Application of Genomic Profiling to Identify Factors that Contribute to Cancer Health Disparities

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Burden of Cancer in the African-American Community

"African-Americans have the highest death rates from all cancer sites combined, and from malignancies of the lung, colon and rectum, breast, prostate, and the cervix of all racial groups in the United States"

From the American Cancer Society

Is Biology a Contributing Factor?

"While data suggest that access to quality care is a factor in cancer disparities, other factors also play a major role, including tumor biology and genetics"

From the AACR Health Disparity Meeting, Atlanta, 2007

- **Race/ethnic disparity in prevalence of basal-like breast tumors *(JAMA 2006, 295: 2492 – 2502)***
  - More common among young African-American women
- **Race/ethnic differences in prevalence of 8q24 cancer susceptibility markers (*Nat Genet 2007, 39: 638 – 44 & 954 – 6; Genome Res 2007, 17: 1717 – 22*)**
  - Risk alleles are more common among African-Americans

A Gene Expression Profiling Study
(Cancer Research 2008, 68, 927-36)

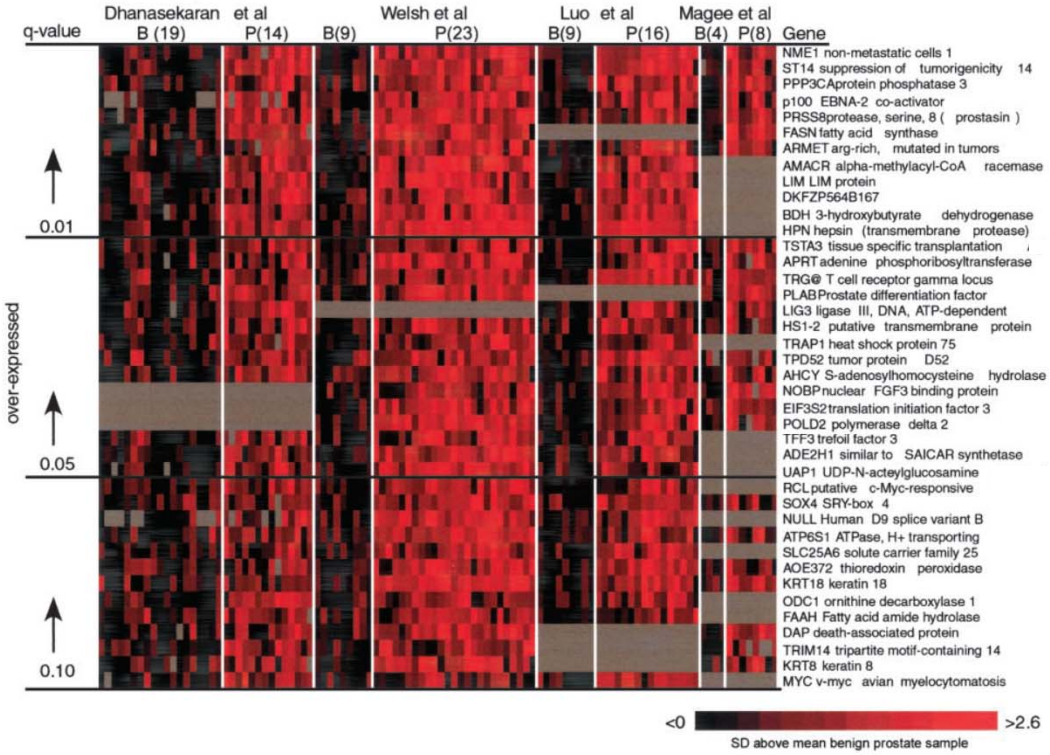
- **Hypothesis: Differences in gene expression will reveal differences in tumor biology between African-American and European-American patients**
- **Gene expression analysis**
  - **33 African-American (AA) patients**
  - **36 European-American (EA) patients**
- **Tumors were matched for clinical parameters**
- **Analysis at gene and pathway level**

