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No evidence of linkage to chromosome 1q42.2–43 in 131 prostate cancer families from the ACTANE Consortium

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Summary Genetic linkage studies worldwide have proposed various chromosomal localizations for prostate cancer susceptibility genes. A recent study found evidence for linkage to chromosome 1q42.2–43. The aim of our study was to attempt to confirm these findings by performing linkage analysis in 131 families with multiple prostate cancer cases selected from the ACTANE (Anglo, Canada, Texas, Australia, Norway, EU Biomed) Consortium. Parametric and non-parametric linkage (NPL) analyses were performed. Two-point LOD scores failed to show evidence of linkage at any marker (maximum two-point LOD score = 0.40 at recombination fraction θ = 0.2 with marker D1S2850). Using a multipoint heterogeneity analysis, the estimated proportion of families linked to this putative locus (α) was 0% (95% CI = 0.00–0.33). Non-parametric linkage analysis also found no evidence of linkage (maximum NPL score = – 0.12, P = 0.55). This analysis of 131 ACTANE families does not support the presence of a locus for a prostate cancer susceptibility gene at 1q42.2–43. Although we cannot rule out the existence of such a locus, analysis indicates that less than 16% of families could be linked to this region. These findings may be a reflection of the locus heterogeneity involved in this disease indicating that there are still other major susceptibility loci to be identified. © 2000 Cancer Research Campaign http://www.bjcancer.com

Many case-control and cohort studies dating as far back as 1956 have observed the familial aggregation of prostate cancer. Segregation analyses (e.g. Steinberg et al, 1990) have given support for the importance of genetic factors in prostate cancer development. Various models for the mode of inheritance have been proposed. A cohort study by Monroe et al (1995) suggested that an X-linked or autosomal recessive susceptibility gene or genes may be involved. However, a complex segregation analysis performed by Carter et al (1992) found evidence for a rare highly penetrant prostate cancer susceptibility gene which is inherited in an autosomal dominant fashion. Two other studies (Gronberg et al, 1997; Schaid et al, 1998) found further support for a high-risk dominant model.

Linkage studies have found some evidence for various loci for major prostate cancer susceptibility genes. The first chromosomal localization of a putative prostate cancer gene, HPC1 (hereditary prostate cancer 1) was suggested by Smith et al (1996) from a genome wide search in 91 prostate cancer families. This study found evidence of linkage of the disease to markers on chromosome 1q24–25, with an estimated 34% of these families being linked. Although three other groups have found some confirmatory evidence for linkage in a similarly small proportion of such families (Cooney et al, 1997; Hsieh et al, 1997; Neuhausen et al, 1999), other studies have failed to find evidence for linkage at this locus (Eeles et al, 1998; Cannon-Albright and Neuhausen, 1997; McIndoe et al, 1997; Thibodeau et al, 1997). A recent meta-analysis combining these published and new data from these groups has estimated that only 6% of families worldwide are linked to this locus (Xu et al, 2000). In a recent genome screen of multiplex sibships with prostate cancer,

Suarez et al (2000) found nominally significant linkage at two distal markers approximately 20cM from the putative HPC1 region.

More recently another prostate cancer susceptibility locus has been described by Xu et al (1998) on the X chromosome at Xq27–28. This locus was estimated to account for approximately 16% of the prostate cancer families studied. A subsequent study by Lange et al (1999) has provided further support for the existence of a prostate cancer susceptibility gene in this region in a linkage study of 153 families with at least two members affected with prostate cancer.

These findings suggest that locus heterogeneity is a feature of this disease and there may be several major susceptibility loci involved.

Berthon et al (1998) reported evidence for linkage to the region 1q42.2–43 from a study of 47 French and German multiple-case families with a maximum two-point LOD score of 2.7 at marker D1S2785. Their heterogeneity analysis estimated that the proportion of families with linkage to this locus could be as high as 50%. In a stratified analysis of nine families with early-onset prostate cancer (age less than 60 years at diagnosis), multipoint LOD and NPL scores of 3.31 and 3.32 (P = 0.001) respectively, were obtained with an alpha of approximately 20%. They named the putative susceptibility gene in this region PCaP (predisposing gene for cancer of the prostate). Gibbs et al (1999) also performed a linkage analysis of this region in 152 prostate cancer families. Both parametric and non-parametric analysis revealed no significant evidence of linkage. Further analysis of family subsets, stratified according to mean age of diagnosis and number of affected members, did not provide any significant evidence for linkage. In a further attempt to confirm the findings by Berthon et al, Whittemore et al (1999) conducted a linkage study in 97 families with at least three affected cases using three markers. Multipoint LOD and NPL scores failed to support linkage, even when analysis was restricted to the 14 families in their

set with early-onset disease. In the genome search by Suarez et al (2000), nominally significant evidence for linkage was found at two markers in the PCaP region in a subgroup of families with late-age-at-onset prostate cancer.

