The Genetics of Prostate Cancer: Clinical Implications

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Facts
• Cancer is caused by interplay of genetic and environmental factors
• The contribution of genetic factors varies between tumors
• Shared genetic factors may increase the risk for more than 1 type of cancer

Early Family Linkage Studies
• Prostate cancer clusters in families
• Most segregation analyses suggested hereditary prostate cancer could be best explained by at least 1 rare dominant susceptibility gene, but this has not yet proven to be the case

Additional Disclosure
• Collaborator with deCODE genetics, Inc.
• Non-paid consultant with no financial interest or support
Early linkage studies of PCa families postulated the existence of several possible susceptibility genes.

Early Targeted Studies

- However, further targeted studies and genome-wide scans revealed difficulties in replication.
- Confirmatory studies have yielded mixed results.

Clinical Studies

Based on Candidate Genes

UPM-3 (Now called PCA3)

- A gene that is 30-100-fold upregulated in prostate cancer.
- Can be detected in prostatic fluid samples.
- Theoretically, it could be used like urinary cytology (i.e., could detect cancer without performing a biopsy).
- Practically it might assist in selecting patients for repeat biopsy.
PCA3 correlates with the probability of a positive biopsy and is independent of prostate volume, PSA, and the number of prior biopsies.
PCA3: Tumor Volume and Gleason Sum

PCA3 Score Before Radical Prostatectomy Predicts Extracapsular Extension and Tumor Volume

Eyal Z. Whitman, Oshri Zarchin, A. Alejandro, Yongjun Chen, Amy Hong, Maria Orsini, George Pricoupenko, Zeev Ben-Hur, J. Christo Kateris, Christopher Glod, Jason A. Bankert, David A. Baez, David N. Wang, Robert Haubner, Susan M. Gapstur, Robert A. Sillanpaa, Howard M. Gershon, David B. Farrow, William F. Miller, Donald J. DeMaria, Michael B. Kattan, Douglas C. Fowke, and Greg W. Lepor

EPCA-2

- Nuclear protein specifically expressed in prostate cancer
- ELISA for 2 epitopes (2.19 and 2.22)
- In serum samples from patients, shows results that are complementary to PSA
- Identifies men with organ-confined and non-organ confined prostate cancer and prostate cancer vs non-prostate cancer.

Leman ES et al J Urol 175:275, abstract 852

Multi-Center Validation

A multicenter evaluation of the PCA3 molecular urine test: Pre-analytical effects, analytical performance, and diagnostic accuracy

Lamy J, Sokol T, Williams L, Paul Lange, Jennifer Strickland, Delta J, Elenji, Jan L, Denis, A. Yu, Blai, Youngsung Ko, Mark Burns, Harry Rittenhouse, Jack Goedert, Robert L. Vessella

*Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD, United States
*Department of Urology, University of Washington, Seattle, WA, United States

Accepted in November 2004, Abstract published November 2005, accepted November 2007, Volume 175, 8 November 2006

EPCA3 in post-DRE urine of PCa patients correlated with pathologic findings of extracapsular tumor extension

Positive end in 10% prostate cancer cases. When combined with serum PSA and biopsy Gleason score, the EPCA-2 ELISA has an accuracy in predicting extracapsular extension in 95%.

Contributions: PCA3 detected in the post-digital rectal examination urine of patients with prostate cancer correlated with pathologic findings. Therefore, it could provide prognostic information. To our knowledge, this is the first report of a marker in urine more than predicts extracapsular extension.
**EPCA-2: A Highly Specific Serum Marker for Prostate Cancer**

Eddy S. Lenaes, Grant W. Cameron, Bruce J. Trock, Lori J. Solow, Daniel W. Chan, Leslie Mangold, Alan W. Partin, and Robert H. Getzenberg

**OBJECTIVES**
- To describe the initial assessment of a new prostate cancer antigen (EPCA-2) in serum samples from men with prostate cancer and controls
- To evaluate the sensitivity and specificity of EPCA-2 in serum samples

**METHODS**
- Serum samples were obtained from 158 men with prostate-specific antigen (PSA) levels greater than 2.5 ng/mL and 46 men with lower PSA levels, and from 50 healthy men.
- Serum EPCA-2 levels were measured using an enzyme-linked immunosorbent assay.

**RESULTS**
- In the group with PSA levels greater than 2.5 ng/mL, EPCA-2 levels were significantly higher than in the control group (p < 0.001).
- The area under the receiver operating characteristic curve (AUC) for EPCA-2 was 0.85 (95% CI 0.78 to 0.92).
- The positive predictive value (PPV) was 82% (95% CI 73% to 90%) and the negative predictive value (NPV) was 75% (95% CI 68% to 81%).

