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Integrated functional analysis of prostate cancer–associated genes: A multi-dataset bioinformatics approach

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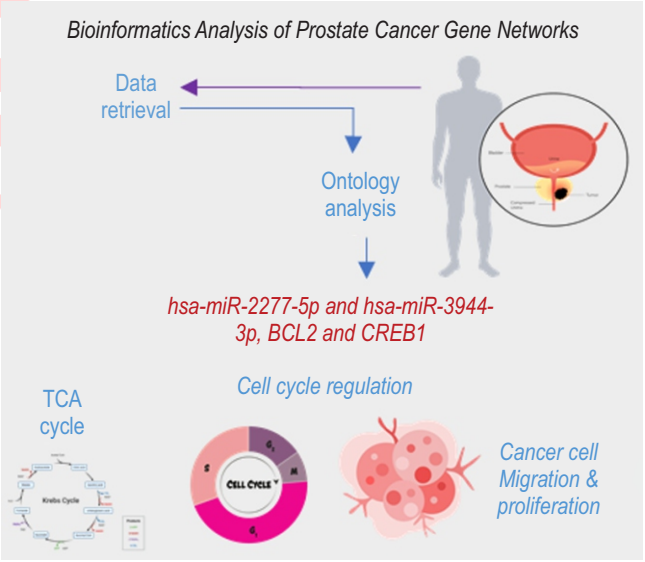
Abstract

Aim: This study aimed to investigate key genetic variants contributing to prostate cancer and their functional significance through integrative bioinformatic and molecular network analyses.

Methodology: GWAS data for prostate cancer were explored to identify important genetic variants and underlying biological pathways. Bioinformatic approaches were applied for enrichment analysis, protein–protein interaction network construction, and clustering to assess gene interactions. Regulatory mechanisms were examined through microRNA and transcription factor interaction analyses, with metabolomic data integrated to assess the impact of genetic variability on prostate cancer metabolism.

Results: Notable associations were identified for hsa-miR-2277-5p and hsa-miR-3944-3p, suggesting potential regulatory significance, although these did not retain significance following multiple testing correction. Reactome Pathway 2024 analysis identified Abacavir Transmembrane Transport as the most significantly enriched pathway (adjusted p = 0.00147; odds ratio = 429.33), alongside additional biologically relevant pathway associations.

Interpretation: This study highlights key genetic factors and regulatory elements potentially contributing to prostate cancer susceptibility and progression. The identified genes, microRNAs, and pathways advance mechanistic understanding of disease vulnerability and may ultimately inform the development of biological markers and targeted therapeutic strategies for prostate cancer.



Key words: Bioinformatics, GWAS, MicroRNA, Prostate cancer, Pathway enrichment

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Introduction

Carcinoma of the prostate is the most common non-cutaneous malignancy in the males and a major health concern (Shu *et al.,* 2025). In 2020, it was estimated that approximately 1.4 million new cases were diagnosed, along with more than 375,000 deaths due to related cases, making it the second most common type of cancer among males after lung cancer and fifth among all cancer deaths among males (Wang *et al.,* 2022). Prostate-specific antigen screening has improved detection rates, yet over diagnosis and overtreatment remain significant clinical challenges, particularly in distinguishing indolent from aggressive disease (Marhold *et al.,* 2022). In the Indian context, though prostate cancer incidence is lower than in Western populations, increasing life expectancy and urbanisation are contributing to a rising disease burden that warrants deeper molecular characterization (Wang *et al.,* 2022). The epidemiology of prostate carcinoma shows considerable geographical and racial differences. The incidence of this cancer is high in Northern/Western Europe, the Caribbean, Australia/NZ, and North America, with age-adjusted rates above 100 per 100,000 in some groups (Bray *et al.,* 2024).

Nevertheless, the rate of new cases being reported in Asia is always lower. Age is recognized as a definitive risk factor for the development of prostatic carcinoma, with a proved 60% prevalence for individuals aged more than 65 years. Family history can be a definite contributing factor as well. Apart from the established germline and somatic mutations, the progression of prostatic cancer has complex molecular pathophysiologies, such as Amplification of Oncogenes, transcriptional dysregulation, and resistance (Cotter and Rubin, 2022). Recent genome-wide association studies conducted between 2021 and 2025 have identified over 260 risk loci for prostate cancer, cumulatively explaining approximately 33% of familial relative risk, yet the functional consequences of most associated variants remain poorly characterized (Bau *et al.,* 2024; Shevach and Cooney, 2025; Shiota *et al.,* 2023). Pathway-level analyses have revealed convergence of these loci on androgen receptor signaling, cell cycle regulation, and DNA damage repair pathways, suggesting that multi-gene network analysis offers a more complete picture of disease biology than single-variant approaches.

