Hum Genet (2006) 119: 400–407
DOI 10.1007/s00439-006-0149-6

ORIGINAL INVESTIGATION

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Genome-wide linkage scan for prostate cancer susceptibility genes in men with aggressive disease: significant evidence for linkage at chromosome 15q12

Received: 3 November 2005 / Accepted: 23 January 2006 / Published online: 1 March 2006

Abstract Epidemiological and twin studies have consistently demonstrated a strong genetic component to prostate cancer (PCa) susceptibility. To date, numerous linkage studies have been performed to identify chromosomal regions containing PCa susceptibility genes. Unfortunately, results from these studies have failed to form any obvious consensus regarding which regions are most likely to contain genes that may contribute to PCa predisposition. One plausible explanation for the difficulty in mapping susceptibility loci is the existence of considerable heterogeneity in the phenotype of PCa, with significant variation in clinical stage and grade of disease even among family members. To address this issue, we performed a genome-wide linkage scan on 71 informative families with two or more men with aggressive PCa. When only men with aggressive PCa were coded as affected, statistically significant evidence for linkage at chromosome 15q12 was detected (LOD = 3.49; genome-wide $p = 0.005$). Furthermore, the evidence for linkage increased when analyses were restricted to Caucasian–American pedigrees ($n = 65$; LOD = 4.05) and pedigrees with two confirmed aggressive cases ($n = 42$, LOD = 4.76). Interestingly, a 1-LOD support interval about our peak at 15q12 overlaps a region of suggestive linkage, 15q11, identified by a recent linkage study on 1,233 PCa families by the International Consortium for Prostate Cancer Genetics. Using a more rigid definition of PCa in linkage studies will result in a severe reduction in sample sizes available for study, but may ultimately prove to increase statistical power to detect susceptibility genes for this multigenic trait.

Keywords Prostate cancer · Linkage mapping · Aggressive disease

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy among men in the United States (Jemal et al. 2003) and the fourth most commonly diagnosed cancer in men worldwide (Parkin 1998). Established risk factors for PCa include older age, African descent, and positive family history for the disease (Steinberg et al. 1990; Narod et al. 1995; Chan et al. 1998). Segregation analyses have generally supported rare autosomal dominant susceptibility alleles (Carter et al. 1992; Gronberg et al. 1997; Schaid et al. 1998). However, some segregation analyses as well as epidemiological and twin studies across different ethnic groups have suggested that familial clustering of PCa may be explained by X-linked and/or recessive mode-of-inheritance susceptibility genes (Monroe et al. 1995; Narod et al. 1995; Cui et al. 2001; Risch 2001).

Numerous genome-wide linkage scans (GWSs) for PCa susceptibility genes have been performed previously. Results from ten GWSs for PCa susceptibility genes, including a GWS from our University of Michigan Prostate Cancer Genetics Project (UM-PCGP) (Lange et al. 2003), have been summarized by Schaid (2004). Results between the linkage studies have been disparate, with no strong consensus between studies regarding the identification of regions containing putative susceptibility genes. These results are indicative of a large amount of genetic heterogeneity of PCa and suggest that large collections of PCa pedigrees will be needed to identify strong candidate regions for PCa susceptibility genes. The International Consortium for Prostate Cancer Genetics (ICPCG) has recently presented results from a GWS based on 1,233 PCa pedigrees. Using parametric and nonparametric linkage analyses, five regions with suggestive linkage (LOD > 1.86) were identified: 5q12, 8p21, 15q11, 17q21, and 22q12. Significant linkage (LOD = 3.57) was detected at chromosome 22q12 in the subset of pedigrees with at least five confirmed cases of PCa.

