



High risk genes predisposing to prostate cancer development—do they exist?

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There is evidence for genetic predisposition to prostate cancer. However, prostate cancer genes have been more difficult to find than genes for some of the other common cancers, such as breast and colon cancer. The reasons for this are discussed in this article and it is now becoming clear that prostate cancer is probably due to multiple genes, many of which are moderate or low penetrance. The advances in the Human Genome Project and technology, especially that of robotics, will help to overcome these problems. *Prostate Cancer and Prostatic Diseases* (2000) 3, 241–247.

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Introduction

Prostate cancer has significant international public health importance. Around 13000 cases are diagnosed each year in the UK and it is responsible for approximately 10000 deaths.¹ In the United States, it is the most common malignancy in men, with over 180000 new cases projected to be diagnosed in 2000.² In Europe, the incidence is increasing by 10–20% every 5y, even when the increase in numbers of prostate cancer cases diagnosed due to screening are removed.³

Little is known about the underlying causes for this disease. Various risk factors⁴ have been proposed such as dietary, endocrine and sexually transmitted agents but as yet none of these environmental factors have been confirmed as a significant cause of prostate cancer.

The prevalence of this disease varies markedly

between different ethnic groups, with the highest frequency found in African-Americans and the lowest frequency in Asian populations.^{5,6} The extent to which this ethnic disparity is attributable to environmental or genetic factors is unknown.

Epidemiological studies of prostate cancer have shown familial clustering of this disease and it is now well recognized that a positive family history of prostate cancer is a strong risk factor. This suggests the existence of underlying genetic predisposing factors. This has led to attempts to map the gene or genes predisposing to prostate cancer within high-risk families. Although various chromosomal loci have been reported as sites for prostate cancer susceptibility genes, results have been conflicting and a high risk gene still remains to be cloned, despite the fact that the first locus was described in 1996. The reasons for this are explored in this review.

Epidemiological evidence

Various case–control^{7–9} (summarised in Eeles¹⁰) and cohort^{11,12} studies have investigated the role of family history as a risk factor for prostate cancer development. Much evidence comes from the study of pedigrees with

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Table 1 Relative risks for prostate cancer in relatives of prostate cancer cases by degree of relationship (from Steinberg *et al*¹³)

Affected relatives	Relative risk (95% CI)
First-degree	2.0 (1.2–3.3)
Second-degree	1.7 (1.0–2.9)
Both first and second-degree	8.8 (2.8–28.1)

Table 2 Age-adjusted relative risk estimates for prostate cancer by number of additional affected family members (from Steinberg *et al*¹³)

Affected relatives (besides proband)	Odds ratio (95% CI)
1	2.2 (1.4–3.5)
2	4.9 (2.0–2.3)
3	10.9 (2.7–43.1)

Table 3 Estimated risk ratios for prostate cancer in first-degree relatives of probands, by age at onset in proband and additional family members (from Carter *et al*¹⁴)

Age at onset of proband	No additional relatives affected	One or more additional first-degree relatives affected
50	1.9 (1.2–2.8)	7.1 (3.7–13.6)
60	1.4 (1.1–1.7)	5.2 (3.1–8.7)
70	1.0 ^a	3.8 (2.4–6.0)

^aReference group.

large numbers of cases, as seen in the Utah population. In families with a positive history of prostate cancer in a first-degree relative (ie brother, father or son), these groups reported an overall three-fold increased risk of the disease, with relative risk estimates ranging from 1.76 to 7.5. As seen in Table 1, risk is less but still significant if only a second-degree relative is affected (grandfather or uncle). Maximal elevation in risk, however, occurs if both first- and second-degree relatives are affected, when the relative risk increases to 8.8.¹² Moreover, this relative risk increases as the number of affected members in the family increases (Table 2): having three first-degree relatives affected gives an 11-fold increased risk for developing prostate cancer.¹²

Early age at diagnosis in the proband was also found to be an important determinant of risk of prostate cancer in relatives. As shown in Table 3, the brother of a proband diagnosed with prostate cancer at age 50 has a relative risk of 1.9-fold of developing the disease compared to a brother of a case diagnosed at age 70.¹⁴

The magnitude of the increased relative risk as the age of the proband decreases and the closeness and number

Table 4 Comparison of segregation analyses

	Carter (1992) ¹⁴	Grönberg (1997) ¹⁵	Schaid (1998) ¹⁶
No. of patients	691	2600	4288
Genetic model	AD ^a	AD	AD
Gene frequency	0.3%	1.7%	0.6%
Penetrance by age 85	88%	63%	89%

All models' risk curves start to rise at 50 y.

