Genetic susceptibility of Prostate Cancer: Genome-wide screen of "non-aggressive" disease

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Background

Research has consistently shown that genetics plays a critical role in prostate cancer (CaP) development, but the identification of CaP genes has proven to be very difficult. Hereditary prostate cancer is a complex disease believed to involve numerous genes and variable penetrance. It has been proposed that studying alternative, highly homogenous phenotypes related to CaP may be a solution for overcoming the apparent heterogeneity that has hindered the identification of susceptibility genes. Several recent studies have applied this idea to "aggressive" or "clinically significant" cases of CaP. Using the resources of the Utah Population Database, we identified two phenotypes often associated with non-aggressive disease that show significant familiality. We present those results here.

Data Resource

- Utah Population Database (UPDB)
  - Records for approximately 2.2 million individuals
  - Up to 9 generations of genealogical data linking individuals into pedigrees
  - Linked to death certificates providing cause of death data since 1904
- Utah Cancer Registry (UCR)
  - Part of Surveillance, Epidemiology and End Results (SEER) program since 1973
  - All cancer events (except basal and squamous cell carcinomas) are recorded
  - Fully linked to UPDB
- 18,894 CaP cases from UCR currently linked to UPDB genealogies

Familial Relative Risk (FRR)

The resources of the UPDB make it possible to make population-based estimates of relative risk for family members of individuals with specific phenotypes. Considering each CaP subgroup to be a unique condition, the table below shows the relative risk to first, second and third degree relatives of cases for developing the same phenotype.

Table 1: Summary of Familial Relative Risks for selected prostate cancer subgroups

Phenotype / Relationship	Subjects	Observed Cases	Expected Cases	FRR	95% CI
All CaP Cases	18,894				
1°		5400	2815.2	1.92	1.87—1.97
2°		5336	4145.4	1.29	1.25—1.32
3°		9397	8527.3	1.10	1.08—1.12
Localized (Non-Metastatic) CaP	7563				
1°		1081	531.1	2.04	1.92—2.16
2°		1316	916.6	1.46	1.36—1.52
3°		2357	2005.0	1.18	1.13—1.22
Regional or Distant Mets.	8974				
1°		1286	670.9	1.92	1.81—2.02
2°		1128	853.5	1.32	1.25—1.40
3°		3097	2692.7	1.15	1.11—1.19
CaP Survival < 5 years	6926				
1°		802	413.0	1.94	1.81—2.08
2°		980	723.1	1.36	1.27—1.44
3°		1834	1645.0	1.11	1.06—1.17
CaP Survival > 10 years	4786				
1°		556	218.3	2.55	2.34—2.77
2°		395	258.2	1.53	1.38—1.69
3°		1302	1007.7	1.29	1.22—1.36
CaP Dx before age 65	4094				
1°		401	121.2	3.31	2.99—3.65
2°		264	157.1	1.68	1.48—1.90
3°		642	514.3	1.25	1.15—1.35

FRR significantly greater than that for general CaP

- All examined subgroups have a significant familial risk component.
- Non-metastatic disease shows a greater a risk to extended family than general CaP.
- Cases diagnosed before age 65 and cases surviving more than 10 years have a risk significantly greater than general CaP for all three relative groups.

Linkage Analysis

Dominant and recessive parametric linkage analyses were performed for the CaP subgroups with survival of greater than 10 years and with localized tumors. All analyses were performed using the MCLINK software package at the Center for High Performance Computing at the University of Utah. Genotyping was performed by the Center for Inherited Disease Research (CIDR) on a full-genome set of 401 STR markers with an average spacing of 9 cM. A summary of the pedigrees used and HLOD tracings are shown below.

Table 2: Summary of pedigree characteristics for linkage analyses

	Phenotype		Summary data for the orignial CaP linkage resource used for this study.
	Non-metastatic CaP	Survival > 10 years	
Pedigrees	47	44	59
Cases	176	150	464
Mean age at diagnosis (years)	69.0	66.6	69.7
Mean case survival (months)	112.9	172.7	106.2
Case subjects genotyped	86	115	246
Other genotyped*	676	594	640

* connecting ancestors of cases, and spouse with up to four children were genotyped when necessary to infer genotypes

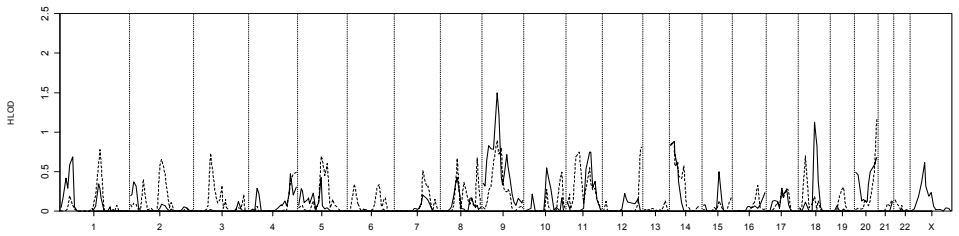

Figure 1: HLOD statistic for linkage to non-metastatic CaP. The solid line represents the dominant model, and the broken line represents the recessive model.

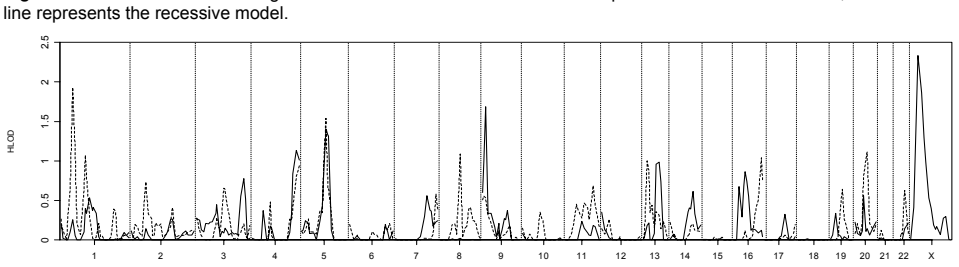

Figure 2: HLOD statistic for linkage to CaP with survival of over 10 years. The solid line represents the dominant model, and the broken line represents the recessive model.

Discussion

- No significant linkage evidence was observed at the genome-wide level for either of the phenotypes examined.
- Best result for the non-metastatic subgroup was HLOD = 1.50 in the dominant analysis at 58 cM on chromosome 9.
- Best result for the long survival subgroup was HLOD = 2.33 in the dominant model at 40 cM on chromosome X.
  - Signal is at Xp21-22, and is not associated with the HPCX locus at Xq27-28.
- Long survival appears to be correlated with early age at diagnosis, which is generally considered to be a trait of hereditary CaP cases.
- The pedigrees and genotypes used in this study were originally ascertained for a linkage analysis of general prostate cancer. Considering only subgroups of the original cases results in fewer cases per pedigree and greater genetic distance between cases, increasing the possibility of confounding due to intra-familial heterogeneity.
- Further research is necessary to identify the genes responsible for hereditary prostate cancer and surmount the overarching problem of CaP heterogeneity.

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