8q24: Prostate Cancer

Matthew Freedman
GAIN II
October 18, 2007
Summary of LOD scores for 11 CaP linkage scans

Adapted from Schaid Hum Molec Genet 13:R103
History of prostate cancer genetics

Where Are the Prostate Cancer Genes?—
A Summary of Eight Genome Wide Searches


Prostate cancer susceptibility genes: Many studies, many results, no answers


REVIEW ARTICLE
Genetics of Prostate Cancer: Too Many Loci, Too Few Genes

Outline

- Whole genome admixture scan
- Fine mapping
- Work in progress
Established risk factors for prostate cancer

- Age
- Family history
- Ethnicity
Prostate cancer: epidemiology

![Incidence rate per 100,000 men](chart)

- **Asian/Pacific Islander**
- **White**
- **Black**

SEER data – 1998-2002
age adjusted
Whole genome admixture scan

- Started 3 years ago

- Risk allele must be differentially distributed between ancestral populations

- Can scan the genome with many fewer markers than for non-admixed pops
Prostate cancer is a strong candidate disease for admixture mapping

- Incidence rates in African-American men ~1.6 fold higher than European-Am men
- Epidemiologic evidence suggests that prostate cancer is even higher in African men
- Prostate cancer has one of the highest heritabilities out of all epithelial cancers
- No gene has been consistently identified
Admixture creates a mosaic

Two African chromosomes

Two European chromosomes

One African, one European chromosome

4 generations ago

3 generations ago

2 generations ago

1 generation ago

Today
How does admixture mapping work?

Disease locus

African chromosome

European chromosome

Men with prostate cancer
The signal of admixture association

- Positive signal at the 60cM position on chromosome (centimorgans).
Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men

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<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases % European ± 1 standard err.</th>
<th>Controls % European ± 1 standard err.</th>
<th>mean age diagnosis (range)</th>
<th>% with Gleason score &gt;7</th>
<th>% with non-local tumors</th>
<th>% with prostate cancer in a first degree relative</th>
<th>Decrease in peak LOD if these samples are removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiethnic Cohort</td>
<td>CA &amp; HI 810</td>
<td>730</td>
<td>23.57 ± 0.50%</td>
<td>25.42 ± 0.57%</td>
<td>68 (46-85)</td>
<td>18%</td>
<td>15%</td>
<td>12%</td>
<td>2.58</td>
</tr>
<tr>
<td>L.A. County Men's Health Study</td>
<td>CA 366</td>
<td>107</td>
<td>22.34 ± 0.83%</td>
<td>26.37 ± 2.13%</td>
<td>63 (42-88)</td>
<td>28%</td>
<td>39%</td>
<td>21%</td>
<td>1.37</td>
</tr>
<tr>
<td>Study Early Onset Pros. Cancer</td>
<td>CA 104</td>
<td>-</td>
<td>20.89 ± 1.37%</td>
<td>-</td>
<td>60 (45-65)</td>
<td>31%</td>
<td>49%</td>
<td>14%</td>
<td>1.01</td>
</tr>
<tr>
<td>PCGP</td>
<td>MI 103</td>
<td>-</td>
<td>19.50 ± 1.01%</td>
<td>-</td>
<td>55 (40-86)</td>
<td>11%</td>
<td>29%</td>
<td>39%</td>
<td>1.15</td>
</tr>
<tr>
<td>Flint Men's Health Study</td>
<td>MI 85</td>
<td>-</td>
<td>18.05 ± 1.21%</td>
<td>-</td>
<td>65 (47-77)</td>
<td>12%</td>
<td>28%</td>
<td>15%</td>
<td>0.06</td>
</tr>
<tr>
<td>Bay Area Men's Health Study</td>
<td>CA 82</td>
<td>36</td>
<td>19.06 ± 1.52%</td>
<td>20.13 ± 2.15%</td>
<td>64 (44-78)</td>
<td>25%</td>
<td>94%</td>
<td>28%</td>
<td>1.16</td>
</tr>
<tr>
<td>Genomics Collaborative</td>
<td>All U.S. 47</td>
<td>-</td>
<td>16.16 ± 1.51%</td>
<td>-</td>
<td>62 (39-81)</td>
<td>14%</td>
<td>38%</td>
<td>28%</td>
<td>0.57</td>
</tr>
<tr>
<td>Combined samples</td>
<td>1,597</td>
<td>873</td>
<td>22.11 ± 0.36%</td>
<td>25.32 ± 0.55%</td>
<td>65 (39-88)</td>
<td>21%</td>
<td>29%</td>
<td>18%</td>
<td>7.14</td>
</tr>
</tbody>
</table>