^aAutosomal dominant.

of the affected family members increases cannot be explained by environmental factors alone, supporting a role for a genetic aetiology. Twin studies also lend support to the existence of an underlying genetic predisposition to prostate cancer. Monozygotic twins have been found to have a four-fold increased concordance rate for the development of prostate cancer compared to dizygotic twins, confirming the importance of genetic factors.¹⁴

Segregation analyses

Segregation analysis involves a study of the family aggregation of prostate cancer to determine the likely mode of inheritance and penetrance of prostate cancer susceptibility genes.

Several segregation analyses have been performed on prostate cancer families. Carter *et al* evaluated 690 families of radical prostatectomy patients.¹⁴ Their data suggested that inherited susceptibility to prostate cancer was due to a rare, highly penetrant autosomal dominant gene with a population frequency of 0.003. The cumulative risk of prostate cancer by the age of 85 was estimated to be 88% in carriers compared to only 5% in non-carriers. The gene accounted for approximately 43% of prostate cancer cases diagnosed under the age of 55 y and 9% of cases in total.

Two further segregation analyses by Schaid *et al*¹⁶ and Grönberg *et al*¹⁷ (Table 4) also proposed similar transmission models; however, the Grönberg model proposed a more common gene with lower penetrance, although the penetrance is still high at 63% by age 80. This latter study is subject to the least bias since it was a systematic analysis of a population-based dataset from a cancer registry, although much of the risk is accounted for by only a few large multiple case families. Although these three studies used different populations, they all produced consistent support for the presence of at least one highly penetrant autosomal dominant prostate cancer susceptibility gene.

Traditionally such genes have been sought using linkage analysis of large pedigrees containing multiple affected cases of the disease. This has been a very successful approach for other common cancers such as melanoma,¹⁸ breast cancer^{19,20} and colon cancer.^{21,22}

Linkage analysis

Based on the findings of these segregation analyses, the search for prostate cancer susceptibility genes commenced. High-risk prostate cancer families for study are selected according to different criteria by different groups. The CRC/UK Familial Prostate Cancer study has selected families fulfilling one or more of the following criteria:¹⁰

1. Multiple-case prostate cancer families with three or more cases at any age.
2. Two or more affected relative pairs where one is under 65 y at diagnosis.

These criteria were chosen because the relative risk of the disease to first-degree relatives is then at least 4-fold. If there are two susceptibility genes of equal effect, there

would then be an 80% power of detecting them ($P < 0.05$; D Easton, *personal communication*). The Johns Hopkins Group¹⁴ have defined hereditary prostate cancer as three or more cases who are first-degree relatives at any age, three cases in three successive generations or brother pairs aged 56 y or less at diagnosis. The majority (97%) of UK families have cases which presented with clinical symptoms. Most of the other clusters in the world, except those from Scandinavia, include a high proportion of PSA-detected cancers as they are from the USA where population screening has been routine for 5 y.

Linkage studies involve genotyping affected individuals (and unaffected, only to infer genotypes of affected deceased individuals) from these informative families for genetic markers distributed across the genome, using either blood or tissue DNA. Blood DNA is usually used in the initial search because paraffin-embedded DNA is so difficult to process. If one or more marker in a region is found to segregate with the disease trait within the family set, this suggests the presence of a potential susceptibility gene in this location. The limit of detection (LOD) score is the logarithm of the odds of linkage and a significant value is considered to be an LOD of > 3.0 ($\log_{10} 3.0 = 1000$ to 1 odds of linkage). A LOD of < -2.0 is evidence against linkage of 100 to one.

Putative loci for prostate cancer genes

To date, four main chromosomal loci have emerged as candidate regions for prostate cancer genes and have been extensively studied by numerous international groups.

