Prostate Cancer

- It is the most frequent cancer (after non-melanoma skin cancer)

- In 2005, more than 232,000 new cases were diagnosed in USA and more than 30,000 will die as a consequence of the disease.
Prostate Cancer

- Most patients are men over 65 years old

- Only 23% are diagnosed before 65.

- Only 4% are diagnosed before 55.

Prostate Cancer

- Epidemiologic data suggest that a strong familial component exists, at least in a subgroup of PC.

- PC familial history in a first-degree relative => a 2-3 times higher RISK

- Families with several affected members and, particularly, with early onset => high RISK for relatives
Models of inheritance

• Carter et al. (PNAS 89:3367-71, 1992) suggest the following model:
  • A rare allele (q = 0.003)
  • Dominant Inheritance
  • 88% life-long penetrance

• The say that this allele would be responsible for:
  • 43% of early-onset cases
  • 9% of total PC cases

Models of inheritance

• More recently, Grönberg et al. (Am J Epidemiol., 146:552-7, 1997) suggest a slightly different model:
  • A more frequent allele (q = 0.0167)
  • Dominant inheritance
  • with lower life-long penetrance: 63%
Loss of Heterozygosity (LOH)

Loss of heterozygosity and other alterations presents in PC have suggested different localizations for genes involved in the disease.

These localizations include:
- chromosome 8 (LOH in 8p22, duplications in 8q)
- 16q
- 17p
- 18q
Loss of Heterozygosity

- So far, these *loci* have not been shown to be major sites for genes involved in PC

Linkage Analysis

* Now replaced by the positional candidate approach

Fig. 2 Schematic of the approach generally utilized for positional cloning.
SIB PAIRS

- General
  - AB CD
  - AC AC (1/4)
  - AD BC BD

- Dominant
  - AB CD
  - AC AC (1/2)
  - AD

- Recessive
  - AB CD
  - AC AC (1/1)

ASSOCIATION STUDIES

- Candidate gene
  - C
  - T

- Phenotype (cancer risk)
  - ≠

- Polymorphism (cancer risk)
By linkage analysis, several loci for PC genes have been identified (however, many contradictory results have been published). The first loci identified were:

- Smith et al. (1996): HPC1 in 1q24-25
- Berthon et al. (1998): PCAP in 1q42.2-43
- Xu et al. (1998): HPCX in Xq27
- Gibbs et al. (1999): CAPB in 1p36

### Table: Average number per family and age of diagnosis

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number of families</th>
<th>Average number per family (range)</th>
<th>Average age of diagnosis (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Affected</td>
<td>Typed*</td>
</tr>
<tr>
<td>North American</td>
<td>79</td>
<td>5.1 (3–15)</td>
<td>3.7 (2–11)</td>
</tr>
<tr>
<td>Swedish</td>
<td>12</td>
<td>3.9 (3–6)</td>
<td>3.6 (3–5)</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>4.9 (3–15)</td>
<td>3.7 (2–11)</td>
</tr>
</tbody>
</table>

*Typed refers to the number of affected family members analyzed.*
Smith et al. (1996): HPC1 in 1q24-25

**Linkage Analysis**

### Parametric Analysis: Two-Point LOD

<table>
<thead>
<tr>
<th>Marker</th>
<th>Distance (cM)*</th>
<th>( \hat{\theta} )</th>
<th>( \hat{\phi} )</th>
<th>( Z ) score</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1S452</td>
<td>0.0</td>
<td>0.94</td>
<td>0.27</td>
<td>2.28</td>
<td>0.01</td>
</tr>
<tr>
<td>D1S219†</td>
<td>1.9</td>
<td>2.31</td>
<td>0.22</td>
<td>2.14</td>
<td>0.02</td>
</tr>
<tr>
<td>D1S212</td>
<td>3.6</td>
<td>2.96</td>
<td>0.19</td>
<td>4.22</td>
<td>0.00001</td>
</tr>
<tr>
<td>D1S2883</td>
<td>0.0</td>
<td>3.66</td>
<td>0.18</td>
<td>4.16</td>
<td>0.000002</td>
</tr>
<tr>
<td>D1S466</td>
<td>5.1</td>
<td>2.41</td>
<td>0.20</td>
<td>4.71</td>
<td>0.000001</td>
</tr>
<tr>
<td>D1S29710</td>
<td>0.9</td>
<td>1.69</td>
<td>0.24</td>
<td>4.05</td>
<td>0.000002</td>
</tr>
<tr>
<td>D1S155</td>
<td>1.5</td>
<td>2.53</td>
<td>0.21</td>
<td>4.62</td>
<td>0.000002</td>
</tr>
<tr>
<td>D1S422</td>
<td>4.4</td>
<td>2.67</td>
<td>0.20</td>
<td>4.26</td>
<td>0.00001</td>
</tr>
<tr>
<td>D1S413†</td>
<td>4.9</td>
<td>1.80</td>
<td>0.21</td>
<td>2.83</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Distances in centimorgans from the preceding marker in the table were derived from the CRIMAP analysis. Markers used in genome-wide scan.
LINKAGE ANALYSIS