The emerging field of perineural invasion — the tendency of prostate cancer to invade nerve fibres — has drawn attention to crosstalk between neurotransmitter signaling systems and tumour biology, an area that has not been systematically explored through integrated bioinformatics (Benzaquen *et al.,* 2024). Furthermore, metabolic reprogramming, particularly involving choline metabolism, has emerged as a hallmark of prostate cancer progression that is detectable through metabolomic profiling and may serve as a non-invasive biomarker (Li *et al.,* 2025). In view of the above, this study was conducted to determine the biological function and regulation of prostate cancer risk loci genes identified through genome-wide association studies using the Enrichr enrichment analysis platform, to investigate the association of gene set with biological terms based on Gene Ontology and various biological pathways, and to explore the regulatory roles of transcription factors and microRNAs in genes associated with prostate cancer—an integrated multi-dataset bioinformatics approach not previously applied to this specific combination of GWAS-derived prostate cancer loci in the Indian research context.

Materials and Methods

A step-wise bioinformatics analysis involving genome-wide association study data, functional enrichment, and network analysis was done to explore the genetic and molecular mechanisms of prostate cancer. Genetic loci that show strong association with prostate cancer were obtained from the GWAS Catalogue (Sollis *et al.,* 2023), a public database that contains known disease-associated loci established by genome wide association studies. These loci were further analyzed using various available tools. The genes were classified based on gene ontology (GO) to identify molecular function, cellular component, and biological processes. The functional enrichment suggested notable groupings of genes that were associated with the pathophysiology of prostate cancer. Pathway analysis was conducted using KEGG. The genes were further analyzed for biological processes using the classification of (Kanehisa *et al.,* 2017) and Reactome (Croft *et al.,* 2011) was carried out to detect the biological pathways with significant association with the input gene set. Post-transcriptional and epigenetic regulation would be analyzed by microRNA enrichment analysis using miRTarBase (Cui *et al.,* 2024) and TargetScan (Min and Yoon, 2010). Moreover, integration with metabolomic data using MetaboAnalyst (Pang *et al.,* 2024) enabled the association of genes identified through GWAS with metabolic pathways, revealing potential biomarkers for the onset and development of disease. This multi-omics approach helps in understanding the targets for developing a predictive and personalized treatment for prostate cancer.

Results and Discussion

Several human microRNAs were found to have significant enrichment scores by Target Scan analysis. Among these, hsa-miR-2277-5p and hsa-miR-3944-3p had higher values of odds ratios and combined scores, reflecting greater regulatory potency (Duca *et al.,* 2021). Although the adjusted p-values were non-significant, enrichment scores tend towards biological significance. Mouse microRNAs showed less significant values, reflecting species-specific regulation of gene targets. The identification of hsa-miR-2277-5p and hsa-miR-3944-3p with elevated odds ratios and combined scores is biologically meaningful even in the absence of post-correction statistical significance, because enrichment scores reflect coordinated regulation of multiple target genes rather than a single association. Both miRNAs have predicted targets involved in cell cycle regulation and apoptotic signaling, which are pathways that converge with the BCL2 and CREB1 hub proteins identified in the PPI analysis. The species-specificity of

enrichment, with mouse miRNAs showing weaker associations, further supports the human relevance of these regulatory predictions and is consistent with the known divergence of miRNA target sites between rodent and primate transcriptomes.