HPC1: hereditary prostate cancer 1 Gene (1q24–25). In 1996, Smith *et al* performed a genome-wide search with linkage analysis in 91 high-risk prostate cancer families.²³ They reported linkage of prostate cancer to chromosome 1q24–25 and named the locus *HPC1*. The maximal multipoint LOD score was 5.43 under heterogeneity (as stated above, a LOD score of over 3 is considered to be statistically significant). Interestingly, two of the linked families were African-American and contributed to over 1.00 of the total LOD score. Although the initial report of linkage to *HPC1* proposed that up to 34% of prostate cancer families could be linked to this locus, a subsequent pooled analysis of 772 families^{24,25} showed the actual proportion to be much lower, at 6%. Subsequent to the first report of linkage, the UK group formed a collaboration with the Canadian and Texan groups, the UK/Canadian/Texan Linkage Consortium,²⁶ and found negative evidence for linkage in the 1q24–25 region in 136 prostate cancer families. The estimated proportion of families linked was 4% and there was no evidence in families with less than three affecteds, but up to 20% could have been linked if there were four or more cases. This was the first study to suggest that *HPC1* may be more likely to be present in larger clusters. Subsequently, other studies have shown that families with male-to-male disease transmission, early age at diagnosis (65 y or less), and with five or more affected members, are more likely to be linked to chromosome 1q24–25.²⁴

Since the initial report²³ on *HPC1*, several groups have aimed to confirm these findings in their family sets. Four studies have shown only weak linkage to the locus using

non-parametric methods.^{27–30} In the study by Cooney *et al*,²⁷ six out of 59 families were African-American and again contributed disproportionately to the observation of linkage, although this did not reach statistical significance. Other studies, however, have failed to find evidence of linkage.^{26,31} A study of 33 potentially *HPC1* linked families indicated that *HPC1* is relatively site-specific, although a moderate but not statistically significant excess of breast and colon cancer was found in the potentially *HPC1*-linked families compared to the unlinked families. The tumours in *HPC1* families tend to be higher grade and therefore would be expected to have a poorer prognosis, but this is not yet known.³² *HPC1* is very unlikely to be a tumour suppressor gene.³³

The gene at the *HPC1* locus has not yet been identified, and indeed the localization information is presently limited.

PCAP. A second putative prostate cancer susceptibility locus (*PCAP*) was reported by Berthon *et al* in 1998 at 1q42.2–43, a locus 60 cM downstream from *HPC1*.³⁴ This group estimated that as many as 40–50% of their French and German families could be linked to this locus. Again the evidence for linkage came predominantly from families with young onset cases (60 y of age or less). However, three subsequent studies^{35–37} of the *PCAP* region have not found significant evidence of linkage, thus failing to confirm this locus. Therefore, although a small proportion of prostate cancer families may be linked to chromosome 1q42.2–43, the proportion is likely to be considerably less than the 40% originally reported.

CAPB. In 1999, evidence for a third locus on chromosome 1 linked to familial prostate cancer was reported by Gibbs *et al*.³⁸ This rare prostate cancer–brain cancer susceptibility locus, *CAPB*, at chromosome 1p36 was identified through linkage studies in 12 high-risk prostate cancer families with at least one family member with primary brain cancer. The overall LOD score in these families was 3.22, and after exclusion of three of the 12 families that had better evidence of linkage to other previously discussed prostate cancer susceptibility loci, a two-point LOD score of 4.74 was achieved. This group therefore concluded that a significant proportion of the families with both a high risk for prostate cancer and a family member with brain cancer showed linkage to the 1p36 region. However, the *CAPB* region was not subsequently confirmed by Berry *et al* in their recent report.³⁰ Our results do not find convincing evidence of linkage, although the LOD score is higher in families with younger average age of onset of prostate cancer, no correlation was found with tumours of any other primary site (Badzioch *et al*, in press).