Smith et al. (1996): HPC1 in 1q24-25

HPC1 locus in 1q24-25 reanalyzed

Xu (AJHG 62 1425-38, 2000)

772 familial CP pedigrees were evaluated

Conclusion: in 6% of the families the disease is linked to HPC1
LINKAGE ANALYSIS
Berthon et al. (1998): PCAP in 1q42.2-43

Characteristics of Genotyped CaP Families

<table>
<thead>
<tr>
<th>Category</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of families analyzed</td>
<td>47</td>
</tr>
<tr>
<td>Total no. of individuals genotyped</td>
<td>194</td>
</tr>
<tr>
<td>Total no. of affecteds genotyped</td>
<td>122</td>
</tr>
<tr>
<td>Average no. of CaP cases/family</td>
<td>3.31</td>
</tr>
<tr>
<td>Average no. of genotyped CaP cases/family</td>
<td>2.60</td>
</tr>
<tr>
<td>Mean age ± SD (in years) at diagnosis</td>
<td>65.9 ± 8.8</td>
</tr>
</tbody>
</table>

They used 3 models with different phenocopy values

- Dominant autosomal inheritance
- Allele frequency: 0.003
- Global penetrance 0.88 (at 85 years)
**LINKAGE ANALYSIS**
Berthon et al. (1998): PCAP in 1q42.2-43

**Age dependent penetrances:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Penetrance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years old</td>
<td>0.01</td>
</tr>
<tr>
<td>40-55 years old</td>
<td>0.1</td>
</tr>
<tr>
<td>55-70 years old</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt; 70 years old</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**Different phenocopy values (penetrance for the healthy allele):**

- **Model 1**: 0.01 for all age classes
- **Model 2**: 10% of the penetrance value for the risk genotype in each age class
- **Model 3**: 0.15 for all age classes
LINKAGE ANALYSIS
Berthon et al. (1998): PCAP in 1q42.2-43
9 EARLY ONSET families:

General results were:

1) They found no LINKAGE in HPC1 region

2) They found LINKAGE in a more telomeric region: 1q42.2-q43

3) They found significative results when using the 9 EARLY ONSET families
LINKAGE ANALYSIS

Berthon et al. (1998): PCAP in 1q42.2-43

Reasons for discrepancies with Smith et al.:

1) They say that several authors failed to find LINKAGE in the HPC1 region
2) Differences in the number of typed families and individuals
3) Differences in population origins: USA/Sweden vs. France/Germany

LINKAGE ANALYSIS

Re-evaluation of the PCAP locus in 1q42-43

Cancel-Tassin et al. (EJHG 9 135-42, 2001)

They evaluate several loci in 64 families and only found linkage for PCAP

They got to the conclusion that PCAP is the main gene in S and W Europe

However, 3 studies with negative results were also published.
## LINKAGE ANALYSIS

