

Le Cancer de la prostate

Apport de la Genetique

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Known predisposing factors for prostate cancer in 2007

Ethnicity

Age adjusted prostate cancer incidence in the US (10^5 inhabitants)

:

- African A. 267
- European A. 170
- Japanese A. 115
- Chinese A. 85

Family history

Twin studies,

concordance rate :

MZ = 0.21 ; DZ = 0.06

Family studies

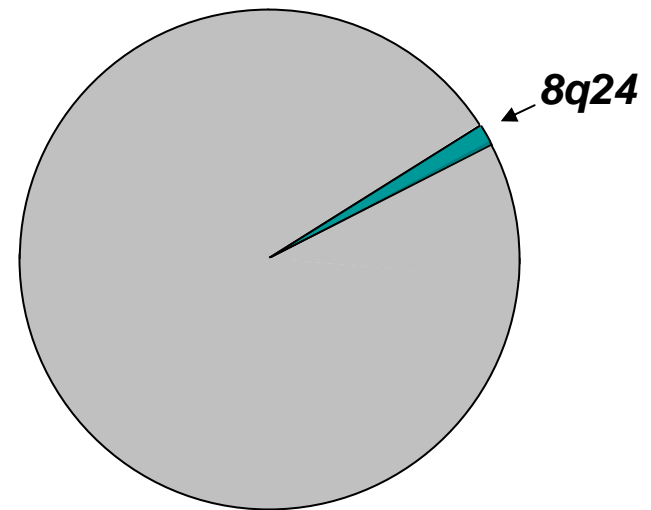
Familial risk* : 1.88

(C.I. 1.80-1.96)

* Familial standardized incidence rate

Familial risk

Linkage studies



97% unexplained

Genome Wide Association Studies for Prostate Cancer

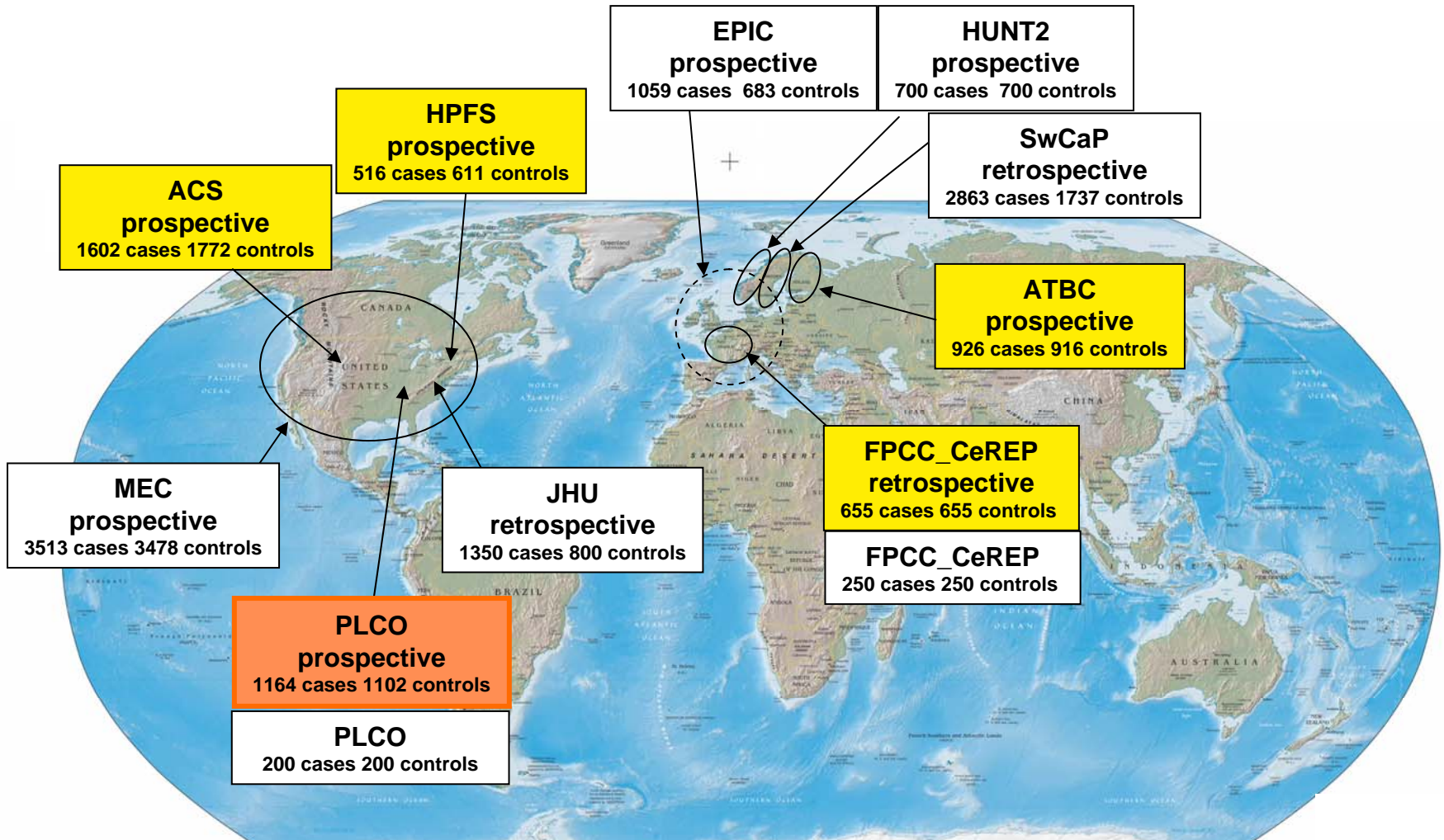
- Achieve an exploration of the entire human genome (minimal functional hypotheses).
- Compare allele frequencies in a group prostate cancer patients and matched group unaffected individuals
 - typically over 500,000 polymorphisms tested for each participants.
 - high throughput genotyping technologies.
 - large number of independent statistical tests.
 - require $p_{\text{value}} < 0.0000001$ to claim significance.
- Are multi-steps programs which demand (very) large groups of cases and controls
 - typically over 10,000 cases and 10,000 controls