One of the difficulties in mapping PCa susceptibility genes is the complex phenotype of the disease. PCa has a full spectrum of clinical presentations from clinically indolent disease to a form of cancer that is widely metastatic at the time of diagnosis. It is possible that different genetic factors contribute to the various types of cancer and thus including men only with one specific phenotype (i.e., clinically aggressive disease) would increase the power to identify aggressiveness loci. Furthermore, it is likely that men from families with a positive history for the disease may often be diagnosed with clinically insignificant PCa due to both increased screening and the higher probability of biopsy. Identifying pedigrees with multiple cases of aggressive disease and reclassifying individuals with less significant disease within these families would lead to pedigrees with more homogeneous phenotypes. Two recent studies (Chang et al. 2005; Stanford et al. 2006), have reported GWSs for aggressive PCa susceptibility genes, where men were only defined as affected if they had an aggressive form of PCa. Using this approach, Chang et al. (2005) found two regions, Xq27-28 and 22q13, with heterogeneity LODs (HLOD), based on a dominant parametric model, greater than 2.0. Stanford et al. (2006) found suggestive linkage (HLOD greater than 2.0 using a dominant parametric model) at 22q11. Interestingly, Stanford et al. (2006) also reported an HLOD of 1.9, using a recessive susceptibility parametric model, at 22q13.

Previously, we described a nonparametric GWS based on 175 PCa pedigrees from the UM-PCGP (Lange et al. 2003). The most significant finding in our report was evidence for suggestive linkage to markers on chromosome 17q21 near the *BRCA1* gene (LOD = 2.36) which increased when the analysis was restricted to the subset of 79 pedigrees with four or more confirmed PCa cases (LOD = 3.27). A combined GWS on 426 PCa pedigrees (Gillanders et al. 2004), including the 175 UM-PCGP pedigrees, gave increased evidence for a 17q21-22 locus based on results from the entire collection of pedigrees (LOD = 3.16) and the subset of pedigrees with four or more confirmed PCa cases (LOD = 3.87). In addition to chromosome 17q21-22, Gillanders et al. (2004) also implicated chromosome 15q11 as a region of linkage (LOD = 2.21 for all 426 pedigrees; LOD = 5.57 for the subset of 225 pedigrees with average age of diagnosis ≥65). Herein, we describe a GWS for susceptibility genes that predispose men to a more aggressive form of PCa using pedigrees from the UM-PCGP. Our results strongly implicate 15q12 as a candidate region for an aggressive PCa gene(s).

Materials and methods

Subjects

Men with PCa who had at least one living relative with PCa were asked to participate in the UM-PCGP and to provide a blood sample, extended family history, and access to medical records. Families were eligible for the current study if they had at least three family members with confirmed PCa or had two confirmed cases in men diagnosed at ≤ 55 years of age and had DNA available on at least two confirmed cases (excluding father–son pairs). PCa diagnoses were confirmed by medical record review when possible, otherwise independent confirmation of the diagnosis by two family members was obtained. All participants gave written informed consent, and all research protocols and consent forms were approved by the University of Michigan Institutional Review Board. DNA samples were collected and genotyped from 640 individuals from 175 PCa families, including 459 diagnosed cases. Characteristics of these 175 families, with respect to ethnicity, average age at diagnosis, number of confirmed cases, male-to-male transmission, were reported previously (Lange et al. 2003).

Definition of aggressive disease

Clinical data was used to classify PCa cases into groups of those with and without aggressive disease. The definition of clinically aggressive disease in this study was similar to the definition used by Chang et al. (2005) and Stanford et al. (2006). Specifically, we assigned affected men to have aggressive PCa if they met at least one of the following requirements: (1) regional or distant stage based on pathology if radical prostatectomy was done, otherwise clinical stage [American Joint Commission on Cancer stage III (T3, N0, M0) or stage IV (T4, N0, M0, or any T, N1, M0 or any T, any N, M1)]; (2) tumor grade Gleason score (a histological measurement of differentiation) at diagnosis ≥7 (or poorly differentiated grade if no Gleason grade was available); (3) pretreatment PSA at diagnosis ≥20 ng/ml; or (4) PCa listed as primary cause of death on death certificate. Men without

any of these criteria were coded as unknown phenotype in the statistical analyses. January 1, 2004 is the last date of new PCa diagnoses in our GWS pedigrees. Although more individuals per family may have joined the study and donated new blood, only bloods collected before May 1, 2000 were genotyped for the GWS marker panel. Pedigrees were included in these analyses if they had at least two genetically related men with aggressive disease and if they were informative for linkage.

