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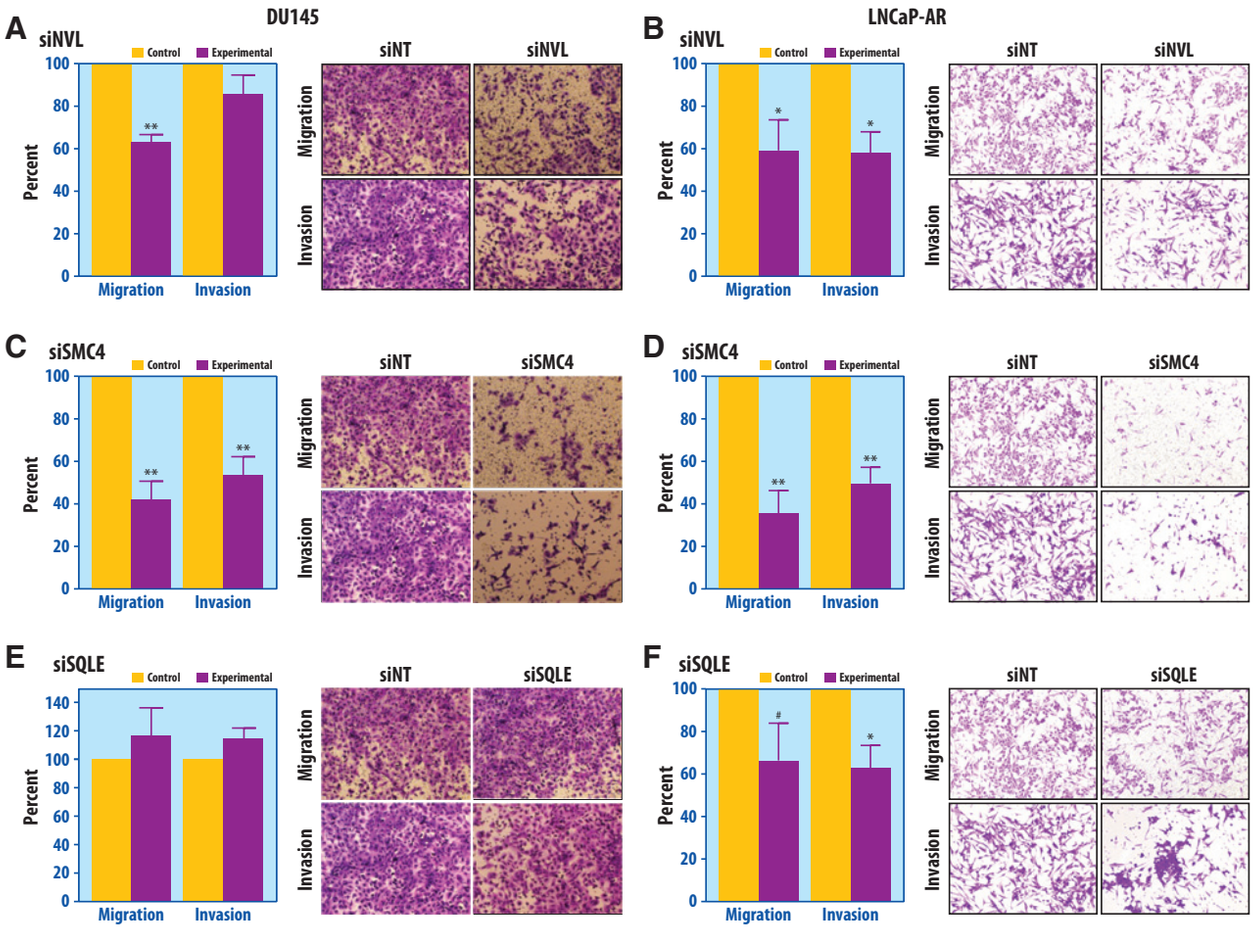

Figure 2.
Invasion and migration after siRNA transfection. Migration and invasion results after individual knockdown of NVL (A and B), SMC4 (C and D), or SQLE (E and F) in DU145 (A, C, E) and LNCaP-AR (B, D, F) cells. Migration and invasion quantified by dye analysis, and representative micrographs shown. Data are normalized to the nontargeting siRNA control (siNT) condition. **, $P < 0.01$ versus siNT; *, $P < 0.05$; #, $P = 0.08$.