Freedman et al., PNAS :14068 (2006)
Genetic position in centimorgans (Chromosome-Position)

LOD score (log base 10 of likelihood)

Chromosome 8 peak

Position on chromosome 8 (in megabases)

Probability density

3.8 Mb

Freedman et al., PNAS :14068  (2006)
A common variant associated with prostate cancer in European and African populations


Convergence of independent methods and data
Outline

- Whole genome admixture scan
- Fine mapping
- Work in progress
Ancestry is a proxy for the causal variant

Magnitude of association with CaP
Do deCODE variants fully explain ancestry risk in African American men?

- DG8S737
- and rs1447295

Causal variant? → Ancestry → CaP

Magnitude of association with CaP
Fine mapping identifies 3 regions contributing to PCa risk
### 7 alleles associated with CaP in a multiethnic cohort

<table>
<thead>
<tr>
<th>Marker</th>
<th>African American</th>
<th>Japanese American</th>
<th>Native Hawaiians</th>
<th>Latinos</th>
<th>European Americans</th>
<th>Pooled OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13254738</td>
<td>1.24 (1.09-1.42)</td>
<td>1.57 (1.33-1.83)</td>
<td>1.46 (1.00-2.12)</td>
<td>1.25</td>
<td>1.11 (0.97-1.26)</td>
<td>1.26 (1.18-1.36)</td>
</tr>
<tr>
<td>rs6983561</td>
<td>1.34 (1.18-1.53)</td>
<td>1.78 (1.47-2.15)</td>
<td>3.17 (1.87-5.36)</td>
<td>1.99</td>
<td>1.16 (0.86-1.58)</td>
<td>1.51 (1.37-1.67)</td>
</tr>
<tr>
<td>Broad11934905</td>
<td>2.45 (1.65-3.62)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.45 (1.65-3.62)</td>
</tr>
<tr>
<td>rs6983267</td>
<td>1.43 (1.17-1.75)</td>
<td>1.22 (1.05-1.42)</td>
<td>1.29 (0.88-1.89)</td>
<td>1.05</td>
<td>1.13 (0.99-1.28)</td>
<td>1.18 (1.09-1.27)</td>
</tr>
<tr>
<td>rs7000448</td>
<td>1.33 (1.12-1.58)</td>
<td>1.23 (1.04-1.46)</td>
<td>1.38 (0.89-2.14)</td>
<td>1.29</td>
<td>1.14 (0.93-1.40)</td>
<td>1.26 (1.15-1.38)</td>
</tr>
<tr>
<td>DG8S737-8</td>
<td>1.25 (1.06-1.49)</td>
<td>1.48 (1.16-1.88)</td>
<td>2.55 (1.33-4.89)</td>
<td>1.46</td>
<td>1.45 (0.96-2.19)</td>
<td>1.39 (1.23-1.57)</td>
</tr>
<tr>
<td>rs10090154</td>
<td>1.11 (0.94-1.32)</td>
<td>1.49 (1.23-1.81)</td>
<td>2.54 (1.61-4.02)</td>
<td>1.98</td>
<td>1.44 (1.17-1.76)</td>
<td>1.43 (1.30-1.58)</td>
</tr>
</tbody>
</table>
Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24

Meredith Yeager1,2, Nick Orr3, Richard B Hayes2, Kevin B Jacobs4, Peter Kraft5, Sholom Wacholder2,

Multiple regions within 8q24 independently affect risk for prostate cancer

Christopher A Haiman1, Nick Patterson2, Matthew L Freedman2,3, Simon R Myers2, Malcolm C Pike1,
Alicja Waliszewska2,4,5, Julie Neubauer2,4, Arti Tandon2,4, Christine Schirmer2,4, Gavin J McDonald2,4,
Steven C Greenway4, Daniel O Stram1, Loic Le Marchand6, Laurence N Kolonel6, Melissa Frasco1,
David Wong1, Lorell C Pooler1, Kristin Ardlie2,7, Ingrid Oakley-Girvan8,9, Alice S Whittemore9,
Kathleen A Cooney10,11, Esther M John8,9, Sue A Ingles1, David Altshuler2,4,12,13,
Brian E Henderson1 & David Reich2,4
Summary: Fine mapping

- Multiple alleles contributing risk in a noncoding region
  - Population attributable risk is large across populations

- Power of studying multiple ethnicities

- Most risk alleles are shared across populations
  (although this is also what we are most powered for)

- MYC is closest gene
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Outline

- Whole genome admixture scan
- Fine mapping
- Work in progress
Now what??