HPCX. In many case–control studies, the relative risk of prostate cancer has been higher for brothers than for fathers of men with the disease. In the study by Schaid *et al*,¹⁶ prostate cancer was 1.5 times more common among brothers than amongst the fathers of men with prostate cancer. These findings could be explained by an X-linked or recessive inheritance of prostate cancer susceptibility in some families. Indeed, in 1998, Xu *et al* proposed a prostate cancer susceptibility locus on the

long arm of chromosome X at Xq 27–28.³⁹ Evidence for linkage was found in a combined study population of 360 North American, Swedish and Finnish families, with a peak two-point LOD score of 4.6. The proportion of families linked to *HPCX* was estimated to be 16%. To date there has only been one follow-up report attempting to confirm linkage of prostate cancer to *HPCX*. Lange *et al*⁴⁰ reported positive LOD scores over a 30cM region containing *HPCX*, with the greatest evidence for linkage in the subset of families with no evidence of male-to-male transmission and early onset disease (under 65 y of age).

Other candidate loci

Overall, the four proposed loci for high-penetrance prostate cancer genes mentioned above appear to account for only a minority of familial prostate cancer clusters and other putative genes have yet to be identified. Recent localization of further prostate cancer susceptibility loci has emerged from genomic screens of large sets of prostate cancer families; a genome-wide search on 162 North American families with three or more members affected with prostate cancer has recently found evidence of linkage to a novel locus at chromosome 20q13, with a maximum two-point LOD score of 2.69, which is below statistical significance.³⁴ Interestingly, the strongest evidence of linkage was found in families with less than five affected relatives, a later average age of diagnosis and no male-to-male transmission.

The results of another genome screen led by Suarez were also published this year.⁴² Their analysis of 504 brothers with prostate cancer identified five new regions of interest based on positive linkage signals: 2q, 12p, 15q, 16p and 16q. This latter region, which was found to have the highest signal, has previously been reported as a candidate area for a tumour-suppressor gene in prostate cancer.^{43,44} Stratification of the sample population in this study identified three further regions of interest: families with a history of breast cancer showed evidence of linkage to chromosome 1q35.1; those with no family history of prostate cancer had linkage to a region proximal to *HPC1*; and those with late onset disease had linkage at chromosome 4q.

Finally, a third genomic scan of 94 prostate cancer families by Gibbs *et al*⁴⁵ has proposed multiple regions of interest, including loci on chromosomes 10, 12 and 14. These new candidate loci for prostate cancer susceptibility genes reported from linkage studies have yet to be confirmed by other groups.

Familial co-aggregation of breast and prostate cancer has also been reported^{46–49} and carriers of mutations in the breast cancer-predisposition genes *BRCA1* and *BRCA2* in breast/ovarian cancer families have been shown to be

at a 3–7-fold risk of prostate cancer.^{50–53} Moreover, the 185delAG Ashkenazi mutation has been reported in one family of that origin with four cases of prostate cancer.⁵⁴ We have therefore assessed the overall contribution of *BRCA1* and *BRCA2* to familial prostate cancer by linkage in a series of multiple case families collected by the UK/Canadian part of the ACTANE Linkage Consortium.

We have also studied two other genes for linkage which are candidates for prostate cancer susceptibility genes because of their involvement in androgen metabolism, but are thought to be lower penetrance genes. The first, *HSD17β2* encodes 17-β-hydroxysteroid dehydrogenase type II and has been isolated from a prostate cDNA library.⁵⁵ It is also expressed in benign and malignant prostate.⁵⁶ The gene product catalyses the conversion of active 17-β-hydroxysteroids into their 17-keto forms and therefore inactivates both androgens and oestrogens.⁵⁷ The *HSD17β2* gene maps to chromosome 16q24.1–q24.2,⁵⁸ a frequently deleted region in prostate tumours.⁵⁹ Moreover, the frequency of loss of heterozygosity at this region is significantly associated with metastatic and clinically aggressive behaviour of prostate cancer.⁵⁹ The second candidate gene is the 5-α-reductase type II gene (*SRD5A2*) which catalyses the conversion of testosterone into the more bioactive androgen dihydrotestosterone (DHT) and maps to 2p23–22.^{60,61} DHT synthesis occurs in prostate tumours and modulation of its activity may be responsible for some of the variations in prostate cancer risk among ethnic groups.^{62,63}

