

# Hereditary Prostate Cancer in DK

Descriptive epidemiology

Molecular biology

Screening

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# Aim

- ❑ Clinical characterization of HPC.
- ❑ Genetic characterization of HPC.

# Introduction

- ❑ Prostate cancer (PC) is frequent and complex disease.
- ❑ Second highest incidence and mortality worldwide.
- ❑ Highest rates in Scandinavia and North America.
- ❑ Lowest rates in Asia.
- ❑ Common among elderly men.
- ❑ - and Afro-American men.

# Definition

- ❑ Sporadic PC: one case in the family.
- ❑ Familial PC: 2-3 cases in the family.
- ❑ Hereditary PC:  $\geq 3$  cases in the family.
  - ❑ 5-10% of all PC
  - ❑ 43% of all PC  $\leq 55$  years (Carter BS et al, 1993)

# HPC definition

Based on family history/pedigree:

- Early onset ( $\leq 55$  y),
- At least 3 PC cases in the family,
- 1 in each 3 generation either maternal or paternal lineage. (Carter BS et al, 1993)

# 1. Descriptive epidemiology

- ❑ Regional epidemiology
  - ❑ Regional PC database.
  - ❑ Cancer Registry/Civil Registration System.
  - ❑ Questionnaire and pedigree.
  
- ❑ National epidemiology
  - ❑ Case-control.
  - ❑ CR/CPR/LPR/PB.

## 2. Regional Description

- ❑ Radical prostatectomy (n = 4-500).
- ❑ No age cut off.
- ❑ Questionnaire and Registries:
  - ❑ 1 relatives plus uncles and grandfather on both sides.
  - ❑  $\geq 2$  PC in the family.
  - ❑ Other cancer diagnoses.
  - ❑ Phenotypes for molecular biology.
- ❑ Aggression parameters: PSA, tumor vol., Gleason, DRE.

# Aim

- ❑ Genetic characterization of HPC.
- ❑ Identify the markers that delineate HPC from sporadic PC.
  - ❑ SNP (single nucleotide polymorphism) in blood.
  - ❑ miRNA in tumor .

# Review

- ❑ S Lindström et al., *The Prostate*, 2006.
- ❑ Litterature review of 79 polymorphism.
- ❑ Inclusion:  $\leq 100$  cases/controls, association in 2 independent studies.
- ❑ 46 polymorphism in case-control PC population of 1,461 PC patients and 796 controls.

# Putative genes

- AR
- SRD5A2
- CYP17
- GSTT1
- MSR1
- CAG repeat
- SNP x 2
- SNP
- Deletion
- SNP

