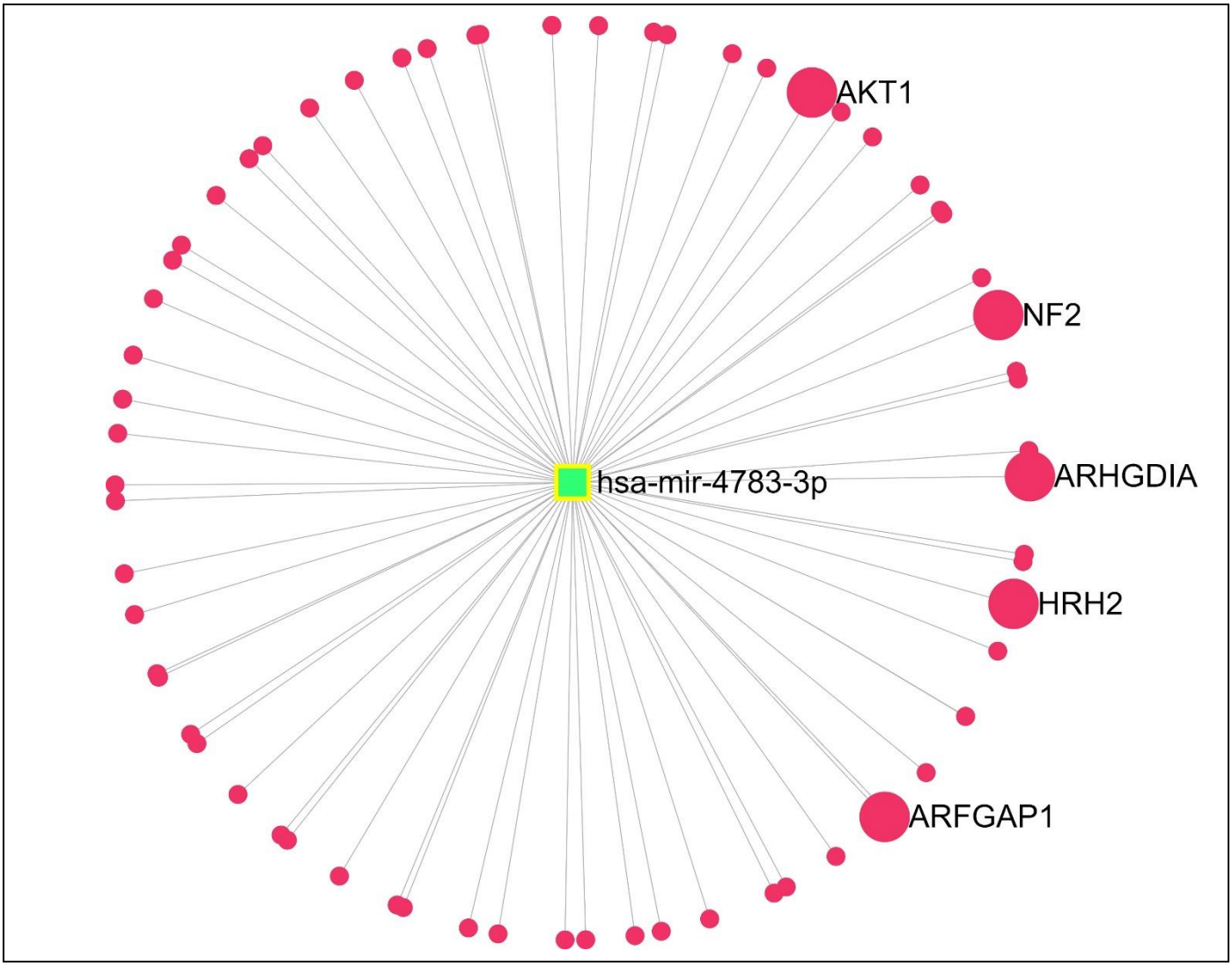

Figure 1. Record of hsa-miR-4783-3p and its target interaction networks. miR-4783-3p-target interaction networks were constructed using the miRNet platform, which incorporates a concentric circle algorithm to structure the network. Each dotted line within the network represents the predicted target genes. In network visualization, a larger dot plot indicates that hsa-miR-4783-3p has a higher potential for direct targeting based on the bioinformatics prediction algorithms used.