Differentially Expressed Genes

- **162 genes differently expressed (FDR ≤ 5%)**
  - **Several metastasis-related genes, e.g., CXCR4, MMP9, AMFR**
- **Differently expressed genes were not shared with the published list(s) of marker genes for prostate tumors**

Marker genes in prostate cancer
Meta-analysis by Rhodes et al.
Cancer Res. 2002, 62, 4427-4433

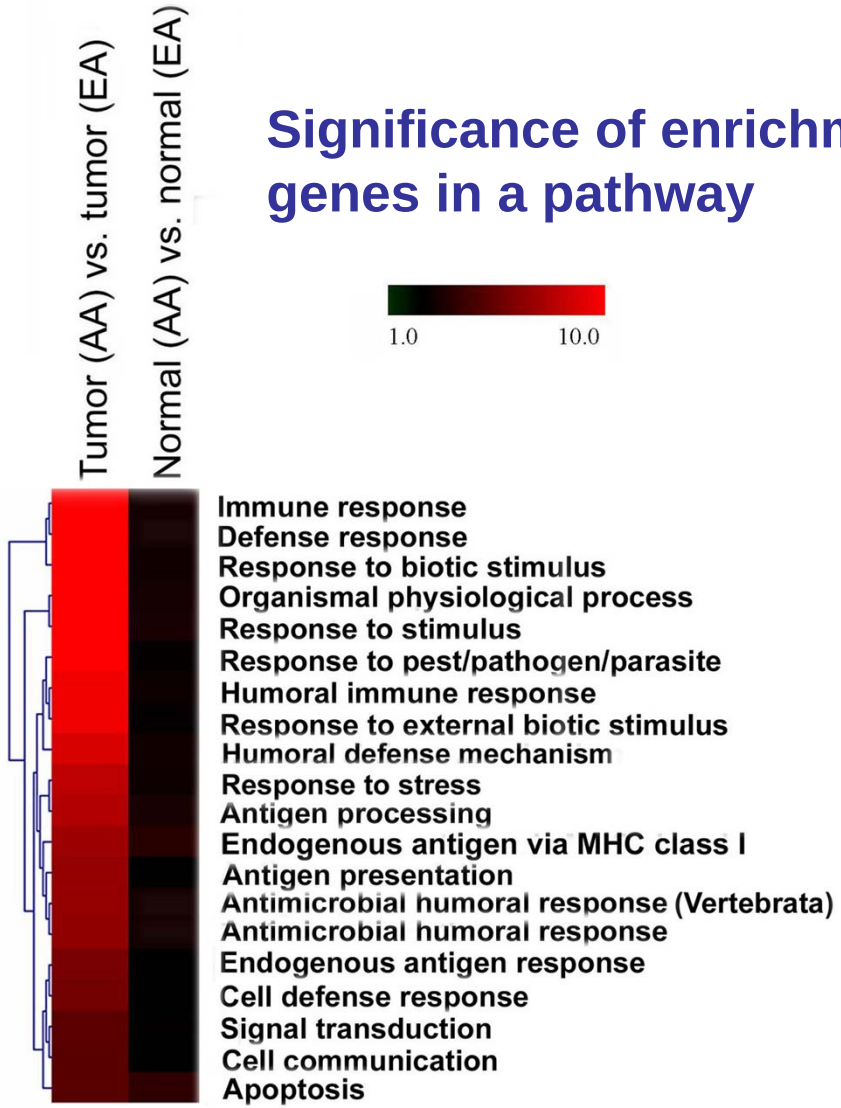
80 marker genes – no overlap



Pathway Analysis: Differences In Immune Response

Significance of enrichment for genes in a pathway

Differently expressed genes



Two-Gene Classifier

Genes

1. Crystalline Beta B2 (*CRYBB2*)
2. Phosphoserine Phosphatase-like (*PSPHL*)

TUMOR (AA) vs. TUMOR (EA)

