

Description of the International Consortium for Prostate Cancer Genetics, and Failure to Replicate Linkage of Hereditary Prostate Cancer to 20q13

Daniel J. Schaid,^{1*} Bao Li Chang,²
and The International Consortium for Prostate Cancer Genetics

¹Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota

²Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, North Carolina

The International Consortium for Prostate Cancer Genetics (ICPCG) is an international collaborative effort to pool pedigrees with hereditary prostate cancer (PC) in order to replicate linkage findings for PC. A strength of the ICPCG is the large number of well-characterized pedigrees, allowing linkage analyses within large subsets. Given the heterogeneity and complexity of PC, the historical difficulties of synthesizing different studies reporting positive and negative linkage replication, and the use of different statistical analysis methods and different stratification criteria, the ICPCG provides a valuable resource to evaluate linkage for hereditary PC. To date, linkage of chromosome 20 (*HPC20*) to hereditary PC has been one of the strongest linkage signals, yet the efforts to replicate this linkage have been limited. This paper reports a linkage analysis of chromosome 20 markers for 1,234 pedigrees with multiple cases of PC ascertained through the ICPCG, and represents the most thorough attempt to confirm or refute linkage to chromosome 20. From the original 158 Mayo pedigrees in which linkage was detected, the maximum heterogeneity LOD (HLOD) score, under a recessive model, was 2.78. In contrast, for the 1,076 pedigrees not included in the original study, the maximum HLOD score (recessive model) was 0.06. Although, a few small linkage signals for chromosome 20 were found in various strata of this pooled analysis, this large study failed to replicate linkage to *HPC20*. This study illustrates the value of the ICPCG family collection to evaluate reported linkage signals and suggests that the *HPC20* region does not make a major contribution to PC susceptibility. *Prostate* 63: 276–290, 2005. © 2004 Wiley-Liss, Inc.

KEY WORDS: HPC20; linkage heterogeneity; familial prostate cancer

INTRODUCTION

Prostate cancer (PC) is the most frequent cancer among men in most developed countries, yet little is known about its causes. Older age, African-American ancestry, and a positive family history of PC have long been recognized as important risk factors. Furthermore, there is a growing body of evidence that genetics is likely to play a key role (for detailed reviews, see References 17,27,36). Familial aggregation studies have generally found consistent levels of PC risk; a recent meta-analysis of 11 case-control studies and two cohort studies that reported the risk of PC according to family history among first degree relatives estimated a pooled odds ratio (OR) of 2.5 (95% CI 2.2–2.8) [20]. In all but one of these studies, the OR was greater if a brother was

affected than if a father was affected. Segregation analyses of the inheritance pattern of PC have generally supported rare autosomal dominant susceptibility alleles, although not all studies have supported a model this simple. For example, Cui et al. [11] concluded that a two-locus model fit best, with early-onset pedigrees

Members of the International Consortium for Prostate Cancer Genetics are listed under heading "The Members of the International Consortium for Prostate Cancer Genetics."

*Correspondence to: Daniel J. Schaid, PhD, Harwick 775, Section of Biostatistics, Mayo Clinic College of Medicine, Rochester, MN 55905.
E-mail: schaid@mayo.edu

Received 8 July 2004; Accepted 7 September 2004

DOI 10.1002/pros.20198

Published online 14 December 2004 in Wiley InterScience
(www.interscience.wiley.com).

more likely explained by an autosomal dominant effect, and late-onset pedigrees more likely explained by either an autosomal recessive or X-linked effect. A recent large study of twins by Lichtenstein et al. [25] based on Swedish, Danish, and Finnish twin registries, estimated that the proband-wise concordance rate (interpreted as the recurrence risk in a co-twin of an affected man) was 21.1% for MZ twins and 6.4% for DZ twins. In a subsequent analysis and interpretation of this same data, Risch [35] suggested that PC may not be explained by independent rare autosomal dominant genes, but maybe by recessive and/or multiple interacting genes. The result from Lichtenstein et al. are remarkably similar to an earlier large study of World War II veteran twins from the USA, which reported a proband-wise concordance rate of 27.1% for MZ twins and 7.1% for DZ twins [32]. Despite this growing evidence that genetics is likely to play an important role in PC, the findings from linkage studies have been disparate.