One-hundred families with multiple cases of prostate cancer were studied. The study group comprised a Canadian group (Quebec City, Montreal and Toronto) (*C*; *n* = 70; 13 had three or more cases, 57 had two cases) and the UK Cancer Research Campaign/British Prostate Group Familial Prostate Cancer Study (UK; *n* = 30; 12 had three or more cases, 18 had two cases). DNA was extracted from whole blood obtained from affected men from these families as previously described⁶⁴ and amplified by PCR at polymorphic sequences close to (within 1 cM), flanking or within the following candidate genes: *BRCA1* (D17S855; THRA1; D17S579; D17S250), *BRCA2* (D13S260; D13S267; D13S171), *SRD5A2* (5-α-reductase II; D2S352) and *HSD17β2* (D16S511). LOD scores at each locus were calculated using the programs LINKAGE⁶⁵ and GENEHUNTER⁶⁶ under the assumption that susceptibility to prostate cancer was due to a highly penetrant dominant gene as predicted by the model of Carter *et al*.¹⁴ The proportion of families that could be due to each of the candidate loci was then estimated using the HOMOG program.⁶⁷ To allow for the possibility that the model is incorrect, model-free analyses were also performed using the program GENEHUNTER.⁶⁶ Haplotype sharing in affected sibling pairs was estimated using SPLINK (D. Clayton, personal communication), both for the complete data set and for men diagnosed at age <70 y.

Table 5 Linkage analysis in prostate cancer clusters: UK/Canadian Prostate Cancer Linkage Consortium

Gene	Number of pedigrees	Total LOD	LOD score under heterogeneity	Estimated proportion linked (α) (95% CI)
<i>BRCA1</i>	85	–4.69	0.16	0.19 (0.00–0.61)
<i>BRCA2</i>	100	–4.29	0.52	0.30 (0.00–0.65)
<i>SRD5A2</i>	100	–5.83	0.62	0.25 (0.00–0.57)
<i>HSD17β2</i>	97	–8.80	0.00	0.00 (0.00–0.27)

Table 6 Haplotype analysis in prostate cancer clusters: UK/Canadian Prostate Cancer Linkage Consortium

Candidate gene	Number of sibling pairs	Number of shared Haplotypes (%)					
		Siblings <70 y at diagnosis			Total—any age at diagnosis		
		0	1	2	0	1	2
<i>BRCA1</i>	Observed	15.7	34.8	15.4	32.2	61.9	28.0
	Expected	15.5	33.0	15.5	30.5	61.0	30.5
<i>BRCA2</i>	Observed	11.7	16.8	6.6	19.7	36.2	16.1
	Expected	8.8	17.6	8.8	18.0	36.0	18.0
<i>SRD5A2</i>	Observed	22.6	31.7	18.7	36.4	62.7	29.0
	Expected	18.3	36.6	18.3	32.0	64.0	32.0
<i>HSD17β2</i>	Observed	22.9	33.1	23.0	35.4	59.1	35.6
	Expected	19.8	39.6	19.8	32.5	65.0	32.5

LOD scores under both homogeneity and heterogeneity are given in Table 5 for the four candidate loci. No locus showed significant evidence of linkage. Although the 95% confidence intervals for the proportion of families linked are wide, the point estimate for each candidate is 0% for *HSD17β2*, 19% for *BRCA1*, 25% for *SRD5A2* and 30% for *BRCA2*. The proportion of familial prostate cancer which may be due to either *BRCA1* or *BRCA2* was estimated to be 30% (95% CI 0–70%). Haplotype sharing in affected sibling pairs is shown in Table 6. In the absence of linkage, both haplotypes are expected to be common to the affected siblings in 25% of cases, and one haplotype is common in 50% of cases due to chance alone. Again, no candidate gene showed significant evidence for linkage to prostate cancer. This result remained true when the analyses were restricted to cases diagnosed below age 70.