# And more....

- HPC1
- PCap
- BRCA I/II

□ P53

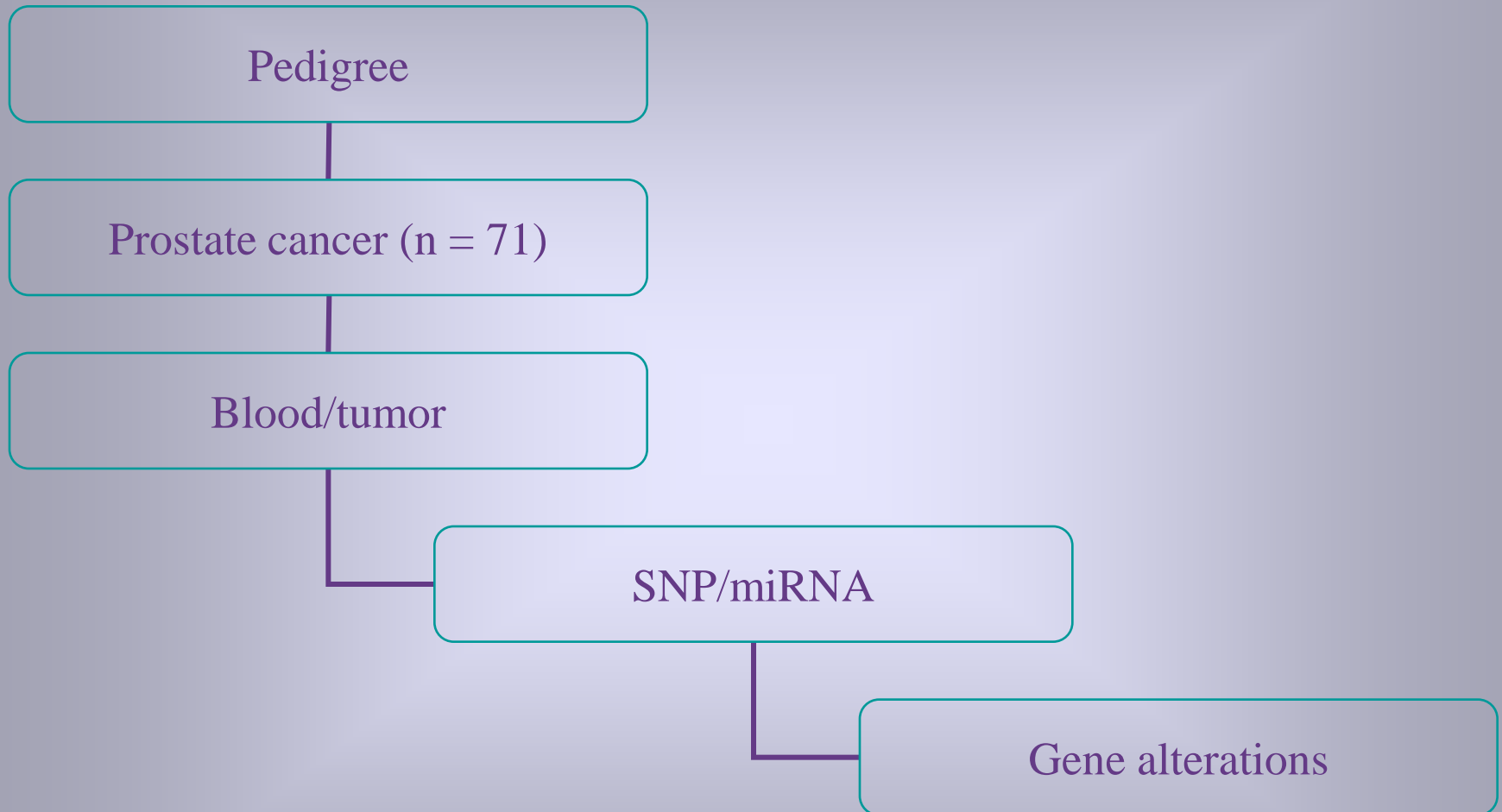
Tumor suppressor

□ RB 1

□ PTEN

Apoptosis

# Method



# Status

- ❑ Data from the various registries.
- ❑ Surveys and charts for pedigrees.
- ❑ Identification of cases.

”To fail to take a good family history is  
bad medicine and someday will be  
criminal negligence”

Childs 1992.

Thank you.

# Appendices

# Background

- Distinct difference between hereditary vs. sporadic cases in colon cancer and breast cancer.
- BRCA1/2 expressed in hereditary BC.
- Functional difference in genes and biology.

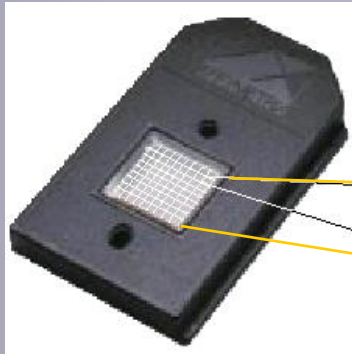
# 1. SNP

- ❑ Single nucleotide polymorphism.
- ❑ 1 every 100-1000 bases.
- ❑ About 5 million SNPs in the human genome.
- ❑ Different SNPs per population.
- ❑ 800.000 identified SNPs.

