Hereditary Prostate Cancer – the Search for the Gene

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Prostate cancer is the most common cancer in men and the second leading cause of cancer-related deaths among men in the United States [1,2]. The presence of Pca in young patients has led researchers to believe that a strong familial component may be involved in its etiology. Mounting evidence – from early twin-based studies to recent molecular biology research – suggests that a significant percentage of Pca patients have a hereditary susceptibility to the disease. Though the cause of the disease is still unknown, it is believed to be multifactorial, with genetic susceptibility as one of several risk factors identified so far. Since the highest rise in incidence of prostate cancer seen in the last three decades was in younger patients with organ-confined and potentially curable disease, it is important to understand and identify the carcinogenesis process that forms the tumor.

The identification of the genetic, biochemical, hormonal and histological mechanisms associated with Pca will provide us with a better understanding and strategy for managing patients and their family members with Pca. This article will review the recent advances in knowledge on the genetic basis of the disease.

Epidemiology

The incidence of Pca in men doubled between the years 1976 and 1994 while mortality increased by only 20%. This trend has been explained by the higher life expectancy and the improved diagnostic tools at the disposal of the clinician, namely the use of the prostate-specific antigen test. The following are some of the more significant risk factors that have been identified in connection with developing Pca:

- **Environmental factors.** The incidence of Pca varies dramatically among different geographic locations. Furthermore, people who migrate from countries with a low incidence of Pca (such as Japan) to countries with high incidence (such as the United States) have developed Pca in proportions commensurate with the incidence levels of the country they migrated to.
- **Race.** The age-adjusted incidence of Pca in African-American men is approximately 50% higher than in Caucasian men. Diet, hormones and genetic difference have all been implicated as an underlying cause [3].
- **Age.** Pca is rare in men under the age of 50 and the incidence and mortality grows rapidly beyond that age. Reports in the current literature have shown that the rise in incidence during the last 25 years has been most pronounced in men younger than 70 [1,2].
- **Hormones.** Eunuchs, prepubertal castrated men and men with congenital defect in the synthesis of androgen do not develop Pca. Moreover, androgen blockade has been shown to be an effective form of treatment in patients with metastatic Pca. Although it is widely accepted that androgens have a role in the pathogenesis of the disease, there is no direct evidence available that links the two.
- **Family history.** A certain percentage of prostate cancer patients show familial clustering. In their study, Carter et al. [4] defined hereditary Pca as a situation where a family experiences one or more of the following features: a) three or more affected members within a nuclear family, b) occurrence of the disease in three successive generations within a family with either paternal or maternal lineage, and c) two affected family members diagnosed to have Pca at the age of 55 or younger. Families who showed clustering of the disease but did not meet the criteria were categorized as Familial Pca and the rest as Sporadic Pca. Carter et al. did not find any significant clinical difference between these three groups. The fact that the hereditary Pca does not differ clinically from sporadic Pca, along with the high incidence and late occurrence of the disease, constitutes a major hurdle in the research of hereditary Pca.

Defining ways of transmission

Several studies have examined the incidence and inheritance pattern of Pca in family relatives of affected individuals [Table 1]. Early studies performed on small groups showed a significantly higher incidence of the disease among family members. However, further research on larger populations was still needed in order to demonstrate that a history of Pca within a family was a risk factor for Pca [2]. Carter and colleagues [5] studied 691 families with a single Pca patient in

Pca = prostate cancer

Table 1. Increased risk and suspected type of inheritance in males, relatives of patients with Pca

Gene freq	Penetrance	Susp inherit	Significance	Affected / fam member	Population	n	Ref.
0.003	88%	Autosomal dominant	RR 1.76 95% CI = 1.28–2.43	119 / 1,642	Radical prostatectomy patients	691	Carter et al. [5]
0.0167	63%	Autosomal dominant	$P < 0.001$ SIR = 1.7	302 / 5,496	National cancer register cohort study*	5,402	Grönberg et al. [8,9]
0.006	89%	Autosomal dominant in patients < 60		5,17 / 17,684	Radical prostatectomy patients	4,288	Schaid et al. [10]
		X-linked or autosomal recessive	RR 1.97	$P < 0.00005$	Population cohort study		Monroe et al. [11]