**CONCLUSION**
- EPCA-2 is a highly sensitive and specific marker for prostate cancer.

**Graphical Representation**
- Graph A: Comparison of PSA levels in normal and prostate cancer patients.
- Graph B: Comparison of EPCA-2 levels in organ-confined and non-organ-confined prostate cancer patients.
TMPRSS2-ETS Gene Fusion

Recurrent Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer


Recurrent chromosomal rearrangements have not been well characterized in common malignancies; the use of transcriptomic approaches to characterize oncogenic chromosomal aberrations on the basis of tumor gene expression. Two ETS transcription factors, ERG and ETV1, were identified as targets in prostate cancer. We identified recurrent gene fusions of the 5′ extended region of TMPRSS2 to ERG or ETV1 in prostate cancer tissues from M. H. Whitaker-Sobotka et al. (2007) in Cancer Res. 67, 9372–9378. The report states that 20 of 29 prostate cancer samples harbor rearrangements in TMPRSS2 and ETV1. We report that the oncogenic transcription factors of TMPRSS2 mediate the oncogenesis of cancerous cells in prostate cancer. These results have implications in the development of carcinogenesis and the molecular diagnosis and treatment of prostate cancer.

Contemporary Strategies in Active Surveillance: erg Fusion Effect on Prostate Cancer Mortality

FUSION STATUS

Cumulative Incidence Ratio: 3.644 (p-value=0.0044, 95%CI=(1.497, 8.870))

M. Rubin et al., Oncogene, 2007

Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer

Transformation signaling in the presence of androgen

ERG oncogenic transcription factor

ETS1 oncogenic transcription factor

Combination of TMPRSS2-ERG and PCA3 significantly improves sensitivity for PCa diagnosis

Urinary Test for Prostate Cancer

Detection of TMPRSS2-ERG Fusion Transcripts and Prostate Cancer Antigen 3 in Urinary Sediments May Improve Diagnosis of Prostate Cancer

Combination of TMPRSS2-ERG and PCA3 significantly improves sensitivity for PCa diagnosis

Multiple Markers in Urine Test

A First-Generation Multiplex Biomarker Analysis of Urine for the Early Detection of Prostate Cancer

Multiple Markers, Including TMPRSS2-ETS Fusions and PCA3

Hypermethylation at GSTP1 in serum predicts early PSA failure following RP.

Hypermethylation at MDR1 was detected in localized PCa. CpG island hypermethylation at several loci was detected with advanced disease.
Gene analysis using PCR is a reliable method for detecting abnormal DNA methylation in voided urine following DRE or prostate needle biopsy.

**Limitations of Linkage and Candidate Gene Studies**

- Linkage analysis has sufficient power to detect highly penetrant genes but has weak power to find susceptibility genes of small-to-moderate effects
- Candidate gene studies do not test most of the genome

**Genetic Variants**

- Prior to 2006, no common genetic variant accounted for a substantial proportion of cases
- In 2006, deCODE genetics discovered genetic variants that point to a complex genetic basis, involving multiple susceptibility loci, i.e., “death by 1000 cuts”
Discovery of 8q24 Risk Alleles

- Discovered and validated 2 sequence variants on chromosome 8q24 (a frequent site of somatic amplification in prostate and colorectal cancer) that are significantly more common in prostate cancer cases than in controls
- This was the first universally replicable prostate cancer susceptibility locus and may account for 8% to 64% of prostate cancer cases


Two 8q24 Alleles Associated with Aggressiveness and Race

- Combined estimated OR of 1.62 (P = 2.7 × 10−11) for DG8S737 -8 and an OR of 1.51 (P = 1.0 × 10−11) for rs1447295 allele 'A'.
- Slight association of DG8S737 -8 with higher Gleason score.
- DG8S737 -8 allele frequency of 16% in the African American population as compared to 5.6% in European/Caucasian population.
- Could account for increased incidence rate of prostate cancer in African Americans.

Amundadottir et al. (2006) Nat Genetics 38: 652-8

Validation Across Multiple Ethnic Cohorts

Replicated SNP rs1447295 in other MEC populations but not African Americans
Other 8q24 Regions

• Subsequent studies revealed additional clusters of variants within 8q24 that independently confer risk for prostate cancer

Tissue Specificity: The General Rule

• In most cases, but not all, the genetic variants are specific for a particular type of cancer
Known Genes in 8q24

- The genomic regions of 8q24 are gene poor and have a high recombination rate.
- The only reported “gene” is a retro-transposed gene, AF268618 (POU5F1) that encodes for a transcription factor, OCT4, proposed as a stem cell marker – embryogenesis and in some tumors.
- Two known genes nearby are c-MYC and FAM84B (NSE2), but no association with these genes has been found.
- deCODE found no differences in expression in carriers and non-carriers of any of the above or of 1447295 (A), HapC, rs16901979.
- The distal end of a fragile site 8C (FRA8C) has been mapped to this region, as well as several integration sites of HPV.

