Serican Journal of Medicine
2026, VOL. 3, NO. 2, 25342
https://doi.org/10.17161/sjm.v3i2.25342

Decoding the Homeobox (HOX) Gene Expression Profile: Implications for Diagnosis, Prognosis and Survival in Prostate Cancer

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ABSTRACT

Objectives: This study provides a comprehensive analysis of the expression profiles and clinical significance of homeobox (HOX) genes in prostate cancer (PCa).

Methods: We utilized large-scale datasets including TCGA-PRAD, DKFZ RNA-seq, and metastatic castration-resistant prostate cancer (mCRPC) cohorts. We screened 228 HOX-related genes for gene expression related to disease progression, diagnosis, and prognosis. Gene expression was compared in patient subgroups stratified by clinical parameters. Survival prognosis was analyzed using the Kaplan-Meier survival curve approach. The AUC value of the altered gene was determined using the Receiver Operating Characteristic (ROC) curve analysis. The effect of castration on HOX-related gene expression was analyzed using the LuCaP35 xenograft dataset.

Results: We identified 42 up-regulated and 56 down-regulated genes with significant differential expression between benign and malignant tissues. Further investigation into 22 key genes revealed their profound impact on diagnosis and prognosis. HOXC6 and NKX2-3 emerged as highly effective diagnostic biomarkers, demonstrating area under the curve (AUC) values of 0.917 and 0.936, respectively. Prognostically, NKX6-1 expression showed the strongest predictive potential for 5-year disease-specific survival (AUC = 0.881), while HOXB7 also served as a critical survival indicator (AUC = 0.909). Conversely, the down-regulation of EVX2 was uniquely associated with all clinicopathological and survival parameters, suggesting a significant tumor-suppressive role. In early-onset PCa, HOXC5, HOXC6, and MEIS2 correlated strongly with tumor mutation burden and biochemical recurrence. In the context of advanced disease, NKX2-3 was associated with Androgen Receptor (AR) activation scores, whereas MEIS2 showed a strong negative correlation. Notably, this study identified HOXB8/HOXD13 genes, like LHX2, as novel and consistent markers, significantly increased in treatment-induced neuroendocrine prostate cancer (t-NEPC).

Conclusion: These findings highlight a distinct subset of HOX genes that govern prostate cancer progression and provide a framework for developing novel diagnostic and prognostic tools tailored to disease stage and subtype.

ARTICLE HISTORY
Received: May 2, 2026
Revised: May 4, 2026
Accepted: May 6, 2026

Introduction

Prostate cancer (PCa) remains a leading cause of cancer-related mortality among men worldwide, characterized by a highly heterogeneous clinical course that ranges from indolent, localized tumors to aggressive, metastatic disease [1]. While androgen receptor (AR) signaling remains the primary driver of prostate development and oncogenesis, the molecular mechanisms governing the transition from primary adenocarcinoma to castration-resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC) are increasingly linked to the reactivation of embryonic developmental programs [2]. At the heart of these programs lie the homeobox (HOX)-containing protein-coding genes [3]. The human genome contains more than 200 functional homeobox genes, with the 39 "canonical" HOX genes organized into four genomic clusters (HOXA, HOXB, HOXC, and HOXD) on different chromosomes [4, 5]. These genes encode transcription factors characterized by a highly conserved 60-amino acid DNA-binding domain known as the homeodomain. During embryogenesis, HOX genes act as "master architects," defining the anterior-posterior body axis and direct-

ing tissue-specific differentiation [6]. In the prostate, specific HOX genes, most notably within the HOXB and HOXC clusters, are essential for the architectural patterning of the prostatic buds [3]. However, once development is complete, many of these genes are silenced or strictly regulated in adult somatic tissues [7]. The "developmental bypass" hypothesis suggests that cancer cells hijack these dormant embryonic programs to promote survival, proliferation, and epithelial-to-mesenchymal transition (EMT) [8].

In prostate cancer, HOX gene dysregulation is not merely a byproduct of genomic instability but a functional driver of progression [9]. Recent studies have identified HOXC6 and NKX2-3 as superior diagnostic biomarkers, often outperforming traditional Serum PSA in distinguishing benign from malignant tissues [10, 11]. The aberrant expression of genes like NKX6-1 and HOXB7 has been strongly correlated with disease-specific survival and biochemical recurrence (BCR) intervals [12, 13]. Conversely, certain homeobox genes like MEIS2 appear to exert tumor-suppressive functions in normal prostate tissue, with their loss marking a critical step toward metastatic progression [14, 15].

A defining feature of PCa is its dependence on androgen signaling [16]. There is a complex, reciprocal relationship between the AR and the HOX network [17]. Certain HOX proteins act as AR co-regulators, either enhancing or inhibiting AR-mediated transcription [17]. For example, HOXC6 is known to be directly regulated by the AR, creating a feed-forward loop that promotes tumor cell viability even under androgen-deprived conditions [18]. This interplay is a key factor in the development of CRPC, where the AR pathway is bypassed or co-opted by developmental transcription factors [16].

As PCa evolves under the selective pressure of potent AR-targeted therapies (such as enzalutamide or abiraterone), a subset of tumors undergoes a lineage switch toward a neuroendocrine (NE) phenotype [19]. This transition is marked by the loss of AR signaling and the acquisition of neuronal markers [20]. Emerging evidence points to homeobox genes like LHX2, HOXB13, and HOXB5 as critical mediators of this plasticity [21-25]. These genes likely facilitate the epigenetic reprogramming required for a cell to abandon its luminal identity and adopt a treatment-resistant neuroendocrine state [26].

Understanding the global expression profiles of the HOX-related genes is essential for identifying the next generation of precision medicine tools. By mapping the transition of HOX expression from early-onset primary tumors to end-stage NEPC, we identified several HOX-related genes as novel therapeutic vulnerabilities and refined their roles as prognostic factors to better predict patient outcomes in this complex disease landscape.

Material and Methods

Gene expression analysis in primary prostate cancer

Gene expression profiles at the mRNA level were assessed using the Cancer Genome Atlas program (TCGA-PRAD) RNA-seq dataset as described in our recent publications [27-33]. The RNA-seq data were converted to $\log_2$(value+1) format before statistical analysis. Two statistical approaches, case-matched pairs and group cohort comparisons, were utilized to compare the differences in gene expression levels between benign and malignant tissues. There were 52 cases of benign-malignant matched tissue pairs in this study. Patients were also stratified by multiple clinicopathological parameters to assess the differences in gene expression levels among subgroups. The AUC value of the altered gene was determined using the Receiver Operating Characteristic (ROC) curve analysis.

Survival outcome assessments

Patient survival outcomes in three categories, namely overall survival, disease-specific survival, and progression-free interval, were analyzed using the minimum p-value approach to obtain the best grouping cut-off values between expression-high and expression-low groups [34]. The Kaplan-Meier survival curve was generated using the bioinformatic platform at the Xiantao Scholar (www.xiantaozi.com) platform as described in our recent publication [27-33].

Gene expression analysis in early-onset and CRPC patients with neuroendocrine features

Gene expression profiles in early-onset prostate cancer patients were assessed in the DKFZ RNA-seq dataset that contains 313 samples from 282 patients [35]. Gene expression levels were assessed in patients with or without biochemical relapses (BCR), E26 transformation-specific (ETS) gene fusion status, or different Gleason score groups.

Gene expression profiling for castration-resistant prostate cancer patients was conducted using the whole exome sequencing data generated by the

SU2C/PCF dream team [36]. Both DKFZ and SU2C/PCF datasets were available on the cBioportal platform [37]. The correlation of gene expression levels with the NEPC and AR scores was calculated using the tools available on the cBioportal platform.

Gene expression profiles in LuCaP35 xenografts after castration

The gene expression data were downloaded from the dataset generated from the experiment using the human prostate cancer LuCaP35 subcutaneous xenograft models [38]. The dataset was downloaded from the NCBI GEO profile GDS4120. Briefly, after castration or sham operation, xenograft tumors were harvested four weeks later, and total RNA extraction was performed using the QIAGEN RNeasy Mini Kit (Valencia, CA). Gene expression levels were assessed using the Affymetrix human genome U133 Plus 2.0 array GeneChip assays.

Statistical analysis

The RNA-seq data for the mRNA expression levels were assessed using the $\log_2$ [TPM + 1] values and presented as the MEAN ± the SEM (standard error of the mean). Statistical analysis was conducted using the ANOVA analysis for multiple group comparisons. The Student t-test was used to determine the significance of the differences between the two groups. The results were visualized using the R package (version 4.2.1) and GraphPad software (version 9.1.0).