Genotyping

Genomic DNA was prepared from blood samples using standard techniques. A total of 405 highly polymorphic microsatellite markers (average heterozygosity = 0.80) were genotyped, resulting in an average marker density of one marker every 8.6 cM. Only 11 genotyping errors out of 12,992 duplicated samples were detected (0.085% genotyping error rate). Details regarding the PCR reactions and allele-scoring techniques are described elsewhere (Lange et al. 2003; Gillanders et al. 2004). Pedigree relationships and conformity of genotype data with Mendelian inheritance assumptions were confirmed previously on these data (Lange et al. 2003).

Statistical analyses

We performed multipoint nonparametric linkage analyses over a 1 cM grid using the computer program Merlin (Abecasis et al. 2002). Specifically, we used the exponential model (Kong and Cox 1997), the "pairs" scoring statistic (Whittemore and Halpern 1994), and equal weights for all pedigrees. Allele frequencies were estimated using all available data from the complete set of 175 UM-PCGP pedigrees. Inter-marker distances and order were provided by the Center for Genetics at Marshfield Medical Research Foundation (research.marshfieldclinic.org/genetics).

To assess the genome-wide statistical significance of our findings (i.e., to determine the probability of observing a LOD score as great or greater than our observed overall maximum GWS LOD score by chance), we performed "gene dropping" under the null hypothesis of no linkage. Specifically, we constructed 1,000 random data sets under the null hypothesis of no linkage and determined the overall maximum LOD score for each random GWS replicate over the same 1 cM grid used in the original scan. Our observed overall maximum GWS LOD score was compared to the distribution of overall maximum GWS LOD scores from the 1,000 replicates, and we calculated an empirical *p*-value corresponding to the genome-wide statistical significance of our findings.

To gain further insight into the characteristics of the pedigrees that linked to specific chromosomal regions of interest, we defined and analyzed subsets of pedigrees based on familial characteristics. Specifically, we stratified pedigrees based on ethnicity, the number of confirmed genetically related aggressive cases (2 vs. ≥3), and the average age-at-diagnosis for the aggressive cases (≤ 65 years vs. > 65 years). Given the modest number of pedigrees with two or more cases of aggressive disease available to us and the impact of multiple testing, subset analyses were only calculated in regions with an observed LOD score greater than 3.0 in the complete collection of "aggressive" pedigrees.

To facilitate direct comparisons between results of the current study and those of Chang et al. (2005) and Stanford et al. (2006), we also performed secondary GWS analyses using the two parametric models used in the latter studies. An autosomal dominant model was used in which the frequency of the susceptibility allele was assumed to be 0.003 and the penetrance for carriers and noncarriers was 1.0 and 0.001, respectively (Smith et al. 1996; Xu et al. 2005). The autosomal recessive model was identical to that used in the recent ICPCG GWS (Xu et al. 2005) in which the susceptibility allele frequency was 0.15, the penetrance for homozygous carriers was 1.0, and the penetrance for heterozygous carriers and homozygous noncarriers was 0.001. Both parametric models were based on segregation analyses using PCa pedigrees for which no distinction was made for PCa severity. The two models were analyzed using the HLOD score approach (Ott 1999).

Results

From the 175 families analyzed in our initial GWS, 91 families were identified that had two or more cases of aggressive PCa. Among these pedigrees, 20 pedigrees were excluded for further analysis because the families were uninformative for linkage when only the aggressive cases were considered. Therefore, the final sample included 71 pedigrees with two or more genetically related aggressive cases that were informative for linkage analysis and consisted of 65 Caucasian–American families, five African–American families, and one Asian–American family. Forty-two pedigrees contained two genetically related confirmed aggressive cases of PCa, 23 pedigrees contained three confirmed aggressive cases, and six pedigrees contained four or more aggressive cases. The average age at diagnosis over all aggressive cases among these 71 pedigrees was 63.3 years, with 41 pedigrees having an average age at diagnosis ≤ 65 years.