Reactome pathway analysis revealed strong enrichment for various metabolism and neurotransmission-related pathways. The Abacavir Transmembrane Transport pathway had the highest enrichment score ($p < 0.05$; OR = 429.33; combined score = 4527.43), followed by the Abacavir ADME and Organic Cation Transport pathways. The involvement of pathways related to neurotransmitters, such as the 'Norepinephrine Neurotransmitter Release Cycle' and 'Na^+/Cl^--dependent Neurotransmitter Transporters, were most noticeable indicating a relation between drug metabolism and neurotransmission processes. The highest enrichment of the Abacavir Transmembrane Transport pathway is at first glance unexpected for a prostate cancer gene set, but is mechanistically interpretable — Abacavir is a nucleoside reverse transcriptase inhibitor that is transported by solute carrier proteins, several of which overlap with the organic cation transporters found in prostate epithelium (Pereira and Vale, 2026). The co-enrichment of norepinephrine neurotransmitter release cycle and sodium/chloride-dependent neurotransmitter transporters is consistent with the emerging evidence that prostate cancer establishes a neuro-oncological niche where perineal invasion and sympathetic signaling promote tumour dissemination (Benzaquen *et al.,* 2024). This finding suggests that the prostate cancer GWAS gene set encodes functional machinery relevant to both drug metabolism and neural signaling, a convergence with clinical significance for drug delivery and tumor microenvironment biology.

KEGG analysis showed that certain biological pathways were significantly enriched even when the FDR values were non-significant. The top pathways with high odd ratios, likely playing a role in metabolism and oncogenic pathways, included Choline metabolism in cancer and Maturity-onset diabetes of the young (MODY) (Knura *et al.,* 2021). The pathways of cardiomyopathy and cancer further highlighted the importance ofsignalling pathways that are also implicated in cases of metabolic and cardiovascular diseases. The enrichment of choline metabolism in cancer as a top KEGG pathway directly connects to the metabolite analysis findings, where choline showed the highest enrichment score among all metabolites. Choline is the substrate for phosphatidylcholine synthesis, which supports rapid membrane biosynthesis in proliferating cancer cells, and choline kinase—the rate-limiting enzyme of this pathway—is overexpressed in prostate cancer and is an established drug target. The co-enrichment of maturity-onset diabetes of the young pathway is noteworthy because the transcription factors HNF1A and HNF4A that define MODY are also expressed in prostate epithelium and regulate genes involved in androgen receptor signaling, reflecting shared transcriptional dependencies between pancreatic beta-cell biology and prostate cancer (Li *et al.,* 2025). The PPI analysis also identified the hub proteins in the network as having a moderate enrichment score. These proteins include *BCL2, HIST1H3A* and *CREB1* in the OR range of 4-5. These proteins are already known to regulate the processes of apoptosis, chromatin regulation, and regulation of transcription. Other proteins in the list include *ITGB1, CDK5, CALM3,* which indicate the regulation of adhesion processes using the integrin pathway. The hub status of BCL2, HIST1H3A, and CREB1 in the PPI network is biologically coherent in the context of prostate cancer. BCL2 overexpression is a well-established mechanism of apoptosis resistance in castration-resistant prostate cancer, and its co-hub relationship with CREB1 is particularly relevant— CREB1 has been shown to directly regulate BCL2 transcription in response to mitochondrial stress, and the CREB1-BCL2 axis drives chemoresistance in RAS-dependent cancers (Man *et al.,* 2025). ITGB1 and CDK5 in the same network reflect the integrin-mediated adhesion and cytoskeletal regulation that prostate cancer cells exploit during invasion and metastasis to bone. CALM3, encoding calmodulin, connects calcium signaling to CDK5 activity, providing a mechanistic link between calcium-dependent neurotransmitter release — enriched in the Reactome analysis — and kinase-driven cell motility (Yang and Tsai, 2022).

Analysis of GO Biological Process showed strong enrichment for terms related to transport. Thiamine transmembrane transport, Polyamine transport, and Xenobiotic transport via blood brain barrier were the most strongly enriched terms (all had $p < 0.05$ and OR > 400). Terms related to neurotransmitters, Dopamine transport and Serotonin uptake, were also strongly enriched, reflecting important roles in transport of nutrients and neurotransmitters across membranes. The strong enrichment of transmembrane transport terms—thiamine, polyamine, xenobiotic, dopamine, and serotonin transport—in GO Biological Process is consistent with the known importance of uptake transporters in prostate cancer pharmacology. Polyamine transport is particularly relevant because prostate tissue has among the highest polyamine concentrations of any tissue in the body, and polyamine biosynthesis supports DNA replication in rapidly dividing cancer cells (Soda, 2022). Xenobiotic transport via blood-brain barrier enrichment may reflect shared transporter expression patterns between the blood-brain barrier and the blood-testis barrier, both of which rely on ABC transporters that are also expressed in prostate tissue and influence drug bioavailability (Lin *et al.,* 2022). GO cellular component analysis indicated localization of gene products in membrane-associated structures. The cytoplasmic face of endoplasmic reticulum membrane had the greatest enrichment score (51.97), followed by Basolateral plasma membrane and Asymmetric synapse. Although non-significant, these suggest functions related to Vesicular transport, Synaptic communication, Intercellular junctional signalling (Table 1).