Results

Multiple HOX-related genes were aberrantly expressed in prostate cancers

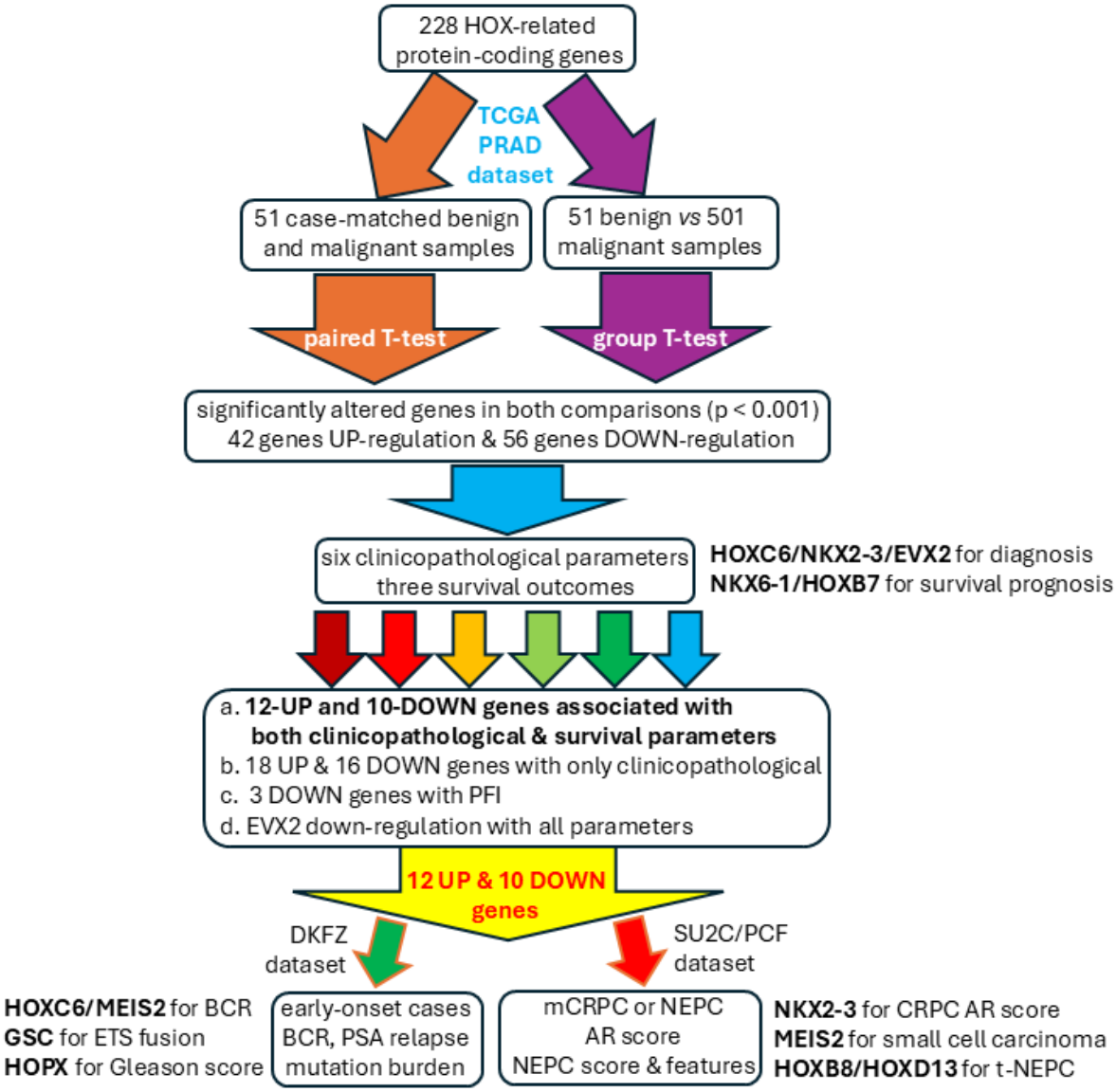
We surveyed the expression profiles of 228 human homeobox (HOX)-containing protein-coding genes [7, 8]. We used the TCGA-PRAD RNA-seq dataset derived from 501 primary prostate cancer patients (Fig 1), which contains 52 case-matched benign and malignant tissues [39]. We first analyzed their differences at the mRNA expression levels in these 52 matched cases using a pair-wise comparison approach, followed by a group comparison approach between benign and malignant tissues (Supplemental Fig S1 and Table S1). From these two approaches, 42 up-regulated genes and 56 down-regulated genes were identified as concomitantly altered in both comparisons (Supplemental Table S2 & S3) with a strong statistical significance ($p < 0.001$)

We then focused our attention on these concomitantly altered (42 UP and 56 DOWN) genes and assessed their association with clinicopathological parameters and survival outcomes. Patients were stratified into high or low expression groups at the median level of gene expression to obtain discrete quantitative data. Among the 42 up-regulated genes (42-UP), 12 genes (HOXC4, HOXC5, HOXC6, HOXC13, NKX2-3, NKX6-1, GSC, ISX, VAX2, BARX1, LHX2, LHX4) were significantly associated with one or more clinicopathological parameters and survival outcomes (12-UP). Eighteen genes (HOXA9, MNX1, NKX2-1, NKX2-2, NKX3-1, LMX1B, SIX1, SIX4, ONECUT2, CUX2, ADNP, ALX4, EN2, GBX2, VAX1, HESX1, SHOX2, MSX1) were only associated with clinicopathological parameters but not survival outcomes (Supplemental Table S4). Among the 56 down-regulated (56-DOWN) genes, ten genes (HOXA2, HOXB7, HOXB8, HOXD3, HOXD13, EVX2, DLX3, MEIS2, HOPX, PAX3) were significantly associated with one or more clinicopathological and survival factors (10-DOWN), and sixteen genes (HOXB2, HOXB4, HOXB5, HOXD8, HOXD9, HOXD11, HOXD12, HOXD13, EVX1, POU3F1, POU5F1, ZEB2, PITX1, VSX1, PKNOX1, POU2F2) were only associated with clinicopathological parameters (Supplemental Table S5). In addition, three down-regulated genes (MEIS1, SIX2, TSHZ3) were only associated with progression-free interval (PFI). Interestingly, EVX2 downregulation was significantly associated with all clinicopathological and survival parameters (Supplemental Table S5). The entire process was illustrated in Fig 1 with the major findings of the gene expression profiling survey.

HOXC6/NKX2-3 gene upregulation exhibits a strong correlation with clinicopathological parameters in prostate cancer