### Xu et al. (1998): HPCX in Xq27

#### Table 1: Characteristics of prostate cancer families

<table>
<thead>
<tr>
<th></th>
<th>JHU</th>
<th>Mayo</th>
<th>Tampere</th>
<th>Unna</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of families</td>
<td>120</td>
<td>123</td>
<td>57</td>
<td>41</td>
<td>356</td>
</tr>
<tr>
<td>Number of individuals typed</td>
<td>766</td>
<td>467</td>
<td>358</td>
<td>246</td>
<td>1700</td>
</tr>
<tr>
<td>Number of affected individuals typed</td>
<td>452</td>
<td>314</td>
<td>137</td>
<td>117</td>
<td>1020</td>
</tr>
<tr>
<td>Avg. number affected family members</td>
<td>5.1 (2-17)</td>
<td>0.0 (2-11)</td>
<td>3.2 (2-9)</td>
<td>2.0 (2-8)</td>
<td>4.2 (2-17)</td>
</tr>
<tr>
<td>Avg. number affected individuals family members</td>
<td>3.2 (2-11)</td>
<td>2.6 (2-7)</td>
<td>2.6 (2-9)</td>
<td>2.8 (2-9)</td>
<td>2.7 (2-11)</td>
</tr>
<tr>
<td>Avg. age at diagnosis (range)</td>
<td>68.1 (68-85)</td>
<td>67.7 (68-85)</td>
<td>68.2 (68-86)</td>
<td>68.0 (68-86)</td>
<td>68.3 (68-86)</td>
</tr>
</tbody>
</table>

#### Table 2: Two-point parametric lod scores

<table>
<thead>
<tr>
<th>Marker</th>
<th>Heterozygosity</th>
<th>JHU (123)</th>
<th>Mayo (123)</th>
<th>Tampere (57)</th>
<th>Unna (41)</th>
<th>All (360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXS994</td>
<td>0.74</td>
<td>4.00 (0.39)</td>
<td>0.31 (0.18)</td>
<td>0.07 (0.22)</td>
<td>0.03 (0.40)</td>
<td>1.00 (0.34)</td>
</tr>
<tr>
<td>DXS1252</td>
<td>0.86</td>
<td>14.0 (1.0)</td>
<td>26.0 (1.0)</td>
<td>0.00 (0.0)</td>
<td>0.86 (0.22)</td>
<td>0.24 (0.40)</td>
</tr>
<tr>
<td>DXS1255</td>
<td>0.86</td>
<td>14.2 (0.3)</td>
<td>19.0 (0.3)</td>
<td>0.00 (0.1)</td>
<td>2.05 (0.14)</td>
<td>0.13 (0.18)</td>
</tr>
<tr>
<td>DXS5751</td>
<td>0.54</td>
<td>14.3 (0.3)</td>
<td>49.0 (0.3)</td>
<td>5.2 (0.1)</td>
<td>1.56 (0.18)</td>
<td>0.63 (0.12)</td>
</tr>
<tr>
<td>DXS9760</td>
<td>0.43</td>
<td>14.6 (0.3)</td>
<td>51.0 (0.4)</td>
<td>7.0 (0.2)</td>
<td>0.79 (0.18)</td>
<td>0.67 (0.12)</td>
</tr>
<tr>
<td>DXS1010</td>
<td>0.70</td>
<td>14.6 (0.3)</td>
<td>62.0 (0.3)</td>
<td>8.0 (0.2)</td>
<td>0.89 (0.18)</td>
<td>1.93 (0.30)</td>
</tr>
<tr>
<td>DXS6885</td>
<td>0.81</td>
<td>14.7 (0.3)</td>
<td>45.0 (0.3)</td>
<td>7.0 (0.1)</td>
<td>0.14 (0.28)</td>
<td>1.07 (0.38)</td>
</tr>
<tr>
<td>DXS9893</td>
<td>0.83</td>
<td>14.8 (0.3)</td>
<td>97.0 (0.3)</td>
<td>0.02 (0.0)</td>
<td>0.00 (0.0)</td>
<td>0.74 (0.36)</td>
</tr>
<tr>
<td>ARMS41 I (5F)</td>
<td>0.68</td>
<td>140.3</td>
<td>110.0 (0)</td>
<td>1.24 (0.0)</td>
<td>1.22 (0.1)</td>
<td>2.41 (0.26)</td>
</tr>
<tr>
<td>DXS7120</td>
<td>0.50</td>
<td>150.4</td>
<td>1.98 (0.0)</td>
<td>0.18 (0.0)</td>
<td>0.00 (0.0)</td>
<td>0.00 (0.0)</td>
</tr>
<tr>
<td>DXS297</td>
<td>0.50</td>
<td>151.0</td>
<td>0.64 (0.0)</td>
<td>0.12 (0.0)</td>
<td>0.12 (0.0)</td>
<td>0.04 (0.0)</td>
</tr>
<tr>
<td>ARMS110-P up 10</td>
<td>0.68</td>
<td>152.5</td>
<td>1.00 (0.0)</td>
<td>0.40 (0.0)</td>
<td>0.05 (0.0)</td>
<td>0.00 (0.0)</td>
</tr>
<tr>
<td>DXS8225</td>
<td>0.80</td>
<td>153.5</td>
<td>1.52 (0.0)</td>
<td>0.29 (0.0)</td>
<td>0.00 (0.0)</td>
<td>0.00 (0.0)</td>
</tr>
<tr>
<td>DXS8225 (2)</td>
<td>0.80</td>
<td>153.5</td>
<td>1.52 (0.0)</td>
<td>1.93 (0.0)</td>
<td>0.46 (0.0)</td>
<td>0.00 (0.0)</td>
</tr>
<tr>
<td>DXS994</td>
<td>0.76</td>
<td>155.3</td>
<td>0.96 (0.3)</td>
<td>5.80 (0.3)</td>
<td>0.48 (0.3)</td>
<td>1.00 (0.50)</td>
</tr>
<tr>
<td>DXS6960</td>
<td>0.67</td>
<td>154.5</td>
<td>0.44 (0.3)</td>
<td>6.04 (0.3)</td>
<td>0.61 (0.4)</td>
<td>1.20 (0.30)</td>
</tr>
<tr>
<td>DXS9760</td>
<td>0.67</td>
<td>154.6</td>
<td>0.2 (0.3)</td>
<td>6.98 (0.3)</td>
<td>0.69 (0.4)</td>
<td>0.12 (0.3)</td>
</tr>
<tr>
<td>DXS1255</td>
<td>0.57</td>
<td>155.5</td>
<td>0.16 (0.3)</td>
<td>3.08 (0.3)</td>
<td>0.98 (0.4)</td>
<td>0.29 (0.3)</td>
</tr>
<tr>
<td>DXS1255 (2)</td>
<td>0.54</td>
<td>156.3</td>
<td>0.31 (0.3)</td>
<td>0.38 (0.3)</td>
<td>0.98 (0.4)</td>
<td>0.48 (0.4)</td>
</tr>
<tr>
<td>ARMS41 (2) (5F)</td>
<td>0.51</td>
<td>157.1</td>
<td>0.02 (0.4)</td>
<td>0.02 (0.4)</td>
<td>0.00 (0.0)</td>
<td>0.03 (0.4)</td>
</tr>
<tr>
<td>DXS7120 (2)</td>
<td>0.20</td>
<td>158.8</td>
<td>0.12 (0.4)</td>
<td>0.57 (0.4)</td>
<td>0.00 (0.0)</td>
<td>0.42 (0.36)</td>
</tr>
</tbody>
</table>