17q: The Second Major Region

Two variants on chromosome 17 confer prostate cancer risk, and the one in TCP2 protects against type 2 diabetes.

UK “Practical” Reports 7 Risk Variants on Chromosome 3, 6, 7, 10, 11, 19 and X

Multiple newly identified loci associated with prostate cancer susceptibility.

Of the 53 SNPs significant at the P < 10^-6 level, 20 were on 8q24 and 6 were on chromosome 17.
Patient Profiling
Prostate Cancer Susceptibility
29 risk variants now identified
Adding Family History as a 6th Risk Factor

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Subjects</th>
<th>Control Subjects</th>
<th>Regression Coefficient</th>
<th>Odds Ratio 95% CI</th>
<th>P Value</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of associated factors</td>
<td>144 (50)</td>
<td>174 (62.3)</td>
<td>0.48</td>
<td>1.82 (1.07-2.98)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>1</td>
<td>178 (59)</td>
<td>181 (58.6)</td>
<td>0.75</td>
<td>2.01 (1.24-3.24)</td>
<td>0.007</td>
<td>0.007</td>
</tr>
<tr>
<td>2</td>
<td>165 (59)</td>
<td>62 (18.6)</td>
<td>0.99</td>
<td>2.71 (1.55-4.76)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>642 (22.1)</td>
<td>68 (18.6)</td>
<td>1.56</td>
<td>4.78 (2.63-8.74)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>616 (22.2)</td>
<td>64 (18.6)</td>
<td>1.56</td>
<td>4.78 (2.63-8.74)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4. Cumulative Effect of Associated Factors on the Risk of Prostate Cancer


Relative risks compared to the general population vary and account for about half of the cases.

deCODE genetics new commercial ProCa test identifies 8 validated variants: 3 on 8q24, 2 on 17q, 1 on 8p15, 1 on 11, and 1 on X.
Genetic Risk Alleles Improve Performance of PSA Isoforms

Profiling for Aggressive Disease

**8q24 & Biopsy Gleason Grade**

Proportion with Gleason ≥7

<table>
<thead>
<tr>
<th>Allele</th>
<th>p value (Region 1)</th>
<th>p value (Region 2)</th>
<th>p value (Region 3)</th>
<th>OR 8q24 (Region 1)</th>
<th>OR 8q24 (Region 2)</th>
<th>OR 8q24 (Region 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs16901979 (Region 1)</td>
<td>0.11</td>
<td>0.26</td>
<td>0.03</td>
<td>4.8</td>
<td>2.6</td>
<td>2.0</td>
</tr>
<tr>
<td>rs16901979 (Region 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs16901979 (Region 3)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Cumulative Model for the Prediction of Pathologic Gleason Score ≥7**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs16901979 8q24</td>
<td>2.0</td>
</tr>
<tr>
<td>rs16901979 8q24 + 1 other allele</td>
<td>2.2</td>
</tr>
<tr>
<td>rs16901979 8q24 + 2 other allele</td>
<td>3.6</td>
</tr>
<tr>
<td>rs16901979 8q24 + 3 other allele</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Genetics of Prostate Cancer

- What are we likely to find in the future, and how are we going to find it?

Following slides courtesy of Douglas A. Easton, PhD, Cambridge University


Prostate cancer genomics: towards a new understanding

John S. Witte
Prostate cancer risk prediction

Current 16 loci

Theoretical maximum

top 1% ~ 3x risk

top 1% ~ 16x risk

Known Breast Cancer Genes

High-risk
Family studies

Rare moderate-risk
Resequencing

Common low-risk
GWAS

Too hard!
Large Genome-Wide Scans Detect More Small-Effect Variants

- In a collaborative study with deCODE genetics (33,000 cases and 45,000 controls), we identified SNPs associated with cancer at multiple sites (lung 1.15, bladder 1.12, prostate 1.07, and cervix 1.31).
- Thus, we have identified genetic variants that confer susceptibility to several cancers that have strong environmental components to their risk.


Implications

- Many new genetic prostate cancer markers
- May provide insights into prostate carcinogenesis and strategies for prevention and treatment
- Some will contribute significantly to patient care