Sequence

Function
Sequencing - ascertain all variation across three regions

- N=48 - across 3 ethnic groups

- Newly discovered and poorly tagged variants will be tested in larger multiethnic cohort
What is the mechanism of risk?

- Possible hypotheses
  - structurally unstable
  - unannotated transcript
    - tiling arrays
  - promoter/enhancer
    - tiling arrays
    - chromatin markers
Hypothesis: structural instability

Are the 8q24 risk alleles associated with somatic 8q amplification?

Being performed on 140 paired normal/tumor samples from the DFCI/Gelb center
**Tiling arrays**

A tiling array is an array that "tiles" oligos across a given region so that it can be interrogated at ultra-high resolution.

We tiled a 5 megabase region at 8q24 with a mean probe spacing of 8bp.

Analyzed cDNA and acetylation.
LnCaP + 20 prostate tissues

Expression of RNA transcripts

Reverse transcribe

Hybridize cDNA

8q24.21 (15kb)

Oligo probes

Expressed transcripts

exon  exon  exon
Blow-up of region - MYC
Transcriptional landscape of 8q24
New transcripts in risk region

Confirmed by RT-PCR in prostate tissue
Currently performing 5' RACE to fully characterize Pseudogene
8q24 regions are bear marks of enhancers

Jerome Eekhoute and Mathieu Lupien
Future directions: what is the region enhancing?

- How is 8q24 influencing expression?
  - Directed
    - 12 transcripts
    - 150 histologically normal prostate samples
  - Unbiased
    - Chromosome Conformation Capture

Expression level

Genotype

AA    AB    BB

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Acknowledgements

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David Reich
Nick Patterson
Simon Myers
Julie Neubauer
Christine Schirmer
Arti Tandon
Gavin McDonald
Neil Hattangadi
Alicja Waliszewska
Kristin Ardlie
David Altshuler

DFCI
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Kathryn Penney
Christine Beckwith
Phil Kantoff
Oliver Sartor
William Oh
Jerome Eekhoute
Mathieu Lupien
Myles Brown

Stanford
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NCCC
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Esther John

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CPDR
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Shiv Srivastava
Albert Dobi
Jennifer Cullen

USC
Brian Henderson
Chris Haiman
Dan Stram
Sue Ingles
Malcolm Pike
### 8q24 variants and clinical parameters

*Kathryn Penney and Mark Pomerantz*

<table>
<thead>
<tr>
<th></th>
<th>PHS (n=598)</th>
<th>DFCI aggressive (n=762)</th>
<th>DFCI RP (n=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis (mean)</strong></td>
<td>(n=598) 68.5</td>
<td>(n=734) 62.2</td>
<td>(n=459) 56.7</td>
</tr>
<tr>
<td><strong>PCa deaths/ long term survivors</strong></td>
<td>156/396</td>
<td>277/168</td>
<td>---</td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td>(n=490) &lt;7 51.4</td>
<td>(n=684) 17.8</td>
<td>(n=460) 41.5</td>
</tr>
<tr>
<td></td>
<td>7 32.9</td>
<td>32.7</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
<td>&gt;7 15.7</td>
<td>49.4</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>PSA at diagnosis</strong>*</td>
<td>(n=221) 9.1</td>
<td>(n=414) 11.0</td>
<td>(n=426) 5.0</td>
</tr>
<tr>
<td><strong>Pathologic stage</strong></td>
<td>---</td>
<td>---</td>
<td>(n=454) 85.9</td>
</tr>
<tr>
<td></td>
<td>T1-T2</td>
<td>T3-T4</td>
<td></td>
</tr>
</tbody>
</table>

*PSA at diagnosis does not include individuals who were diagnosed with metastases*
8q24 and PCa mortality

Kathryn Penney and Mark Pomerantz

N=433 PCa deaths and N=564 > 10 year survivors
Adjusted for age at diagnosis and cohort