*Maximum lod score under heterogeneity with the maximum likelihood estimate of the recombination fraction (\(\theta\)) calibrated using MAPMAKER. Distance on cM from Xpter. **These markers were not genotyped in this group. ***Three markers were not genotyped in this group.
Xu et al. (1998): HPCX in Xq27

Table 3: Two-point affected sibpair analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>cM</th>
<th>Mean IBD</th>
<th>P-value</th>
<th>lod</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXS2954</td>
<td>140.0</td>
<td>0.54</td>
<td>0.08</td>
<td>0.42</td>
</tr>
<tr>
<td>DXS1222</td>
<td>140.9</td>
<td>0.51</td>
<td>0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>DXS2205</td>
<td>142.3</td>
<td>0.53</td>
<td>0.15</td>
<td>0.24</td>
</tr>
<tr>
<td>DXS6572</td>
<td>143.6</td>
<td>0.56</td>
<td>0.005</td>
<td>1.41</td>
</tr>
<tr>
<td>DXS5679</td>
<td>144.8</td>
<td>0.55</td>
<td>0.047</td>
<td>0.60</td>
</tr>
<tr>
<td>DXS1623</td>
<td>146.1</td>
<td>0.57</td>
<td>0.005</td>
<td>1.43</td>
</tr>
<tr>
<td>DXS1660</td>
<td>147.3</td>
<td>0.55</td>
<td>0.039</td>
<td>0.67</td>
</tr>
<tr>
<td>DXS8647</td>
<td>148.8</td>
<td>0.55</td>
<td>0.023</td>
<td>0.66</td>
</tr>
<tr>
<td>AFMA117sf5</td>
<td>149.3</td>
<td>0.58</td>
<td>0.013</td>
<td>0.96</td>
</tr>
<tr>
<td>DXS1260</td>
<td>150.4</td>
<td>0.60</td>
<td>0.00006</td>
<td>3.11</td>
</tr>
<tr>
<td>DXS287</td>
<td>151.0</td>
<td>0.60</td>
<td>0.025</td>
<td>0.82</td>
</tr>
<tr>
<td>AFMR19yb10</td>
<td>152.5</td>
<td>0.57</td>
<td>0.007</td>
<td>1.26</td>
</tr>
<tr>
<td>DXS2889</td>
<td>152.5</td>
<td>0.57</td>
<td>0.003</td>
<td>1.26</td>
</tr>
</tbody>
</table>