The maximum LOD score based on nonparametric and parametric models for each of the 23 chromosomes are presented in Table 1. In Fig. 1, the nonparametric results from our GWS of 71 families with aggressive PCa is compared with the nonparametric results from our GWS analyzing the complete set of 175 UM-PCGP pedigrees without regard to disease severity (results very similar to results published previously in Lange et al. 2003). The most significant evidence for linkage with aggressive PCa was detected at 15q12 with a

Table 1 Maximum nonparametric and parametric LOD scores for aggressive disease, and their associated location, by chromosome

Chromosome	Kong and Cox		Recessive			Dominant		
	Maximum LOD	Location (cM)	Maximum HLOD	α	Location (cM)	Maximum HLOD	α	Location (cM)
1	0.29	3.5	0.25	0.15	156	1.07	0.34	4
2	0.66	237	0.55	0.25	166	1.29	0.34	86
3	1.21	163.5	1.18	0.38	162	0.26	0.17	168
4	0.93	13	0.88	0.36	14	0.73	0.31	9.5
5	0.69	81.5	0.52	0.19	120	0.45	0.22	78
6	2.09	30	1.52	0.42	28	1.11	0.32	30
7	0.67	169	0.41	0.17	169	0.66	0.27	13
8	0.31	104	0.28	0.14	50	0.10	0.09	118
9	0.18	46	0.25	0.15	134	0.09	0.08	140
10	0.34	126.5	0.40	0.18	124	0.07	0.05	71
11	0.43	13	0.37	0.17	120	0.62	0.21	113
12	0.72	75	0.45	0.21	75	0.87	0.31	75
13	0.59	5.5	0.49	0.26	6	0.70	0.24	93
14	0.60	97	0.62	0.23	55	0.76	0.26	40
15	3.49	15	3.37	0.56	15	1.69	0.38	17
16	0.32	53	0.26	0.17	52	0.11	0.12	58.5
17	0.72	53	0.76	0.28	28	0.64	0.24	54
18	1.03	101	0.96	0.30	102	0.96	0.30	102
19	0.30	59	0.27	0.16	57	0.33	0.14	42
20	0.86	95	0.14	0.11	96	1.52	0.38	93.5
21	0.45	29.5	0.37	0.18	20	0.62	0.22	35
22	0.00	–	0.00	0.00	–	0.00	0.00	–
23	0.34	23	0.90	0.38	23	0.77	0.24	24

nonparametric LOD score of 3.49 near marker D15S1002. In contrast, evidence for linkage in the complete set of 175 pedigrees at this location was modest (nonparametric LOD = 0.83). Suggestive evidence for linkage with aggressive PCa was also observed at chromosome 6p22-23 (nonparametric LOD = 2.09) near marker D6S289; again the evidence in the complete collection of 175 pedigrees was modest (LOD = 0.58) at this location. Nonparametric LOD scores greater than 1.0 in the aggressive GWS were also detected at 3q24 (LOD = 1.21), 6q23 (LOD = 1.07), and 18q22 (LOD = 1.03). Aggressive disease did not appear to contribute disproportionately to the overall evidence for linkage at 17q21-22 that was observed in the complete set of 175 pedigrees (nonparametric LOD = 0.72 in the 71 aggressive PCa pedigrees versus nonparametric LOD = 2.51 in all 175 pedigrees).

To assess the global statistical significance of our findings, we used gene-dropping simulations under the null hypothesis of no linkage to create 1,000 random replicate data sets. Only 5/1,000 random GWSs had a maximum LOD score as large, or larger, than our observed maximum GWS LOD of 3.49 at 15q12, resulting in an overall genome-wide empirical significance level of $p = 0.005$ for our findings. The global statistical significance of our LOD of 2.09 at 6p22-23 was estimated to be approximately $p = 0.15$.

Linkage analyses were also performed using subsets of the 71 aggressive pedigrees at 15q12 (Fig. 2). The evidence for linkage at 15q12 increased when analyses were restricted to the 65 Caucasian–American pedigrees (nonparametric LOD = 4.05). Analysis of the 42 families with only two genetically related aggressive PCa cases resulted in a nonparametric LOD = 4.76 at 14 cM compared to the 29 families with ≥3 aggressive PCa cases in which the maximum nonparametric LOD = 0.28 over the 15q12 interval. The LOD scores were similar for the 41 pedigrees with average age of diagnosis ≤ 65 years (maximum 15q nonparametric LOD = 2.43 at 25 cM) and the 30 pedigrees with average age of diagnosis >65 (maximum 15q nonparametric LOD = 2.15 at 9 cM) although the peak values were located approximately 15 cM apart. LOD scores for both subsets only tapered off modestly at 15 cM, which is the position of the peak location for all 71 families. Given that multiple subsets of pedigrees were analyzed at 15q12, the impact of multiple testing should be considered when appraising the magnitude of the LOD scores for the different subsets of pedigrees in this region.

