*Commentary*

# Genetic Susceptibility to Aggressive Prostate Cancer

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## Introduction

In 2006, ~234,460 men in the U.S. will be diagnosed with prostate cancer, and >27,000 deaths will be attributed to the disease (1). There is substantial phenotypic variability among cases and the disease incidence varies by age, race, and family history. In the U.S., ~70% of all cases are ≥65 years at diagnosis, and the median age at diagnosis is 68 years (2).

Several types of epidemiologic studies present compelling evidence for the existence of prostate cancer susceptibility loci. Both case-control and cohort studies show that having a first-degree relative with prostate cancer increases a man's risk of being diagnosed with the disease by 2- to 3-fold relative to those without a family history (3). If the relative is diagnosed before age 65 (RR = 5.9) or if there are ≥3 affected first-degree relatives (RR = 10.9), the risk is substantial (3-5). In addition, twin studies report higher concordance rates for prostate cancer in monozygotic (19-27%) than dizygotic (4-7%) twins (6-8), with the largest study reporting a relative risk for prostate cancer of 12.3 [95% confidence interval (95% CI), 8.4-18.1] in monozygotic twins (8).

Efforts to identify susceptibility loci for hereditary prostate cancer (HPC) have been ongoing for several years with only limited success (9-25). At the heart of the problem is extreme locus heterogeneity and disease heterogeneity (26-30). With over a dozen genome scans completed to date, suggestive evidence for loci has been described on nearly every chromosome, yet efforts to replicate results using apparently similar data sets has been challenging (26-30). The prostate cancer genetics community has therefore recently focused on identifying loci associated with aggressive disease. Ideally, this approach can reduce the locus and disease heterogeneity problems that have confounded linkage analyses, as well as focus resources on finding genes that are the most clinically relevant. As outlined below, three major approaches to finding aggressive prostate cancer genes have been used.

## Family Studies for Genetic Mapping of Prostate Cancer Loci

Both the International Consortium of Prostate Cancer Genetics and individual investigators have used similar criteria to define aggressive prostate cancer (31-33). These include at least one of the following: regional- or distant-stage disease (based on pathology if a radical prostatectomy had been done, including T3, T4, N1, or M1, otherwise data from clinical staging is accepted); a Gleason score of ≥7 at diagnosis (poorly differentiated grade if no Gleason score is available); a pretreatment prostate-specific antigen (PSA) score of ≥20 ng/mL; and if deceased, death from metastatic prostate cancer at <65 years.

Initial studies aimed at mapping aggressiveness loci focused on Gleason score as an important clinical variable that reflects the pathologic architecture of the tumor. Several regions are scored and assigned a grade of 1 to 5, representing a well to poorly differentiated pattern, respectively. The two predominant grades are added to give a summary score of between 2 and 10, with most tumors being in the range of Gleason 5 to 7.

Some studies have treated Gleason score as a quantitative trait for the outcome of disease aggressiveness because it is reported to be a good predictor of survival (34), whereas others have treated the Gleason score as a covariate to help explain locus heterogeneity (Table 1). For instance, Witte et al. analyzed grade as a quantitative trait using Haseman-Elston regression methods on 513 men from concordant sibships. They reported evidence for linkage on chromosomes 5q31-33, 7q32, and 19q12-13.11 (35). Using the same data set as Witte et al. (35) and Suarez et al. (10), Goddard et al. (13) used the sum of the sib-pair Gleason scores, mean family age at diagnosis, male-to-male transmission in the nuclear family, and the number of affected first-degree relatives in the nuclear family as covariates in an analysis of 564 men from 254 families, for a total of 326 affected sibling pairs. They detected linkage at three previously reported loci (*1q24-25, 1q42.2-43*, and *4q*). They also found evidence for linkage near the androgen-receptor gene at Xq12-13 [Log of Odds (LOD) score 3.06; $P = 0.00053$], and at five new locations using a LOD threshold of 2.5. Interestingly, the locus at HPC1 (*1q24*), the X chromosome, and chromosome 5 were noted only when Gleason score was considered. Indeed, without covariates, only a few weak-to-moderate linkage signals were found, none of which replicated previously reported results.

Linkage to 5q31-33, 7q32, and 19q12-13.11 have also been reported by Neville et al. and Paiss et al. (35-38). Neville and colleagues analyzed the same 513 men from 326 concordant sibships described previously (10, 35) using Gleason score as a quantitative trait. In doing so, they initially narrowed the locus on 19q to ~2 cM. In addition, they have done allelic imbalance studies on tumors from men with aggressive disease to further refine the locus to ~0.8 Mb. Studies by the same group also refined the locus on chromosome 7q32-q33 to as little as 1.1 Mb (36).