*Distance in cM from Xpter. Affected sibpair analyses were performed using ANALYZE. All possible sibpairs were used in the analysis, however, a weight of \((n-1)/n\) was given to the sibship of multiple sibs, where \(n\) is the number of sibs.
Xu et al. (1998): HPCX in Xq27

Re-evaluation of the HPCX locus in Xq27

It was confirmed by two independent studies:

Lange et al. (Clin Cancer Res, 5 4013-20, 1999)

Peters et al. (Hum Hered 51 107-13, 2001)
Gibbs et al. (1999): CAPB in 1p36

- They used different liability classes to establish age dependant penetrance
- They performed a genomewide linkage analysis with 70 families and 387 markers 10 cM apart
- They found different regions with LOD scores > 1

Assuming heterogeneity, they reached a LOD score of 1.65 in 1p36 with a value of 0.435 for \( \alpha \) (fraction of linked families)
Gibbs et al. (1999): CAPB in 1p36

• They decided to “stratify” the families

• For BRCA1 and BRCA2 families had been selected according to:
  - “early-” or “late-onset”
  - by the joint presentation of breast and ovary cancer

• they stratified the families according to:

  - age of diagnosis
  - by the joint presentation of prostate and brain cancer
## LINKAGE ANALYSIS

Gibbs et al. (1999): CAPB in 1p36

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean Age at Diagnosis (years)</th>
<th>LOD Score at $\Theta = 0$</th>
<th>NPLpairs Score (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset PC:</td>
<td>63.5</td>
<td>3.65</td>
<td>1.844 (.043)</td>
</tr>
<tr>
<td>Late-onset PC:</td>
<td>69.6</td>
<td>-1.84</td>
<td>-.450 (.673)</td>
</tr>
</tbody>
</table>

And what’s new after 2000?
Loss of Heterozygosity

On one hand, a very prevalent LOH was described:

- Dai et al. (2001) observed LOH in 17q21, distal to BRCA1
- This LOH is present in 54 out of 126 prostate cancer cases (43 %)

LINKAGE ANALYSIS

On the other hand, Tavtigian et al. (2001) found a new locus in 17p by linkage analysis en 17p and...

…THEY FOUND THE GENE !!!
Tavtigian et al. (2001): ELAC2 because it is homologous to E.coli ElaC gene.

Table 1 - Two-point linkage evidence at chromosome 17p

<table>
<thead>
<tr>
<th>Marker</th>
<th>Distance (cM)</th>
<th>Max. lod* (θ)</th>
<th>Heterogeneity lod (θ, 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D17S786</td>
<td>0.11 (0.17)</td>
<td>0.10 (1.00)</td>
<td>0.4 (0.0)</td>
</tr>
<tr>
<td>D17S562</td>
<td>0.69 (0.26)</td>
<td>0.64 (1.00)</td>
<td>0.3 (0.0)</td>
</tr>
<tr>
<td>D17S786</td>
<td>0.00 (0.0)</td>
<td>0.00 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>D17S562</td>
<td>1.41 (0.25)</td>
<td>1.41 (0.25)</td>
<td>0.2 (0.0)</td>
</tr>
</tbody>
</table>

*Maximum lod scores interpolated using the standard quadratic function.
Tavitgian et al. (2001): It is expressed in all tissues

They found two mutations in the gene (in two different pedigrees):

1. 1641insG

Out of 5 men >45 with the mutation: 3 had PC and 2 had enhanced levels of PSA
Tavtigian et al. (2001):

They found two mutations in the gene (in two different pedigrees):

2. Arg781His

- Founder individual: a man with children with 5 different women.
- Affected individuals in all family branches.
- 6 out 12 affected members bore the mutation

BESIDES, THEY FOUND TWO COMMON VARIANTS:

1. Ser217Leu
2. Ala451Thr
GENE!!!

Tavtigian et al. (2001):