NVL, *SMC4*, and *SQLE* in the metastatic cascade using transwell invasion and migration assays after transient siRNA knockdown in the prostate cancer cell lines DU145 and LNCaP-AR. In addition, we included *TPX2* in our *in vitro* studies as a positive control for a prognostic outlier gene with a demonstrated impact on oncogenic phenotypes (33). Knockdown efficiency was 64% for NVL in DU145 cells, and otherwise >75% for all genes in both cell lines (Fig. 1A and B). Knockdown of *TPX2* strongly induced cell death (Fig. 1C and D) and inhibited proliferation (Fig. 1E and F) in both cell lines, as expected (33). *NVL* and *SMC4* knockdown had a mild inhibitory effect on proliferation in LNCaP-AR cells (Fig. 1F). We next tested these three genes in an *in vitro* model of the metastatic process; the cell death induction by TPX2 was such that there were insufficient cells for invasion or migration assays for both cell lines. We observed that knockdown of *NVL* resulted in decreased migration in DU145 cells (Fig. 2A), and decreased migration and invasion in LNCaP-AR cells (Fig. 2B). *SMC4* knockdown significantly decreased both migration and invasion in both cell lines (Fig. 2C and D). Knockdown of *SQLE* nonsignificantly increased migration and invasion in DU145 cells (Fig. 2E), and significantly decreased migration and invasion in LNCaP-AR cells (Fig. 2F). These results confirm that NVL, SMC4, and SQLE have biologic roles in the metastatic process in prostate cancer.

Clinical validation

To validate the prognostic significance of the outlier genes, we examined them in three independent clinical datasets from different institutions: MCII, TJU, and CCF. Focusing on the four prognostic outlier genes we studied *in vitro*, outlier expression of each gene individually had strong prognostic association with metastatic progression with HRs 3.7–11 (Fig. 3A–D). To understand the role of these four prognostic outlier genes after metastasis, we examined the expression of each candidate gene in metastases versus primary tumors in the Oncomine prostate cancer datasets. Indeed, each gene has significant overexpression in metastases versus primary tumor in nearly all datasets, indicating an ongoing contribution to metastatic prostate cancer (Fig. 3E). These results indicate that outlier expression of *NVL*, *SMC4*, *SQLE*, or *TPX2* has strong prognostic association with metastatic progression after prostatectomy, and that these prognostic outlier genes continue to have a role in metastatic prostate cancer.

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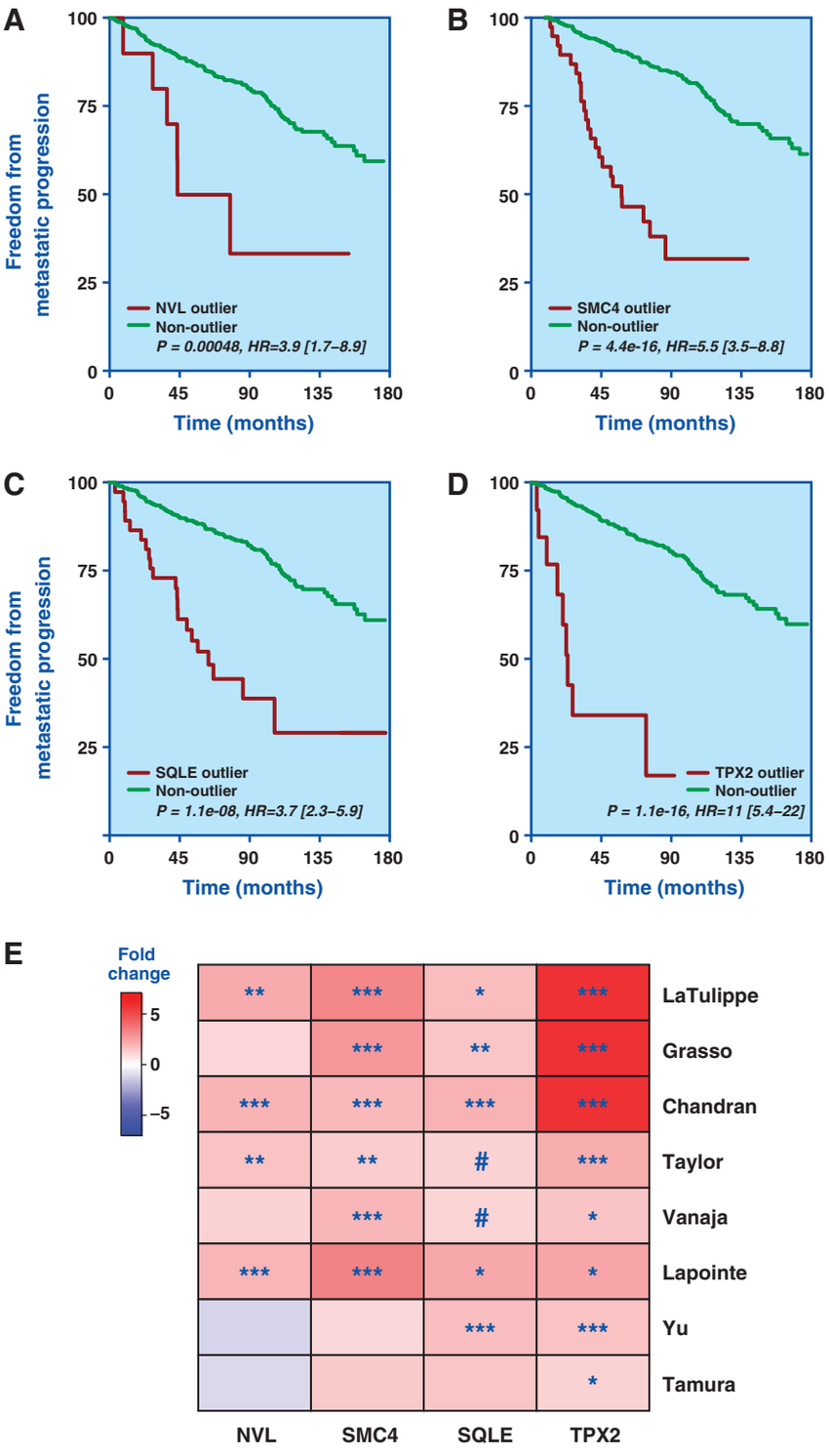