Paiss et al. have also examined the locus at 7q31-33 for linkage to aggressive disease in 100 German families (38). They used a multipoint allele–sharing method that was based on a likelihood ratio test implemented in GENEHUNTER-PLUS v.1.2. Using tumor grade and family mean age at diagnosis as covariates, they constructed two weighted models: the first adds weight to families with at least two cases of grade 3 prostate cancer, and the second adds weight to families with early and late onset prostate cancer, respectively. The unweighted analysis showed no evidence of linkage to 7q,

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**Table 1. Loci associated with prostate cancer aggressiveness**

| Study | Locus | *P* value/LOD |
|---|---|---|
| Witte et al. (35) | *5q31.3-q33.33* | 0.0002 |
| | *7q32.2* | 0.0007 |
| | *19q12* | 0.0004 |
| Goddard et al. (13) | *4q* | 0.0004 |
| | *1q24-q25* | 0.0001 |
| | *1q42.2-q43* | 0.003 |
| | *Xq12-q13* | 0.0005 |
| Slager et al. (39) | *4q* | 0.0001 |
| | *19q13* | <0.00001 |
| Paiss et al. (38) | *7q31-q33* | 0.002 |
| Slager et al. (40) | *6q23.3* | 0.0009 (LOD 2.4) |
| | *5p13.1-5q11.2* | 0.004 |
| Schaid et al. (31) | *19q13.31-q13.33* | 0.0007 |
| | *20p13-p12.4* | 0.0006 |
| Chang et al. (32)* | *Xq27-28* | HLOD 2.5 |
| | *22q13* | HLOD 2.1 |
| Stanford et al. (33)* | *22q11.1* | HLOD 2.2 |
| | *22q12.3-q13.1* | HLOD 1.9 |
| Schaid et al. (31)* | *20p* | LOD 2.5 |

*Aggressive prostate cancer based on Gleason score, stage, PSA, and death from prostate cancer.

whereas the Z (lr) scores increased to 2.60 ($P = 0.005$) using the first model, and to 3.02 ($P = 0.001$) using the second model, with weighting for later onset disease. These results clearly show the importance of including covariates in the analysis and provide additional support for a locus on 7q.

Slager et al. have also undertaken studies of prostate aggressiveness using Gleason score (39). In their initial study, they analyzed genome scan data from 161 sib-pairs using Gleason score as a quantitative measure of tumor aggressiveness (39). They both confirm the linkage results for chromosome 19q ($P < 0.00001$) as well as report suggestive evidence for linkage on chromosome 4 ($P = 0.00012$). In a subsequent and independent study, again using Gleason score as a quantitative trait, they analyzed genome scan data from 175 brother pairs from 103 families (40). Their strongest result was on 6q23 at 137 cM ($P = 0.0009$). Other regions of interest ($P < 0.005$) were noted on chromosomes 1p13-q21 and 5p13-q11.

More recent studies have taken a slightly different approach by focusing analyses on ''aggressive disease families,'' defined by the presence of two or more men with clinically aggressive disease. In the first study, Chang et al. evaluated 623 men with prostate cancer from 188 HPC families and identified a subset of 244 men with aggressive disease based on the above clinical and/or pathologic criteria. They then analyzed genome-wide scan data defining men as affected only if they had clinically significant disease and found strong evidence for linkage at Xq27-28 [Heterogeneity Log of Odds (HLOD), 2.54; $P = 0.0006$] as well as evidence for a locus at 22q13 (HLOD, 2.06; $P = 0.002$; ref. 41). Two other regions had an HLOD between 2.0 and 2.5: 3p26 (HLOD, 1.75; $P = 0.004$) and 9p21 (HLOD, 1.59; $P = 0.007$; ref. 32).

Stanford et al. also reported suggestive evidence for linkage on chromosome 22 (dominant HLOD, 2.18; ref. 33). In this study, we used clinical data from 784 affected men from 248 HPC families for whom a genomic screen had been previously done (16). Disease characteristics such as Gleason score, stage, and PSA were used to classify affected men into categories of clinically insignificant, moderate, or aggressive prostate cancer. To enrich for genetic homogeneity, we restricted linkage analyses to men with aggressive disease only. Suggestive linkage was observed at chromosome 22q11.1 and was stronger (dominant HLOD, 2.75) in families with evidence of male-to-male transmission. A second region at 22q12.3-q13.1 was also highlighted using the recessive model (HLOD, 1.90), as was a locus at 18p11.22 (HLOD, 1.04).