CGEMS prostate cancer project

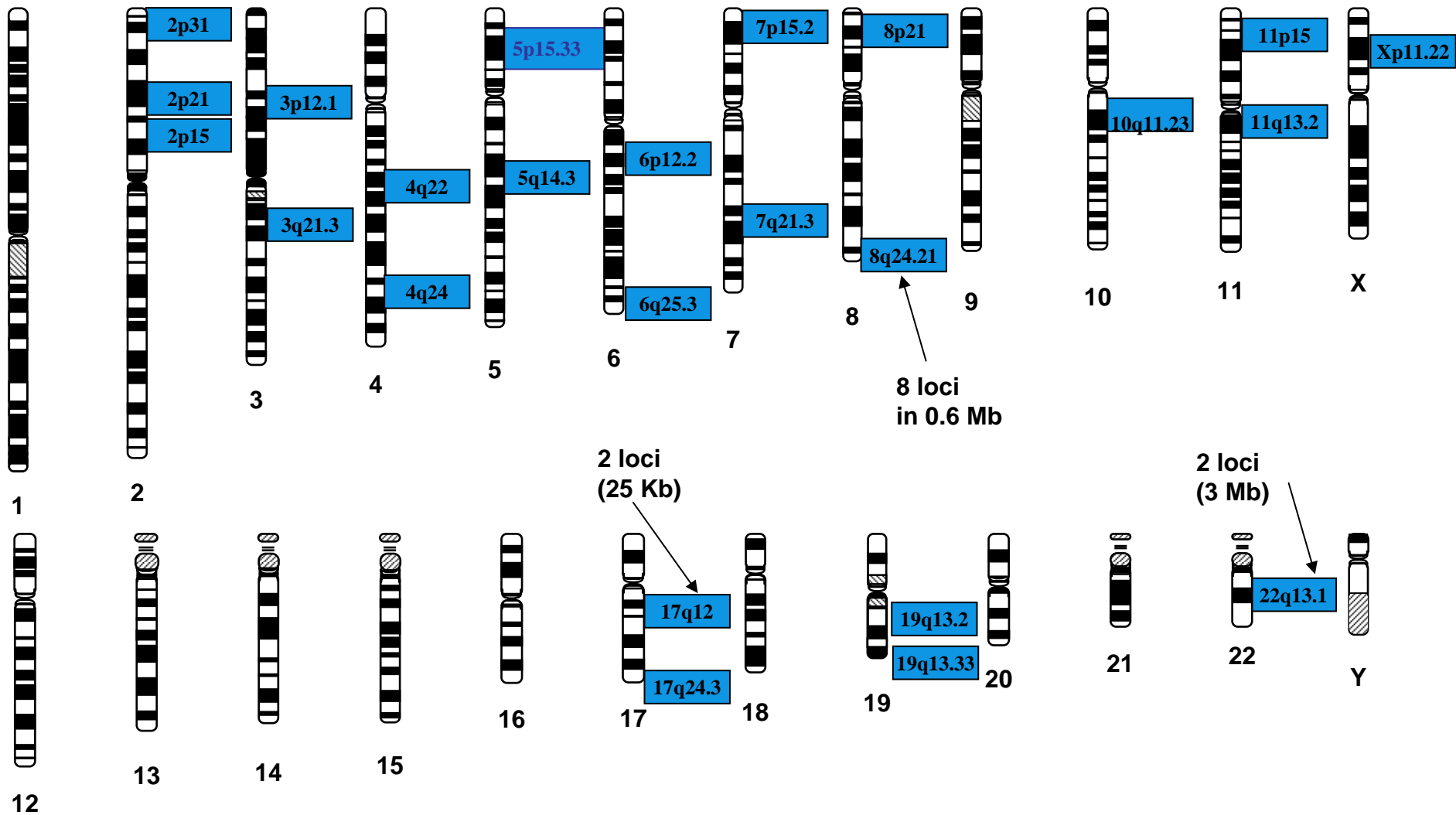
Total

~14,800 prostate cancer patients

~12,900 controls