Figure 3.
Clinical validation. A–D, Kaplan–Meier analysis of freedom from metastatic progression by individual outlier status in the pooled three validation cohorts for NVL (A), SMC4 (B), SQLE (C), and TPX2 (D). E, heatmap of differential expression of the four prognostic outlier genes studied in metastatic samples compared with primary tumor samples, across the eight Oncomine prostate cancer cohorts with $n > 20$; red indicates overexpression in metastatic samples; #, $P < 0.1$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Prognostic outlier score

While we focused *in vitro* studies on a small subset of the prognostic outlier genes, our initial hypothesis that prognostic outlier status could be an important prognostic tool was not limited to *NVL*, *SMC4*, *SQLE*, and *TPX2*. Therefore, we extended our clinical validation analyses to the entire list of 20 prognostic outlier genes. As individual patients may have outlier status of more than one prognostic outlier gene, we first defined a prognostic outlier score as the number of prognostic outlier genes with outlier status. Clinicopathologic variables Gleason score, positive surgical margins, seminal vesicle invasion, and lymph node involvement were significantly different among the prognostic

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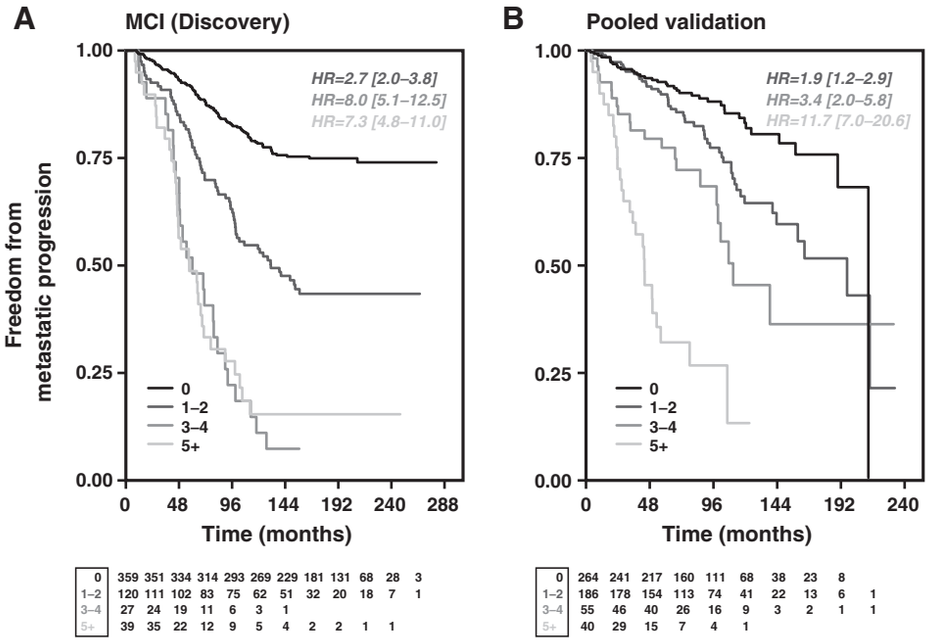