Linkage of PC susceptibility was first reported for chromosome 1q23-25 (*HPC1* region) [42]. However, follow-up studies provided conflicting conclusions. Because of these early studies, the International Consortium for Prostate Cancer Genetics (ICPCG) was formed in order to bring together many of the groups investigating the genetic linkage of PC. This collaboration led to the combination of 772 families from nine international groups in an effort to evaluate the strength of evidence for linkage to *HPC1*. An advantage of this collaborative effort was the ability to create homogeneous subsets of a large number of pedigrees, in an effort to control the large amount of heterogeneity that is likely to dilute linkage signals. Some weak confirmatory linkage evidence was found, with a heterogeneity LOD score (HLOD) of 1.4 [47]. The evidence of linkage to *HPC1* was found to be greater among 491 pedigrees with male-to-male disease transmission, with an HLOD = 2.6. Thus, this study provided some supportive evidence for a PC susceptibility gene, although the fraction of such families that segregate this gene is likely to be small.

Other chromosomal regions have been reported to be linked to PC susceptibility, including chromosome 1q42.2-43 (*PCAP*) [4]; chromosome Xq27-28 (*HPCX*) [49]; chromosome 1p36 that may be involved in families with both brain and PC (*CAPB*) [16]; chromosome 8p22-23 [50]; chromosome 17p (*HPC2* region) [43]; chromosome 7q in Jewish families [15]; and chromosome 20q13 (*HPC20*) [3]. Possible candidate genes harboring disease-associated variants have been suggested for *HPC1* (*RNASEL*), 8p (*MSR1*), and *HPC2* (*ELAC2*), although none have been definitively established. In addition to these early reports, ten genome-scans have been recently published, of which eight were summarized in

Reference 13, and all ten summarized in Reference 36. Three chromosomes, 4, 6, and 7, had LOD scores of at least 1.0 across five independent studies, and two chromosomes, 11 and 16, had LOD scores of at least 2 for two independent studies. Perhaps one of the most remarkable observations was that no single chromosome provided consistent strong linkage evidence, say LOD scores at least 3.0, across two or more studies. Given the large amount of heterogeneity of PC, subset analyses are warranted, stratifying by factors such as age at diagnosis, amount of family history, and severity of disease. However, such an analysis would require pooling of a large number of families to achieve large enough subsets to have adequate power to evaluate linkage, which this ICPCG study achieves.

This report has two aims. The first aim is to describe the large international collaborative effort by the ICPCG to study PC genetics. The second aim is to evaluate linkage for chromosome 20q13, in an effort to replicate the findings of Berry et al. [3]. This initial study, conducted at the Mayo Clinic, analyzed 162 families. Evidence of linkage to markers on chromosome 20 was found, with a maximum HLOD of 1.08 under a dominant model, and 2.94 under a recessive model. The linkage evidence was strongest among families with an average age at diagnosis 65 years, fewer than five men affected, and no male-to-male disease transmission. Interestingly, these results are consistent with segregation results from Cui et al. [11], which suggested that for older-onset disease, a recessive model is more likely. Attempts to replicate the chromosome 20 region have thus far produced only very weak linkage evidence. In a study of 159 families, Zheng et al. [51] found a maximum HLOD of 0.08 for a dominant model and an HLOD of 0.42 for a recessive model, with the strongest evidence in the same types of families as those found by Berry et al. In another study of 172 families, Bock et al. [5] found an HLOD of 0.08, with stronger evidence provided by a subset of 16 African-American families (HLOD = 0.86). Finally, in a study of 66 families [7], HLODs of 0.03–0.11 were found, depending on the assumed penetrance. Interestingly, the four genes *CSEIL*, *ZNF217*, *MYBL2*, and *STK15* within 20q13 have been shown to be over-expressed in PC, and two of these (*MYBL2* and *STK15*) are over-expressed in prostate metastases [1]. However, linkage to *HPC20* has yet to be confirmed, and no susceptibility genes in this region have been identified.