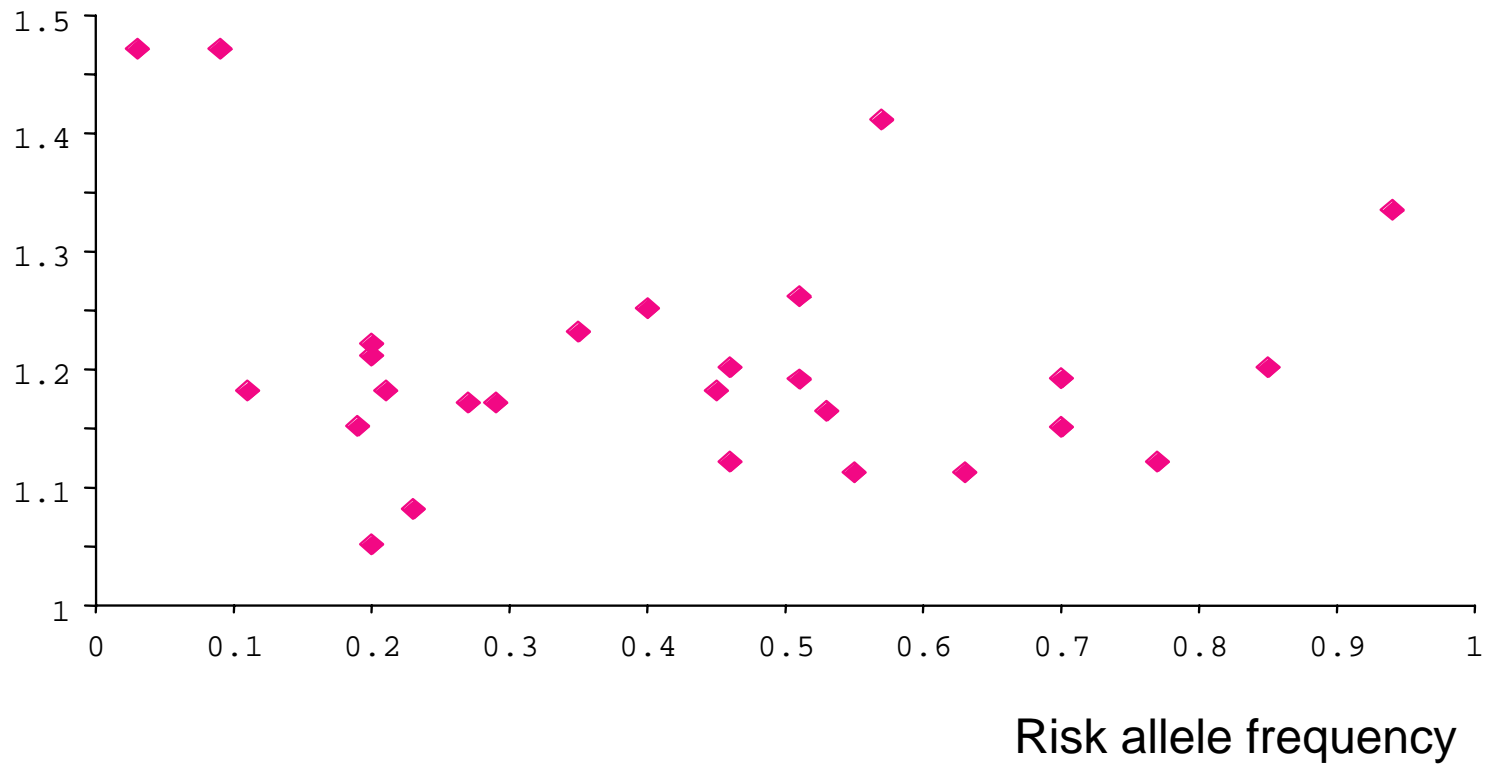


Susceptibility loci for prostate cancer Association studies

