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Genetic etiology of hereditary prostate cancer

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1. ABSTRACT

Prostate cancer (PC) is a pervasive disease both in terms of incidence and mortality, yet little is known about its etiologic factors. Twin and segregation studies provide evidence for an inherited genetic component to the etiology of PC, yet over a dozen family-based genetic linkage analyses have not been able to consistently identify susceptibility loci. This chapter will review these studies, describe the challenges of this endeavor, and describe efforts to confront these challenges, such as using larger sets of families and more homogeneous subgroups.

2. INTRODUCTION

Prostate cancer (PC) is the most common non-cutaneous cancer and the second leading cause of cancer deaths among men in the United States (US) (1). In 2006, an estimated 234,460 men will be diagnosed with PC and 27,350 men will die of the disease (2). In spite of the pervasiveness of PC, little is known about its etiologic factors. Incidence rates increase steeply with age beginning at 45, and incident rates are 60% higher for blacks compared to whites in the US (1,3). There are considerable differences in incidence rates worldwide: incidence rates are 24- to 60-times higher in Western countries such as the US, Canada, and Sweden than in Asian countries such as Japan, India, and China (4). Besides age, race, and country of origin, however, the only other well-established risk factor for PC is a family history of the disease. A family history of PC in a first-degree relative is associated with a 2-3 fold significant increase in relative risk (3,5-6). Moreover, if the relative is diagnosed before age 65 or if there are three or more affected first-degree relatives, the risk is even higher (RR=5.9 and 10.9, respectively) (7-9). The aggressiveness of prostate cancer varies widely. Some tumors progress to invasive, potentially life-threatening disease, whereas others stay latent for the remainder of an individual's lifetime.

Diet, smoking, and other shared environmental exposures may explain some of the familial clustering of PC, but clearly there is also an hereditary component to the disease (7,10). In this review, we will describe the twin and segregation studies that provide evidence for a genetic etiology of PC. We will then describe the efforts to

Table 1. Segregation analyses of prostate cancer (PC)

Parameter		Carter, 1992 (21)	Grönberg, 1997 (31)	Schaid, 1998 (20)	Verhage, 2001 (19)	Cui, 2001 (23)	Gong, 2002 (28)	Valeri, 2003 (18)
Number of PC families		691	2,857	4,228	1,199	1,476	1,719	691
Country		US	Sweden	US	US	Australia	US, Canada	France
Population-based		No	Yes	No	No	Yes	Yes	No
Mean age-at–diagnosis		59	n/a	66	65	61	n/a	69
Transmission model		AD	AD	AD[a]	AD	AD+AR[b]	MF	AD
Penetrance estimates (%)	≤Age 55	4	2	3	12	7 (AD), 23 (AR)[c]	n/a	3
	≤Age 85	88	63	89	97	27 (AD), 100 (AR)	n/a	99
Frequency of disease allele (%)		0.3	1.7	0.8	0.4	1.7 (AD), 8.4 (AR)[d]	2.4 (AD), 32.0 (AR)	0.03

n/a = not available; AD = autosomal dominant; AR = autosomal recessive; MF = multifactorial, [a] Results from segregation analyses including only probands diagnosed at <66 years, [b] Results from the best fitting two-locus segregation models by Cui *et al.* are given, [c] Penetrances for the AD and AR component of the best fitting two-locus model are given for ages 60 and 80,[d] Two-locus multiplicative model.

identify PC susceptibility loci using family-based genetic linkage analysis, and the challenges involved with this endeavor. Finally, we will propose future directions to overcome some of these challenges. In addition to this review, several other papers have been written about the search for PC susceptibility loci and may be of interest to the reader (11-14).