The results of the GWSs using dominant and recessive parametric models to analyze the data from the 71 aggressive PCa families are presented in Fig. 3. The maximum evidence for linkage for both the dominant and recessive models occurred at 15q12 (HLOD = 1.69 and HLOD = 3.37, respectively). Additional HLODs greater than 1.0 were observed for the dominant model at 1p36 (HLOD = 1.07), 2p14 (HLOD = 1.29), 2q37 (HLOD = 1.21), 6p22-23 (HLOD = 1.11), and 20q13 (HLOD = 1.52). Additional HLODs greater than 1.0 for the recessive model occurred at 3q24 (HLOD = 1.18) and 6p22-23 (HLOD = 1.52).

Discussion

In this GWS based on 71 pedigrees containing two or more cases of aggressive PCa, evidence for linkage

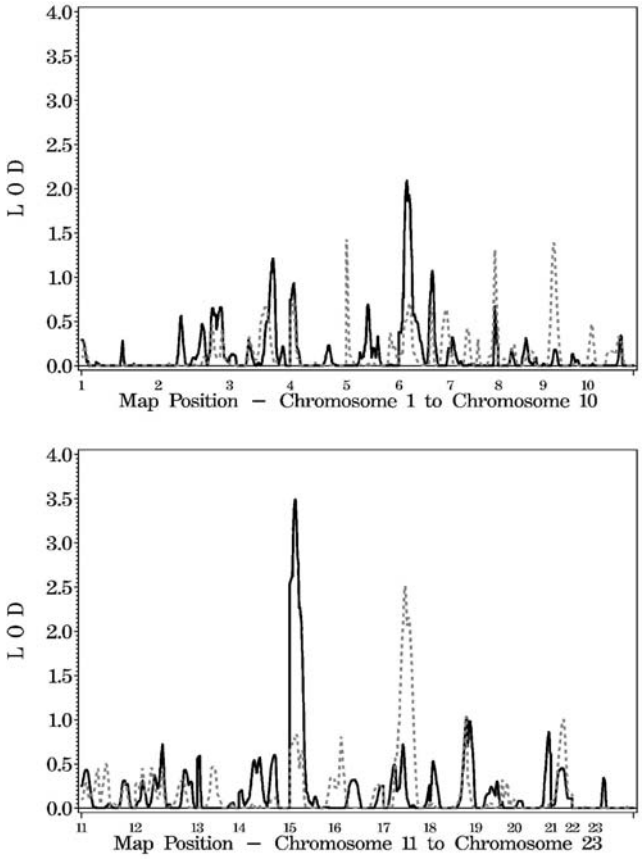

Fig. 1 Results from our genome-wide nonparametric linkage scan for PCa susceptibility genes in 175 UM-PCGP families with two or more PCa cases using different clinical criteria. The *gray hashed line* represents our LOD score results from the complete set of 175 pedigrees. The *black solid line* represents our LOD score results from the 71 informative pedigrees with two or more aggressive cases where men without aggressive PCa were recoded as disease status unknown

(LOD = 3.49, genome-wide $p = 0.005$) to 15q12 markers reached genome-wide statistical significance. In addition to the results at 15q12, suggestive evidence for linkage was also found at 6p22-23 (LOD = 2.09; genome-wide $p = 0.15$). The 15q12 region is in close proximity to a region that has been recently implicated as a possible candidate region for a generalized PCa locus by a large collaborative linkage study from the ICPCG (Xu et al. 2005). The ICPCG presented linkage results from 1,233 PCa pedigrees, including the 175 UM-PCGP pedigrees included in this study, and found suggestive evidence of linkage to 15q11 (HLOD = 2.10 for the recessive parametric model), with the linkage peak approximately 10 cM distal to our linkage peak. The 175 UM-PCGP pedigrees contributed the strongest evidence for linkage (HLOD = 1.06) among the ten different groups at this location. The linkage peaks from our study and from the ICPCG have overlapping 1-LOD support intervals. The linkage evidence at 15q11 in the ICPCG study was strongest when analyzing pedigrees with less than five confirmed cases and when using the recessive parametric model we used in the current study. Similar to the results from the ICPCG, we also found greater evidence for linkage at 15q12 in our pedigrees when analyzing men with aggressive PCa using the recessive parametric model (HLOD = 3.37) than when using the dominant parametric model (HLOD = 1.69).