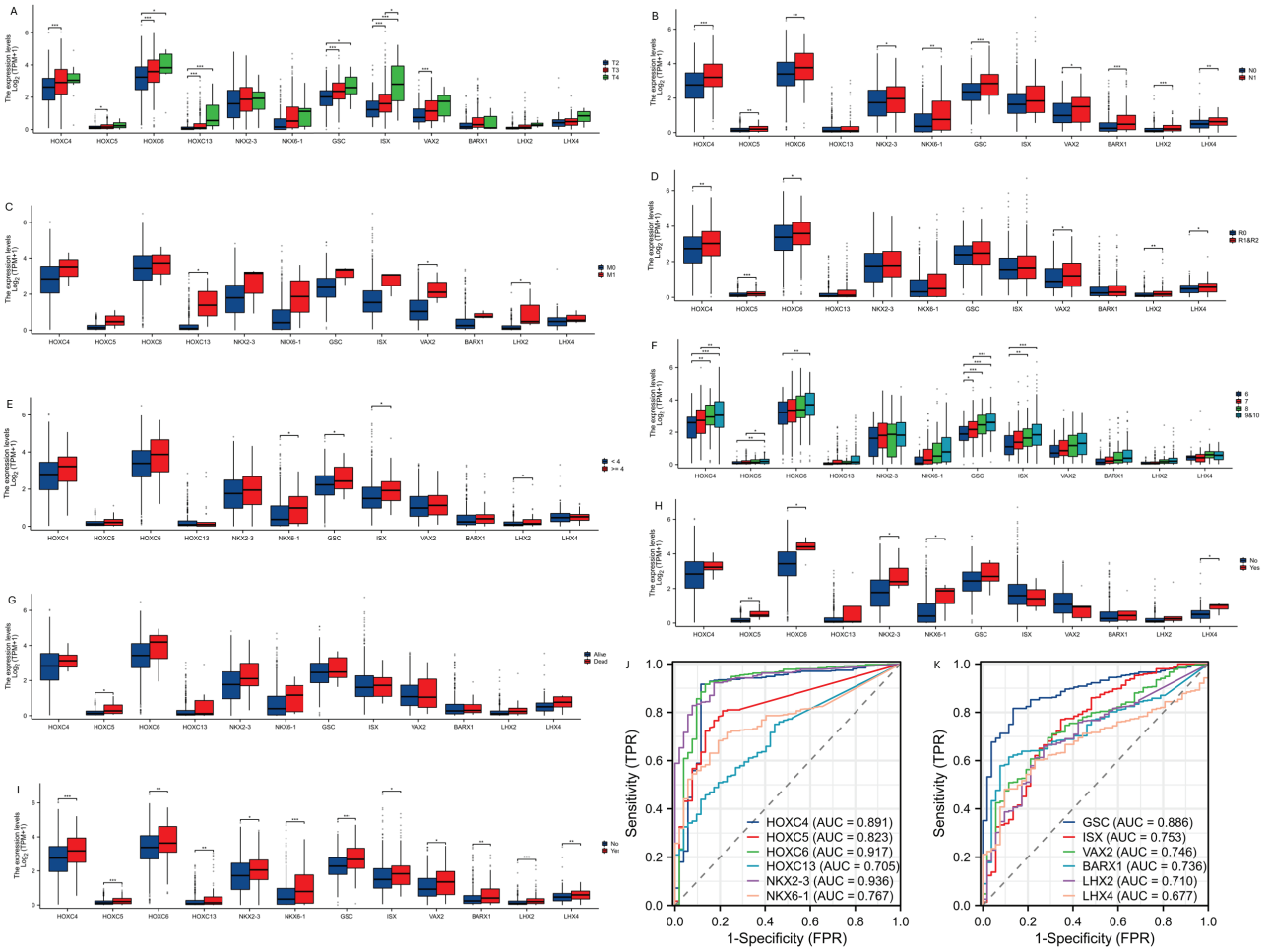
To evaluate the clinical significance in detail, we used a continuous quantitative data approach to examine the expression differences in subgroups based on pathological stage, lymph node invasion, distal metastasis, residual tumors post-surgery, serum PSA level before surgery, Gleason score, overall survival, disease-specific survival, and progression-free survival. Among the 12 up-regulated genes (12-UP), HOXC6 gene expression was at the highest levels and exhibited a strong elevation along with increasing tumor stage (Fig 2A), positive lymphatic invasion (Fig 2B), post-surgery residual tumors (Fig 2D), higher Gleason scores (Fig 2F), worse disease-specific survival outcome (Fig 2H), and shorter progression-free interval (Fig 2I), but not with distal metastasis (Fig 2C) and prior-surgery PSA levels (Fig 2E). These data were supported by previous reports [10, 40-42].

Fig 1. Schematic illustration of the data mining process. A total of 228 HOX -related family genes were screened over the TCGA-PRAD RNA-seq dataset, and 42-UP and 56-DOWN genes were identified in primary prostate cancers. Of these significantly altered genes, 12-UP and 10-DOWN genes were found to be tightly associated with clinicopathological parameters and patient outcomes.



Four HOX genes (HOXC5, BARX1, LHX2, LHX4) were expressed at relatively lower levels with a moderate upregulation (Fig 2A). However, HOXC13 & ISX gene expression was drastically upregulated in late stage (pT4) compared to early stage pT2 diseases (Fig 2A), but was not associated with lymph node invasion (Fig 2B), distal metastasis (Fig 2C), or residual tumor post-surgery (Fig 2D). HOXC13, VAX2, and LHX2 were largely increased in cases with distal metastatic diseases (Fig 2C). HOXC4, HOXC6, GSC, and ISX gene expression was gradually elevated along with the higher Gleason scores (Fig 2F). None of these 12-UP genes were associated with patient overall survival outcomes (Fig 2G); however, five (HOXC5, HOXC6, NKX2-3, NKX6-1, and LHX4) of these 12-UP genes were expressed at a significantly higher level in patients with disease-specific death (Fig 2H). Interestingly, all these 12-UP genes showed a significantly higher level in relapsed patients compared to disease-free patients (Fig 2I).

Fig 2. Gene expression comparisons for the 12-UP genes in clinical subgroups. A Group cohort comparison was used to compare gene expression levels among different pathological stages (**A**, case numbers: 190-296-11), between cases with or without lymph node invasion (**B**, case numbers: 351-80), with or without distal metastasis (**C**, case numbers: 459-3), with or without residual tumor after surgery (**D**, case numbers: 319-154), prior surgery PSA level below or above 4 (**E**, case numbers: 420-27), among different Gleason score (**F**, case numbers: 46-251-65-138), overall survival (**G**, case numbers: 494-10), disease-specific survival (**H**, case numbers: 497-5), or progression-free survival (**I**, 410-94) using the TCGA-PRAD RNA-seq dataset. Panel **J** & **K**, ROC analysis was conducted to determine the predictive potential in distinguishing benign from tumor tissues. The 95%CI for the AUCs: HOXC4, 0.832-0.950; HOXC5, 0.770-0.875; HOXC6, 0.867-0.968; HOXC13, 0.642-0.768; NKX2-3, 0.909-0.963; NKX6-1, 0.716-0.817; GSC, 0.848-0.924; ISX, 0.679-0.828; VAX2, 0.682-0.810; BARX1, 0.681-0.792; LHX2, 0.643-0.776; LHX4, 0.619-0.735. ANOVA test, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

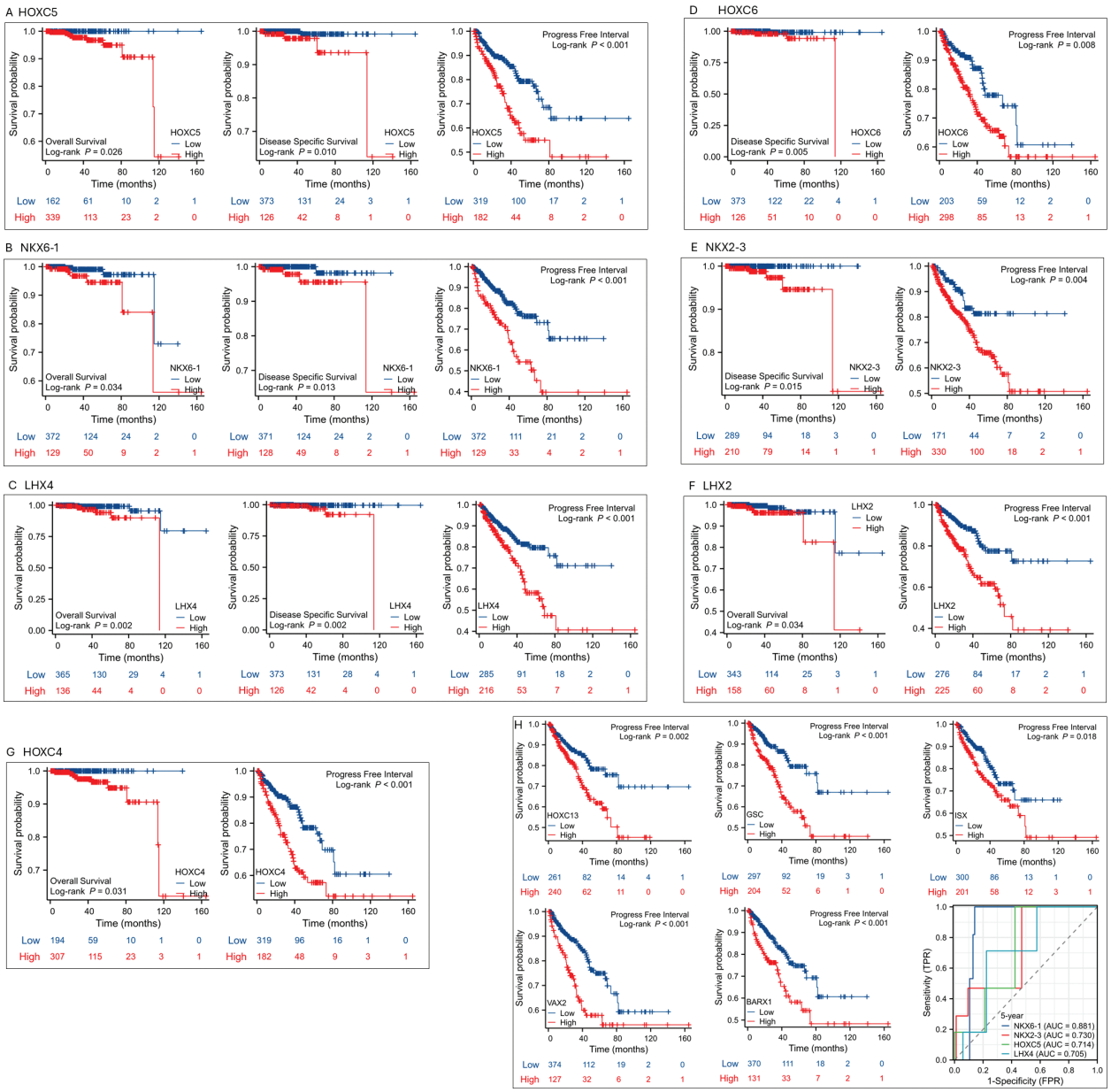


We then conducted an ROC analysis to determine the impact of gene expression levels on distinguishing benign and malignant tissues. Among these 12-UP genes, HOXC6 and NKX2-3 gene expression showed very high AUC values (0.917-0.936, Fig 2J), followed by HOXC4, GSC, and HOXC5 (Fig 2K). These data suggest that HOXC6 and NKX2-3 gene expression is tightly associated with prostate cancer progression. Indeed, recent reports showed that HOXC6 and NKX2-3 expression are clinical biomarkers for prostate cancer diagnosis [11, 18, 43-47].