METHODS

Ascertainment of Families

The ICPCG provides infrastructure and scientific leadership to facilitate collaborative studies across a large number of groups studying the genetic basis of

PC. An important aim of the ICPCG is to provide mechanisms to replicate linkage findings for hereditary PC in a large collection of well-characterized pedigrees, given the historical difficulty of any single group of investigators replicating a linkage finding for this complex disease [13,30,36]. Eleven groups participated in this combined linkage analysis of chromosome 20q13, with a total of 1,234 hereditary PC pedigrees. Although the methods of pedigree ascertainment and confirmation of PC diagnoses differed somewhat across the different groups, only affected men with their PC diagnosis confirmed by medical records or death certificates were included in this analysis. The research protocols and informed consents were approved by each group's institutional review boards. The 11 groups that participated in this linkage analysis are briefly summarized below.

ACTANE (Anglo/Canadian/Texan/Australian/Norwegian/EU Biomed). Details of ACTANE ascertainment are provided by Edwards et al. [14]. A summary of the participating groups are as follows:

- **Anglo (UK):** The UK Familial Prostate Cancer Study ascertains blood samples from families in which three or more men are affected with PC, or in which two relatives are affected with PC with at least one diagnosed at age <65 years. Over 80% of the cases in the UK series had presented symptomatically and had clinically detectable disease. All cases were verified by histology report or death certificate.
- **Canada:** Families with at least two affected men with PC were recruited in Montreal over the years 1992–1999. Families were identified through a PC clinic associated with McGill University, through referral by urologists elsewhere in Canada and through the Patient Advocates for Advanced Cancer Treatment (PAACT). At least 50% of the cases were detected as a result of PSA screening.
- **Texas:** Index cases were patients referred to the University of Texas M.D. Anderson Cancer Center, Houston, TX. Diagnoses of PC were subsequently confirmed by pathological review. Approximately 40% were clinically detected.
- **Australia:** Families were ascertained from a population-based case-control study conducted in Melbourne, Sydney, and Perth between 1994 and 1998 [11]. All probands had histopathological confirmation of PC with Gleason scores of >4. Affected family members' diagnoses were verified on the National Cancer Registry or by medical record where possible. Approximately 65% of all cases were clinically detected.
- **Norway:** Families were ascertained through the Department of Medical Genetics at the Norwegian

Radium Hospital. Diagnoses of PC were confirmed by medical records or the Norwegian Cancer Registry. Families were also ascertained via urology clinics in Ullevaal Hospital. All Norwegian cases presented symptomatically.

- **EU Biomed:** These families were collected from major urological centers over Europe. For this study, none were large enough to include in this linkage analysis.

BC/CA/HI (British Columbia, California, Hawaii). Families were ascertained to have three or more medically verified diagnoses of PC among first- or second-degree relatives. The families were identified from a multiethnic case-control study conducted in Hawaii, Los Angeles, San Francisco, and Vancouver [44], as well as from screens of the British Columbia Cancer Registry and the San Francisco-Oakland Cancer Registry and from publicity in the San Jose Mercury News. Most families fulfilled one or more of the proposed criteria for families in which PC is likely to be hereditary (i.e., three or more affected individuals within one nuclear family, affected individuals in three generations, and/or two or more individuals affected at <55 years of age). For further details, see Reference 18.