The primary focus of this chapter is the genetic etiology of hereditary prostate cancer (HPC). A definition of HPC provided by Carter *et al.* in 1993, now referred to as the "Hopkins Criteria," includes families meeting at least one of the following criteria: (a) three or more first-degree relatives with PC, (b) PC in three successive generations through the paternal or maternal lineage, and/or (c) two first-degree relatives diagnosed with PC at an early age (≤55 years) (15). In comparison, "familial" PC does not meet these strict criteria, but includes families with two first-degree (diagnosed after age 55) or one first-degree and two or more second-degree relatives with PC. "Sporadic" PC, which includes men with no family history of the disease, most likely accounts for the majority of PC cases (75% to 85% of all cases in the general population). Familial PC is estimated to account for 10% to 20% of all cases of PC and HPC for 5% to 10% of all cases of PC in the general population. Even though HPC is less common, if the estimates by Carter *et al.* are true, then, given the incidence estimates above, about 23,000 men will be diagnosed with HPC in 2006 alone. HPC is likely caused by rare, highly penetrant alleles at multiple susceptibility genes, which are currently the subject of intensive genetic mapping and linkage efforts. Once HPC genes are identified and associated mutations are characterized, genetic screening for PC susceptibility will become a reality.

3. AGGREGATION STUDIES

Familial aggregation studies provide evidence for a genetic component to disease etiology. In twin studies, for example, when monozygotic twins are more often concordant for a trait than dizygotic twins, there is evidence for a genetic component. Several twin studies related to PC have been completed. The first by Grönberg *et al.* looked at 458 PC cases from a registry of 4,840 male twin pairs in Sweden (16). They found that 1.0% of all monozygotic twins were concordant for PC, whereas only 0.2% of all dizygotic twins were concordant. Page *et al.* found similar results in their study of 1,009 twin pairs in a US twin registry, of which at least one member had PC (17). They reported that 16.7% of the monozygotic twins and 3.7% of dizygotic twins were concordant for PC. Lichtenstein *et al.*, in the largest twin study reported to date, looked at the concordance of all cancers in 44,788 pairs of twins from Sweden, Denmark, and Finland (10). They found 18% of the monozygotic twins and 3% of dizygotic twins were concordant for PC, similar to the findings of Page *et al.* Lichtenstein *et al.* estimated that 42% (95% CI 20%-50%) of all PC risk may be attributed to inherited genetic variants, including rare, highly penetrant mutations and less common low-to-moderate penetrant genetic polymorphisms. (The penetrance of a gene refers to the likelihood that a person carrying a mutation in that gene will develop the characteristic(s) or phenotype associated with that mutation.)

4. SEGREGATION STUDIES

Complex segregation analyses support a genetic component to PC and provide evidence for the penetrance and the frequency of the high-risk alleles in the population, as well as the mode of inheritance. The mode of inheritance refers to how an allele is transferred from an affected parent to their offspring; such as through autosomal dominant, autosomal recessive, or X-linked, transmission. Most of the segregation analyses for PC, summarized in Table 1, show evidence for a rare (allele frequency of <1%), highly penetrant (lifetime risk of about 90%), autosomal dominant gene (18-21).

The first segregation analysis by Carter *et al.* used 691 prostate cancer families in the US, with an average age of diagnosis of 59.3 (21). They found strong evidence for an autosomal dominant mode of inheritance, with an estimated allele frequency of 0.3%. The proportion of gene carriers predicted to develop PC by the age of 85 years was estimated to be 88%. Grönberg *et al.*, in a set of 2,857 families in Sweden, also found evidence for a major gene with an autosomal dominant mode of inheritance. However, they estimated a higher allele frequency of 1.7% and a lower lifetime penetrance of 63%. Two US studies and one French study have also found evidence for an autosomal dominant gene, with allele frequencies and lifetime penetrance rates similar to those in the Carter study