The most striking result from our study is that the evidence for 15q12 linkage was derived almost entirely from the set of 42 pedigrees with two aggressive cases (LOD = 4.76) and that there was little evidence for linkage (LOD = 0.28) in the 29 pedigrees with three or more aggressive cases. Given the complex etiology of PCa, one might reason that the set of pedigrees with three or more aggressive cases would be a more a priori powerful set of pedigrees for detecting aggressive PCa

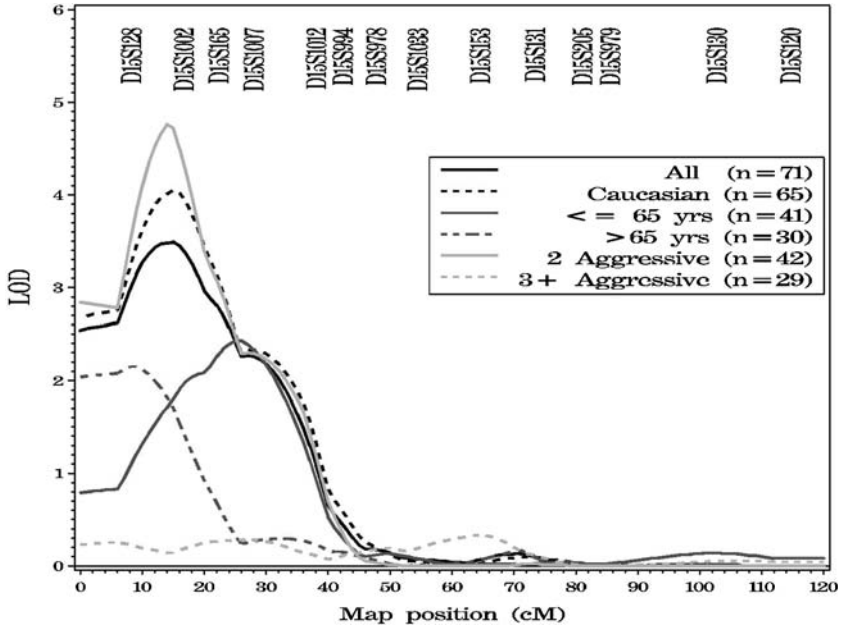

Fig. 2 Results from our nonparametric linkage analyses at chromosome 15 using subsets of the 71 aggressive pedigrees. We present results from the complete set of 71 aggressive pedigrees, from the subset of 65 Caucasian aggressive pedigrees, and from subsets of aggressive pedigrees stratified by average age at diagnosis and number of aggressive cases