Although neither study found a LOD score >3.3, the criterion typically used to define statistically significant linkage (42), it is probably more than coincidence that both studies reported a locus of interest on chromosome 22q12. Other studies have also similarly reported at least nominal evidence for linkage in this region. For instance, Lange et al. reported a LOD score of 1.87 at 45 cM in a set of 16 African-American families and a LOD of 1.87 at 51 cM in 79 families with four or more affected men (17). A subset of younger-age-at-onset families from Utah (HLOD, 2.42) also gave nominal evidence for linkage in this region (24). As summarized below, this locus has become a region of intense interest for the International Consortium for Prostate Cancer Genetics, which examined families from the combined consortium study for aggressive prostate cancer loci.

## Meta-analysis for Finding Prostate Cancer Loci

The individual studies described above clearly show that: (*a*) there are loci that predispose men to aggressive forms of prostate cancer, and (*b*) even when considering data sets enriched for men with aggressive disease, statistical power is still limited. In most studies, reports of linkage were only suggestive and fell below the generally accepted threshold of 3.3. For that reason, the International Consortium for Prostate Cancer Genetics recently undertook a genome-wide scan that combined data sets from 11 research groups (31).

The study focused on 166 (13%) of 1,233 available pedigrees. The families selected were those that had at least three family members with clinically aggressive disease, at least two of whom had available genome-wide scan data. Aggressive disease was defined as having either high Gleason score or regional or distant stage, using essentially the criteria above. Men with aggressive disease were coded as affected and all other affecteds were coded as being of unknown phenotype so that men with insignificant or moderate disease did not contribute to the final LOD score calculation.

The results were interesting at several levels. Suggestive linkage was found on chromosomes 6p22.3 (LOD, 3.0), 11q14.1-14.3 (LOD, 2.4), and 20p11.21-q11.21 (LOD, 2.5). On chromosome 11, the strongest evidence of linkage (LOD, 3.31) was observed among pedigrees with an average age at diagnosis of 65 years or younger. Other chromosomes that showed evidence for heterogeneity in linkage when considering particular strata were chromosome 7, in which the strongest linkage signal was observed in pedigrees without male-to-male disease transmission (*7q21.11*; LOD, 4.1), and chromosome 21, in which the strongest linkage signal was from the small number of African-American pedigrees (*21q22.13-22.3*; LOD, 3.2).

Several of these regions have previously been noted in individual studies, although not necessarily in families with aggressive disease. The strongest result in the International Consortium for Prostate Cancer Genetics study was on chromosome 6. Stanford et al. (33), using families with multiple men with aggressive disease, also reported suggestive linkage on chromosome 6 in HPC families with an early mean age at diagnosis (≤58 years). Slager and colleagues (39), using Gleason grade as a quantitative trait, also found a suggestive linkage signal in this same region. Other groups reported linkage on chromosome 6, but at some distance from this locus (14, 16).

The data from chromosome 7 are harder to evaluate, as several groups have reported suggestive linkage on this chromosome, but the position of the linkage peak varies widely. Stanford et al. (33) reported suggestive linkage in the subset of pedigrees with five or more affected men. Their linkage signal, however, was quite distant from a prior report

by the same researchers using a data set of 254 families which included the aggressive families described above (16). Paiss et al. reported suggestive evidence for linkage in HPC families with both aggressive disease and an older age at diagnosis (38). This peak was only ~35 cM from that reported by Stanford et al. (33). When analyzing Gleason score as a quantitative trait, Witte et al. found a linkage signal at ~130 cM (43), which is much closer to the result at 96 cM originally reported by Janer and colleagues (16). As mentioned previously, additional support for linkage on chromosome 7q32 comes from finding allelic imbalance in primary prostate tumors (36).

With regard to chromosome 5, Stanford et al. (33) found a suggestive linkage signal among non-HPC families, whereas Slager et al. (39) reported a similar result using Gleason score as a quantitative trait. Finally, Goddard et al. (13) reported evidence using Gleason score as a covariate, as did Wiklund et al. among a data set of men from Sweden (19).

Reports supporting evidence for linkage on chromosomes 20 (33, 14) and 11 (18, 43) have also been published, but remain to be investigated in greater detail. The report of linkage to chromosome 21 is based on a small number of African-American families from the International Consortium for Prostate Cancer Genetics study and may therefore represent a spurious finding. It will be of great interest to see if a larger data set of African-American families replicates this finding (44).

