Molecular and Clinical Correlates of High PSMA/*FOLH1* mRNA Expression in Primary and Metastatic Prostate Cancer

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BACKGROUND

- The *FOLH1* gene encodes prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein that is highly expressed in most prostate cancer cells.
- PSMA expression can increase in metastatic castration resistant prostate cancer (mCPRC) but can be lost with the emergence of treatment-induced AR negative or neuroendocrine prostate cancer.
- PSMA is now a target for diagnostic imaging and treatment in prostate cancer. ^{177}Lu-PSMA-617, a β-emitting PSMA targeted radioligand, has demonstrated improved survival for patients with mCRPC. Additionally, other novel therapeutics targeting PSMA including alternative radioligands, antibody drug conjugates, and bispecific antibodies are currently under development.
- Characterizing the molecular profile of high and low PSMA/*FOLH1* expressing tumors will be critical to optimizing patients selection for PSMA targeted treatments alone and in combination with other therapeutic strategies.

OBJECTIVES

- Primary objectives:
  - Evaluate *FOLH1* mRNA expression across tumor sites in patients with prostate cancer.
- Secondary objectives:
  - Evaluate commonly occurring DNA alterations in tumors with high and low *FOLH1* expression.
  - Evaluate *FOLH1* expression in tumor with high and low AR and NEPC signature scores.
  - Evaluate overall survival in patients with high and low *FOLH1* expression.

METHODS

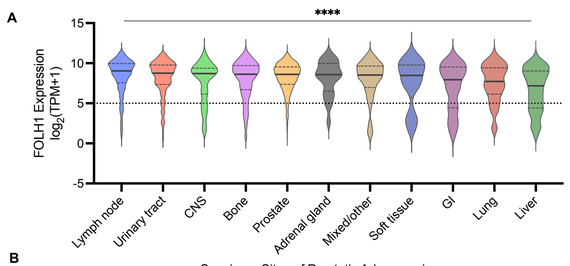
- NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed for prostate cancer patient specimens (n=7,558) through Caris Life Sciences (Phoenix, AZ).
  - *FOLH1*-High/Low expression were defined as percentile of RNA transcripts per million (TPM):
  Q1: < 25th (Low), Q2: 25th - 50th , Q3: 50th - 75th , Q4: ≥75th (High)
- Androgen receptor (AR), neuroendocrine (NEPC), and T-cell inflamed RNA signature scores were calculated. *FOLH1* was removed from the AR signature gene list.
- Tumor cell PD-L1+ expression (≥2+, ≥5%; SP142) was assessed by IHC.
- Kaplan-Meier estimates for real-world overall survival (OS) were calculated from time of diagnosis to last contact (death).

RESULTS

Table 1: Baseline demographics.

Cohort Characteristics	N (%)
Samples	7558 (100%)
Median Age (range)	68.0 (35- >89)
Histology	**N (%)**
Prostatic adenocarcinoma	100.0 %
Neuroendocrine prostate cancer	0.0 %
Mixed tumors	4.6 %
NOS	57.0 %
Specimen site	**N (%)**
Prostate	4495 (62.5 %)
Metastasis	2697 (37.5 %)
Lymph node	832 (11.6 %)
Bone	568 (7.9 %)
Liver	359 (5.0 %)
Urinary tract	340 (4.7 %)
Lung	116 (1.6 %)
Gastrointestinal	53 (0.7 %)
CNS	49 (0.7 %)
Soft tissue	30 (0.4 %)
Adrenal gland	22 (0.3 %)
Mixed/other sites	238 (4.6 %)

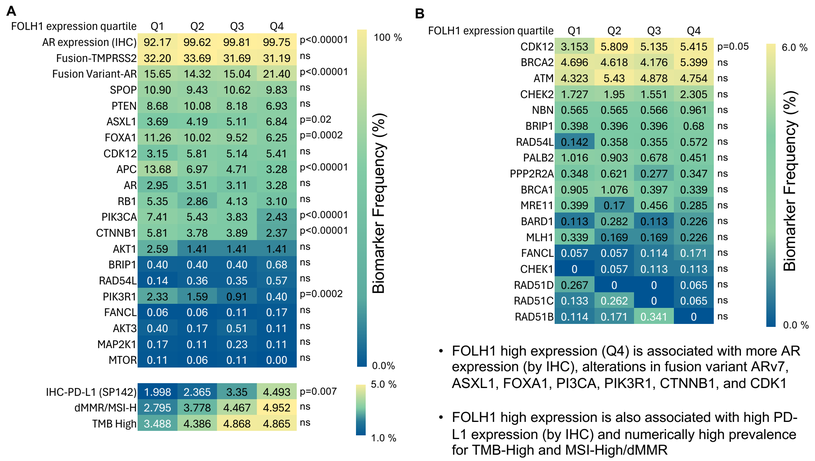
Figure 1: *FOLH1* expression by specimen site. A) *FOLH1* expression across specimen sites. ****Pairwise q-value <0.0001 across all specimen sites. B) Median *FOLH1* expression and patient sample count, across specimen sites. * For prostate gland compared to each specimen site (Mann-Whitney U pairwise statistical test, q-value <0.05).