Because of the higher alpha score (proportion of families that may be linked) for *BRCA2*, and the single report of the presence of the Ashkenazi *BRCA1* mutation in one prostate cancer family, the entire coding region of *BRCA1* and 2 was analysed by CSGE in 38 familial prostate cancer clusters from the UK set and no mutations were found in *BRCA1*, but two novel deleterious deletions were found in *BRCA2*.⁶⁸ These were found in two families with affected sibling pairs. In both cases, the brother with prostate cancer of older onset carried the mutation, whilst the other did not and they did not share a haplotype. However, the brother who carried the mutation had loss of heterozygosity of the wild-type *BRCA2* allele in the tumour, implying, together with the nature of the mutation, that it was cancer-causing.

Why are prostate cancer-predisposition genes so hard to find?

The above linkage reports have produced mixed results, with no convincing evidence for the role of any one particular locus in the predisposition to prostate cancer. From epidemiological and segregation analysis data alone, there is strong evidence that high-risk prostate cancer genes almost certainly exist, so why have they not yet been found? The greatest linkage evidence (which still only suggests that the locus accounts for 6% of families worldwide), is for the 1q24–25 gene. There may be several reasons why this gene has not yet been cloned: the original region of interest was very large (50cM) compared with many other reports of linkage

(eg the region to locate *BRCA2* was about 3cM), and so a larger region has to be sequenced in families to discover the candidate code; there have been discrepancies about the exact position of the peak of linkage from different groups; many suggest it is distal to the original peak reported, and it is not clear whether the 1q42 locus is a separate locus to the 1q24 gene locus.

Other factors are also thought to contribute to the problem of confirming linkage: population and ethnic differences between the sample sets are inevitable and undoubtedly complicate the mapping process. Prostate cancer is a common disease and low LOD scores may occur due to the presence of phenocopies, ie men who have developed disease that is sporadic and not due to an inherited germline mutation. Prostate cancer typically occurs at a late age, thus it is often difficult to have DNA available from living affected men for more than one generation. The lack of distinguishing features between the hereditary and sporadic forms of the disease is another problem. No significant differences have been found overall between the two groups in terms of clinical stage, pathological stage, Gleason score, tumour volume or pre-operative PSA value.⁶⁹ Furthermore, the family studies have been collected using different case-clustering criteria and mode of presentation. It is possible that PSA-detected prostate cancer may in some instances behave differently from clinically presenting disease.

Finally, and perhaps most importantly, genetic heterogeneity is a feature of this disease; in other words multiple prostate cancer susceptibility genes are thought to exist. Thus, any one prostate cancer susceptibility locus may be responsible for only a small proportion of families affected by hereditary prostate cancer in general. In the presence of such genetic heterogeneity, it may be difficult for different groups to replicate linkage to an infrequent locus which may account for only a small proportion of families. Evaluation of extended pedigrees with stratified analysis of family subsets and meta-analyses of large datasets are therefore crucial in the successful confirmation of prostate cancer susceptibility loci. Ultimately the only definite evidence will come from direct mutation analysis. Our results above for linkage to four candidate genes illustrate this point. Despite negative evidence for linkage and a possible alpha (proportion of families linked) of 30% for *BRCA1* and 2, in a preliminary study of 38 familial clusters, the frequency of germline mutations is 0% for *BRCA1* and 5% for *BRCA2*. We now believe, since this study was performed, that the other two candidates are more likely to be low

penetrance genes. Such genes are more optimally located by association studies of normal variations in these genes (polymorphisms—see the review of Neuhausen, this volume of the journal), in large series of preferably >1000 prostate cancer case blood DNA samples *vs* ethnically matched controls. This has tremendous implications for the direction of genetic predisposition research in prostate cancer over the next 5 y. An extensive candidate gene approach, even for higher risk genes, may soon be necessary if the proportion of families due to each gene is low. For low-penetrance genes, an association study approach is needed, but this will require large DNA sample banks and well characterized clinical data. Advances in robotic technology will greatly help this process.

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Note added in proof: Since submitting this article, Tavtigian SV *et al.* have presented at the American Society of Human Genetics (October 2000) early data suggesting that there may be a gene on 17p (*HPC2*) (A strong candidate prostate cancer predisposition gene at chromosome 17p. *Am J Hum Genet* 2000; **67**(Suppl): 11 abstract 7). Two mutations have been found in this gene in families with numerous cases of prostate cancer. It is uncertain whether this gene will transpire to be a moderate or high risk gene.

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