BESIDES, THEY FOUND TWO COMMON VARIANTS:

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2. Ala451Thr

AND THEY OBTAINED SIGNIFICATIVE RESULTS FOR BOTH OF THEM IN ASSOCIATION STUDIES (more than 4000 individuals): p=0.0261, OR 2.4 and p=0.0223, OR 3.1

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ALSO, THE GENE FOR THE HPC1 LOCUS WAS FOUND:

IT IS THE GENE CODING FOR L RIBONUCLEASE: 

\textit{RNASEL}

The enzyme regulates cell proliferation and apoptosis

A germline mutation + LOH => Tumour suppressor gene
SOME NEW LOCI WERE ALSO IDENTIFIED IN 2000...

Another genomewide scan: Aggresiveness (Witte et al. 2000)
Rare, highly penetrant loci

162 families (USA)
Model = Smith
Lodscore > 3

504 sibs. (USA)
Lodscore = 3

...AND A NEW LOCUS WAS FOUND IN 8p22-23 (Xu et al., 2001)

And, again, a gene was identified within this locus:

**MSR1**

Six rare missense mutations were found to cosegregate with PC in several families.

And N174Y was present in 4.4% of PC patients and in 0.8% of unaffected men (p=0.009).
The only 3 genes identified so far by linkage analysis are:

* **ELAC2 (17p11):** It is believed to play a role in cell cycle progression

* **RNASEL (1q24.25):** Endoribonuclease with antiviral and pro-apoptotic activity.

* **MSR1 (8p22-23):** A macrophage specific receptor that binds different ligands.

- So far, none of the genes involved in hereditary PC seems to be a major cause of sporadic tumours (>90% of all PC).

- For this reason, new approaches are being considered:

  - Two of them are:
    - Studies on inactivation-hypermethylation.
    - Association studies
Epigenetic changes in prostate tumours:

<table>
<thead>
<tr>
<th>GENE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTP1 (11q13)</td>
<td>Inactivated in most tumours</td>
</tr>
<tr>
<td>Cav1 (7q13.2)</td>
<td>Hypermetilated in recurrent tumours</td>
</tr>
<tr>
<td>P16 (9p21)</td>
<td>Hypermetilated in most tumours</td>
</tr>
<tr>
<td>ER (11q13)</td>
<td>Inactivated in advanced tumours</td>
</tr>
<tr>
<td>ECAD (16q22.1)</td>
<td>Inactivated in advanced tumours</td>
</tr>
<tr>
<td>CD44</td>
<td>Inactivated in primary tumours and in metastases</td>
</tr>
</tbody>
</table>

ASSOCIATION STUDIES

- Common, low penetrant alleles.

- Androgen receptor: 2 trinucleotides CAG and GGC.
- PSA: SNP in the promoter
- SRDA2 (steroid 5-a reductase type II, membrane-bound): V89L and A49T
ASSOCIATION STUDIES

• Androgen receptor: 2 trinucleotides CAG and GGC (both in exon 1).

CAG expansion => Kennedy’s disease

CAG (polyglutamine) < 20 and GGC (polyglycine) < 16 are associated to a HIGHER PROSTATE CANCER RISK

ASSOCIATION STUDIES

• Androgen receptor

PC is more prevalent in the Afro-American than in the white population

CAG
In Africans and descendents: 80% < 20 repeats.
In Non-Africans: 50% < 20 repeats.

(Kittles et al. 2001)
ASSOCIATION STUDIES

- Androgen receptor

PC is more prevalent in the Afro-American than in the white population

GGC
In Africans and descendents:
  50% < 14 repeats.
In Non-Africans:
  13% < 14 repeats.
(Kittles et al. 2001)

ASSOCIATION STUDIES

- Androgen receptor (AR) and PSA

The AR effect is more evident for individuals with the GG genotype for the PSA gene SNP:

Each reduction in one CAG repeat => a 7% enhancement in serum PSA levels (in individuals who are GG for the PSA SNP).

(Xue et al. 2001)
Zeegers et al. (Cancer Epidemiol. Biomarkers Prev., 2004) performed a meta-analysis and found a very modest association. They question its biological impact.