* Nationwide cancer register (Sweden)
Affected/fam member = Pca-affected family members/all male family members, Susp inherit = suspected type of inheritance, Penet = estimated penetrance by the age of 85. Gene freq = estimated gene frequency in the population.

each. All patients were managed by radical prostatectomy for localized Pca between 1982 and 1989. The study was designed to estimate the risk of developing the disease in different family members of affected individuals, and segregation analysis was performed to assess possible Mendelian inheritance in cases with familial clustering. Five models of inheritance were examined: sporadic, Mendelian (dominant, co-dominant, recessive) and environmental. A total of 119 affected men were identified among 1,642 relatives of 691 patients. Carters' group found that early age at onset of disease and multiple affected family members were the main factors that define the risk of developing Pca in other family members. Among the five models of inheritance tested the one that best explained familial clustering of Pca was autosomal dominant inheritance with high penetrance (88% by the age of 85) of a rare allele. Carter and colleagues considered this allele to be responsible for 43% of Pca patients diagnosed under the age of 55 (2% of cases) and for only 9% of the total number of Pca patients.

Walsh and Partin [6] and Isaacs et al. [7] from the Johns Hopkins Institute found that familial Pca comprises up to 25% of all Pca cases, while the subgroup of the hereditary form involves only 9%. In families with Pca clustering, first-degree relatives have an increased risk of developing Pca (76% higher than the control). In examining family history for cancer in other organs, they found familial Pca to be site specific with the exception of central nervous system tumors. Thus family members of Pca patients did not have an increased risk for cancer at other sites, except for a significantly higher risk for primary CNS tumors. The main disadvantage of these studies is the bias of ascertainment for younger and healthier Pca patients who were managed by radical prostatectomy.

Grönberg et al. [8] from Sweden conducted a cohort study using the national cancer registry. They followed 5,402 families of patients with biopsy-proven Pca. Among the 5,496 sons of affected men, 302 (5.49%) developed Pca. This was significantly higher than the incidence of Pca in Swedish men ($P < 0.001$). When affected fathers were diagnosed before they reached 70 years, the risk for their sons was increased inversely to the fathers' age at diagnosis. In a later study, this group [9] examined the type of inheritance using segregation analysis in 2,857 nuclear families of the former 5,496 sons of patients. Seven possible models of inheritance were examined, with the dominant inheritance model giving the best fit. These authors observed that penetrance of the gene was lower than that reported by Walsh and colleagues (0.63 vs. 0.88) and the gene frequency in the Swedish population higher (0.0167 vs. 0.003).

Schaid et al. [10] surveyed 4,288 men who had radical prostatectomy for localized Pca. Using complex segregation analysis they examined familial clustering of Pca for type of inheritance. No single mode of transmission could explain the variety of familial clustering found in the study group, but when observing families of patients diagnosed under the age of 60 a rare autosomal dominant susceptibility gene gave the best fit. The predicted allele frequency in the population was found to be 0.006 and the penetrance by the age of 85 was 89%. They also found that brothers of probands had a higher risk of developing Pca than their fathers. This implied an X-linked or autosomal recessive mode of inheritance. The authors suggested that the lower compliance and response rate among fathers could explain this observation. Monroe and coworkers [11] performed a population cohort study and found that across all ethnic groups the risk of developing Pca was significantly higher when a first-degree relative was affected, and that the risk for the proband's brother was twice as high as the risk for the proband's father ($P < 0.00005$). Based on their findings they concluded that either X-linked or recessive inheritance accounts for the transmission of hereditary/familial Pca.

In summary, the genetic basis of familial Pca is still poorly understood. Most researchers agree that hereditary Pca is a complex genetic disease involving several genes and environmental factors. Alternatively, a cascade of multiple genetic mutations in the same gene is another possible model in the process of prostate carcinogenesis. The different types of inheritance that were found in patients with Pca [Table 1] reflect the expected genetic heterogeneity found with the disease. The complex inheritance of hereditary Pca is yet to be unraveled.