CeRePP (Centre de Recherche pour les Pathologies Prostatiques), France. Families with at least three affected men were selected for linkage analysis, including the 37 French pedigrees that were analyzed in a previous genome-wide screen [4]. All families were from south and west Europe; some families from France appeared to originate from Spain and Portugal. For this analysis, two other families originating from North Africa (one from Tunisia and one from Algeria) were also included. All affected men who were genotyped had their PC confirmed by a pathological record. For further details, see References 7,8.

JHU (Johns Hopkins University). All hereditary PC families, each having at least three first-degree relatives affected with PC, were collected and studied at the Brady Urology Institute at Johns Hopkins Hospital (Baltimore, MD). Families were ascertained from three sources. A majority of them were ascertained through referrals generated as a response to a letter to 8,000 urologists throughout the country. The second source was from family history records of the patient population seen at Johns Hopkins Hospital for treatment of PC. The third source was the respondents to articles published in a variety of lay publications describing the PC family studies. PC diagnosis was verified by medical records for each affected male studied. Further details can be found in Reference 48.

Mayo (Mayo Clinic). All men who received either a radical prostatectomy for clinically localized PC in the Department of Urology, or radiation therapy in the Division of Radiation Oncology, Mayo Clinic, were sent a family cancer-history survey [37]. From the surveys, families were selected for further follow-up because they reported at least three men with PC in the family, of which two men may be alive for recruitment. Family histories were confirmed and extended by telephone interviews. Additional men were referred for the Mayo Prostate Cancer Family Study, primarily through the Department of Urology. Medical records were reviewed for all Mayo Clinic patients, and medical records and paraffin-embedded tumor blocks were requested for all men seen outside of the Mayo medical system. For further details, see References 2,3,12,37. In the initial report of linkage to chromosome 20, 162 families were used [3]. However, after completing all markers for the genome screen, three families were identified to have questionable paternity, via relationships checks by the software Relpair [6]. In addition, medical records were not available to confirm PC for one family. These four families were excluded from this current pooled analysis.

Michigan (University of Michigan). Men with PC who had at least one living affected relative were asked to participate in the University of Michigan Prostate Cancer Genetics Project by providing a blood sample, extended family history, and access to medical records. Eligibility criteria for inclusion of a family in the current study included: having at least three family members with confirmed cases of PC or having two confirmed cases occurring in men ≤ 55 years old and having available DNA on at least two confirmed cases (excluding father-son pairs). For further details, see Reference 24.

PROGRESS (Prostate Cancer Genetic Research Study, Fred Hutchinson Cancer Research Center). Two hundred seventy one HPC families were ascertained from throughout North America and several other countries by advertising a toll-free number via public media, health-related publications, and the internet, as well as communications with urologists, other health-care professionals, and PC support groups as described previously [26]. To be eligible for the study, families were required to meet at least one of the following criteria: (1) have three or more first-degree relatives with PC; (2) have three generations with PC, either through paternal or maternal lineage; or (3) have two first-degree relatives with PC diagnosed before age 65 or who were African-American. All PC survivors and selected unaffected men and women were invited to join the Prostate Cancer Genetic

Research Study (PROGRESS). On average, eight members of each family completed a study questionnaire on medical and family cancer history and provided a blood sample. Medical records and death certificates were used to confirm PC diagnoses. For further details, see Reference 19.

Tampere (University of Tampere), Finland. Ten multiplex PC families were selected from a total of 57 families previously used for *HPC1* and *HPCX* linkage analyses [39,49]. None of these families exhibited bilineality of PC history. The remaining 47 families were not genotyped because there were only 1 or 2 sampled affected persons per family. Families were selected based on informativeness for linkage analyses, which was evaluated by the number of affected relatives in the families and the number of affected relatives for whom a blood sample was available for genotyping. At least three members per family had to be affected with PC and blood specimens had to be available for at least three affected relatives per family. All affected men were either first- or second-degree relatives of the probands. A detailed description of the original collection of 57 families, confirmation of diagnoses through the Finnish Cancer Registry or hospital medical records, and prostate specific antigen (PSA) testing for unaffected males in the families is presented elsewhere [38,39].