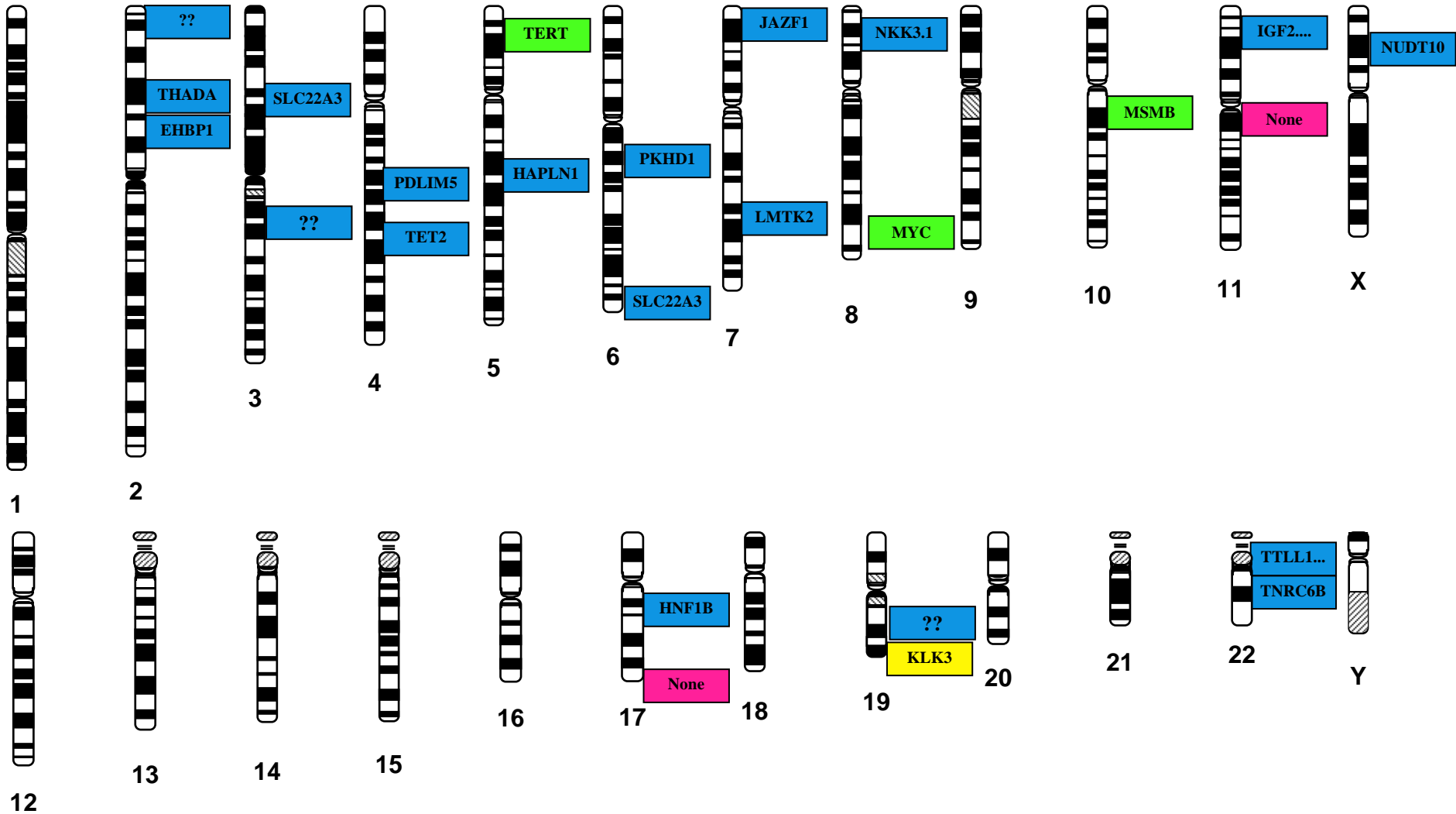


Risk allele frequency versus odds ratio for prostate cancer associated loci