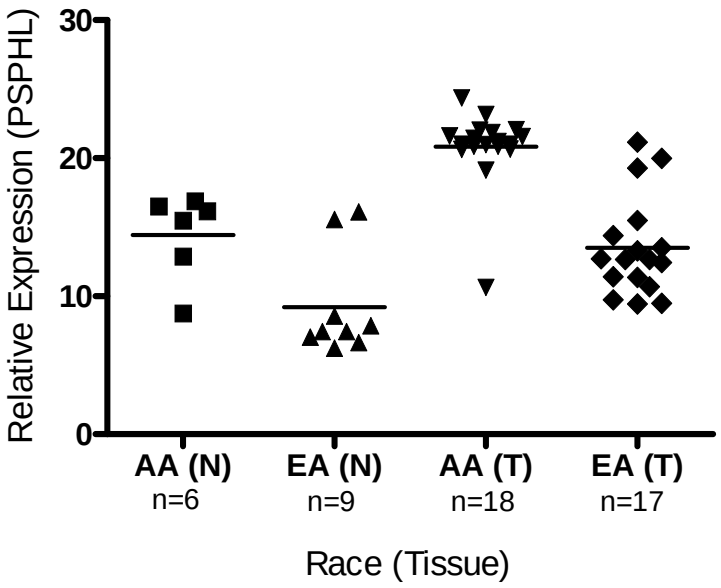
Test Set

True/Predicted	African-American	European-American	Total	% Accuracy
African-American	30	3	33	91%
European-American	2	34	36	94%

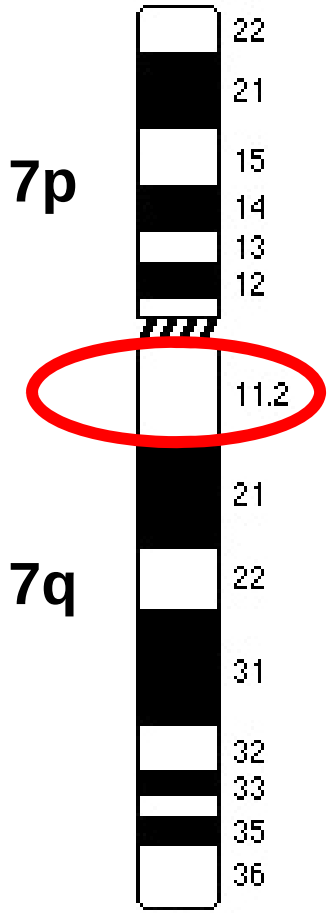
Blinded Independent Validation Set

True/Predicted	African-American	European	Total	% Accuracy
African-American	30	4	34	88%
European	0	5	5	100%

PSPHL (Phosphoserine Phosphatase-like)



Comparisons	Fold Change	*P*-value
EA Tumor vs. non tumor	20	<0.0001
AA Tumor vs. non tumor	84	0.009
Normal AA vs. EA	38	0.015
Tumor AA vs. EA	161	<0.0001

