Abstract

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Characterization of 1577 Primary Prostate Cancers Reveals Novel Biological and Clinicopathologic Insights into Molecular Subtypes.

Tomlins SA[1], Alshalalfa M[2], Davicioni E[2], Erho N[2], Yousefi K[2], Zhao S[3], Haddad Z[2], Den RB[4], Dicker AP[4], Trock BJ[5], DeMarzo AM[5], Ross AE[5], Schaeffer EM[5], Klein EA[6], Magi-Galluzzi C[6], Karnes RJ[7], Jenkins RB[8], Feng FY[9].

Author information

Abstract

BACKGROUND: Prostate cancer (PCa) molecular subtypes have been defined by essentially mutually exclusive events, including ETS gene fusions (most commonly involving ERG) and SPINK1 overexpression. Clinical assessment may aid in disease stratification, complementing available prognostic tests.

OBJECTIVE: To determine the analytical validity and clinicopatholgic associations of microarray-based molecular subtyping.

DESIGN, SETTING, AND PARTICIPANTS: We analyzed Affymetrix GeneChip expression profiles for 1577 patients from eight radical prostatectomy cohorts, including 1351 cases assessed using the Decipher prognostic assay (GenomeDx Biosciences, San Diego, CA, USA) performed in a laboratory with Clinical Laboratory Improvements Amendment certification. A microarray-based (m-) random forest ERG classification model was trained and validated. Outlier expression analysis was used to predict other mutually exclusive non-ERG ETS gene rearrangements (ETS^+) or SPINK1 overexpression ($SPINK1^+$).

OUTCOME MEASUREMENTS: Associations with clinical features and outcomes by multivariate logistic regression analysis and receiver operating curves.

RESULTS AND LIMITATIONS: The m-ERG classifier showed 95% accuracy in an independent validation subset (155 samples). Across cohorts, 45% of PCas were classified as $m\text{-}ERG^+$, 9% as $m\text{-}ETS^+$, 8% as $m\text{-}SPINK1^+$, and 38% as triple negative ($m\text{-}ERG^-/m\text{-}ETS^-/m\text{-}SPINK1^-$). Gene expression profiling supports three underlying molecularly defined groups: $m\text{-}ERG^+$, $m\text{-}ETS^+$, and $m\text{-}SPINK1^+$/triple negative. On multivariate analysis, $m\text{-}ERG^+$ tumors were associated with lower preoperative serum prostate-specific antigen and Gleason scores, but greater extraprostatic extension ($p<0.001$). $m\text{-}ETS^+$ tumors were associated with seminal vesicle invasion ($p=0.01$), while $m\text{-}SPINK1^+$/triple negative tumors had higher Gleason scores and were more frequent in Black/African American patients ($p<0.001$). Clinical outcomes were not significantly different among subtypes.

CONCLUSIONS: A clinically available prognostic test (Decipher) can also assess PCa molecular subtypes, obviating the need for additional testing. Clinicopathologic differences were found among subtypes based on global expression patterns.

PATIENT SUMMARY: Molecular subtyping of prostate cancer can be achieved using extra data generated from a clinical-grade, genome-wide expression-profiling prognostic assay (Decipher). Transcriptomic and clinical analysis support three distinct molecular subtypes: (1) $m\text{-}ERG^+$, (2) $m\text{-}ETS^+$,

and (3) m-SPINK1$^+$/triple negative (m-ERG$^-$/m-ETS$^-$/m-SPINK1$^-$). Incorporation of subtyping into a clinically available assay may facilitate additional applications beyond routine prognosis.

KEYWORDS: ERG; ETS; Microarray; Prognosis; Prostate cancer; SPINK1

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