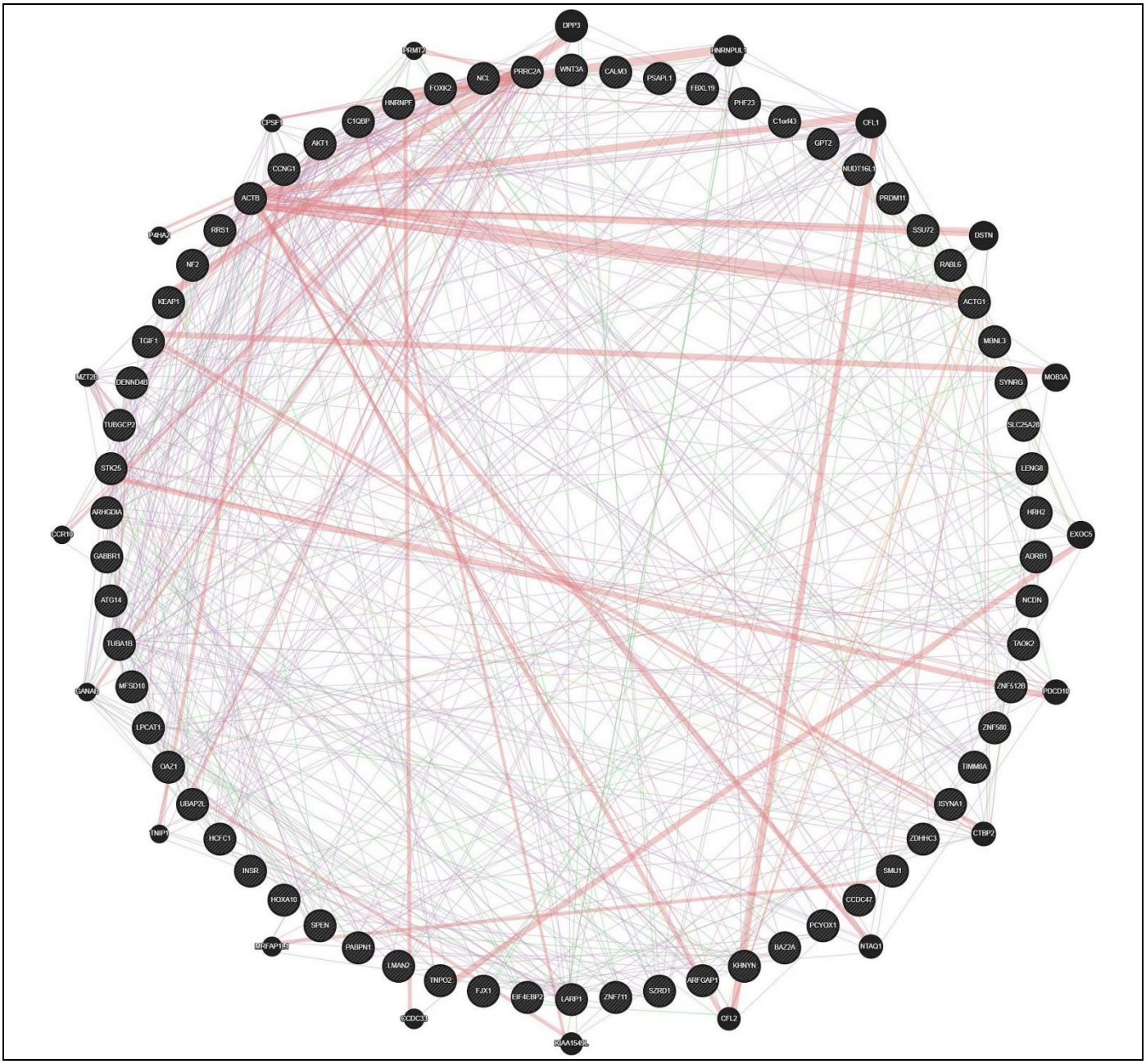

Figure 2. Predicted association networks of the hsa-miR-4783-3p target gene set. The networks were constructed using the GeneMANIA database with : Co-expression; : Physical interactions; : Predicted; : Genetic interactions. Each dark spot represents a gene symbol name.

Then, the effect of individual pathways on PCa was searched by the published literature using keywords.

2.3. Expression validation

We validated the expression levels of the identified genes using GEPIA, a web server for RNA sequencing expression data analysis. GEPIA's capabilities in tumor/normal differential expression analysis and profiling by cancer type were instrumental in determining the expression patterns of our key genes in PCa samples[12].