Figure 4.
Prognostic outlier score analysis. A and B, Kaplan–Meier analysis of freedom from metastatic progression by prognostic outlier score of 0, 1-2, 3-4, or ≥5 in the discovery (MCI) cohort (A) and the pooled validation cohort (B).

outlier score groups, whereas age, PSA, stage, and extracapsular extension were not (Supplementary Table S2). The prognostic outlier score results in well-stratified patient groups in both the discovery (MCI; Fig. 4A) and the pooled validation cohorts (Fig. 4B). Multivariable analysis in both the discovery (MCI) cohort and the pooled validation cohort (Supplementary Table S3) showed outlier score to be one of the most significant predictors of 10-year metastatic progression with an OR 1.5 per each additional outlier in both the discovery and the pooled validation cohorts ($P < 0.0001$). In addition, we found that this was also true for overall survival (Supplementary Fig. S4).

Given the novelty of our prognostic outlier gene approach compared with prior biomarker discovery efforts in prostate cancer, we hypothesized that the prognostic outlier score could supplement existing prostate cancer prognostic instruments. In fact, the prognostic outlier score was a significant predictor of metastatic progression independent of Decipher, CAPRA-S, or mCCP score in a multivariable model (Table 2) and significantly increased ROC AUC when integrated into each score (Supplementary Fig. S5; Table 2; refs. 18, 25–28). With the addition of prognostic outlier score, the AUC of Decipher increased from 0.768 to 0.791 ($P < 0.05$), mCCP from 0.710 to 0.782 ($P < 0.005$), and CAPRA-S from 0.715 to 0.75 ($P < 0.001$). Thus, outlier status of the prognostic outlier genes is strongly associated with poor outcomes in high-risk prostate cancer after prostatectomy, and provides information independently of published prognostic instruments.

Table 2. Outlier score and other prostate cancer signatures

	Published signatures		
	Decipher	**mCCP**	**CAPRA-S**
ROC AUC			
Published signature	0.768	0.710	0.715
+ Outlier score	0.791	0.783	0.785
P value	0.042	0.0032	0.00098
MVA with published signature and outlier score			
Published signature *P* value	2.56E−05	0.000997	0.000184
OR (95% CI)	2.6 (1.7–4.1)	2.4 (1.4–3.9)	2.2 (1.5–3.4)
Outlier score, *P* value	0.00557	4.03E−05	8.68E−05
OR (95% CI)	2.8 (1.4–5.8)	4.8 (2.3–10.1)	4.2 (2.1–8.7)

Abbreviations: AUC, area under the curve; MVA, multivariable analysis; ROC, receiver-operating curve.

Discussion

High-risk prostate cancer carries a significant risk of metastatic progression after prostatectomy, and therefore better prognostic biomarkers and therapeutic strategies are needed (2, 3). Molecular biomarkers are a promising class of prognostic biomarker candidates, but these studies in prostate cancer have been limited by follow-up insufficient for study of metastatic progression or survival because of the long disease course (16). Separately, outlier analysis has identified preeminent prostate cancer genes *TMPRSS2-ERG* fusions and *SPINK1* (19, 20), but has been limited to comparisons of cancer versus normal samples. These two approaches have been very fruitful in the prostate cancer translational research.

In this study, we sought to address both prognostic and therapeutic needs in high-risk prostate cancer by applying the novel prognostic outlier gene approach. We identified 20 prognostic outlier genes in the discovery cohort, many of which are well-known cancer genes, but several of which have not been studied in prostate cancer. We defined a prognostic outlier score as the number of prognostic outlier genes with outlier status, and demonstrated that each additional prognostic outlier gene with outlier status associates with more aggressive clinical behavior. Indeed, increasing prognostic outlier score was one of the most significant predictors of metastatic progression and overall survival after prostatectomy. The prognostic outlier score predicted outcomes independently from the published prognostic instruments Decipher, CAPRA-S, and mCCP score, and added to the prognostic ability of these tools.