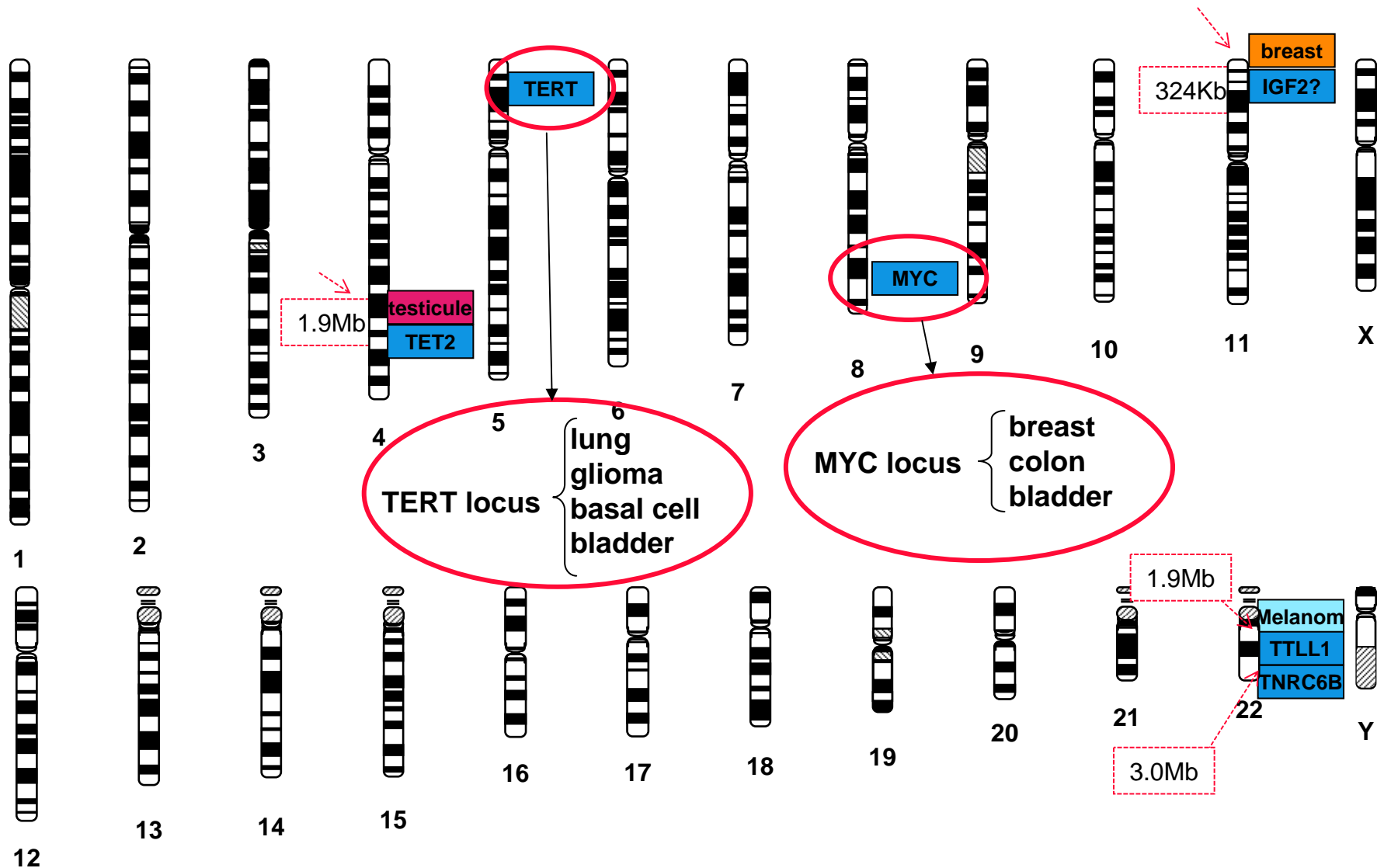
Per allele odds ratio



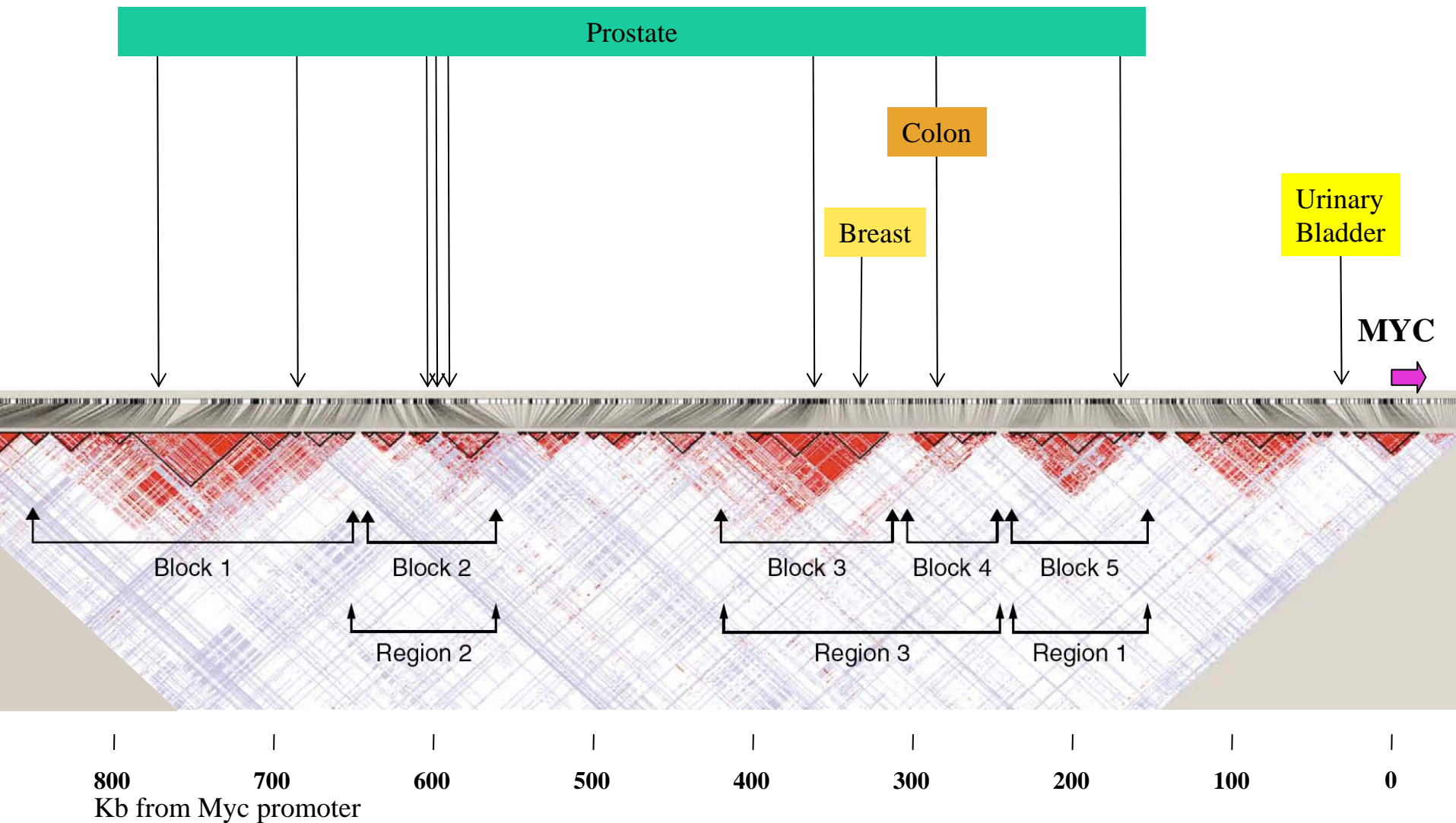
Candidate Target Genes