Table 2. Sites linked to hereditary prostate cancer

Ref.	N / # families	Suspected site	Locus name	Inheritance	Remarks
Walsh & associates [12–14]	604 / 66	1q24-25	HPC1	Autosomal dominant	More than 5 affected family members, age < 55
Borton et al. [19]	194 / 47	1q42.2-43	HPC2 or PCAP	Autosomal dominant	
Gibbs et al. [21]	/ 12	1p36	CAPB	Autosomal dominant	Familial clustering of PCA & primary brain tumors
Xu et al. [22]	1,989 / 360	Xq27-28	HPCX	X-linked	

N / #families = number of family members who had a genome-wide screen / number of families.

Searching for the gene

Epidemiological studies supporting the existence of hereditary forms of Pca have led to the initiation of genome-wide searches for loci contributing to hereditary Pca. Attempts at genetic mapping and characterization of genes predisposing to Pca have yielded four reported loci [Table 2]. In November 1996 Smith et al. [12] published their study implicating a locus on the long arm of chromosome 1 (1q24-25, hereditary prostate cancer 1, HPC1) in familial clustering of Pca. They examined 79 North American and 12 Swedish pedigrees – each having at least three affected first-degree family members. The average age at diagnosis was 65 years, but 34 patients were younger than 55. A genome-wide screening performed in 66 of the North American pedigrees has shown possible linkages of hereditary Pca to chromosome 1q24-25 (two-point LOD 2.75 with the marker *D1S218*). Using multiple markers for this suspected region in 25 additional families provided a statistically significant evidence for linkage (LOD score of 5.43 in the region between markers D1S2883 and D1S422) in this region. Smith et al. reported significant locus heterogeneity and found that only 34% of the pedigrees were linked to HPC1. Further studies based on this pool of patients [13,14] showed that linkage of Pca to HPC1 was even stronger in a specific subgroup of families (five or more affected family members, patients younger then 55 at diagnosis, advanced stage, or higher grade of malignancy). The results of Smith and coworkers were followed by several confirmatory reports. Cooney et al. [15] investigated 20 families that met the criteria for hereditary Pca (three or more affected family members, three successive generations affected in one pedigree, or two family members diagnosed before the age of 55). They found convincing evidence for linkage between HPC1 and Pca (NPL Z score = 1.72 P = 0.0451 for marker *D1S466*). A similar study done by Neuhausen et al. [16] in high risk families from Utah, USA, confirmed these findings as well. However, two additional studies failed to reproduce these results [17,18]. Eeles and coworkers [17] did not find significant evidence of linkage to HPC1 in the families and concluded that HPC1 is responsible for only a minority of familial prostate cancer. Mcindoe et al. [18] found negative LOD scores to the putative HPC1 locus in 49 families and concluded that other susceptibility genes may play a role in the families they studied. Berton et al. [19] studied 47 French-German families with three or more affected family members who had pathological evidence of Pca. In a genome-wide search they determined linkage to a second locus on the long arm of chromosome 1 (1q42.2-43) and suggested the name PCAP or HPC2 as the second putative susceptibility locus for Pca. A subset of nine families presenting with early-onset disease has shown a strong linkage to this locus (multi-point LOD = 3.31 and NPL = 3.32, P = 0.001) further supporting the existence of PCAP. No evidence of linkage to HPC1 was found, thus implying that two separate sites on chromosome 1 might be linked to Pca.

Gibbs et al. [20] were not able to reproduce these results when they investigated 152 pedigrees of families with Pca clustering. They suggested a possible linkage in a small proportion of families compatible with genetic heterogeneity. Their research emphasized the need for further confirmatory studies of this site. In a small subgroup of families the same researchers [21] found an association between Pca and primary brain tumors, a phenomenon that was reported previously by Isaacs et al. [7]. In their work, which included 141 pedigrees of families with hereditary Pca (early-age onset defined as lower then 60), the genome-wide scan yielded a potential new hereditary Pca susceptibility locus mapped to the short arm of chromosome 1 at 1p36. This region is known for loss of heterozygosity in several primary brain tumors. Of 141 families studied, 38 had a history of brain tumor in a family relative and 12 families had either confirmatory medical records or two first-degree family members supporting the history. The study of this subgroup of families yielded a peak LOD score of 3.22 at recombination fraction (θ) of 0.06 with marker *D1S507* located in 1p36. When excluding three families that have a greater linkage to HPC1 or HPC2, the remaining nine families had a multi-point analysis giving a two-point LOD score of 4.74 at θ = 0.0 with marker *D1S1407* further supporting linkage to locus 1p36.