GO: Molecular Function analysis identified a strongly overrepresented category of prostaglandins and monoamines transmembrane transporters (Adj P = 0.0044). This was coupled with an overrepresentation of quaternary ammonium group transmembrane transporters and thiamine transmembrane transporters, consistent with a functional enrichment in membrane transporters. Binding functions, such as insulin-like

Table 1: Enriched molecular function along with the p – values

Names	p-value	Adjusted p-value	Odds Ratio	Combined score
Cytoplasmic side of endoplasmic reticulum membrane (GO:0098554)	0.02125	0.242	51.97	200.15
Basolateral plasma membrane (GO:0016323)	0.03227	0.242	7.56	25.95
Asymmetric synapse (GO:0032279)	0.1978	0.5793	4.7	7.61
Adherensjunction (GO:0005912)	0.2201	0.5793	4.16	6.29
Postsynaptic density (GO:0014069)	0.2214	0.5793	4.13	6.22

Table 2: Enriched molecular function along with the p – values

Names	p-value	Adjusted p-value	Odds Ratio	Combined score
Prostaglandin transmembrane transporter activity (GO:0015132)	0.000144	0.004388	143.07	1265.68
Monoamine transmembrane transporter activity (GO:0008504)	0.000144	0.004388	143.07	1265.68
Quaternary ammonium group transmembrane Transporter Activity (GO:0015651)	0.000354	0.007188	85.82	682.02
Thiamine transmembrane transporter activity (GO:0015234)	0.008224	0.1254	155.96	748.73
Pyrimidine nucleoside transmembrane Transporter Activity (GO:0015214)	0.01149	0.1334	103.96	464.29

Table 3: Enriched metabolites along with the p – values

Names	p-value	Adjusted p-value	Odds Ratio	Combined score
Choline (HMDB00097)	0.04363	0.2182	23.97	75.06
Manganese (HMDB01333)	0.274	0.5386	3.22	4.17
Phosphate (HMDB01429)	0.4208	0.5386	1.88	1.62
Guanosine triphosphate (HMDB01273)	0.5363	0.5386	1.33	0.83
Magnesium (HMDB00547)	0.5386	0.5386	1.32	0.82

growth factor binding and actinin binding, further implied a link between growth and structural processes (Table 2). The strongest molecular function enrichment for prostaglandin and monoamine transmembrane transporter activity directly connects the GWAS gene set to arachidonic acid metabolism and monoamine neurotransmitter uptake—two biological processes with established roles in prostate cancer biology (Siech *et al.,* 2022).

Prostaglandin E2, synthesised from arachidonic acid by COX-2, promotes prostate cancer proliferation and immune evasion, and genes regulating prostaglandin transport influence tissue concentrations of this pro-tumorigenic mediator (Jara-Gutiérrez and Baladrón, 2021). The insulin-like growth factor binding enrichment links to the IGF1 receptor signaling pathway, which cooperates with the androgen receptor to promote prostate cancer cell survival and is associated with aggressive disease phenotypes (Siech *et al.,* 2022). Analyses of cell markers showed an overrepresentation of liver stem cells, Sertoli cells, and brush/tuft cells of lungs with high odds ratios and combined scores. Progenitor or stem cells like trophoblast stem cells and intestinal stem cells were overrepresented, and this can be attributed to activation of developmental and regenerative gene expression programs related to cellular plasticity. The overrepresentation of liver stem cells, Sertoli cells, and lung brush cells in the cell marker analysis indicates that the prostate cancer GWAS gene set shares expression signatures with progenitor and specialised cell types across multiple tissues (Nandagopal *et al.,* 2024). Sertoli cell gene expression patterns overlap significantly with prostate luminal epithelial cells due to their shared androgen-regulated transcriptional programmes, making this enrichment biologically coherent. The co-enrichment of trophoblast and intestinal stem cell signatures suggests activation of a broader epithelial progenitor programme, consistent with the cancer stem cell hypothesis in prostate cancer where a small population of cells with stem-like properties drives tumour maintenance and therapy resistance (Chu *et al.,* 2024). The results of the metabolite analysis showed that choline had the highest degree of enrichment (p-value < 0.05; OR = 23.97),