The aim of our study was to attempt to confirm the findings of Berthon et al (1998) by performing linkage analysis in 131 prostate cancer families from the ACTANE Consortium using microsatellite markers in the 1q42.2–43 region.

MATERIALS AND METHODS

Family selection

A total of 131 families were selected from the ACTANE Consortium (excluding Canada) for this study. The criteria for selection were: three or more relatives affected with prostate cancer in a family, or a relative pair affected with the disease, one or both of whom were aged 65 years or less at diagnosis. The ACTANE consortium is a collaboration between the Cancer Research Campaign (CRC)/British Prostate Group (BPG) UK Familial Prostate Cancer Study (Anglo) and other groups worldwide with prostate cancer family sets from Canada, Texas, Australia, Norway, EU Biomed. Families were collected as follows:

UK group
All families were recruited through collaborating urologists, geneticists and oncologists via the CRC/BPG UK Familial Prostate Cancer Study. Within these families 97% of cases were clinically detected and the remaining 3% were diagnosed as a result of a prostate-specific antigen (PSA) screen. Details of family history were obtained from questionnaires completed by the index case. Cases of prostate cancer were confirmed by pathology reports, self-report, medical records or death certificates.

Texan group
Index cases were patients referred to the UTMD Anderson Cancer Centre, Houston, Texas, whose diagnoses of prostate cancer were subsequently confirmed by pathology review.

Australian group
Families were recruited from the 'Risk factors for Prostate Cancer' study which is a population-based case-control study conducted in Melbourne, Sydney and Perth. All probands had histopathological confirmation of prostate cancer. Reported prostate cancer cases in family members were confirmed wherever possible by matching against the National Cancer Registry and National Death Index.

Norwegian group
Families were recruited from the cancer genetics clinic at the Norwegian Radium Hospital and were included if prostate cancer affected: at least three relatives in the same lineage regardless of age of onset; or a relative pair with one aged 65 years or younger at diagnosis. Diagnosis in the prostate cancer cases was verified from the medical records. For family members reported by the cases to have prostate cancer, the diagnosis was verified by the National Cancer Registry or by the medical records when possible.

EU Biomed group
These families were collected from major urological centres across Europe. These centres have been participating in the

Table 1 Family breakdown by centre, age and number of affected members

Number of cases	UK	Texas	Australia	Norway	EU Biomed	Total
Two affected	32	3	14	1	1	51
Three or four affected	32	5	24	2	4	67
Five or more affected	5	5	1	2	0	13
Total	69	13	39	5	5	131
[a] Age < 65	30	3	22	3	2	60
[a] Age ≥ 65	39	10	17	2	3	71

[a]Age figures refer to average age at diagnosis of affecteds.

collection of families for the analysis of high- and low-penetrance genes in prostate cancer. Only those cases in whom the diagnosis of prostate cancer could be verified from histological or medical records were included in the analysis. Breakdown of families by centre, number of affected members and age at diagnosis is shown in Table 1.

Full approval for this study was obtained from the Research Ethics Committee.

Genotype analysis

DNA for analysis was extracted from lymphocytes from blood samples provided by both affected and unaffected family members in the study. All individuals were genotyped using four polymorphic markers spanning the PCaP candidate region of 1q42.2–43 as reported by Berthon et al (1998). The dinucleotides used were D1S2850-11.2cM-D1S2785-1.2cM-D1S321-6.0cM-D1S2842. Sex-averaged distances between markers were taken from genetic maps from the Marshfield Medical Research Foundation (Broman et al 1998). Samples from all collaborating groups were genotyped at one centre.