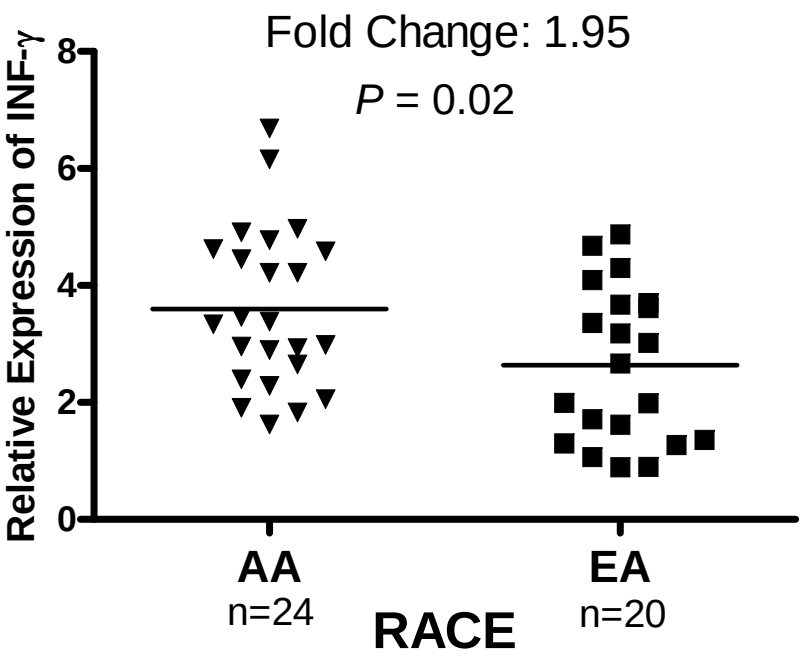


- **Advanced PCa**
- **Williams Beuren Syndrome**

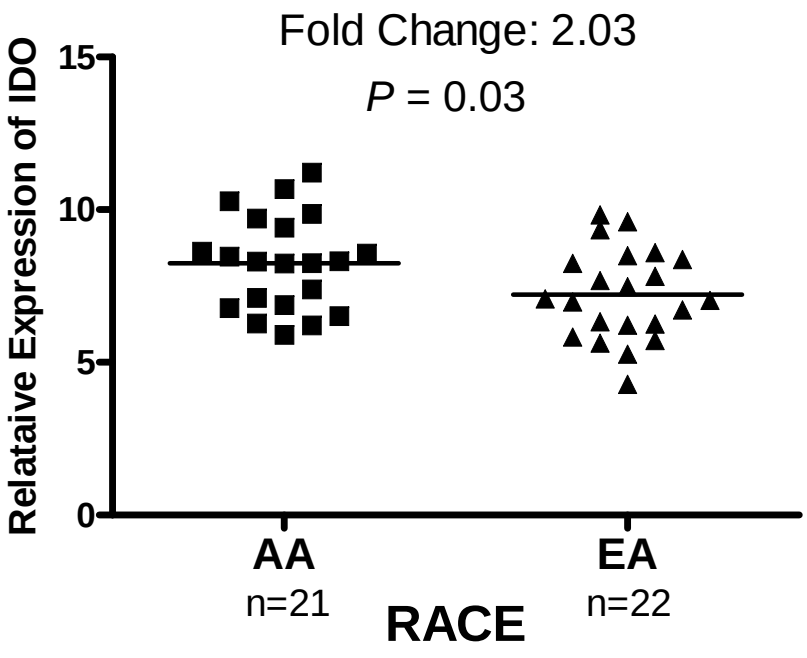
Interferon γ Signature in Tumors

Numerous interferon-regulated genes were found to be more highly expressed in tumors of African-American patients: A viral signature?

Interferon γ



Indolamine 2,3-dioxygenase



Conclusions

- **Numerous genes were differently expressed in prostate tumors comparing African-American and European-American patients**
  - Increased expression of metastasis-promoting genes in tumors from African-American men
  - A two-gene tumor signature differentiates between the two patient groups
- **Indication of distinct tumor microenvironment**
  - Differences in tumor immunobiology and presence of interferon γ signature
- **Immune-related differences could be predisposing to tumor progression and may affect therapy outcome**

Future Course

- **Examine immunobiology of tumors in African-American patients**
  - **Immune tolerance**
    - Indoleamine 2,3-dioxygenase & tryptophan availability
    - Immune cell profiling of tumors (with A. Hurwitz)
  - **Interferon γ signature**
    - Serum markers in case control study
    - Presence of viral sequences in tumors from viral infections (e.g., XMRV) or endogenous retroviruses (e.g., HERV-K)

      (with M. Linehan, H. Young, R. Silverman, N. Bannert, others)

- **Investigate the function of *PSPHL***

  with Jun Luo, William Isaacs (JHU)

Gene Expression Profiling Study: A Collaboration

Contributors at NCI

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Extramural

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Tissue resource: NCI Collaborative Prostate Cancer Tissue Resource