Table 2. Putative hereditary prostate cancer susceptibility loci

Study	Country	Number of HPC families or sibships	Gene	Locus	Max. Multipoint LOD, HLOD, NPL, or Z-score
Smith, 1996 (30)	US, Sweden	91 families	HPC1	1q24-25	5.43
Berthon, 1998 (44)	France, Germany	47 families	PCAP	1q42.2-43	3.10
Xu, 1998 (48)	US, Sweden, Finland	360 families	HPCX	Xq27-28	3.85
Gibbs, 1999 (54)	US, Canada	12[a] families	CAPB	1p36	3.22
Berry, 2000 (58)	US	162 families	HPC20	20q13	3.02
Suarez, 2000 (36)	US	504 sibships	*	16q23.2	3.15
Xu, 2001 (63)	US	159 families	MSR1	8p22-23	1.84
Tavtigian, 2001 (67)	US	33 families	HPC2/ELAC2	17p11	4.53
Hsieh, 2001 (88)	US, Canada	98 families	*	19p13.3	2.87
Friedrichsen, 2004 (83)	US	36 Jewish families	*	7q11-21	3.01
Gillanders, 2004 (89)	US	426 families	*	17q22	3.16
Xu, 2005 (81)	Several North American and European countries	1,233 families (ICPCG)	*	22q12	3.57
Larson, 2005 (90)	US	201 sibships	FHIT	3p14.2	3.83

* A specific gene has not yet been identified, [a] Only families with both brain and prostate cancer were included

18-20). Conlon *et al.* also found evidence for dominantly inherited loci using Monte Carlo Markov Chain (MCMC) segregation analysis to determine the contribution of quantitative trait loci (QTLs) to HPC (22).

Other possible modes of transmission have been identified through segregation analyses. Cui *et al.* in a study of 1,476 Australian men found evidence for a dominantly inherited model, but only for men who were diagnosed before age 60. For older-onset cases, a recessively inherited or X-linked model provided the best fit. The estimated allele frequency for the dominant model was the same as Grönberg *et al.* (1.7%), with an estimated lifetime penetrance of 70%; the estimated allele frequency for the recessive model was 8.7%, with an estimated lifetime penetrance of 100% (23). Some studies that examined PC risks in fathers compared to brothers of men with the disease, support an X-linked or recessive model of inheritance (24-27). Gong *et al.* found that a multifactorial model, which assumes the risk of PC within families is determined by both environmental and genetic factors, better explained the results than did the simple Mendelian models (28).

Taken together, these segregation analyses provide convincing evidence that PC is, at least partly, inherited as a Mendelian autosomal trait with high lifetime penetrance. These findings stimulated the next step, family-based linkage studies, to identify HPC susceptibility genes.

5. LINKAGE STUDIES

Genetic linkage analysis detects the tendency for two genetic loci to pass together from one generation to the next. The closer two loci are on a given chromosome, the more likely they are to show linkage. Family-based linkage studies generate LOD or HLOD scores, which reflect the "closeness" or linkage between known genetic markers (microsatellites or SNPs) and unknown disease alleles (using disease status as a proxy) among family members. In general, a LOD score of 3.3 or higher for a genome-wide scan is considered strong evidence for linkage, and a LOD score of 1.9 or higher is considered to be suggestive for linkage (29). The LOD score can also be calculated under the assumption that there is heterogeneity (HLOD), such that a subset of families, but not all of them, may provide evidence for linkage to a particular locus. Several loci which may harbor HPC susceptibility genes, have been identified and are summarized in Table 2.

5.1. HPC1

Smith *et al.* were the first to report a PC susceptibility locus, 1q24–25, which they named HPC1 for hereditary prostate cancer 1 (30). They used 91 hereditary PC families from the US and Sweden, and achieved a maximum multipoint HLOD score of 5.43 under the assumption of heterogeneity. These investigators later found evidence that linkage to HPC1 was provided primarily by large families (≥5 affected members) with an early average age-at-diagnosis (31). Carpten *et al.* subsequently described germline mutations in the ribonuclease L gene (RNASEL), located within the 1q24-25 region (32). They found two different mutations in two of the 26 probands studied. Two studies confirmed linkage to the 1q24–25 locus (33-34), but other studies did not (35-40).

Ostrander *et al.*, in reviewing PC susceptibility genes (11), mention several subsequent studies of HPC1 that may help explain these inconsistent replication results. The first study they describe is by Neuhausen *et al.* in an analysis of 41 Utah families (41). This study confirmed linkage at HPC1 by reporting two- and three-point LODs of 1.73 ($p = 0.005$) and 2.06 ($p = 0.002$). Ostrander *et al.* propose this study was able to achieve these results through two means. First, the study had very large families (mean number of 10.7 affected men per family), which may have increased power to detect HPC beyond sporadic cancers. Second, the linkage model was adjusted to fit the true age of diagnosis observed in the Utah families, which might mean that model misspecification is contributing to the contradictory linkage results (11).