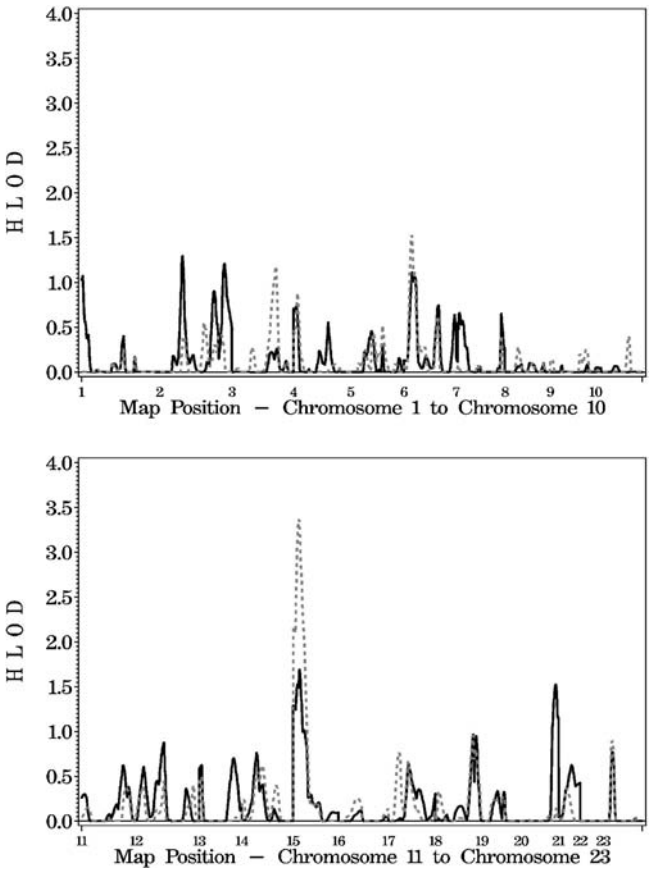

Fig. 3 Results from our parametric GWSs for the 71 informative pedigrees with two or more aggressive PCa cases. Results from the dominant mode-of-inheritance model are shown using a *black solid line* and results from the recessive mode-of-inheritance model are shown using a *gray hashed line*

susceptibility genes. Segregation analyses and epidemiological studies suggest the presence of multiple PCa susceptibility loci. Collections of pedigrees with large numbers of aggressive cases will likely be more biased toward detecting highly penetrant susceptibility genes. One plausible explanation for the apparent discrepancy in results between the two subsets of pedigrees is genetic heterogeneity; specifically pedigrees with three or more aggressive cases may be less likely to link to 15q11-12 than pedigrees with just two aggressive cases. Given the relatively small number of pedigrees and the multiple numbers of subsets analyzed at 15q11-12, another obvious explanation for the apparent difference in results between the subset of pedigrees with two or more aggressive cases and the subset of pedigrees with three or more affecteds is random chance. In any case, our results suggest that validation studies of our 15q12 findings should include a wide range of pedigrees in terms of numbers of aggressive cases and not just focus on pedigrees with large numbers of aggressive cases.

We did not find any evidence supporting the regions identified by Chang et al. (2005) and Stanford et al. (2006) on chromosomes 22q11, 22q13, or Xq27-28. Our observed LOD scores were 0.00 across all three regions. Chang et al. reported HLODs for the dominant parametric model across the genome and for these models the HLOD scores at both 15q12 and 6p22-23 were, by inspection, both approximately 0.40. Results were not presented in these regions for either a recessive parametric model or for any nonparametric models. Stanford et al. (2006) presented results for both a nonparametric model and the two parametric models described in the current study. No evidence for linkage was reported at either 15q12 or 6p22-23 for any of the models. There are some differences between the John Hopkins pedigrees used in Chang et al. (2005) and the UM-PCGP pedigrees that may contribute to the different results observed in our two studies. The Hopkins pedigrees tend to be larger, have more PCa cases per pedigree, and have PCa cases in more generations than the UM-PCGP pedigrees (Smith et al. 1996; Lange et al. 2003; Gillanders et al. 2004). Average age at diagnosis, percent of families that are African–American, and percent of families with evidence for male-to-male transmission are very similar between the pedigree sets used by the two studies. PROGESS pedigrees used in Stanford et al. (2006) tend to have similar characteristics to those observed for UM-PCGP pedigrees, with the exception that UM-PCGP has a higher proportion of African–American pedigrees.

It is also important to consider that different groups may use different definitions of aggressive disease. For example, although Chang et al. (2005) used a very similar definition that is used in the present study, they also included a subset of men with stage II cancer (T2C N0 M0 or PCa involving both lobes of the prostate) in their category of aggressive disease. Men with progressive disease after primary therapy indicated by either bone scan or biochemical recurrence (rise in serum PSA) were also included in addition to those men who ultimately died of cancer. The definition being used by Stanford et al. (2006) is identical to the one used in this report except that only men who died from metastatic PCa before age 65 years were considered to have clinically aggressive disease. We chose not to use this age restriction because we considered that death due to PCa at any age was indicative of aggressive disease and that this definition was overly restrictive as less than 15% of deaths from PCa occurred before age 65 years in our GWS families. In any case, it is clear that not all PCa is the same and it is highly plausible that future success in mapping PCa susceptibility genes will be contingent upon using more restrictive classification rules for defining the phenotype.