NKX6-1 expression exhibited a strong power for survival prognosis

We performed a survival analysis of these 12-UP genes using the Kaplan-Meier curve approach. As shown in Fig 3A-3C, higher levels of three genes (HOXC5, NKX6-1, and LHX4) showed a signifi-

Fig 3. Survival analysis for the 12-UP genes in prostate cancers. Gene expression data for the HOX-related family genes, including HOXC5 (**A**), NKX6-1 (**B**), LHX4 (**C**), HOXC6 (**D**), NKX2-3 (**E**), LHX2 (**F**), HOXC4 (**G**), as well as other five genes (**H**), were extracted from the TCGA-PRAD RNA-seq dataset to perform the Kaplan-Meier survival analysis on the Xiantao scholar platform with a minimum *p*-value approach [34]. ROC analysis was conducted to determine the predictive potential for the 5-year disease-specific survival outcome (last panel in **H**).



cantly worse outcome in overall, disease-specific, and progression-free survivals. Four genes (HOXC6, NKX2-3, LHX2, and HOXC4) were associated with worse survival outcomes in disease-specific and progression-free survivals (Fig 3D-3G). Five genes (HOXC13, GSC, ISX, VAX2, BARX1) were only associated with progression-free outcomes (Fig 3H). A time-dependent prediction for 5-year disease-specific survival showed that NKX6-1 gene expression had the strongest predictive potential (AUC = 0.881) (Fig 3H, last panel). These data indicate that NKX6-1 expression might serve as a novel prognostic marker of prostate cancer survival outcome.

EVX2 gene downregulation was associated with prostate cancer progression

Among the 10 down-regulated genes (10-DOWN), three genes (HOXD13, EVX2, MEIS2) were

Fig 4. Gene expression comparisons for the 10-DOWN genes in clinical subgroups. Group comparisons for the gene expression (log_2 [value + 1]) was conducted between different groups stratified by clinicopathological categories, including tumor vs normal (**A**), among different pathological stage (**B**), with or without lymph node invasion (**C**), with or without distal metastasis (**D**), with or without residual tumor after initial surgery (**E**), prior surgery PSA level below 4 or above 4 (**F**), among different Gleason score groups (**G**), overall survival status (**H**), disease-specific survival outcome (**I**), progression-free survival (**J**). ROC analysis was conducted to determine the predictive potential in distinguishing benign from tumor tissues (**K** & **L**). Case numbers in subgroups were listed in Figure 2. The 95%CI for the AUCs: HOXA2, 0.527-0.698; HOXB7, 0.558-0.718; HOXB8, 0.570-0.740; HOXD3, 0.504-0.680; HOXD13, 0.813-0.931; EVX2, 0.809-0.923; DLX3, 0.705-0.840; MEIS2, 0.767-0.916; HOPX, 0.584-0.731; PAX3, 0.635-0.786. ANOVA test, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

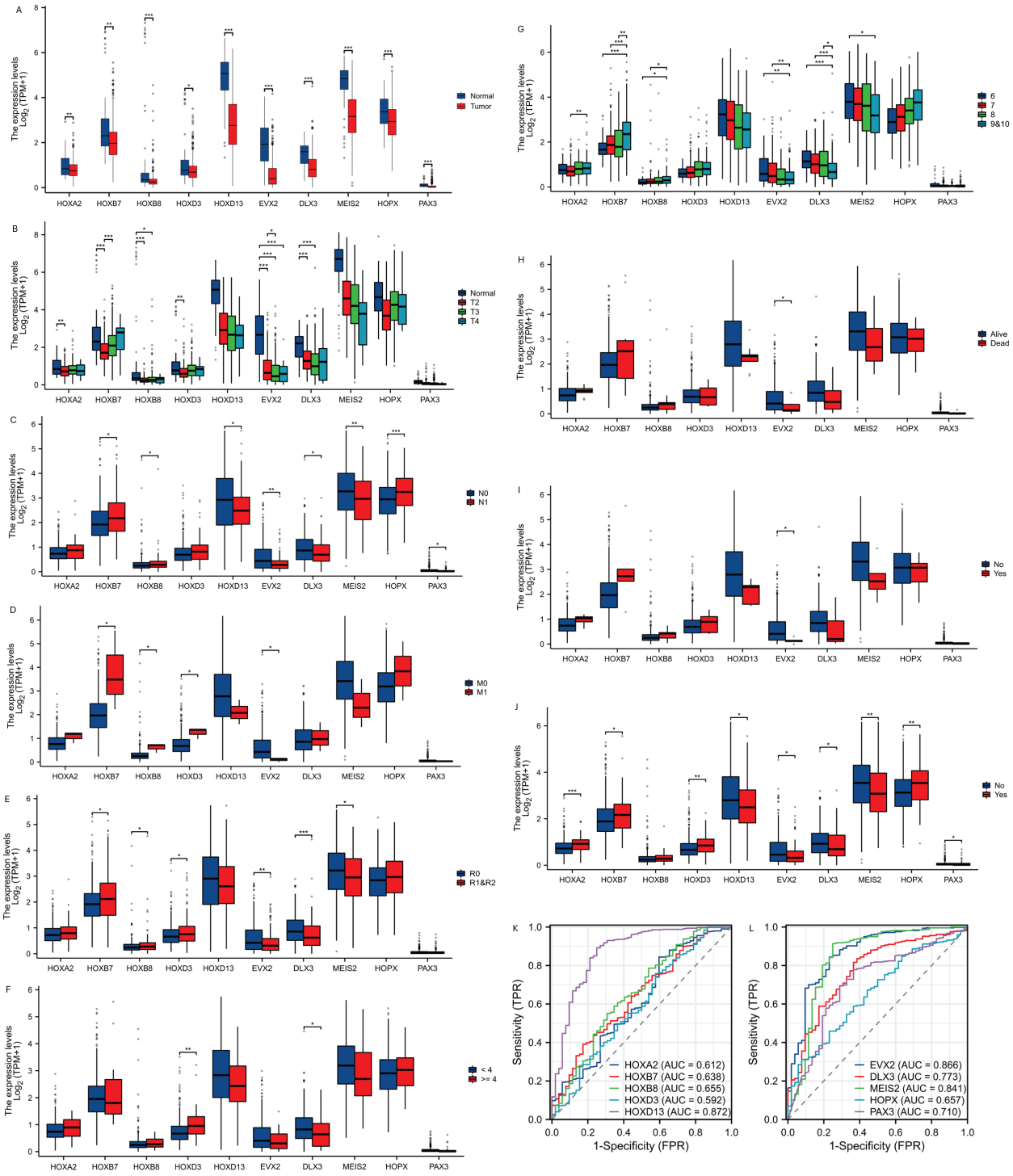
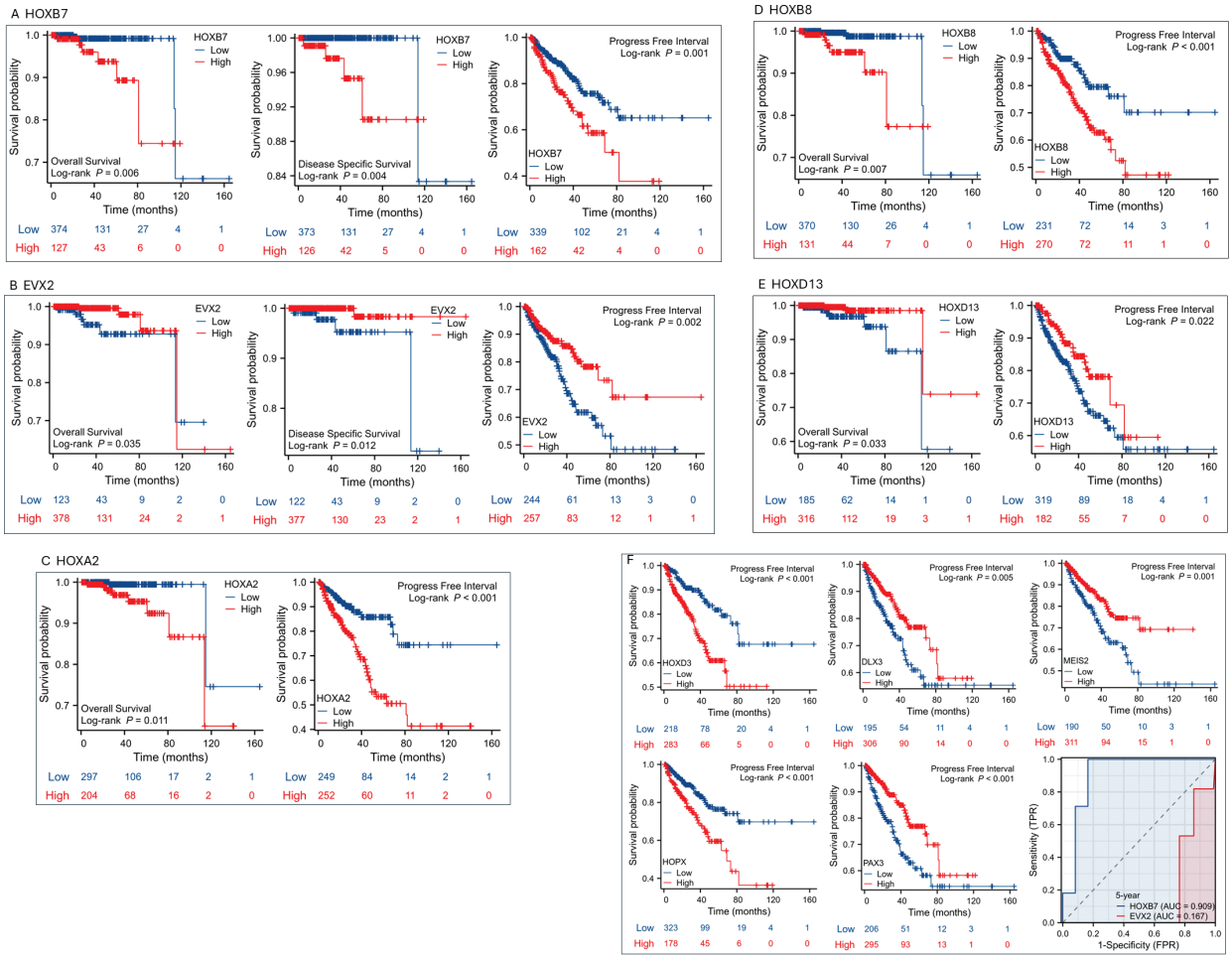