PCR was performed as follows: one primer of each pair was radiolabelled with ^{32}P using ^{32}P (γ-dATP) and T4 polynucleotide kinase (PNK) in the presence of PNK-ligase buffer; the reaction mixture contained 1.5 μl of KCL Tris PE Buffer (× 10), 0.60 μl 1.0 mM MgCl$_2$ (Perkin Elmer) for markers D1S321 and D1S2785 / 2.0 mM MgCl$_2$ for marker D1S2850/ 1.5 mM MgCl$_2$ for marker D1S2842, 0.15 μl (final concentration 1.0 mM) total deoxynucleotide triphosphates (Stratagene), 0.15 μl of each primer (Oswel) at final concentration of 0.30 μM, 0.6 units Perkin Elmer gold Taq Polymerase, 5 μl genomic DNA (5 ng μl^{-1}) and water to a total volume of 15 μl. PCR was performed on a Hybaid thermocycler using annealing temperatures optimized for each primer, for a total of 35–40 cycles. PCR products were loaded onto 6% denaturing polyacrylamide gels. Controls of known size were loaded at regular intervals to act as size markers. Gels were run at 80 W for 2.5–3.0 h, dried and then exposed to X-ray film for 12 h to 3 days. Alleles were then scored visually by one observer and confirmed by a second observer. Allele scores were assigned on the basis of comparison with the CEPH family member 1347-02 who was used as a control individual. Control allele frequencies for each marker were derived from the CEPH family database (Dausset et al, 1990)

Statistical analysis

Linkage of prostate cancer to the region 1q42.2–43 was first assessed by parametric LOD score analysis, based on the prostate-cancer-

susceptibility model suggested by Carter et al (1992). This model assumes that prostate cancer susceptibility is due to a dominant gene with a population frequency of 0.003 and an overall penetrance of 88% by 85 years of age in carriers. This was also the basis of the models used by Berthon et al (1998) in their linkage analysis. Two-point LOD scores were calculated using Fastlink (Cottingham et al, 1993; Schäffer et al, 1994). Multipoint heterogeneity LOD (HLOD) scores were computed using Genehunter (Kruglyak et al, 1996) over the 18 cM distance spanned by the four markers. Families too large for exact computation by Genehunter were analysed using Vitesse (O'Connell et al, 1995).

Due to doubt regarding the appropriate model for age-specific prostate cancer susceptibility, non-parametric linkage scores were calculated to compare identical-by-descent sharing among all affecteds in a pedigree, with that expected under no linkage.

Analysis was performed across the whole family set and then in subsets stratified according to: number of affected men per family; and average age at diagnosis (age < 65 years and age ≥ 65 years).

RESULTS

LOD scores from the two-point parametric analysis are given in Table 2. The results show no evidence for linkage at any marker. The largest positive LOD score was 0.40 at DIS2850 with recombination fraction $\theta = 0.2$.

Non-parametric multipoint analysis using Genehunter found no evidence of linkage to 1q42.2–43 at marker D1S2785 either for all families combined (multipoint NPL score = –0.12, $P = 0.55$) or separately, according to number of cases affected per family: two cases (multipoint NPL score = –0.44, $P = 0.67$); three or four cases (multipoint NPL score = 0.08, $P = 0.46$); ≥ five cases (multipoint NPL score = 0.30, $P = 0.35$). Analysis was also performed in family subsets according to average age at diagnosis: under 65 years (multipoint NPL score = 0.12, $P = 0.45$) and 65 years and over (multipoint NPL score = –0.27, $P = 0.60$).

The results of the multipoint heterogeneity analyses are shown in Tables 3 and 4. The results do not provide any evidence of linkage at 1q42.2–43, the overall HLOD score for all 131 families was 0.00 and the estimated proportion linked (α) was 0 (95% CI = 0.00–0.33). For families with five or more cases, the HLOD was 0.01, with $\alpha = 0.16$ (95% CI = 0–1); for families with only two cases the HLOD was also 0.00, with $\alpha = 0$ (95% CI = 0.00–0.57). Analysis stratified by age at diagnosis showed that for the 60 families that had at least two members diagnosed at age 65 years or less, HLOD was 0.00 ($\alpha = 0$) while the HLOD for the other 71 families was 0.01 ($\alpha = 0.07$).

The results presented in Table 4 have assumed that the candidate gene lies midway between markers D1S2785 and D1S321, as was suggested by the peak LOD scores obtained in this region by Berthon's group. Therefore, we also performed heterogeneity and

Table 2 Two-point LOD scores for four markers on chromosome 1q42.2–43

Marker	Recombination fraction (θ)						
	0.0	0.01	0.05	0.1	0.2	0.3	0.4
D1S2850	–2.53	–2.04	–0.82	–0.07	0.40	0.31	0.10
D1S2785	–11.39	–9.64	–5.94	–3.57	–1.31	–0.42	–0.08
D1S321	–0.89	–0.65	–0.07	0.26	0.38	0.24	0.07
D1S2842	–8.45	–7.38	–4.72	–2.85	–1.00	–0.28	–0.05