# 1. miRNA

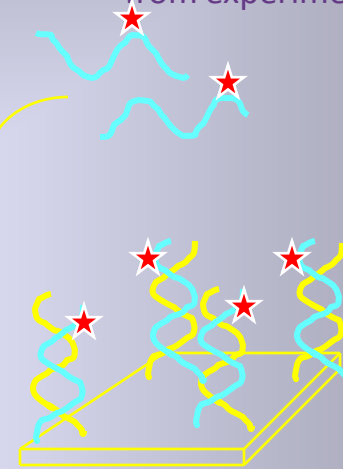
- ❑ microRNA.
- ❑ Small non-coding, single strand copy of DNA.
- ❑ ↓Regulates gene expression.
- ❑ 200 identified miRNAs.

# GeneChip<sup>®</sup> Expression Analysis Process

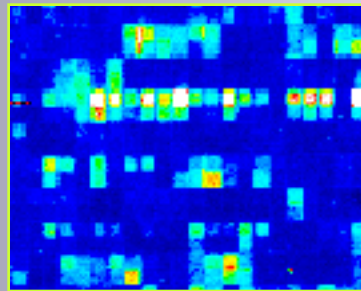


each probe cell contains millions of copies of a specific oligonucleotide probe

Biotinylated RNA target from experimental sample

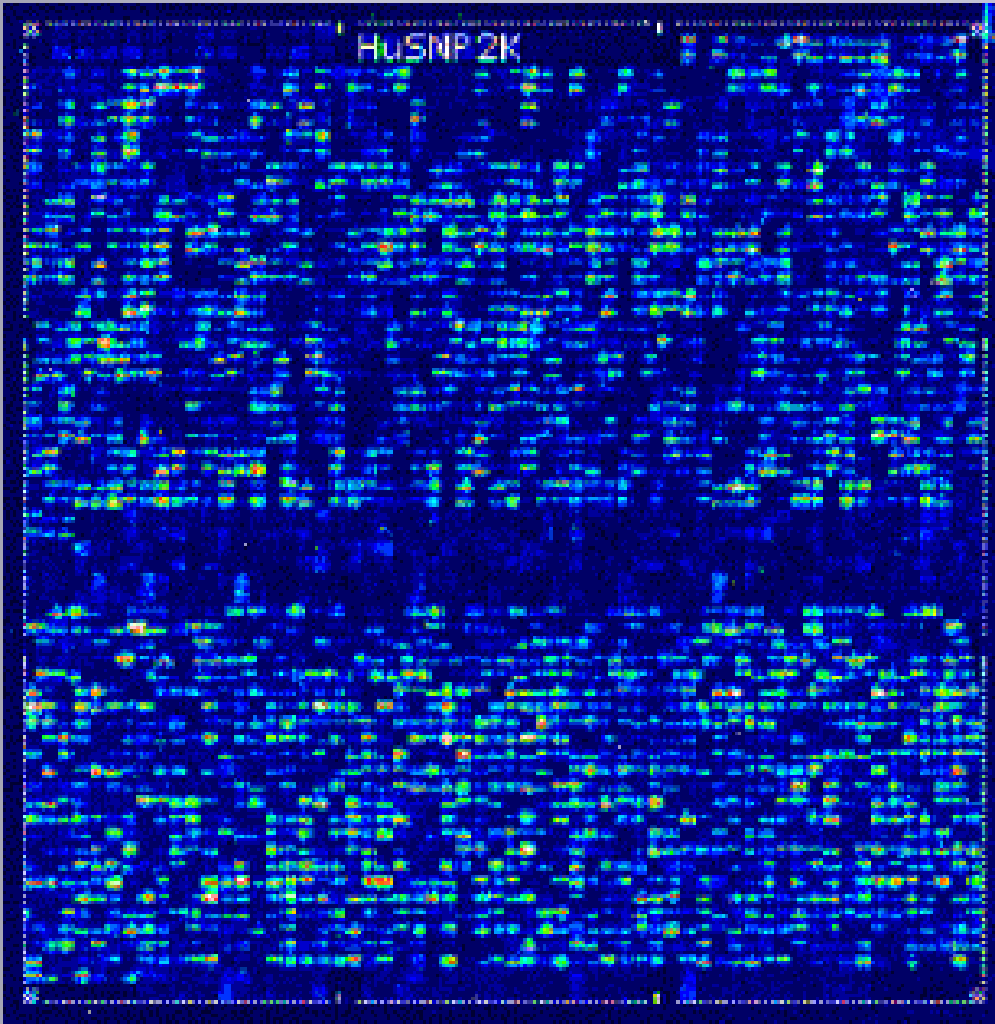


Streptavidin - Phycoerythrin Conjugate



Scanning identifies hybridization levels

# HuSNP probe array GeneChip



1494 SNP's

24 multiplex  
PCR reactions

~ 1300 calls

~ 400 heterozygous  
loci

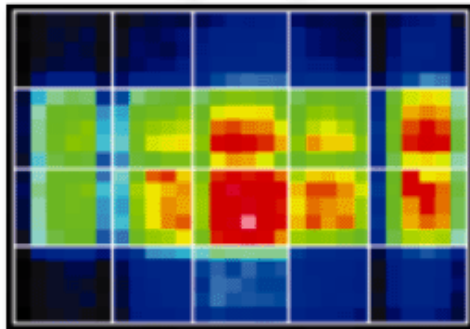