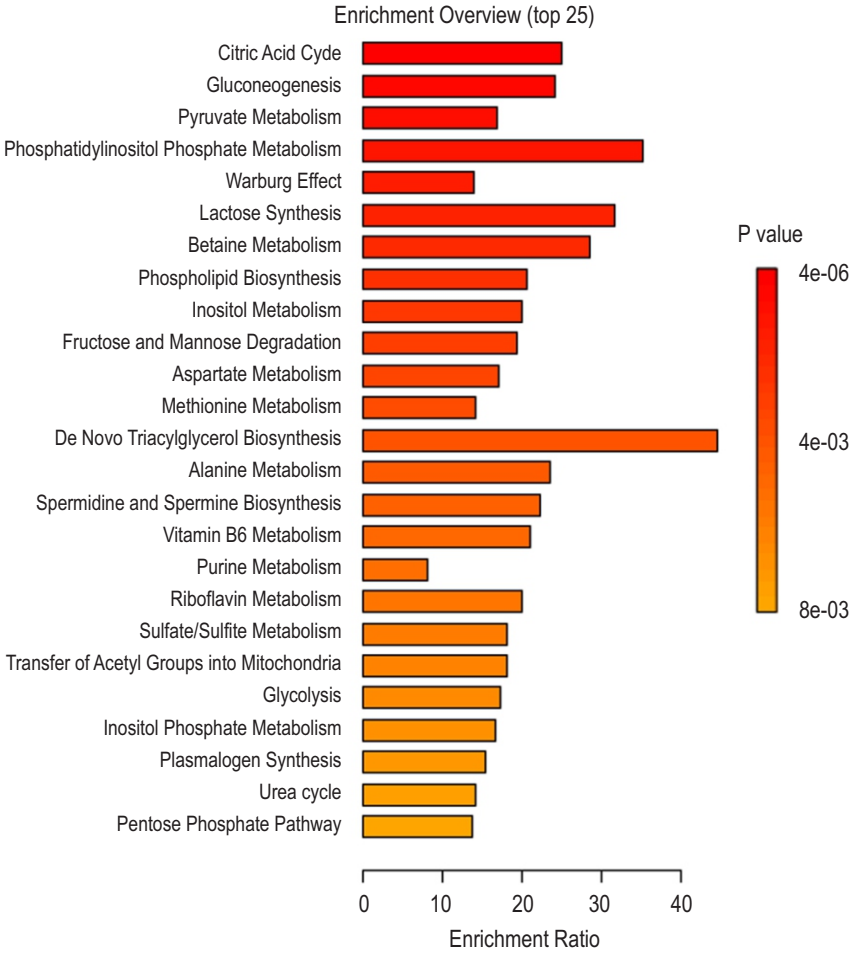

Fig. 1: Top 25 enriched pathways are shown in the enrichment overview. The pathways were significantly enriched, with the highest enrichment ratios and lowest p-values.

proposing potential involvement in choline-related metabolism such as biosynthesis of membranes and methylation. The other compounds that had a low degree of enrichment included Manganese, Phosphate, GTP, and Magnesium. (Table 3). Choline's position as the highest-enrichment metabolite with an odds ratio of 23.97 is clinically significant because choline PET imaging is already an established diagnostic modality for prostate cancer staging and recurrence detection, and elevated tissue choline reflects the accelerated phosphatidylcholine synthesis that characterises rapidly dividing prostate cancer cells (Detti *et al.,* 2023). The co-enrichment of manganese, phosphate, GTP, and magnesium — though at lower significance — reflects the metalloprotein and nucleotide dependencies of the mitochondrial respiratory chain, which are consistent with the Warburg effect and Citric Acid Cycle enrichments identified in the metabolic pathway modelling (Li *et al.,* 2025).