The HPC1 locus has also been examined by the International Consortium for Prostate Cancer Genetics (ICPCG) (42). This consortium includes investigators from North America, Australia, Finland, Norway, Sweden, and the United Kingdom who combined their individual data sets to create one set of 772 PC families, which includes the families in the initial linkage paper by Smith *et al.* (30). This large number of families may have yielded increased power to detect HPC beyond sporadic cancers, as in the

Utah study. The overall HLOD was 1.4, with an estimated proportion of linked families of 6%. In addition, the ICPCG tried to reduce genetic heterogeneity by looking at more homogeneous subsets of families. Genetic heterogeneity occurs when multiple genotypes are responsible for the same disease phenotype. A more homogenous set of families, then, may be enriched for linkage. The ICPCG analysis focused on a subset of 48 large (≥5 affected men), younger average-age-of-diagnosis (<65 years) families, whose disease was not potentially due to X chromosome mutations. This analysis resulted in an HLOD of 2.25 (p=0.001) for HPC1 (42).

Goode *et al.* also tried to reduce heterogeneity by limiting their analyses to families with more aggressive disease phenotypes (43). By doing so, they confirmed linkage between HPC1 and more aggressive PC. In this case, the relationship was strongest in families with a median age-at-diagnosis ≤65 years (non-parametric LOD (NPL) =3.48) (43).

Based on these analyses, Ostrander *et al.* (11) developed a set of guidelines for detecting and verifying linkage results for a complex disease, such as PC. These principles include (1) using large data sets of well-characterized families, particularly families with large numbers of affected men; and (2) using family history of other cancers and clinical features of PC, such as Gleason score to evaluate disease aggressiveness, to create more homogenous subsets of families. These guiding principles are the motivation for the studies we propose later in the chapter.

5.2. PCAP

Berthon *et al.* found linkage to 1q42.2–43 (PCAP) in 47 French and German families (44). The strongest evidence for linkage to PCAP was among families with early-onset PC (< 60 years), with a maximum two-point LOD score of 2.7 and NPL score of 3.1 (p=0.001). Cancel-Tassin *et al.* were able to confirm this finding (35), but most studies have found no evidence for linkage (37-38,45-47).

5.3. HPCX

Xu *et al.* combined families from four investigators in Finland, Sweden, and the US, then stratified these families based on apparent mode of transmission. Stratifying families based on their apparent mode of transmission is an attempt to create more homogeneous subsets of families; such parametric analyses can provide greater power to detect linkage. The strongest evidence for linkage was in 360 PC families with evidence for male-to-male transmission, with linkage to Xq27–28 (HPCX) with a maximum two-point LOD score of 4.60 (48). Evidence for male-to-male transmission indicates the HPCX gene is likely not transferred through an X-linked mode of inheritance. Several studies have confirmed this result (49-52), but others have not (35,38,53).

5.4. CAPB

Gibbs *et al.* (54) hypothesized a possible shared locus for prostate and primary brain cancers because an excess of brain and central nervous system cancers had been reported previously in HPC families (55-56). They found linkage to a PC-brain cancer susceptibility locus at 1p36 using 94 families with a family history of PC, 12 of which also reported a family history of primary brain cancer (54). The overall LOD score was 3.22 in these 12 families, and increased to 3.65 when the analysis was limited to six families with an earlier average age at PC diagnosis (≤65 years). The ACTANE consortium confirmed linkage to CAPB, with an HLOD of 1.93 in 127 families that were not selected for brain cancer (57). Berry *et al.* examined the CAPB region in 13 PC families with at least one case of brain cancer and found no evidence for linkage (37).