2.4. Prediction of regulatory relationships

We employed TargetScan to understand the potential regulatory relationships between hsa-miR-4783-3p and its target genes. This tool predicts miRNA targets on the basis of the conservation of sites matching the seed region of each miRNA, aiding in exploring binding affinities and interactions[13].

2.5. Identification of shared miRNA targets

We used ShinyGO to identify other miRNAs sharing targets with hsa-miR-4783-3p. By integrating

our gene list with miRTarBase data within ShinyGO, we explored the broader regulatory network, highlighting the convergence of multiple miRNAs on shared gene targets. This analysis used the false discovery rate (FDR) to assess the statistical significance of shared target associations among miRNAs[14].

3. RESULTS AND DISCUSSION

3.1. Screening of the target genes of hsa-miR-4783-3p and their regulatory networks

Our research successfully identified 66 target genes under the influence of hsa-miR-4783-3p, as shown in Figure 1. Furthermore, we identified four key types of connections among the target genes: co-expression, physical interaction, predicted interactions, and genetic interactions (Figure 2). These connections offered valuable insights into the potential relationships and functional associations among the target genes, which could provide a comprehensive framework for understanding the mechanisms influencing PCa biology.

Co-expression emerged as the predominant association, representing approximately 55.72% of the interactions. Co-expressed genes could serve as a molecular signature reflecting specific PCa subtypes or disease stages, with potential clinical implications for patient stratification and prognosis. This pattern displayed coordinated expression of these genes, indicating shared regulation or involvement in related biological pathways.

Physical interactions formed the second largest group, comprising approximately 42.67% of the networks. These direct protein-protein and protein-DNA binding connections are crucial for cellular signaling and gene regulation. Mapping these interactions could elucidate the key pathways driving PCa progression. Disrupting critical physical interactions may represent a viable therapeutic strategy. The prevalence of these associations implies that the target genes of hsa-miR-4783-3p are closely involved in the development and progression of PCa.

In addition, we identified a smaller proportion of predicted interactions (1.19%) based on computational analyses. Although experimental validation is essential, these predictions offer initial hypotheses for further investigation because they may uncover novel gene associations influencing PCa development and therapeutic response.

Genetic interactions, although a minor fraction at 0.41%, indicated synergistic effects where multiple genes collectively influenced phenotypes beyond their individual impacts. Elucidating these complex relationships could shed light on the intricate genetic underpinnings of prostate cancer progression.

Collectively, these insights could facilitate the development of molecular signatures, identification of therapeutic targets, and, ultimately, the tailoring of interventions based on each patient's unique molecular profile.

3.2. Identification of the functions of critical target genes related to prostate cancer

Among the 66 target genes analyzed, five were particularly significant in PCa progression using the Reactome database: *AKT1*, *ARFGAP1*, *ARHGDIA*, *HRH2*, and *NF2*, as detailed in Table 1. These genes were selected for their differential expression in PCa tissues compared with normal tissues and their involvement in significant pathways relevant to PCa. As shown in Table 2, our selection of these genes was further supported by a comprehensive literature review, which underscored their roles in PCa biology and their potential as therapeutic targets.

Our pathway examination revealed that the target genes of hsa-miR-4783-3p are mainly associated with pathways such as GLUT4 translocation, VEGFA-VEGFR2 signaling, eNOS activation, and nitric oxide

Table 1. List of hsa-miR-4783-3p target genes associated with prostate cancer

Target genes	Associated pathway
AKT1 (↑)	Translocation of GLUT4 to the plasma membrane
AKT1 (↑), ARFGAP1 (↓)	Membrane Trafficking
AKT1 (↑)	VEGFA-VEGFR2 Pathway
AKT1 (↑), ARFGAP1 (↓)	Vesicle-mediated transport
AKT1 (↑)	eNOS activation and regulation
AKT1 (↑)	BH4 synthesis, recycling, salvage, and regulation
AKT1 (↑)	Metabolism of nitric oxide
HRH2 (↓)	Histamine receptors
ARHGDIA (↑), NF2 (↑)	Signaling by Rho-GTPases

Notes: Gene expression changes were determined using GEPIA analysis. AKT1: V-akt murine thymoma viral oncogene homolog 1; ARFGAP1: ADP-ribosylation factor GTPase activating protein 1; NF2: Neurofibromin 2 (Merlin); HRH2: Histamine receptor H2; ARHGDIA: Rho GDP dissociation inhibitor (GDI) alpha; GLUT4: Solute carrier family 2 (facilitated glucose transporter), member 4; VEGFA: Vascular endothelial growth factor A; VEGFR2: Vascular endothelial growth factor receptor 2; eNOS: Endothelial nitric oxide synthase; BH4: Tetrahydrobiopterin; ↑: Up-regulation; ↓ Down-regulation.