And, unfortunately:

no breakthroughs in 2005
They only found some evidence of linkage to: 1p13-q21, 5p13-q11 and 6q23.
A Combined Genomewide Linkage Scan of 1,233 Families for Prostate Cancer–Susceptibility Genes Conducted by the International Consortium for Prostate Cancer Genetics

Juanfeng Xu,1 Lathezar Dimitrov,1 Bao-Li Chang,1 Tamara S. Adams,1 Aubrey R. Turner,1 Deborah A. Meyers,1 Rosalind A. Erbes,2 Douglas F. Easton,3 William D. Foulkes,2 Jacques Simard,2 Graham G. Giles,2 John L. Hopper,2 Louise Mahle,2 Pal Moller,3 Tim Bishop,3 Chris Evans,4 Steve Edwards,2 Julia Meitz,2 Sarah Bullock,2 Questa Hope,2 The ACTANE Consortium,5 Chih-Long Hsieh,7 Jerry Halpern,7 Raymond N. Balzer,7 Ingrid Oakley-Girvan,7 Alice S. Whittemore,7 Charles M. Fowling,6 Martha Geitzler,6 Sarah D. Isaac,2 Patrick C. Walsh,5 Kathleen E. Wiley,5 William B. Isaacs,4 Stephen N. Thibodeau,5 Shannon K. McDonnell,5 Julie M. Cunningham,5 Katherine E. Zataras,5 Scott Helbling,5 Daniel J. Schaid,7 Danielle M. Friedrichsen,6 Kerry Deutsch,7 Suzanne Kolb,7 Michael Badzioch,2,8 Gail P. Javik,9 Manta Janes,5 Leroy Hood,10 Elaine A. Ostlund,10 Janet L. Stanford,10 Ethan M. Lange,7 Jennifer L. Beebe-Dimmer,7 Caroline E. Mohai,7 Kathleen A. Cooney,10 Tarja Ilonen,8 Agnes Baftes-Bonnie,8 Henna Fredriksson,9 Mika P. Mutikainen,9 Terje U. Tammela,8 Joan Bailey-Wilson,10 Johanna Schleutker,8 Christiane Maier,10 Kathleen Herkner,10 Josef J. Hoegel,10 Walther Vogel,10 Thomas Paise,9 Fredrik Wilkund,10 Monica Emanuelsson,10 Elisabeth Stenman,10 Bjorn-Anders Jonsson,10 Henrik Grafberg,10 Nicola J. Camp,10 James Fanhani,11 Lisa A. Cannon-Albright,11 and Daniele Seminara12,2
... but the only significant linkage was at 22q12.

ASSOCIATION STUDIES


Association of Hereditary Prostate Cancer Gene Polymorphic Variants With Sporadic Aggressive Prostate Carcinoma

Ferrin C. Noonan-Wheelers,1 William Wu,1 Kimberly A. Roehl,2 Aleksandra Klim,3 John Haugen,1 Brian K. Suarez,1,4 and Adam S. Kibel1,4

They look for common variants in the genes shown to be involved in hereditary PC (ELAC2, RNASEL, and MSR1) to see if they were associated with sporadic PC.
The results were negative, except for RNASEL D541E.

Genetic Variation in the HSD17B1 Gene and Risk of Prostate Cancer

They study only one gene but with a different approach.
ASSOCIATION STUDIES

They look for LD and use tag-SNPs

(a) Haplotype blocks

(b) Mosaic chromosomes in population

TRENDS in Genetics
A comprehensive haplotype analysis of CYP19 and breast cancer risk: the Multiethnic Cohort

Christopher A. Haiman\textsuperscript{1,7}, Daniel O. Stram\textsuperscript{1}, Malcolm C. Pike\textsuperscript{1}, Laurence N. Kolonel\textsuperscript{2}, Noel P. Burt\textsuperscript{2}, David Altshuler\textsuperscript{3,4,5,6}, Joel Hirschhorn\textsuperscript{3,4,7} and Brian E. Henderson\textsuperscript{1}

<table>
<thead>
<tr>
<th>Haplotypes\textsuperscript{2}</th>
<th>Haplotype frequencies</th>
<th>OR\textsuperscript{a} (95% CI)</th>
<th>OR\textsuperscript{a} (95% CI)</th>
<th>All groups combined OR\textsuperscript{a} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a 133423</td>
<td>78.6</td>
<td>83.5 (Ref)</td>
<td>85.5 (Ref)</td>
<td>1.22 (1.07--1.40)</td>
</tr>
<tr>
<td>3b 232324</td>
<td>11.1</td>
<td>8.9</td>
<td>3.6</td>
<td>0.58 (0.35--0.96)</td>
</tr>
<tr>
<td>3d 143243</td>
<td>5.0</td>
<td>3.3</td>
<td>6.2</td>
<td>1.02 (0.66--1.58)</td>
</tr>
<tr>
<td>3e 332343</td>
<td></td>
<td></td>
<td></td>
<td>1.28 (1.01--1.62)</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Cases (n = 254), Controls (n = 673)

\textsuperscript{2}ORs adjusted for age, race, and study.
ASSOCIATION STUDIES

They found no significant differences between cases and controls.