Other analytical approaches have been used to identify PCa genes that contribute to a clinically aggressive phenotype. Several studies, including a report using a subset of UM-PCGP pedigrees (Slager et al. 2006), have performed quantitative trait linkage analyses using Gleason grade as a clinical marker for severity (Witte et al. 2000; Neville et al. 2002, 2003; Paiss et al. 2003; Slager et al. 2003). Several regions, most notably 7q32 and 19q12, have been implicated by multiple studies.

For these analyses, evidence for linkage using Gleason grade as a quantitative trait is supported by both increased allele sharing between family members concordant for Gleason grade as well as decreased allele sharing between family members discordant for Gleason grade. Individuals without disease are only used to infer identity-by-descent information between affected relatives. These studies are likely better powered than our current approach to detect genes that modify disease severity conditional on having PCa and less powered for finding genes that specifically predispose men to aggressive forms of the disease given that our approach focuses specifically on the degree of allele-sharing between men with aggressive disease. The current study found no significant evidence for linkage to either 7q32 or 19q12.

PCa is a multifactorial trait and has a highly variable degree of severity. To date, little success has been achieved in mapping PCa genes through linkage analyses and subsequent follow-up candidate gene studies. A small number of linkage studies have resulted in the identification of a few candidate genes, including *RNASEL* on chromosome 1 (Carpten et al. 2002), *ELAC2* on chromosome 17 (Tavtigian et al. 2001), and *MSR1* on chromosome 8 (Xu et al. 2002). However, confirmation studies have produced mixed results (Schaid 2004) and these genes do not appear to explain a significant fraction of the genetic susceptibility to this disease. Focusing on aggressive PCa could be an important step for identifying PCa susceptibility genes. From an epidemiological and medical standpoint, it makes sense to focus on identifying genes that predispose individuals to forms of PCa that severely impact life expectancy and quality of life. From a genetic and statistical standpoint, reducing the heterogeneity in the phenotype can increase the power to identify PCa genes. The classical example demonstrating the importance of identifying pedigrees with homogeneous phenotypes was the cloning of the *BRCA1* gene for breast cancer susceptibility (Hall et al. 1990). The identification of this gene was facilitated by focusing on pedigrees with early age at onset of the disease. We have made great strides recently in our ability to detect cancerous lesions in the prostate early in the disease process. The clear benefit from this greater ability to detect cancerous lesions is quicker intervention and greater cure rates. The problem for geneticists is that we are often faced with the dilemma of how to deal with the different severities of PCa, especially when there is considerable variability within PCa families. It is highly plausible that men from a family with positive history for the disease are diagnosed at a high-rate of insignificant PCa partially due to increased screening and the higher probability of biopsy. Silverberg et al. (2001) have shown that even a small amount of phenotype misclassification can have a serious consequence on statistical power to detect linkage. Thus, focusing attention on aggressive disease represents a potentially powerful alternative approach for mapping PCa susceptibility genes. However, such a focus would dramatically reduce the sample sizes available to individual investigators in terms of numbers of informative pedigrees and numbers of PCa cases per pedigree. As discussed in Leal and Ott (2000), there is a trade-off between the cost of reducing sample size and the benefit of focusing on more homogeneous subsets of pedigrees. Large linkage consortiums, such as the ICPCG, should make subset analyses, such as those that focus solely on aggressive disease, more palatable. However, it remains to be seen whether focusing on aggressive PCa will ultimately lead to greater success for mapping PCa susceptibility genes.

Acknowledgments We express our gratitude to the many families who have participated in the University of Michigan Prostate Cancer Genetics Project (UM-PCGP) as well as project coordinators Caroline Mohai, Carrie Couyoumjian, and Alicia Mastronardi. We also express our appreciation to two anonymous reviewers for their insightful comments regarding an earlier version of this manuscript. This research was funded by US Public Health Service National Institutes of Health Grants CA 079596 and CA 089600.

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