Prostate cancer susceptibility loci associated with other cancer types

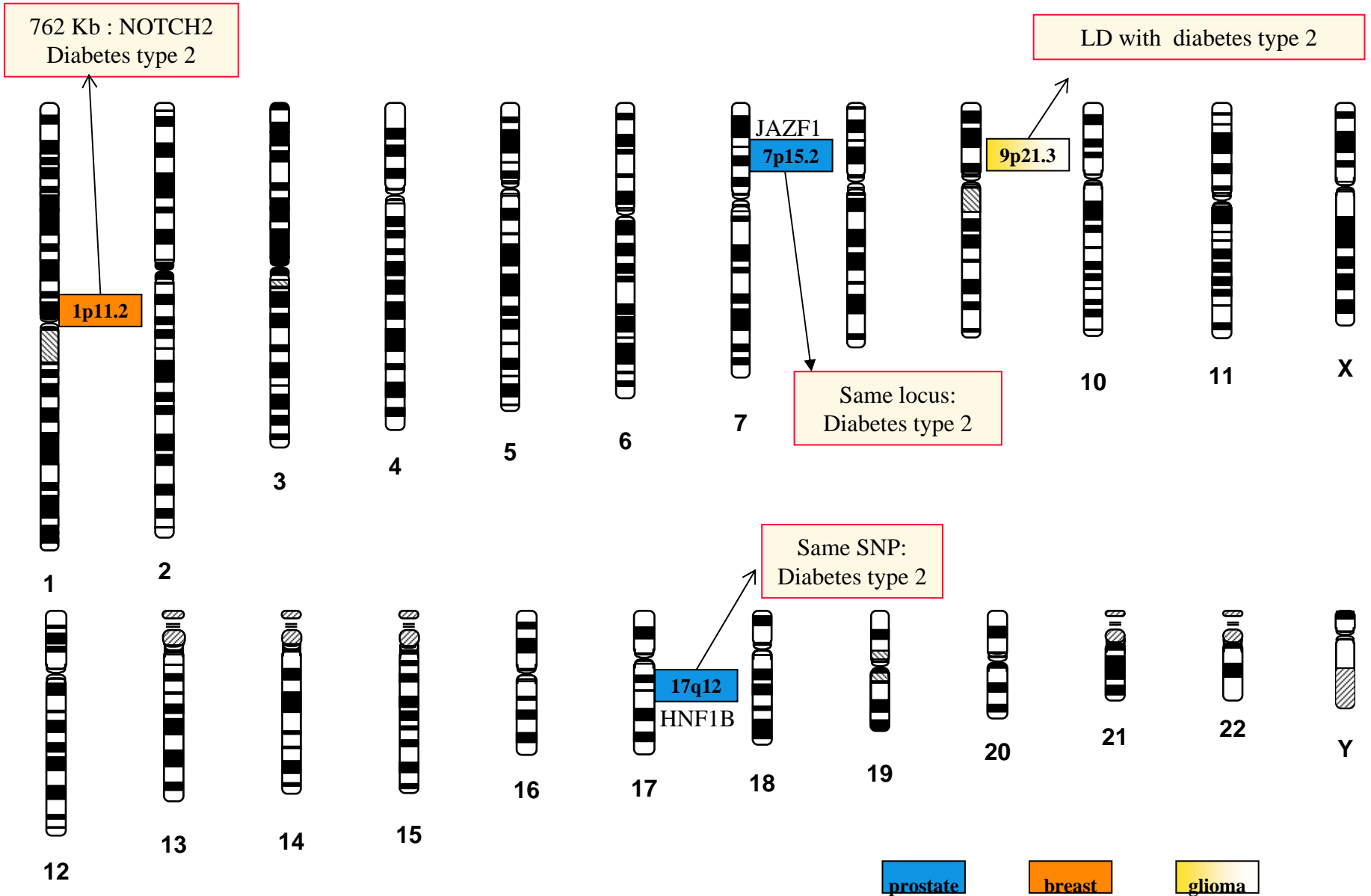


A 800 Kb region upstream of Myc associates with multiple cancer types and demonstrates multiple independent hits for prostate cancer