Fig 5. Survival analysis for the 10-DOWN genes in prostate cancers. Gene expression data for the HOX-related family genes, including HOXB7 (**A**), EVX2 (**B**), HOXA2 (**C**), HOXB8 (**D**), HOXD13 (**E**), as well as five genes (**F**), were extracted from the TCGA-PRAD RNA-seq dataset to perform the Kaplan-Meier survival analysis on the Xiantao Scholar platform with a minimum *p*-value approach [34]. ROC analysis was conducted to determine the predictive potential for the 5-year disease-specific survival outcome (last panel in **F**).



expressed at a higher level in normal prostate tissues compared to the other seven down-regulated genes and were decreased sharply in malignant tissues (Fig 4A), indicating a potential tumor suppressive role. Interestingly, only EVX2 expression was significantly associated with all clinicopathological parameters, such as late stage (Fig 4B), lymphatic invasion (Fig 4C), distal metastasis (Fig 4D), post-surgery residual tumors (Fig 4E), higher Gleason scores (Fig 4G), overall survival (Fig 4H), disease-specific survival (Fig 4I), and progression-free interval (Fig 4J), except prior-surgery PSA level (Fig 4F). These data indicate that EVX2 downregulation is strongly associated with prostate cancer progression and survival outcomes. In addition, DLX3 gene expression was also significantly reduced when compared among different pathological stages (Fig 4B), lymphatic invasion (Fig 4C), distal metastasis (Fig 4D), post-surgery residual tumor (Fig 4E), prior surgery PSA level (Fig 4F), higher Gleason score (Fig 4G), and progression-free interval (Fig 4J), except overall and disease-specific survival outcomes (Fig 4H & 4I). However, the PAX3 gene was expressed at very low levels in both normal and malignant prostate tissues without any significant association with clinicopathological parameters (Fig 4A-4I), which was not in line with a previous report [48]. A ROC analysis revealed that HOXD13, EVX2, and MEIS2 gene expression had very high AUC values between 0.872 -0.841 (Fig 4K & 4L). These data strongly suggest that EVX2 gene downregulation in prostate cancer is associated with disease progression, similar to HOXD13 and MEIS2 [14, 49].

HOXB7 showed an opposite trend between gene expression and disease progression

We surprisingly found that four genes (HOXB7, HOXD3, HOPX, and HOXA2) out of the 10-DOWN genes showed an inconsistent trend along disease progression in different stages. In detail, HOXB7 gene expression was significantly reduced in early-stage T2 diseases compared to normal prostate tissues; however, its expression was significantly increased in late-stage T3-T4 diseases (Fig 4B), N1 diseases (Fig 4C), M1 diseases (Fig 4D), post-surgery residual tumors (Fig 4E), higher Gleason score cases (Fig 4G), and relapsed cases (Fig 4J). HOXD3 expression was increased in M1 diseases (Fig 4D), post-surgery residual tumor (Fig 4E), and higher prior-surgery PSA levels (Fig 4F). HOPX expression was significantly increased in N1 diseases (Fig 4C) and relapsed cases (Fig 4J). HOXA2 expression was increased in Gleason score 9-10 cases (Fig 4G) and relapsed cases (Fig 4J). These data suggest that these four genes (HOXA2/HOXB7/HOXD3/HOPX) might be differently regulated by distinct mechanisms at different stages of tumor progression. These data suggest that loss of expression of these three genes has the potential to distinguish malignant from benign prostate tissue. Interestingly, these data are in line with previous reports about HOXD13 and MEIS2 gene expression in prostate cancers [14, 15, 49-54].

HOXB7 expression exerted a strong potential in survival prognosis

Kaplan-Meier survival analysis revealed that HOXB7 and EVX2 were both strongly associated with all three survival parameters. Higher HOXB7 expression was associated with worse outcomes (Fig 5A); however, higher EVX2 expression was associated with better outcomes (Fig 5B). In addition, HOXA2/HOXB8 expression was associated with disease-specific survival and progression-free interval (Fig 5C & 5D). Higher HOXD13 expression was associated with favorable outcomes in overall survival and progression-free interval (Fig 5E). The other five genes, HOXD3/HOPX versus DLX3/MEIS2/PAX3, showed an opposite significance in progression-free interval (Fig 5F). A time-dependent prediction model showed that HOXB7 expression had the highest AUC value of 0.909 for 5-year disease-specific survival (Fig 5F, last panel). These data suggest that HOXB7 expression is a strong prognostic factor for patient survival outcome, which is in line with a recent report [13].

Table 1. Correlation of HOX-related genes with tumor mutation burdens.

Gene ID	Spearman	p value	Pearson	p value	R^2
HOXC5	0.55	1.15E-10	0.5	1.23E-8	0.25
HOXC6	0.58	5.75E-12	0.53	1.03E-9	0.28
HOXC13	0.29	1.52E-3	0.4	1.07E-5	0.16
NKX2-3	0.45	4.78E-7	0.35	1.11E-4	0.12
NKX6-1	0.35	1.05E-4	0.28	2.17E-3	0.08
GSC	0.38	2.47E-5	0.34	1.52E-4	0.12
ISX	0.44	6.64E-7	0.37	3.43E-5	0.14
VAX2	0.46	2.77E-7	0.33	2.68E-4	0.11
BARX1	0.29	1.76E-3	0.2	3.14E-2	0.04
LHX2	0.31	7.15E-4	0.23	1.13E-2	0.06
LHX4	-0.11	2.59E-1	-0.13	1.59E-1	0.02
HOXA2	-0.04	ns	-0.05	ns	0
HOXB7	0.19	4.04E-2	0.25	5.93E-3	0.06
HOXB8	0.02	ns	0.05	ns	0
HOXD3	0.17	ns	0.12	ns	0.01
HOXD13	-0.3	1.01E-3	-0.2	3.07E-2	0.04
EVX2	-0.34	2.06E-4	-0.23	1.47E-2	0.05
DLX3	-0.39	1.91E-5	-0.26	5.17E-3	0.07
MEIS2	-0.54	4.24E-10	-0.34	1.81E-4	0.12
HOPX	0.4	1.06E-5	0.35	1.20E-4	0.12
PAX3	-0.14	ns	-0.02	ns	0

MEIS2 expression is inversely associated with tumor mutation burden and biochemical recurrence in early-onset patients

Early-onset disease is a subtype of aggressive prostate cancer with unique genetic alterations [55, 56]. We analyzed the expression profiles of the 12-UP and 10-DOWN genes using the DKFZ RNA-seq dataset derived from 292 patients with early-onset prostate cancers [35]. Our analysis discovered a strong positive correlation (correlation coefficients > 0.5, R^2 > 0.1) between two genes (HOXC5 and HOXC6) and tumor mutation burden. In contrast, a strong negative correlation was found between MEIS2 expression and tumor mutation burden (Table 1). Meanwhile, the other five genes (NKX2-3, GSC, ISX, VAX2, and HOPX) showed a moderate correlation (correlation coefficients 0.3-0.5, R^2 > 0.1) with tumor mutation burden in these patients.