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We found that three prognostic outlier genes that are unstudied in prostate cancer contribute to oncogenic phenotypes in two prostate cancer cell lines. *TPX2* knockdown induced cell death as our positive control for a prognostic outlier gene with an impact on oncogenic phenotypes (33); *NVL*, *SMC4*, or *SQLE* knockdown significantly decreased migration and/or invasion in one or both cell lines used. The molecular mechanisms of these prognostic outlier genes are not yet clear. NVL is a member of the AAA ATPase superfamily with two predominant isoforms in the nucleolus and nucleoplasm, is reportedly involved in ribosomogenesis, and an essential component of the TERT holoenzyme (42, 43). Interruption of either of these functions could potentially have significant impact on tumor cell biology. However, this is the first report to implicate NVL in cancer biology, and further study is required. SMC4 is an ATPase core protein of the condensin I and II complexes that capture and condense chromatids in the early stages of mitosis (44). SMC4 has been implicated in colorectal, liver, and breast cancer (45–47), but has not been studied in prostate cancer or implicated in the metastatic cascade. In addition, SMC4/condensin interacts with the genomic transcriptional insulator CTCF, and thus may be required for oncogenic gene silencing (48). SQLE is a cholesterol biosynthesis enzyme that has been implicated in several cancers other than prostate, and, interestingly, is located in the chromosome 8q24 Myc oncogene amplicon (49–51). *SQLE* knockdown had an impact in LNCaP-AR but not DU145 cells, which is likely reflective of the much more significant role of steroid hormone signaling in LNCaP-AR cells. Although some molecular details about each gene are known, the prognostic performance demonstrated in our study provides strong motivation for further investigation in prostate cancer.

Although our study is able to leverage the power of several large cohorts, there are potential limitations with our data. We cannot account for all inter- and intracohort variation from factors such as warm/cold ischemia time, different tissue fixation and processing procedures, relative ratios of different cells (e.g., tumor, stroma, benign glands, inflammatory cells, etc.) and different patient characteristics and treatment protocols at each institution. However, we attempted to mitigate these effects by performing all RNA processing and microarray hybridization in the same CLIA-certified laboratory, and by using multivariable analysis and stratification to account for measured and unmeasured confounders, respectively. In addition, we note that a study specifically examining the effects of ischemia time on gene expression found <1% of genes significantly changed, and there is no overlap with the prognostic outlier genes identified in this study (52).

In summary, we have performed a novel analysis in a large high-risk prostate cancer cohort with long follow-up to identify 20 prognostic outlier genes as potential biomarkers and therapeutic targets. *In vitro* validation of three prognostic outlier genes unstudied in prostate cancer, *NVL*, *SMC4*, and *SQLE*, confirmed that these genes play a causal role in the metastatic cascade, and therefore may be further explored for therapeutic intervention. Importantly, the prognostic performance of outlier status of the 20 prognostic outlier genes was validated as one of the strongest prognostic predictors of metastatic progression across three independent clinical datasets comprising more than 500 patients, and provided prognostic information independent of three published prognostic instruments. On the basis of these findings, prognostic outlier genes may serve as an important novel class of cancer genes for biomarker and therapeutic discovery in prostate cancer.

Disclosure of Potential Conflicts of Interest

Shuang G. Zhao reports receiving travel reimbursement from Genome Dx Biosciences. E.M. Schaeffer, A.E. Ross, A.P. Dicker, P.L. Nguyen, and F.Y. Feng are consultant/advisory board members for Genome Dx Biosciences. E.A. Klein reports receiving research funding from Genome Dx Biosciences. R.J. Karnes reports receiving research travel reimbursement and funding from Genome Dx Biosciences. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.R. Evans, V. Kothari, G. Sun, A. Larm, V. Mondine, E.M. Schaeffer, A.E. Ross, R.B. Den, R.J. Karnes, E. Davicioni

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.G. Zhao, J.R. Evans, V. Kothari, G. Sun, A. Larm, V. Mondine, E.M. Schaeffer, E.A. Klein, R.B. Den, A.P. Dicker, R.J. Karnes, N. Erho, P.L. Nguyen, F.Y. Feng

Writing, review, and/or revision of the manuscript: S.G. Zhao, J.R. Evans, A.E. Ross, E.A. Klein, R.B. Den, A.P. Dicker, R.J. Karnes, N. Erho, P.L. Nguyen, E. Davicioni, F.Y. Feng

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Study supervision: S.G. Zhao, J.R. Evans, P.L. Nguyen, F.Y. Feng

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The Landscape of Prognostic Outlier Genes in High-Risk Prostate Cancer

Shuang G. Zhao, Joseph R. Evans, Vishal Kothari, et al.

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