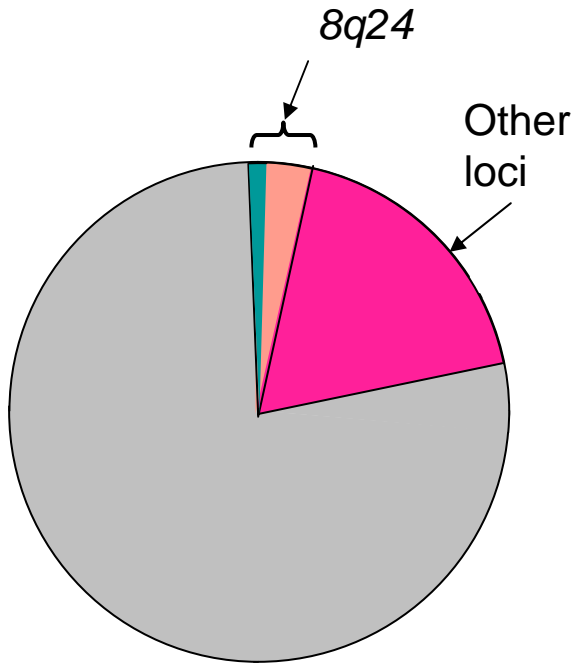
Some evidence for ovary, kidney, larynx, thyroid

Associations with diabetes type2



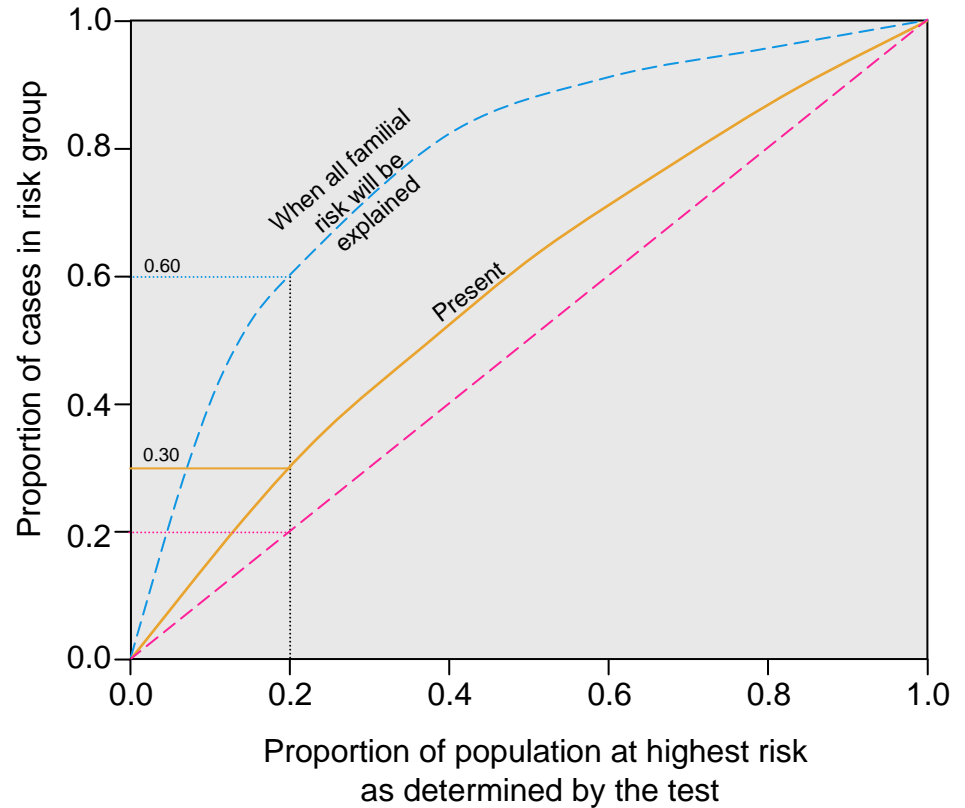
Prostate Cancer

Proportion of familial risk explained



77% unexplained

ROC curve for a genetic test based on the known susceptibility loci



Conclusion

- GWAS for prostate cancer have led in three years to the identification of 33 independent susceptibility loci. This number is likely to increase.
- Each locus provides a new lead to the understanding of prostate cancer initiation and progression. For most loci, the target gene has not yet been established, but will soon be.
- Two susceptibility loci are shared between prostate cancer and diabetes type 2, thus revealing shared (opposing) mechanisms.
- The two major cancer susceptibility loci in humans (TERT and MYC) include prostate cancer and many other cancer types.
- Only a small proportion of familial risk may be explained by the known susceptibility loci. This proportion is likely to increase
- The implementation of genetic tests in early detection programs is not likely to provide a major improvement in the near future.
- Genetic tests have not yet been validated for individual risk assessment of prostate cancer.