Table 2. List of predicted pathways and their related roles in prostate cancer

Key pathways	Function in prostate cancer
Translocation of GLUT4 to the plasma membrane	Involvement in castration-resistant prostate cancer (CRPC) phenotype transition[21].
Membrane trafficking	Play a crucial role in regulating cellular signaling, angiogenesis, metastasis, and drug resistance, contributing to tumor progression[22].
VEGFA-VEGFR2 pathway	Multidimensional effects of metastatic PCa[23].
Vesicle-mediated transport	Impacting the development of the microenvironment surrounding the prostate tumor results in augmentation of tumor growth, invasion, bone metastasis, and resistance to therapeutic drugs[24].
eNOS activation and regulation	Facilitating the proliferation of PCa stem cells and concurrently fostering the progression of metastatic CRPC[25].
BH4 synthesis, recycling, salvage, and regulation	Impact on the tumor angiogenesis process[26].
Metabolism of nitric oxide	Promoting prostate tumor carcinogenesis, which is characterized by genetic instability and the development of a secretory phenotype that stimulates tumor growth[27].
RHO GTPase pathway	Crucial in facilitating various essential processes such as migration, invasion, and prostate tumor cell diapedesis[28].
Histamine receptors	Contributions to the growth of PCa[29].

metabolism, which are implicated in processes such as angiogenesis, metastasis, and drug resistance. Together, our study not only identified key genes regulated by hsa-miR-4783-3p but also highlighted their potential as therapeutic targets in PCa. However, experimental validation is still required to fully understand their specific functions and interactions in PCa.

3.3. Pairing analysis of target genes and hsa-miR-4783-3p in the seed match region

TargetScan examination of the predicted consequential pairing between hsa-miR-4783-3p and its target genes within the seed match region is a pivotal aspect of our study. The seed match region of hsa-miR-4783-3p, located between positions 2-8 from its 5' end, is notably significant because of its high conservation and crucial role in target recognition. The analysis involved a detailed evaluation of the base pairing within the seed region of hsa-miR-4783-3p and the complementary sequence in the mRNA of the target genes, as presented in Table 3.

Our pairing analysis provided insights into the potential binding interactions between hsa-miR-4783-3p and its target genes, indicating a higher likelihood of effective miRNA-mediated regulation. These findings indicate direct interactions between miRNA and its target genes, which could significantly influence the expression and functionality of these genes. However, experimental validation is essential to confirm these predictions and fully understand the mechanisms of miRNA-target interactions in PCa.