5.5. HPC20

Berry *et al.* found linkage to 20q13 (HPC20) using 162 North American families with <5 members affected with PC, a later average age-at-diagnosis (> 65 years), and no evidence for male-to-male transmission (58). These findings were confirmed by some (59-60) but not other investigators (61-62).

5.6. MSR1

Xu *et al.* found linkage to the macrophage scavenger receptor gene (MSR1) region at 8p22–23 (63). They used 159 HPC families and 21 microsatellite markers, spanning a 35 cM area. Evidence for linkage was found to be particularly strong in families with a later mean age-at-diagnosis (> 65 years). This locus has been confirmed in some (64-65) but not all (66) studies.

5.7. HPC2/ELAC2

Tavtigian *et al.* found linkage to the 17p11 region (HPC2/ELAC2) using a genome-wide scan of eight large Utah pedigrees (67). They then used fine mapping in a larger set of 33 families, which resulted in a maximum 2-point LOD score of 4.53 (67). Of 436 families screened for mutations in the HPC2 gene, 3 (0.7%) have been found to carry these mutations (67-70). Although these mutations are rare, there are 2 missense mutations which may be important with sporadic cancer (71-72). The HPC2/ELAC2 gene has been successfully cloned within the linked locus. Linkage to HPC2/ELAC2 has not been replicated in other studies (70,73).

5.8. HPC Aggressiveness Loci

Several linkage analyses incorporating clinical data to search for loci associated with more aggressive phenotypes have been completed, with results summarized in Table 3. Witte *et al.* analyzed Gleason score as a quantitative trait and reported strong evidence for linkage on chromosomes 5q31, 7q32-q34, and 19q12 (74). The findings on chromosome 7 were confirmed by Paiss *et al.* (75), and the findings on chromosome 19 were confirmed by Slager *et al.* (76) who also reported evidence for linkage on chromosome 4q (76). Goddard *et al.* analyzed the same data set as Witte *et al.* (77). They showed the importance of using covariates to detect linkage for HPC by regressing linkage information on pair-specific covariates. Using Gleason score as a covariate, linkage was detected on chromosome 1q24-25 (LOD=3.25) and 1q42.2-43

Table 3. Putative aggressive hereditary prostate cancer susceptibility loci

Study	Country	Number of HPC families or sibships	Gene	Locus	Max. Multipoint LOD, HLOD, NPL, Z-score, or p-value[a]
Witte, 2000 (74)	US	326 sibships	*	5q31.3-q33.33	p=0.0053
			*	7q32.2	p=0.0076
			*	19q12	p=0.0088
Goddard, 2001 (77)	US	326 sibships	*	4q	2.80
			HPC1	1q24-q25	3.25
			PCAP	1q42.2-43	2.84
			AR	Xq12-q13	3.06
Slager, 2003 (76)	US	161 families	*	4q	p=0.00012
			*	19q13	p<0.0001
Paiss, 2003 (75)	Germany	100 families	*	7q31-q33	3.02
Chang, 2005 (79)	US	188 families	HPCX	Xq27-28	2.54
			*	22q13	2.06
Slager, 2006 (78)	US	175 sibships	*	6q23.3	p=0.0009
Stanford, 2006 (80)	US	248 families	*	22q11.1	2.18
			*	22q12.3-q13.1	1.90

* A specific gene has not yet been identified, [a] p-value provided when LOD score was not available; p=0.001 corresponds to LOD=3.

(LOD=2.84); and using age-at-diagnosis as a covariate, linkage was detected on chromosome 4q (LOD=2.8). Without the use of covariates no linkage signals were detected. Slager *et al.* used Gleason score as a quantitative trait and found evidence of linkage to 6q23 (78).