Ulm (University of Ulm), Germany. Families were ascertained into the University of Ulm Prostate Cancer Genetics Projects. The collection of PC families has been described in detail previously [33]. Briefly, the probands' self-reported family history of PC has been used as a guide for recruitment of affected and relevant unaffected relatives. Families with at least two relatives with both histologically confirmed PC and available DNA were recruited. The families were all Caucasian and originated from all over Germany, with the majority resident in the Southern part. For additional details, see Reference 34.

Umeå (Umeå University), Sweden. Families with hereditary PC have been collected since 1995 and have been ascertained mainly by collaborating urologists and oncologists throughout Sweden. All diagnoses of PC in the families were confirmed both by reference to the Swedish National Cancer Registry and direct examination of medical records. The majority of the cases (79%) had clinical symptoms at diagnosis and 60% of the cases were diagnosed with a locally advanced or metastatic tumor. Blood has been collected for DNA extraction, both from affected men and their spouses and from the children, so that inferred genotypes can be determined. For the present study,

families having a minimum of three men affected with PC, in which we have at least two affected men with known or inferred genotypes, were selected. For additional details, see Reference 45.

Utah (University of Utah). The Utah pedigrees were ascertained from the Utah Population Database, which combines a genealogy containing approximately eight generations of Utah pioneers and their descendants with a cancer registry containing ~30 years of complete cancer registration for the state of Utah [40]. Approximately, 298 families have been ascertained by observation of a significant excess of PC cases among descendants of a single founder, with no age-at-diagnosis criteria. Of these, genotyping has been completed on ~140 pedigrees. Because the Utah pedigrees are considerably larger than those submitted by the rest of the consortium, they were split into independent sub-pedigrees to be small enough to be analyzed by Genhunter-Plus [23], the analysis tool chosen for the consortium data set. Pedigrees were split using an algorithm that creates independent sub-pedigrees containing at least three affected individuals of no more than second degree relationship. Some pedigrees yielded no sub-pedigrees, while others yielded one or more. Because only phenotype, and not genotype, information was used, the splitting was done in an unbiased manner. A portion of the sub-pedigrees were still too large for analysis by Genhunter-Plus and were further trimmed using the automatic trimming function in Genhunter. In some cases, this automatic trimming produced pedigrees with little linkage information because it deleted unaffected members who were necessary to infer the genotype of a deceased case with PC.

Genotyping and Marker Map

The genetic markers used in this analysis are presented in Table I. These markers represent a combination of markers that were genotyped by different groups for either their genome scans, fine-scale mapping, or both. Details of genotyping methods can be found in previous publications by the respective groups.

A consensus map of the genetic markers from the different groups was created as follows. A total of 45 different markers on chromosome 20 were used by ICPCG members. For our analysis, the order of these markers was determined from UCSC Goldenpath (version hg13, released November 14, 2002). The marker distance was based on the de Code map [22]. All markers except one were successfully mapped to Golden path or de Code maps. For the unmapped marker, its primer information was used with an ePCR procedure to map this marker to the physical map of

Golden path. The map position of this marker was determined by interpolation from flanking markers. Because some groups did not have either the first or last markers from this consensus map, dummy non-informative markers (i.e., homozygous for all subjects) were used as anchors for these groups (see Table I). This allowed us to align all group's linkage files to the consensus map, allowing for different groups using different markers. All groups computed LOD scores at 1 cM intervals along the consensus map, using the Genhunter-Plus software [21,23].

Definition of Affection Status and Classification of Pedigrees

Affected individuals were defined as those men affected with PC that had been confirmed by either medical records or death certificates. Affected individuals without either medical records or death certificate confirmation were considered as unknown affection status (hence, self-reported PC, or PC based solely on family-history interviews were considered unknown). Because of this restricted definition, some pedigrees had fewer counts of affected men than previously reported in publications by the respective groups. Furthermore, because some groups allowed self-report as unaffected, while others required verification by PSA screening, all unaffected subjects were coded as unknown affection status. This decision was made in order to have a standard definition of affection status across all participating groups. Hence, all analyses were based on the sharing of marker genotypes among affected individuals, with no consideration of the phenotype for unaffected individuals.