# HuSNP probe array GeneChip

5 different 20 nucleotide probes with different locations of the SNP base position within the 20 bases

-4	-1	0	+1	+4
MMA	MMA	MMA	MMA	MMA
PMA	PMA	PMA	PMA	PMA
PMB	PMB	PMB	PMB	PMB
MMB	MMB	MMB	MMB	MMB

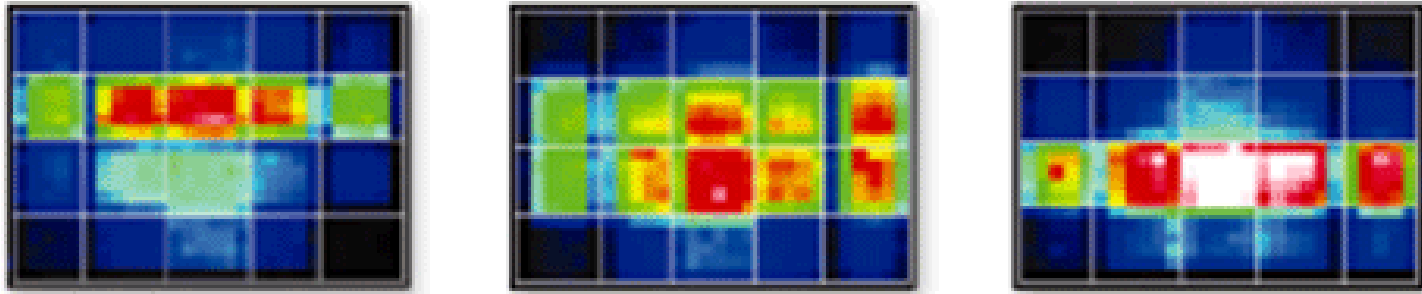
GGTGATTATG<sup>A</sup><sub>G</sub>ACCTACTAT

CCACTAATAC<sup>A</sup>TGGGATGATA  
CCACTAATAC<sup>T</sup>TGGGATGATA  
CCACTAATAC<sup>C</sup>TGGGATGATA  
CCACTAATAC<sup>G</sup>TGGGATGATA



The hybridization signal shows an AB genotype of the interrogated SNP

# HuSNP probe array GeneChip



Hybridizations of one SNP marker for 3 individuals genotypes AA, AB and BB respectively

# Affymetrix single features