MICROARRAYS

They look for genes over- or under-expressed in PC compared to normal tissue.
They found several genome regions with gene over- or under-expressed in tumours.

The main differential flat region (DFR) identified in this study was one in the long arm of chromosome 16:

16q12.2
Systematic Replication Study of Reported Genetic Associations in Prostate Cancer: Strong Support for Genetic Variation in the Androgen Pathway

Sara Lindström,1 S. Lily Zheng,2 Fredrik Wiklund,3 Björn-Anders Johansson,1 Hans-Olov Adami,1 Katarina Augustsson-Båtner,1 Anthony J. Brookes,1,5 Jielin Sun,2 Bao-Li Chang,1 Weimin Liu,2 Ce Li,7 William B. Isaacs,6 Jan Adolfsdotter,2 Henrik Grönberg,2,6 and Jianfeng Xu2

1Department of Radiation Sciences, Oncology, University of Umeå, Umeå, Sweden
2Center for Human Genetics, Wake Forest University School of Medicine, Winston-Salem, North Carolina
3Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Sweden
4Center for Genetics and Bioinformatics, Karolinska Institute, Stockholm, Sweden
5Department of Genetics, University of Leicester, Leicester, United Kingdom
6Department of Urology, Johns Hopkins Medical Institutions, Baltimore, Maryland
7OncoLogic Center CLINTEC, Karolinska Institute, Stockholm, Sweden

BACKGROUND. Association studies have become a common and popular method to identify genetic variants predisposing to complex diseases. Despite considerable efforts and initial promising findings, the field of prostate cancer genetics is characterized by inconclusive reports and no prostate cancer gene has yet been established.

METHODS. We performed a literature review and identified 79 different polymorphisms reported to influence prostate cancer risk. Of these, 46 were selected and tested for association in a large Swedish population-based case-control prostate cancer population.

RESULTS. We observed significant (P < 0.05) confirmation for six polymorphisms located in five different genes. Three of them coded for key enzymes in the androgen biosynthesis and response pathway: the CAG repeat in the androgen receptor (AR) gene (P = 0.03), one SNP in the CYP17 gene (P = 0.04), two SNPs in the SRD5A2 gene (P = 0.02 and 0.02, respectively), a deletion of the GSTT1 gene (P = 0.006), and one SNP in the MSTR gene, IVS5-59C > A, (P = 0.009).

CONCLUSIONS. Notwithstanding the difficulties to replicate findings in genetic association studies, our results strongly support the importance of androgen pathway genes in prostate cancer etiology. Prostate 66: 1728–1743, 2006. © 2006 Wiley-Liss, Inc.
CONCLUSIONS

• The great heterogeneity makes the use of linkage analysis difficult.

• Some linkage results might even been erroneous.

• In any case, population differences should be taken into account. Subgroups according to different features (age of onset, joint presentation with another type of cancer, aggressiveness, etc.) could be made.
CONCLUSIONS

• An effort is being done on association studies.

• New SNPs described within the Human Genome Project are being used.

• As well as new technologies, such as microarrays for large scale studies.

CONCLUSIONS

• A recent systematic replication study supports the importance of the Androgen pathway.

• They found positive results for:
  - AR gene (CAG repeat)
  - SRD5A2 (steroid 5 alpha reductase)
  - CYP17 (17-alpha-hydroxylase)
  - GSTT1 (Glutathione S-Transferase Θ1)
  - MSR1 (Macrophage Scavenger Receptor1)
Final Conclusions

- Genetic factors account for a substantial fraction of all prostate cancer.
- No prostate cancer gene had yet been established.
- Association studies are identifying genetic variants (such as those in the androgen pathway) that predispose to prostate cancer.

End of the First Day of the PhD Course on Cancer Genetics

Questions???