A pedigree was classified as hereditary PC (HPC) if it met the criteria of Carter et al. [9]. At least one of the following three criteria must have been met: (1) three consecutive generations of PC along a line of descent; (2) at least three first-degree relatives with a diagnosis of PC; (3) two or more relatives with a diagnosis of PC at age ≤ 55 years. Furthermore, because linkage of PC susceptibility to chromosome X has been reported [49], pedigrees were classified according to paternal transmission (yes vs. no). Pedigrees classified as "yes" for paternal transmission were consistent with autosomal dominant transmission, allowing for incomplete penetrance. For example, pedigrees would be classified as "yes" if a father and son both had PC, or if the father was unaffected, but paternal cousins both had PC. Pedigrees that had clear X-transmission were classified as "no" for paternal transmission. Pedigrees that did not have sufficient information to distinguish incomplete penetrance for an autosomal dominant susceptibility allele versus X-transmission (e.g., nuclear families with unaffected fathers) were considered as

TABLE I. Chromosome 20 Markers Used by Members of the ICPCG

| Marker | Position (cM) | ACTANE | BC/CA/HI | CeRePP | JHU | Mayo | Michigan | PROGRESS | Tampere | Ulm | Umeå | Utah |
|---------|---------------|--------|----------|--------|-----|------|----------|----------|---------|-----|------|------|
| D20S117 | 2.9 | d | d | d | + | + | + | d | + | + | + | d |
| D20S473 | 10.82 | | | | | | | + | | | | |
| D20S889 | 11.93 | | | | + | + | + | | + | + | + | |
| D20S482 | 13.21 | + | | | | | | | | | | |
| D20S95 | 18.4 | | | | | | | + | | | | |
| D20S115 | 24.66 | | | | + | + | + | | + | + | + | |
| D20S177 | 27.52 | | | | | | | | | + | | |
| D20S851 | 27.69 | + | | | | | | | | | | |
| D20S186 | 34.58 | | | | + | + | + | | + | + | + | |
| D20S604 | 35.78 | + | | | | | | + | | | | |
| D20S852 | 39.56 | | | | | | | | | + | | |
| D20S112 | 44.35 | | | | + | + | + | | + | + | + | |
| D20S470 | 44.46 | + | | | | | | + | | | | |
| D20S471 | 49.03 | | | | | | | | | + | | |
| D20S912 | 50.95 | | | | | | | | | + | | |
| D20S477 | 51.9 | + | | | | | | + | | | | |
| D20S195 | 57.66 | | | | + | + | + | | + | + | + | |
| D20S478 | 60.72 | + | + | | | | | + | | | | |
| D20S107 | 61.78 | | | | + | + | + | | + | + | + | |
| D20S170 | 63.29 | | | | | | | | | | | + |
| D20S119 | 69.4 | | | | + | + | + | | + | + | + | |
| D20S481 | 69.4 | + | + | | | | | + | | | | |
| D20S891 | 72.46 | | | | + | | + | | + | | + | |
| D20S178 | 73.83 | + | | | + | + | + | | | | | + |
| D20S866 | 75.75 | | | | | | | | | | | + |
| D20S887 | 76.13 | + | | + | + | + | + | | | | | |
| D20S109 | 77.86 | + | | | | + | + | | | | | |
| D20S196 | 78.47 | + | | + | + | + | + | | | + | | + |
| D20S857 | 80.74 | | | + | | | | | | | | |
| D20S893 | 81.65 | + | | | | + | + | | | | | |
| D20S902 | 83.04 | | | | + | | + | | + | | + | |
| D20S480 | 83.19 | + | + | | | | | + | | | | |
| D20S120 | 86.68 | + | | | + | + | + | + | | | | + |
| D20S100 | 88.96 | | | | + | + | + | | + | + | + | |
| D20S149 | 92.09 | | | | | + | | | | | | |
| D20S430 | 93.75 | | | | | | | | | | | + |
| D20S171 | 98.63 | + | + | d | + | + | + | + | + | + | + | + |

+, marker genotyped; d, dummy non-informative anchor marker.

unknown and were combined with the no paternal transmission group for this analysis.