Metabolic pathways, like Citric Acid Cycle, Gluconeogenesis, and Warburg Effect ($p < 0.00001$), Lipid and amino acid metabolism pathways, namely Phospholipid Biosynthesis and Aspartate metabolism, were also identified to be enriched. Secondary pathways, namely Urea cycle, Pentose Phosphate Pathway ($p < 0.01$), reinforced the idea that overall metabolism was being repurposed; however, these did not reach statistical significance (Fig. 1). The enrichment of Warburg Effect, Citric Acid Cycle, and Gluconeogenesis pathways together describes the metabolic flexibility that is characteristic of prostate cancer — cells can shift between oxidative phosphorylation and aerobic glycolysis depending on substrate availability and androgen signaling status (Schiliro and Firestein, 2021). Phospholipid biosynthesis enrichment directly connects to the choline metabolite finding, since choline is the rate-limiting substrate for phosphatidylcholine production. The pentose phosphate pathway enrichment supports nucleotide biosynthesis for rapidly dividing cancer cells, and aspartate metabolism provides the carbon backbone for purine and pyrimidine synthesis (Vidal-Cruchez and Ben-Sahra, 2026). This pattern of metabolic pathway enrichment is consistent with the integrated

signaling-metabolic network view of cancer biology and supports the use of metabolic targeting strategies alongside conventional androgen deprivation therapy (Lin *et al.,* 2022).

The above multiple layers of enrichment analyses together demonstrate a clear nexus of transport processes, energy metabolism, and cell signaling. The common theme of transmembrane transport protein activity, neurotransmission, and/or choline metabolic processes emphasizes the metabolic diversity of examined gene set. It is pertinent to note that Reactome and GO analysis results matched on neurotransmission/ nutrient transport. This perhaps suggests a possible crosstalk between neurosystems and metabolic pathways (Benzaquen *et al.,* 2024). The consistency of transport-related enrichment across Reactome, GO Biological Process, and GO Molecular Function analyses — covering Abacavir transmembrane transport, organic cation transport, thiamine transport, polyamine transport, prostaglandin transport, and monoamine transport—constitutes robust multi-platform validation that membrane transport machinery is centrally implicated in the prostate cancer gene set. This convergence is not coincidental; many solute carrier proteins that mediate these transport activities are under androgen receptor transcriptional control, providing a direct mechanistic link between the hormonal landscape of prostate cancer and the functional enrichments observed here (Benzaquen *et al.,* 2024).

BCL2, CREB1 and *ITGB1* were identified as hubs, proposing a regulatory mechanism in apoptosis, transcription, and cell adhesion, which has been previously shown for these proteins in relation to metabolic adaptation and stress response (Man *et al.,* 2025; Marhold *et al.,* 2022). The inclusion of stem cell-related signatures in the liver, lung, and reproductive cell lineages suggests the involvement of gene-expression profiles that may be associated with either regeneration or malignancy (Barata *et al.,* 2023; Chu *et al.,* 2024; Sato *et al.,* 2017). Though some of the paths failed to cross strict post-correction statistical significance thresholds, their biological plausibility with established cascades of signaling and metabolism supports their validity. Specifically, the relevance of choline and thiamine transport mechanisms with enrichment of terms suggestive of MODY and cancer in the KEGG database reflects shared metabolic vulnerabilities (Li *et al.,* 2025; Lin *et al.,* 2022).

In conclusion, the bioinformatic analysis describes a pattern of modified metabolism and signaling pathways mediated by transport function, neurotransmitter control, and cellular plasticity. These data provide a preliminary molecular platform which may inform future research endeavors aimed at investigating underlying mechanisms related to observed transcriptomics and metabolomics modifications. This current study is purely bioinformatics-based and does have verification by experimental or clinical methods. As a result, these current results should be considered preliminary and may not be entirely accurate regarding biological or clinical truths. Further study is needed for these observations to be supported.

The novelty of this study lies in its application of a multi-dataset enrichment approach to prostate cancer GWAS-derived loci, simultaneously interrogating GO, Reactome, KEGG, miRNA, PPI, cell marker, and metabolite databases to generate an integrated molecular portrait. Previous bioinformatics studies on prostate cancer have typically focused on one or two analytical dimensions; the multi-platform convergence demonstrated here —particularly the consistent identification of transport, neurotransmitter, and choline-related biology across independent databases — provides greater confidence in these findings than any single analysis could achieve. Future experimental validation should prioritise the choline kinase-CREB1-BCL2 axis as a tractable therapeutic target and investigate the perineural invasion gene signature identified here in patient-derived prostate cancer organoid models.

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