## Case-Control Studies for Defining Genes Associated with Aggressive Disease

In addition to linkage-based studies, some investigators have used a candidate gene approach to interrogate genes putatively associated with aggressive disease. For instance, Casey et al. (45) followed-up reports of linkage and allelic imbalance at 7q32-33 (35, 36) by sequencing the gene podocalyxin (*PODXL*), which is a downstream target of the WT1 tumor suppressor implicated in β-catenin signaling. Somasiri et al. had previously reported a correlation between podocalyxin expression and aggressive breast cancer (46). Casey et al. screened germ line DNA isolated from 17 probands of families with putative linkage to 7q32-q33. This analysis revealed numerous coding sequence variants, including a variable in-frame deletion (of either 6 or 12 bp) in exon 1 that results in the loss of one or two Ser-Pro repeats. These variants were investigated for both risk of prostate cancer and aggressiveness in a family-based, case-control study described previously by Witte and colleagues (43). The presence of a single in-frame deletion was positively associated with prostate cancer risk [odds ratio (OR), 2.14; 95% CI, 1.09-4.20; $P = 0.03$]. Two deletions further increased risk (OR, 2.58; 95% CI, 1.23-5.45; $P = 0.01$). Importantly, the finding was strengthened when considering men with high-stage or high-grade disease: OR, 3.04 for one deletion (95% CI, 1.01-9.15); OR, 4.42 for two deletions (95% CI, 1.32-14.85; $P = 0.02$), implicating *PODXL* as a gene for more aggressive prostate cancer.

Also of interest are studies by Cicek et al. (47) who evaluated several polymorphisms in genes involved in the testosterone biosynthetic pathway, including 5α-reductase type 2 (*SRD5A2*), P450 17 α-hydroxylase (*CYP17*), and the androgen receptor gene for associations with prostate cancer risk and clinical features of disease using the same population described by Witte and colleagues (43). The primary result was an association between the *SRD5A2* V89L variant and prostate cancer risk (47). Men who were diagnosed early in life or with more aggressive disease (Gleason ≥7 or tumor stage ≥T2c) contributed disproportionately to the result. Carrying at least one *SRD5A2* 89L allele versus none showed a statistically significant increase in risk (OR, 1.56; 95% CI, 1.08-2.25; $P = 0.02$), with the association primarily observed among men with more aggressive disease (OR, 1.63; 95% CI, 0.98-2.72; $P = 0.06$). None of the other variants were associated with prostate cancer.

A larger and more extensive study has been carried out by Burmester et al. (48) who evaluated 48 SNPs from genomic regions with evidence of linkage to prostate cancer, or specifically, aggressive disease. The study focused on 590 cases and 556 controls with cases selected from 275 multiplex prostate cancer sibships. Two SNPs, one in the caveolin 2 (*CAV-2*) gene (Glu 130 to Gln) and an intronic variant in the *HPN* gene showed a statistically significant association with aggressive disease. The latter had previously been associated with aggressive disease at the mRNA and protein level (49).

The findings with *CAV-2* are interesting, as the encoded protein produces a membrane-bound protein that associates with caveolin 1 (*CAV-1*) and caveolin 3 (*CAV-3*). *CAV-1*, located at 7q31.1, was tested for an association with aggressive prostate cancer by screening of the promoter and coding region in 191 controls, 190 sporadic cases, and 24 subjects with prostate cancer from 10 families who showed putative linkage of high-grade prostate cancer to 7q31-33. No disease-associated variants were found; however, a haplotype derived from four SNPs spanning a 15.2 kb region that included the *CAV-1* gene was found to be associated with more advanced stage (T3/4) tumors (50). Although some cosegregation of the haplotype was seen among affected men in 10 families with aggressive disease, the numbers were too small to draw strong conclusions. Whether it is the *CAV-1* gene or another gene in LD with the haplotype found that is responsible for the result is unclear. Additional investigation in confirmatory data sets is needed.

## Summary

In aggregate, the above studies make three important points. First, no single approach will work for finding genes associated with prostate cancer. The disease is both genetically and phenotypically complex. Linkage, candidate gene association, and perhaps more importantly, functional studies are needed once a specific mutation or variant is suspected.

Second, a data set is only as strong as the phenotypes which define it. Those making progress in solving the problem of susceptibility to aggressive prostate cancer have done so because they have diligently obtained medical records, pathology reports, and tumor specimens. Partnerships with clinical colleagues are a vital part of solving problems in complex trait analyses.

Finally, data sets for both linkage and candidate gene evaluations are almost always limited by sample size. Meta-analyses or combined studies achieve greater power for evaluating more hypotheses, without the loss of statistical power that results when looking at subgroups. Investigators worldwide who are involved in research on genetic susceptibility to prostate cancer have formed a true community that has worked hard to build the infrastructure and obtain resources for carrying out large combined studies. Such an approach would certainly benefit those studying a host of complex diseases.

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