Linkage Analysis Methods

The linkage analyses for each set of families were performed by each group using a common method of analysis, implemented in Perl scripts to facilitate consistency and automation. The output files containing pedigree-specific LOD scores were sent to the Data Coordinating Center, which then combined the data for the linkage analyses. The planned analyses were developed and approved by members of the ICPCG.

The allele frequencies for each marker in each group were estimated by counting alleles across all families,

ignoring genetic relationships. Because there were few families within each participating group that had a non-Caucasian race background, allele frequencies were estimated from the pool of all data within a group, ignoring race. Although not optimal, this provides more robust allele frequency estimates, particularly for the many alleles of some of the microsatellite markers. Four parametric models were used for chromosome 20—two dominant and two recessive models. The first autosomal dominant was the “Smith” model that was used to map *HPC1* [42], with two liability classes. The frequency of the susceptibility allele was 0.003. Affected men were placed in the first liability class, for which the penetrance was 0.001 for

non-carriers and 1.0 for carriers. All unaffected subjects were placed in the second liability class, for which the penetrance was 0.5 for all genotypes (i.e., non-informative). The second autosomal dominant model had six liability classes. The allele frequency was the same as the two-liability model, but the five age-specific liability classes, which allowed a more refined age-dependent dominant model, were derived from complex segregation analysis [10] and data from the surveillance, epidemiology, and end results (SEER)—see Reference 47 for details. The respective penetrances for non-carriers and carriers were: (0.00038, 0.0018) for affected men with age at diagnosis ≤ 49 years; (0.00061, 0.0084), age 50–59; (0.0032, 0.03), age 60–69; (0.0082, 0.04), age 70–79; (0.0086, 0.015), age ≥ 80 ; unaffected subjects were placed in the sixth liability class, for which the penetrances were again set equal to 0.5 for all genotypes to be non-informative. The autosomal recessive models were variants of the above two dominant models, except that the susceptibility allele frequency was set to 0.15 and the penetrance for heterozygous carriers set equal to the penetrance for homozygous non-carriers. The allele frequency of 0.15 was based on segregation analyses of the Mayo Clinic family cancer-history survey, assuming a recessive model, without Hardy–Weinberg equilibrium [37]. All parametric analyses utilized the HLOD score [31].

The nonparametric (model-free) allele-sharing methods of Kong and Cox [21] were used, and we report the KC-LOD score based on the exponential allele-sharing model, as implemented in the combined software of Genehunter-Plus and ASM. All linkage results were based on multipoint calculations by the Genehunter-Plus software [23]. Families were weighted equally, and the score function “all” was used, which provides more evidence for linkage than the “pairs” option whenever most affecteds in a pedigree share the same allele identical by descent.

RESULTS

Pedigree Characteristics

The number of pedigrees contributed by each group, and the characteristics of the pedigrees, are presented in Table II. Among the total of 1,234 pedigrees, the mean age at diagnosis of the cases was 65 years. This mean varied across the groups from 64 to 69 years. For analysis purposes, we chose three age groups, based on the distribution of the pedigree average age at diagnosis over all groups. The extreme lowest and highest age groups were chosen to represent approximately the lower and upper 20% of the distribution. The three age groups were: mean age ≤ 60 years (221 pedigrees), mean age 60–70 years (792 pedigrees), and mean age > 70 years (221 pedigrees). The mean number of men