Evidence for yet another Pca susceptibility gene has been provided by Xu and colleagues [22]. They reported a region on chromosome X (Xq27-28) that had linkage to hereditary Pca in approximately 16% of cases. This locus was named HPCX. They assembled 360 pedigrees with Pca clustering from North America, Sweden and Finland in a multi-center study. A genome-wide screen of the 66 North American families

HPC1 = hereditary prostate cancer 1

implicated a locus on Xq27-28 as possibly linked to hereditary Pca. A maximal LOD score of 4.6 at $\theta = 0.26$ was observed with marker *DXS1113*. Parametric multi-point linkage analysis in 319 families under assumption of heterogeneity gave a LOD score of 3.85, further supporting an X-linked gene in the pathogenesis of Pca. The proportion of families with Pca clustering linked to this site was estimated to be 16% – ranging between 15% in American families and 41% in Norwegian families, with 30% of them linked to HPC1. A confirmatory study by Lange et al. [23] on 153 pedigrees could not reproduce these findings.

Epidemiological data suggest that a strong familial component is involved in the etiology of a subset of cases of Pca, particularly those diagnosed at a younger age. However, the study of hereditary Pca had to overcome three major obstacles: the high incidence of sporadic Pca in the population, the late onset of the disease, and the evidence of genetic heterogeneity documented in many of the linkage analyses as well as in epidemiological studies. Therefore, it is not surprising that several confirmatory studies failed to reproduce linkage of Pca to one of the four loci that were mapped to date [Table 2]. Genetic heterogeneity explains the number of sites suspected of linkage to Pca and the different Mendelian inheritance found. It appears that it is just a matter of time until we encounter more sites suspected to be linked to Pca.

Modes of Inheritance

Two types of inheritance have been implicated in hereditary Pca so far: autosomal dominant and X-linked.

- **Autosomal dominant.** Autosomal dominant inheritance was estimated as responsible for 9% of Pca diagnosed under 85 years of age, and 43% when diagnosed before the age of 55. Three sites on chromosome 1 were linked to Pca – two on the long arm (HPC1, HPC2) and one on the short arm (CAPB). The majority of studies to date, including several confirmatory studies, were done on HPC1. Penetrance ranged between 63% and 89% by the age of 85 and the frequency in the population was 0.003–0.0167. Families with a history of Pca and primary brain tumor tend to be linked to the short arm of chromosome 1 (CAPB).
- **X linked.** One locus on chromosome X was identified as linked to Pca (HPCX). Several genes at Xq27-28 have been mapped to Pca, and they should be evaluated as potential prostate cancer susceptibility genes.

Conclusion

The recognition that Pca has a strong familial component paved the way for the search of Pca susceptibility genes. Four loci have been mapped to date and the efforts for finding more Pca susceptibility genes should be continued. Searching for the loss of heterozygosity and linkage analysis in the DNA of families with early-age Pca (< 55 years old) and overwhelming family clustering of Pca (> 5 members) might provide researchers with additional new sites involved in the pathogenesis of Pca. Identification and cloning of genes in these loci along with the characterization of specific causative mutations will allow us to fully understand the role of proteins and their normal biological function in the prostatic cell. Moreover, identification of the genes and their specific mutations within a family will permit accurate genetic counseling and screening programs. This will ensure that susceptible individuals will benefit from earlier screening while eliminating any unnecessary tests for those members that do not bear any risk. There is evidence that genetic counseling and screening programs could have beneficial psychological effects in families with multiple cases of Pca [24].

Family practitioners as well as urologists should be aware of the possibility of hereditary prostate cancer. A thorough family history must be taken with an evaluation of both the paternal and maternal lineage. Families demonstrating clustering of the disease should be enrolled in a screening program and followed closely with repeated prostate-specific antigen measurements and digital rectal examinations. The ultimate goal is to have the ability to identify those individuals within a family that is genetically susceptible to Pca in order to provide timely screening and prevention practices.

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