Further analysis revealed that five genes (HOXC5, HOXC6, VAX2, HOPX, plus HOXB7) showed a moderate negative correlation with biochemical relapse-free interval after initial surgery (Table 2).

Table 2. Correlation of gene expression with BCR-free interval.

Gene ID	Spearman	p	Pearson	p	R^2
HOXC5	-0.38	6.51E-5	-0.37	1.13E-4	0.13
HOXC6	-0.43	3.67E-6	-0.4	3.00E-5	0.15
HOXC13	-0.36	1.55E-4	-0.24	0.012	0
NKX2-3	-0.26	6.72E-3	-0.3	1.80E-3	0.09
NKX6-1	-0.17	ns	-0.21	3.03E-2	0.02
GSC	-0.24	1.39E-2	-0.25	1.15E-2	0.06
ISX	-0.17	ns	-0.13	ns	0
VAX2	-0.38	5.80E-5	-0.41	1.34E-5	0.16
BARX1	-0.36	1.89E-4	-0.19	ns	0.01
LHX2	-0.34	3.95E-4	-0.33	4.91E-4	0
LHX4	0.14	ns	0.04	ns	0
HOXA2	0.02	ns	-0.03	ns	0
HOXB7	-0.28	3.73E-3	-0.35	2.81E-4	0.12
HOXB8	-0.11	ns	-0.13	ns	0
HOXD3	-0.11	ns	-0.12	ns	0
HOXD13	0.31	1.14E-3	0.27	4.64E-3	0.08
EVX2	0.34	4.60E-4	0.33	5.21E-4	0
DLX3	0.3	1.96E-3	0.24	1.32E-2	0
MEIS2	0.49	1.58E-7	0.5	4.68E-8	0.24
HOPX	-0.4	2.13E-5	-0.43	5.78E-6	0.17
PAX3	0.19	4.68E-2	0.1	ns	-0.01

Table 3. Correlation of AR score with gene expression.

Gene ID	Spearman	p-value	Pearson	p-value	R^2
HOXC4	0.11	n.s.	0.08	n.s.	0
HOXC5	0.06	n.s.	0.04	n.s.	0
HOXC6	0.28	4.44E-6	0.29	1.16E-6	0.09
HOXC13	-0.1	n.s.	-0.25	3.51E-5	0.06
NKX2-3	0.34	1.82E-8	0.36	1.26E-9	0.13
NKX6-1	0.13	2.98E-2	0.12	n.s.	0.01
GSC	0.13	3.76E-2	0.19	1.75E-3	0.04
ISX	0.38	1.13E-10	0.29	2.45E-6	0.08
VAX2	0.17	6.98E-3	0.17	6.55E-3	0.03
BARX1	-0.03	n.s.	-0.04	n.s.	0
LHX2	-0.13	3.94E-2	-0.37	5.63E-10	0.14
LHX4	0.05	n.s.	0.04	n.s.	0
HOXA2	-0.33	2.67E-8	-0.25	3.19E-5	0.06
HOXB7	-0.38	1.08E-10	-0.37	4.91E-10	0.14
HOXB8	-0.29	1.25E-6	-0.34	1.01E-8	0.12
HOXD3	-0.07	n.s.	-0.08	n.s.	0.01
HOXD13	-0.21	6.17E-4	-0.37	3.10E-10	0.14
EVX2	-0.15	1.70E-2	-0.22	3.00E-4	0.05
DLX3	-0.34	1.94E-8	-0.38	2.25E-10	0.14
MEIS2	-0.51	5.85E-19	-0.56	1.51E-23	0.32
HOPX	0.02	n.s.	0.07	n.s.	0
PAX3	-0.23	1.74E-4	0.2	9.02E-4	0.04

Interestingly, MEIS2 expression exhibited a strong positive correlation with biochemically relapse-free interval (Table 2), indicating that loss of MEIS2 expression is associated with a quick BCR relapse. Consistently, MEIS2 expression was significantly reduced in BCR-relapsed patients compared to BCR-free patients (Fig 6A). These data suggest that the MEIS2 gene might play a suppressive role in biochemical relapse of prostate cancer in the early onset patients, as reported in regular patients [14, 15, 49, 51, 54].

ETS family gene fusions occur in approximately 50% of prostate cancers, acting as a major oncogenic driver and diagnostic biomarker [57]. We then analyzed these HOX genes altered in early-onset patients in different ETS status. As shown in Fig 6B, GSC/BARX1 expression was significantly increased in patients with ETS fusion, although BARX1 expression level was very low in general.

We then compared the HOX gene expression in relation to the Gleason score. Compared to the lower group (Gleason score 3+3/3+4), the higher group (Gleason score 4+3/4+4/4+5/5+4/5+5) patients showed a significantly higher expression of HOXC5/HOXC6/GSC/VAX2/BARX1/HOPX genes, while MEIS2 gene expression was significantly reduced in the higher Gleason score group (Fig 6C). These data further support the notion of MEIS2 downregulation in prostate cancer progression.

MEIS2 expression was negatively correlated with AR score in castration-resistant metastatic prostate cancer

The clinical obstacle of prostate cancer management is the castration resistant progression in late stages. In castration-resistant prostate cancers (CRPC), the AR signal pathway is reactivated due to diverse mechanisms [58, 59]. We therefore evaluated the correlation of the 12-UP & 10-DOWN genes with AR activation score in CRPC cases using the SU2C/PCF RNA-seq dataset [36]. Our results showed that MEIS2 expression showed a strong negative correlation with the AR score (correlation coefficient > 0.5, $R^2 = 0.32$), while the NKX2-3 gene was positively correlated with the AR score (Table 3).

To assess the androgen regulation in the expression of these AR score-correlated genes, we analyzed the expression profiles of these AR score-correlated

Fig 6. HOX family gene expression in early-onset prostate cancers. Gene expression data for the listed genes were extracted from the DKFZ RNA-seq dataset and compared between subgroups with or without biochemical relapses (**A**, case number: 81-24), ETS fusion (**B**, case number: 86-32), and different Gleason scores (**C**, case number: 82-36). Student *t*-test, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.001$.