Additional clinical factors beyond Gleason score were recently utilized in two genomic scans. Clinically significant (aggressive) disease was defined as a Gleason score ≥ 7, or regional/distant stage, or diagnostic PSA ≥ 20 ng/ml, or rising PSA after treatment or death from metastatic PC. Considering only men with more aggressive features as affected, Chang *et al.* identified linkage in the Xq27-28 region (HLOD=2.54) and the 22q13 region (HLOD=2.06) (79). Linkage analyses of 123 HPC families with at least 2 or more men with aggressive PC (80) suggested loci at chromosomes 22q11.1 (HLOD=2.18) and 22q12.3-q13.1 (HLOD=1.90). Significant linkage at 22q12 (LOD=3.57) was also reported by a combined ICPCG linkage analysis of 269 HPC families with at least five affected members (81). Taken together, these results suggest that focusing on men with clinically significant PC may be an important approach in the search for susceptibility genes that contribute to development of aggressive disease phenotypes.

6. CHALLENGES WITH HPC

In summary, although multiple segregation analyses have provided evidence for major PC susceptibility genes, few loci have been consistently identified using linkage analysis in over a dozen independent studies. Several of the challenges of studies of genetic etiology of disease are clearly demonstrated by the efforts to find genetic susceptibility loci for HPC, such as genetic heterogeneity, model misspecification, phenotypic variation, and false-positive results (29). There are three common reasons given for why these problems arise in the study of PC families (82). The first is that sporadic disease is common. An estimated one in six men will be diagnosed with PC at some point in their lives (2). This inevitably results in a high rate of phenocopies, or PC cases with different environmental and/or genetic causes. Thus, there may be no easily discernible phenotype difference between sporadic cases and hereditary cases of PC. A second complication is that the median age-at-diagnosis for PC is 69 years for whites and 66 years for blacks (1). This means there is a dearth of data (i.e., DNA for genotyping) from probands' previous generations. Finally, the introduction of the prostate-specific antigen (PSA) screening test in the late 1980s has led to an increase in the number of asymptomatic PC cases who would not have been diagnosed clinically in the absence of PSA testing. This may lead to a time-dependent phenocopy rate that is contributing to disease heterogeneity (82).

The guiding principles described previously, namely using larger sets of families and more homogeneous subgroups, may help overcome these challenges. The study that identified the CAPB locus by focusing on HPC families with another primary cancer, and the studies incorporating disease characteristics are good examples of the benefit of following these principles (54,80). Another example is provided by Friedrichsen *et al.*, who identified a significant locus on 7q (NPL=3.01) by defining a homogeneous subset of 36 HPC families of Ashkenazi Jewish descent (83).

More recently, the ICPCG consortium, described above, used the largest set of families to date, 1,233 families collected from multiple investigators worldwide, to try to overcome genetic heterogeneity (81). The ICPCG was able to maintain good statistical power and stratify the data set into several homogenous subsets, including families with large numbers of affected individuals (5 or more) or early ages-at-diagnosis (≤65). This approach identified significant linkage at 22q12, with a LOD score of 3.57 (81).

7. DISCUSSION

Although this chapter has focused on linkage studies searching for highly penetrant genetic mutation in HPC families, such mutations are rare. The majority of prostate cancers are sporadic. A low penetrance PC susceptibility gene may increase the risk of PC while not causing the pattern of disease seen in HPC families. Because of their higher frequency, these less penetrant genes may be more important from a public health perspective in the etiology of PC. In particular, the

possible interaction between low-to-moderately penetrant alleles and environmental factors that may alter their activity is another important avenue of research. We emphasized the search for highly penetrant susceptibility genes for HPC because once these genetic variants are found, genetic screening for PC susceptibility can become a reality. In addition, knowledge of the underlying molecular biology of HPC is expected to shed light on genes and pathways that may also play key roles in the pathogenesis of familial and sporadic PC. Some evidence for this notion already exists as some loci mapped using HPC families have genetic variants that have been associated with increased relative risks for sporadic PC, such as MSR1 and HPC2. We refer the reader to several reviews for more information on low penetrance PC susceptibility genes (84-85), and to current efforts to take a more systematic approach to finding common alleles that confer modest susceptibility to cancer, as opposed to high penetrance alleles (86-87).

Once highly penetrant susceptibility genes for HPC are found, studies will be needed to characterize the specific mutations so that genetic screening for PC susceptibility can become a reality. In addition, replication and association studies will be needed to fully characterize the roles of specific genetic mutations in the etiology of PC.

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