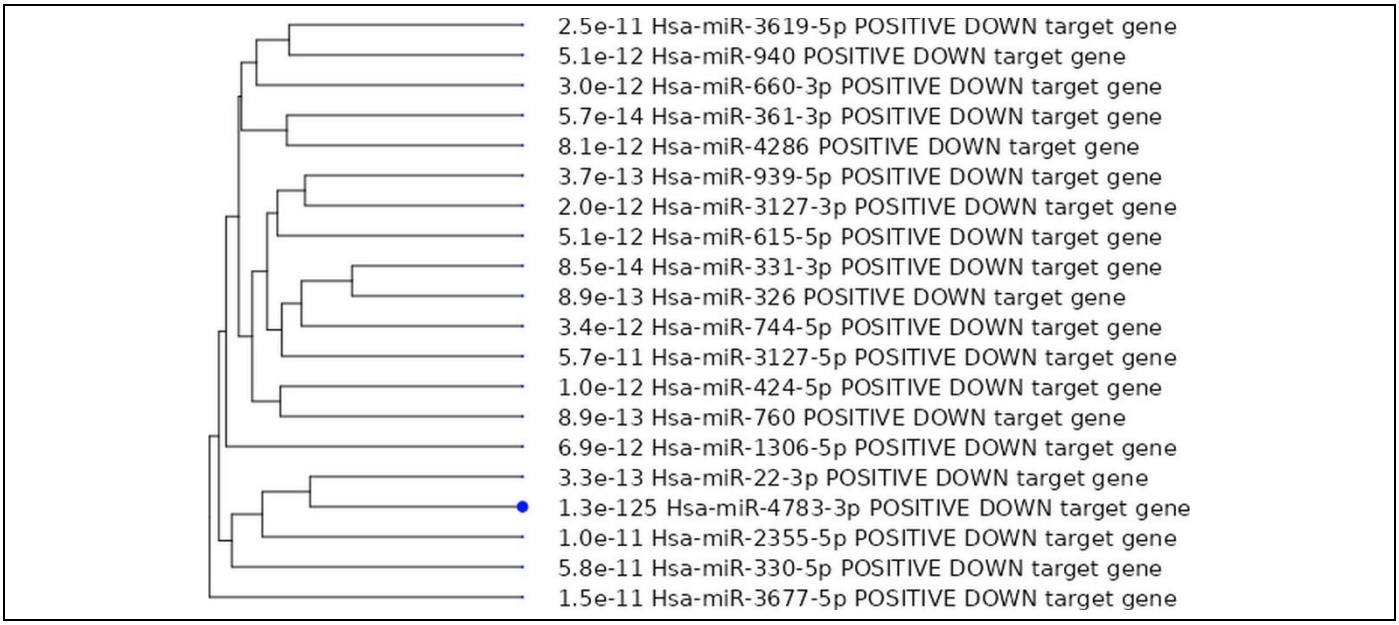

Figure 3. A hierarchical clustering tree summarizing the correlation between miRNAs and shared target genes. Larger dots represent more statistically significant interactions, as determined by the lower adj. p-values from FDR.

3.4. Exploring the association between miRNAs and shared target genes

Upon detailed analysis of the target genes validated by miRTarBase, it became evident that most of these genes function as downstream targets in the regulatory network influenced by hsa-miR-4783-3p. As illustrated in Figure 3, this observation underscores the critical role of hsa-miR-4783-3p in the complex regulatory landscape of PCa. The hierarchical clustering tree effectively summarizes the correlations among various miRNAs, including hsa-miR-4783-3p, and reveals their shared target genes. This visualization represents the interconnected regulatory pathways, highlighting the central role of hsa-miR-4783-3p in these networks.

Interestingly, our analysis of the predicted target genes revealed a robust association with hsa-miR-4783-3p. Among the evaluated miRNAs, hsa-miR-4783-3p demonstrated the highest enrichment, both in terms of the false discovery rate and fold enrichment, for its predicted target genes. This statistically significant correlation demonstrates a powerful and potentially pivotal regulatory relationship between hsa-miR-4783-3p and these target genes in PCa.

Furthermore, we identified shared target genes between hsa-miR-4783-3p and other pathogenic miRNAs, confirming potential interactions and demonstrating cooperative regulatory roles among these miRNAs in PCa progression. The identification of these shared gene targets brings into focus the intricate and interwoven regulatory networks that govern the functions of these miRNAs in the PCa complex milieu. Such insights are invaluable for understanding the multifaceted nature of miRNA-mediated regulation in cancer and could pave the way for new therapeutic interventions targeting these specific miRNA-gene interactions.

3.5. Discussion

To date, there is limited evidence from the literature showing hsa-miR-4783-3p's involvement in PCa development or progression. However, our study presents several important findings that advance the understanding of the potential roles of hsa-miR-4783-3p in prostate cancer:

(1): We identified 66 target genes systematically regulated by this miRNA, which may be involved in critical biological processes and pathways implicated in PCa progression. Among these genes, *AKT1*, *ARFGAP1*, *ARHGDIA*, *HRH2*, and *NF2* emerged as particularly relevant, associated with pathways such as GLUT4 translocation, VEGFA-VEGFR2 signaling, and eNOS activation, which drive PCa progression, metastasis, and therapeutic resistance (as shown in Table 1&2). The involvement of these genes in key pathways highlights the potential multifaceted roles of hsa-miR-4783-3p in regulating cellular processes that drive PCa development and metastasis through its potential binding interactions (Table 3). However, experimental validation of these predicted interactions is necessary to fully elucidate the mechanisms underlying the regulatory roles of hsa-miR-4783-3p in PCa.