	Lymph node	Urinary tract	CNS	Bone	Prostate	Adrenal gland	Mixed/ Other	Soft tissue	GI	Lung	Liver
FOLH1 Median Value (TPM)	518.2*	434.4	417.1	394.5	390.9	373.1	359.9	358.0	245.5	209.6*	143.1*
Count (N)	832	340	49	568	4495	22	328	30	53	116	359

- *FOLH1* mRNA expression varies significantly across different specimen sites of prostatic adenocarcinoma, with the highest expression in lymph node and lowest in liver.
- Compared to prostate gland (primary disease site), Lymph node had significantly more enrichment of *FOLH1* transcript, while liver and lung had significantly less *FOLH1* enrichment in the entire prostate adenocarcinoma cohort

Figure 2: Genomic alterations associated with *FOLH1* expression quartiles. A) Frequency of gene alterations, AR expression (by IHC), and Immunotherapy-Related Markers. 2) Frequency of homologous recombination repair gene alterations (PROFOUND and TALAPRO-2 gene sets).



- FOLH1 high expression (Q4) is associated with more AR expression (by IHC), alterations in fusion variant ARv7, ASXL1, FOXA1, PI3CA, PIK3R1, CTNNB1, and CDK1
- FOLH1 high expression is also associated with high PD-L1 expression (by IHC) and numerically high prevalence for TMB-High and MSI-High/dMMR

Figure 3: *FOLH1* mRNA expression correlation with A) AR signaling score (p<0.0001) and B) NEPC score. Spearman's rank Correlation analysis was performed to obtain correlation coefficient (p<0.0001)

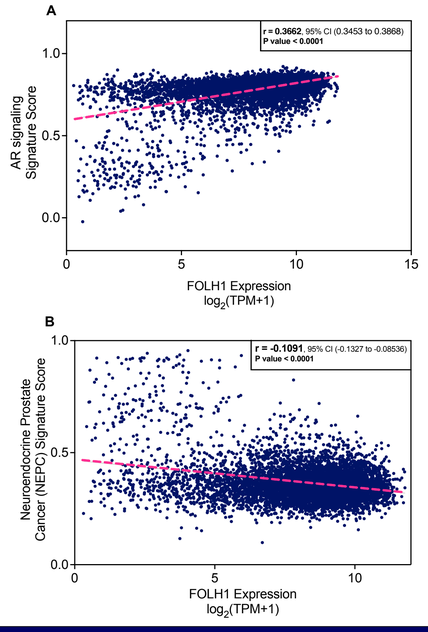
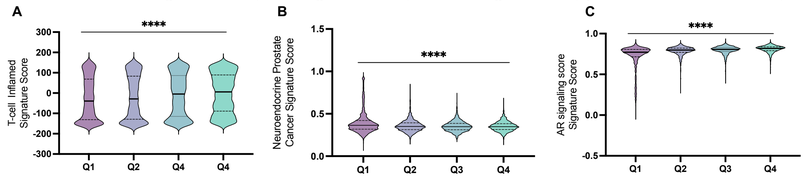
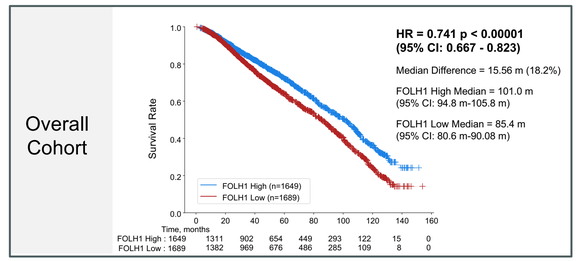


Figure 4: Comparison of transcriptomic signatures across *FOLH1* expression quartiles. A) T-cell inflamed signature, 2) AR signature, 3) NEPC signature. (q-value <0.0001 for all)



RESULTS

Figure 5: Overall survival among *FOLH1* high (quartile 4) and low groups (quartile 1).



CONCLUSIONS

- This is the largest analysis to date of *FOLH1*-related genomic/transcriptomic features and survival outcomes in prostate cancer.
- Relative to the prostate gland, *FOLH1* expression varied by metastatic site, with highest expression in lymph nodes, and lowest expression in GI, lung, and liver metastases.
- High *FOLH1* expression significantly correlated with *AR-V7* and *ASXL1* alterations, and a depletion of *APC*, *FOX1A*, *PIK3CA*, *CTNNB1*, and *PIK3R1* alterations.
- *FOLH1* mRNA expression was associated with higher AR signaling, T cell inflammation, and lower NEPC signaling.
- High *FOLH1* expression was associated with greater OS overall, and in men with primary and metastasis sequencing.
- Tumors with high *FOLH1* are molecularly distinct, providing insights for unique therapeutic strategies in this group.

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