Table 3 Multipoint linkage analysis of 131 families (non-parametric analysis)

Marker and relative position (cM)	Multipoint Lod score	α	MultiPoint HLOD score	Multipoint NPL score	*P*
D1S2850:					
0.00	–5.31	0.12	0.05	0.09	0.46
2.25	–4.72	0.11	0.03	0.05	0.48
4.50	–5.01	0.09	0.02	0.01	0.49
6.75	–5.98	0.07	0.01	–0.03	0.51
9.00	–7.86	0.05	–0.00	–0.08	0.53
D1S2785					
11.25	–12.41	0.04	–0.00	–0.12	0.54
11.50	–12.12	0.04	–0.00	–0.12	0.54
11.75	–11.91	0.03	–0.01	–0.12	0.55
11.99	–11.74	0.03	–0.01	–0.13	0.55
12.24	–11.62	0.03	–0.01	–0.13	0.55
D1S321					
12.49	–11.54	0.03	–0.01	–0.13	0.55
13.68	–10.78	0.02	–0.01	–0.17	0.56
14.87	–10.34	0.02	–0.01	–0.21	0.58
16.06	–10.15	0.02	–0.01	–0.24	0.59
17.25	–10.16	0.01	–0.01	–0.27	0.60
D1S2842					
18.44	–10.38	0.01	–0.01	–0.31	0.62

Table 3 Multipoint linkage analysis of 131 families (non-parametric analysis)

Families	Multipoint Lod score	HLOD score[a]	α	(95% CI) NPL score	*P*
All 0.55	–11.91	0.00	0.00	(0.00–0.33)	–0.12
Two cases 0.67	–2.33	0.00	0.00	(0.00–0.57)	–0.44
Three/four cases 0.46	–8.95	0.01	0.07	(0.00–0.43)	0.08
five-plus cases 0.35	–0.62	0.01	0.16	(0.00–1.00)	0.30
Age ≤ 65 0.45	–7.07	0.00	0.00	(0.00–0.43)	0.12
Age > 65 0.60	24.84	0.01	0.07	(0.00–0.49)	20.27

[a]Assuming heterogeneity

sub-group analyses, maximizing the position of the putative susceptibility gene over the whole 18 cM region. Results showed little change: the maximum HLOD score was only 0.37 ($\alpha = 0.32$), obtained at the location of marker D1S2850, in families containing three or four cases.

DISCUSSION

Analyses of the set of 131 ACTANE prostate cancer families overall showed no significant evidence of linkage to 1q42.2–43 region using four markers flanking the putative PCaP region (two-point LOD = –0.89 to –11.39, across the region of maximum multipoint LOD reported by Berthon et al, 1998). Overall the estimated proportion of families linked was zero, although we could not confidently exclude values less than one-third. Stratification of the family set into sub-groups according to average age at

diagnosis and number of affected family members also yielded no evidence of linkage.

Our findings are similar to those of Gibbs et al (1999) and Whittemore et al (1999) who also failed to find evidence of linkage after analysis according to a similar stratification. Such conflicting evidence regarding linkage to this region on chromosome 1 may be influenced by various factors, particularly with respect to the sample set. Indeed, some differences exist in the profiles of families used in this study. Berthon's group used 47 families of French and German origin only while our study comprised 131 families of both European and North American origin. All French and German families studied had a minimum of three members affected with the disease, while we included families with only two members affected. However, it seems unlikely that these differences alone could account for the discrepancy in results found between the two groups. Whittemore et al (1999) used only three markers to genotype 82 families of predominantly American origin. Similarly, out of the 152 families used in the study by Gibbs et al (1999) only six were of non-white origin, the rest were white American. Thus our study used a wider cross-section of families of diverse international origin.

Berthon et al (1998) also looked for loss of heterozygosity (LOH) at 1q42.2–43 in addition to linkage. Allelic loss in this region was seen in 11 tumours, of which five also had overlapping alterations in the 1q24–25 area. This finding of LOH is of particular interest because there is another putative locus, HPC1 at 1q24–25 (Smith et al, 1996). We have yet to carry out LOH studies, but this will be undertaken as part of a future study.

In conclusion, this analysis of 131 multiple-case prostate cancer families failed to show evidence of linkage at chromosome 1q42.2–43. It is becoming increasingly evident from the results of recent linkage studies in this field that several major loci may be involved in the increased susceptibility to inherited prostate cancer. Thus, 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 further extended pedigrees and meta-analyses of large data sets are therefore crucial in the successful identification of prostate-cancer-susceptibility loci.

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APPENDIX

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