(2): We acknowledge the limitations of our research, including the predictive nature of our evaluation and the reliance on computational tools with inherent limitations. Although informative, the predictive nature of our study necessitates experimental validation to confirm the biological and clinical significance of the identified miRNA-target interactions. Reliance on computational tools, subject to the limitations of their datasets, underscores the need for caution in interpreting our results[15–17]. Future research should transition from *in-silico* methodologies to *in- vitro*

Table 3. Analysis of predicted consequential pairing in the seed region

Positions 731–738 of AKT1 3′ UTR: 8mer	Positions 1130-1136 of ARHGDIA 3' UTR: 7mer-A1
5' ...UCUUGGUGACUGUCC**CACCGGGA** **|||||||** 3' CGUCUGCGCGGGGUU**GUGGCCC**C	5' ...CCUGCUUCUUUUCUG**ACCGGGA**A **||||||** 3' CGUCUGCGCGGGGUUG**UGGCCC**C
Position 1626-1633 of ARFGAP1 3' UTR: 8mer	**Positions 173–179 of HRH2 3' UTR: 7mer-m8**
5' ...AAGGUGCUGAGAAGC**CACCGGGA** **|||||||** 3' CGUCUGCGCGGGGUU**GUGGCCC**C	5' ...GAGUUGGUCUUCCCU**CACCGGG**C **|||||||** 3' CGUCUGCGCGGGGUU**GUGGCCC**C
Positions 394–400 of the NF2 3′ UTR: 7mer-A1	**Positions 3556-3563 of NF2 3' UTR: 8mer**
5' ...GCCACUUCUCCUGCU**ACCGGGA**C **||||||** 3' CGUCUGCGCGGGGUUG**UGGCCC**C	5' ...GCAGAAGCCCCACAG**CACCGGGA** **|||||| |||||||** 3' CGUCUGCGCGGGGUU--**GUGGCCC**C

Notes: A 7mer-A1 is a type of miRNA target site (bottom) that consists of a 7-nucleotide sequence within the 3' UTR of an mRNA molecule (top) with an "A" (adenine) at the first position of the miRNA binding site. A 7mer-m8 is another type of miRNA target site that contains a 7-nucleotide sequence within the 3' UTR. An 8mer is a type of miRNA target site that consists of an 8-nucleotide sequence within the 3' UTR of mRNA.

and *in-vivo* validations, employing techniques such as luciferase reporter assays or CRISPR-Cas9 gene editing[18,19]. Integrating multi-omics datasets will not only validate our findings but may also reveal additional regulatory layers[20].

(3): Furthermore, future studies should explore the interplay between hsa-miR-4783-3p and other miRNAs identified as pathogenic in our research. Understanding their synergistic or antagonistic interactions could provide deeper insights into PCa progression. Collectively, our findings highlight the complex and multifaceted nature of hsa-miR-4783-3p's potential involvement in PCa.

4. CONCLUSION

In conclusion, our comprehensive bioinformatics study provides novel insights into the potential involvement of hsa-miR-4783-3p in PCa pathogenesis. The identification of 66 key target genes, including *AKT1*, *ARFGAP1*, *ARHGDIA*, *HRH2*, and *NF2*, and their associations with critical pathways driving cancer progression, metastasis, and therapeutic resistance, implicate hsa-miR-4783-3p in the complex regulatory networks underlying PCa biology. The results of this study lay a solid foundation for future experimental validation of predicted miRNA-target interactions and their functional implications. This enhanced understanding holds significant relevance for advancing diagnostic and therapeutic strategies tailored to the molecular signatures of PCa, with the goal of improving clinical outcomes for patients.

5. ACKNOWLEDGMENT

Minh Trong Quang was funded by the Master, PhD Scholarship Program of Vingroup Innovation Foundation (VINIF), code VINIF.2021.ThS.69 and VINIF.2022.ThS.054. In addition, we extend our sincere gratitude to Dr. Minh Nam Nguyen (University of Health Sciences – Vietnam National University Ho Chi Minh City) for his invaluable comments that significantly enhanced the quality of this manuscript.

Conflict of interest
The authors declare that they have no competing interests.

Funding
This research received no external funding.

Ethics approval
Not applicable.

Article info:
Received May 4, 2024
Accepted June 25, 2024

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