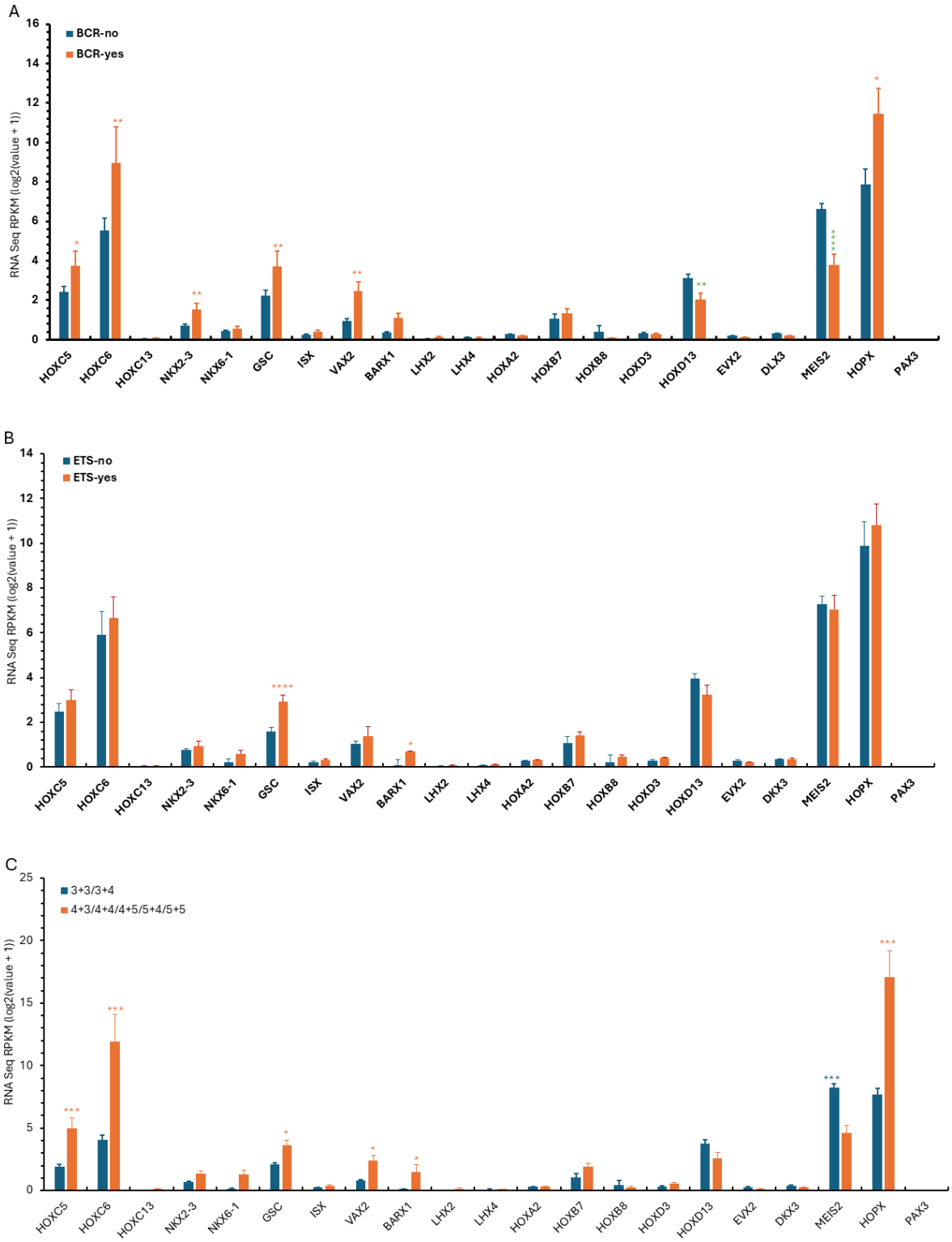


Fig 7. A-B: Gene expression in LuCaP35 xenograft tissues after castration. MEIS2 **(A) and** NKX2-3 **(B)** expression data were extracted from the NCBI GEO profiles of GDS4120 [38]. **C-L: HOX-related gene expression in t-NEPC tissues**. Gene expression data at the mRNA levels were extracted from the whole exome sequencing dataset generated by the SU2C/PCF dream team available on the cBioportal platform [36]. CRPC patients were stratified into two subgroups without neuroendocrine features (panel **C**, **E-H**). Further stratification was made by separating NEPC cases into CRPC-NE and small cell carcinoma (panel **D**, **I-L**). The asterisk indicates a significant difference. Student *t*-test (panel A – H) and ANOVA analysis (panel I – L), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. n.s., no significant difference.

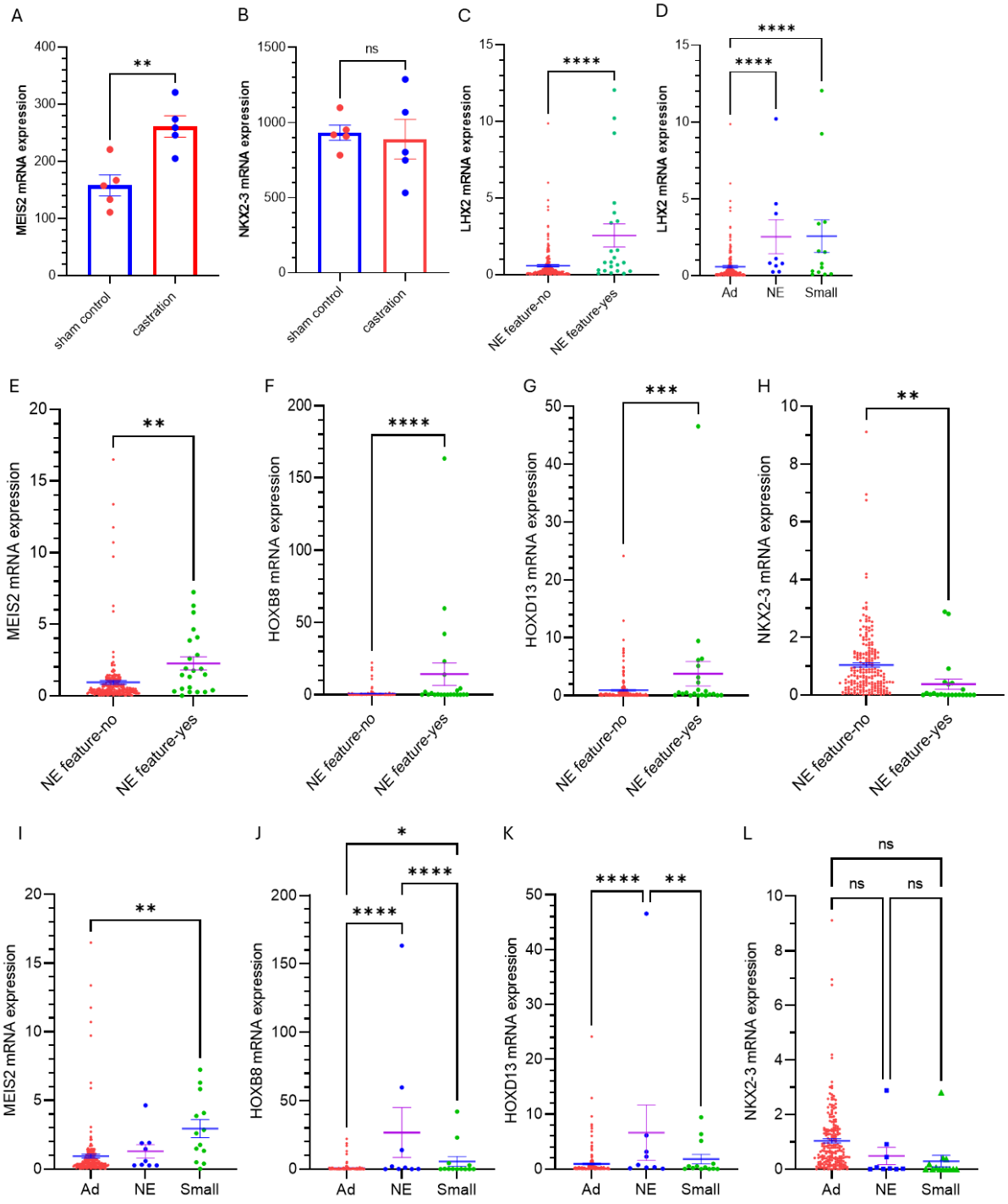


Table 4. Correlation of NEPC score with gene expression.

Gene ID	Spearman	p-value	Pearson	p-value	R^2
HOXC4	-0.2	9.60E-4	-0.08	n.s.	0.01
HOXC5	-0.17	5.04E-3	-0.03	n.s.	0
HOXC6	-0.3	9.56E-7	-0.25	3.04E-5	0.06
HOXC13	-0.03	n.s.	0.24	5.88E-5	0.06
NKX2-3	-0.56	6.61E-23	-0.48	1.20E-16	0.23
NKX6-1	-0.12	4.37E-2	-0.05	n.s.	0
GSC	-0.35	8.45E-9	-0.28	5.33E-6	0.08
ISX	-0.27	1.16E-5	-0.19	1.76E-3	0.04
VAX2	-0.31	3.50E-7	-0.14	2.51E-2	0.02
BARX1	-0.03	n.s.	0.05	n.s.	0
LHX2	0.29	1.38E-6	0.57	6.66E-24	0.32
LHX4	0.02	n.s.	0.03	n.s.	0
HOXA2	0.13	3.60E-2	0.16	8.38E-3	0.03
HOXB7	0.07	n.s.	0.22	3.67E-4	0.05
HOXB8	0.02	n.s.	0.44	6.60E-14	0.19
HOXD3	-0.03	n.s.	0.18	3.79E-3	0.03
HOXD13	0.14	2.42E-2	0.37	3.90E-10	0.14
EVX2	0.19	1.50E-3	0.23	1.79E-4	0.05
DLX3	0.06	n.s.	0.21	7.27E-4	0.04
MEIS2	0.38	1.29E-10	0.43	3.07E-13	0.18
HOPX	-0.2	1.10E-3	-0.21	6.02E-4	0.04
PAX3	0.14	2.19E-2	0.22	2.79E-4	0.05

genes in the GEO dataset of GDS4120 derived from LuCaP35 xenograft tumors [38]. Our results showed that MEIS2 gene expression was significantly increased in LuCaP35 xenograft tissue after castration compared to sham control; however, NKX2-3 expression only had a slight reduction with statistical significance after castration (Fig 7B). These data indicated that MEIS2 gene expression might be modulated by the androgen signal pathway, pending further mechanistic investigation.

HOXB8/HOXD13 genes were strongly correlated with neuroendocrine progression

At the end stage of CRPC, neuroendocrine progression occurred in about 25% cases after long-term anti-AR therapy [60, 61]. We asked if those 12-UP & 10-DOWN genes were associated with neuroendocrinal progression index, a.k.a. the NEPC score [36]. Our results showed a strong inverse correlation between NKX2-3 expression and the NEPC score, while LHX2, MEIS2, HOXB8, and HOXD13 genes were positively correlated with the NEPC score (Table 4), of which LHX2 upregulation was recently reported to promote NEPC progression [21].

We then compared the expression levels of these genes between CRPC cases with or without NE features. In line with the recent report [21], LHX2 gene expression was significantly increased in t-NEPC and small cell carcinoma (Fig 7C & 7D). Consistent with the correlation results (Table 4), MEIS2, HOXB8, and HOXD13 gene expression was significantly increased in CRPC-NE cases (Fig 7E-7G), while NKX2-3 expression was significantly reduced in CRPC-NE cases (Fig 7H). Interestingly, after stratifying the CRPC-NE cases into treatment-induced NEPC (t-NEPC) and small cell carcinoma (SCC), MEIS2 expression was significantly increased only in SCC tissues (Fig 7I). Interestingly, HOXB8 and HOXD13 expression was significantly increased in t-NEPC but decreased in SCC tissues (Fig 7J & 7K), but NKX2-3 expression had no significant difference among these tissue types (Fig 7L). These data indicate that MEIS2 gene

expression is associated with small cell carcinoma, while HOXB8 and HOXD13 are solely associated with t-NEPC progression.

Discussion

The homeobox (HOX) family consists of highly conserved transcription factors that orchestrate embryonic development and cellular identity [5]. Our analysis of the TCGA-PRAD dataset, encompassing 501 primary cases, reveals a profound transcriptional reprogramming of the HOX landscape in prostate malignancy. The identification of 42 up-regulated and 56 down-regulated genes suggests that PCa is characterized not by a single genetic "hit," but by a systemic disruption of the homeodomain-containing protein network.

The quest for reliable PCa biomarkers beyond the limited specificity of PSA has led to the identification of HOXC6 and NKX2-3 as premier candidates [10, 11, 43]. With AUC values exceeding 0.91, overexpression of HOXC6 and NKX2-3 genes offers a robust mechanism for distinguishing benign from malignant tissue. Our data confirms that HOXC6 expression scales linearly with tumor stage and Gleason score. Mechanistically, HOXC6 is known to regulate genes involved in cell proliferation and survival, such as FGFR7 and IGFBP3 [62, 63]. Its elevation in relapsed patients highlights its role not just in presence, but in the aggressive potential of the primary tumor.

Interestingly, while NKX2-3 provides exceptional diagnostic accuracy (AUC = 0.936, 95%CI = 0.909-0.963), its biological role in the prostate is less defined than the HOX clusters [11]. Our correlation analysis with AR scores suggests it may be a downstream effector of androgen signaling, acting as a bridge between hormonal drive and developmental gene reactivation.

One of the most striking findings of this study is the predictive power of NKX6-1 and HOXB7 in patient outcomes. NKX6-1 emerged as the strongest predictor for 5-year disease-specific survival (AUC = 0.881). While typically associated with pancreatic beta-cell development [64], its aberrant expression in the prostate likely represents a "lineage infidelity" where the cancer cell adopts developmental programs that confer a survival advantage under stress [12]. Interestingly, our results showed a significant HOXB7 downregulation in prostate cancer tissues compared to benign counterparts, but its expression was sharply increased in late-stage disease or along with cancer progression. This distinct dysregulation during disease progression indicates a distinct mechanism for HOXB7 expression in prostate cancer that deserves further mechanistic investigation.

While much focus is placed on oncogenic drivers, the sharp downregulation of EVX2, MEIS2, and HOXD13 points to a loss of critical developmental checkpoints. EVX2's significant association with every clinicopathological parameter, except prior surgery PSA, suggests it may be a more accurate "silent" driver of progression than traditional clinical markers. The loss of EVX2 likely removes inhibitory signals that normally maintain the differentiated state of the prostatic epithelium. HOXD13 expression has been shown to suppress prostate cancer metastasis [49], and its knocking down led to increased cell growth in prostate cancer cells [50], supporting the notion that HOXD13 might serve as a tumor suppressor in prostate cancers. MEIS2 expression has been shown to modulate prostate cancer progression [14], and its downregulation was due to epigenetic silencing in prostate cancers [15].

Early-onset prostate cancer is often more aggressive and genetically distinct [35]. Our analysis using the DKFZ RNA-seq dataset identified a core triad, HOXC5, HOXC6, and MEIS2, that correlates strongly with Tumor Mutation Burden (TMB). The correlation between these genes and biochemical recurrence (BCR) suggests that in younger patients, HOX gene dysregulation is intrinsically linked to genomic instability. MEIS2, in particular, appears to act as a protective factor [14]; its reduction in BCR-positive patients suggests that MEIS2 might normally function to maintain genomic integrity or suppress the metastatic cascade. Notably, HOPX gene expression was significantly higher in patients with BCR relapse and higher Gleason scores. HOPX expression was also significantly correlated with shorter BCR relapse-free interval and higher tumor mutation burden, acting like a tumor driver in these early-onset patients. Similar inconsistent findings were also found in regular primary prostate cancers, where HOPX expression was significantly downregulated in general but significantly increased in lymph node invasion and disease relapse patients. These unique correlations of HOPX expression with clinicopathological parameters in prostate cancers await further mechanistic illustration.

The progression to CRPC is the primary clinical hurdle in PCa management [59]. Our results demonstrate that the HOX network is not static; it evolves

alongside the Androgen Receptor (AR) signaling axis. HOXC6 and NKX2-3 show strong positive correlations with AR activation scores, which is in line with a previous report that HOXC6 is an androgen-regulated gene [59]. Conversely, genes like MEIS2 show a strong negative correlation ($R^2 = 0.32$). This suggests that as tumors become more aggressive and potentially lose canonical AR signaling, they downregulate "differentiating" factors like MEIS2 [15].

At the end stage of the disease, approximately 25% of cases undergo neuroendocrine prostate cancer (NEPC) trans-differentiation [61]. This study identifies LHX2 as a pivotal marker for this transition, as reported recently [21]. LHX2 was significantly increased in both treatment-induced NEPC (t-NEPC) and small cell carcinoma (SCC), supporting the notion that LHX2 is a core component of the neuroendocrine "master switch." On the other hand, HOXB8 and HOXD13 genes were uniquely elevated in t-NEPC but not in SCC, which implies that the pathway to neuroendocrine features via androgen-deprivation therapy (t-NEPC) is molecularly distinct from the "de novo" small cell pathway.

Conclusion and Future Directions

The aberrant expression of HOX genes in prostate cancer provides a molecular roadmap of the disease's lifecycle, from the diagnostic utility of HOXC6/NKX2-3 in primary tumors to the prognostic significance of NKX6-1/HOXB7, and finally to the neuroendocrine trans-differentiation mediated by LHX2. Future therapeutic strategies should consider the HOX-AR axis. Since many of these developmental factors are transcription factors, traditionally "undruggable," targeting their downstream effectors or utilizing PROTAC technology to degrade these developmental drivers could represent the next frontier in PCa treatment. Furthermore, the use of HOX-based diagnostic panels could significantly refine the "active surveillance" vs. "radical intervention" decision-making process, sparing patients from over-treatment while identifying aggressive disease earlier than PSA alone.

Acknowledgements

The results shown in this study are in part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

Declarations

Ethical Approval: not applicable
Funding support: None
Availability of Data and Materials: Not applicable

Author Contributions

W Liu and S Tang conducted data analysis of the GEO data profiles and the TCGA datasets. M Mirza and B Li drafted the manuscript. All authors approved the submission.

Conflict of Interest

The authors declared no commercial or financial relationships construed as a potential conflict of interest.

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