per pedigree with PC confirmed by medical records or death certificates was 3.8, and this mean ranged from 2.8 to 5.8 across the different groups. Although the prior ICPCG combined linkage analyses for *HPC1* stratified pedigrees according to ≤ 4 versus ≥ 5 affected men per pedigree, our larger number of pedigrees allowed us to stratify according to more extreme family history. Here, we stratified according to ≤ 3 affected men (672 pedigrees); 4–5 affected men (413 pedigrees); and ≥ 6 affected men (149 pedigrees). There were 836 pedigrees that met the Carter criteria for HPC, and 398 that did not. Furthermore, there were 587 pedigrees that met the definition of paternal transmission of PC, and 647 pedigrees that did not. Finally, 1,156 pedigrees were classified as of Caucasian ancestry, 40 pedigrees had African or African-American ancestry, and 38 pedigrees had other racial ancestry (e.g., Asian, Hispanic).

Linkage Results

To evaluate replication of linkage for chromosome 20, we present the linkage results separately for the pedigrees from the Mayo Clinic that generated the hypothesis, and for the ICPCG pedigrees excluding the Mayo Clinic series. In addition, we present results for the full dataset. For the purpose of this report, we use “ICPCG-Other” to denote the set of ICPCG pedigrees after removing the Mayo pedigrees. The Mayo pedigrees are reanalyzed here, because these analyses are for affecteds only, in contrast to the initial report that used phenotype data for all pedigree members, even those without genotype data. Hence, the results for the Mayo pedigrees serve as a reference when examining the linkage results for the independent set of ICPCG-Other pedigrees. The parametric and model-free LOD scores are presented in Figure 1. For the Mayo pedigrees analyzed by the two-liability model, the max HLOD was 2.78 for the recessive model and 1.24 for the dominant model, with both maxima occurring at 73 cM. The max KC-LOD was 2.22 at 64 cM. The markers flanking these maxima can be found in Table I. In contrast, the ICPCG-Other pedigrees show no linkage evidence for any model (HLOD 0.44 under the dominant model, 0.06 under the recessive model, and KC-LOD of 0.01). Figure 1 shows that the ICPCG-Other pedigrees have somewhat less than expected allele sharing in the region where the Mayo pedigrees have excessive allele sharing (at the region around 70 cM). The combined dataset also showed no evidence of linkage to chromosome 20.

Linkage Results: Subsets

The original report for linkage of the Mayo pedigrees found greater evidence of linkage in pedigrees with either a later average age at diagnosis, fewer affected

TABLE II. Characteristics of Pedigrees From ICPCG Used for Chromosome 20 Linkage

| Pedigree characteristic | ACTANE | BC/CA/HI | CeRePP | JHU | Mayo | Michigan | PROGRESS | Tampere | Ulm | Umeå | Utah | Total |
|-------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|-------------|---------------|---------------|---------------|---------------|
| No. pedigrees | 54 | 98 | 65 | 182 | 158 | 126 | 248 | 10 | 143 | 50 | 100 | 1,234 |
| Mean age diagnosis | 63.4 (50, 74) | 66.6 (54, 80) | 66.3 (55, 80) | 64.1 (43, 76) | 65.7 (47, 75) | 62.8 (43, 77) | 64.1 (47, 78) | 68 (56, 76) | 64.3 (51, 82) | 68.4 (56, 78) | 69.4 (60, 80) | 65.1 (44, 82) |
| Mean (range) | | | | | | | | | | | | |
| ≤60 | 11 | 11 | 10 | 40 | 22 | 34 | 58 | 1 | 32 | 2 | 0 | 221 |
| 60-70 | 38 | 58 | 44 | 124 | 108 | 83 | 153 | 5 | 92 | 30 | 57 | 792 |
| >70 | 5 | 29 | 11 | 18 | 28 | 9 | 37 | 4 | 19 | 18 | 43 | 221 |
| Number affected | | | | | | | | | | | | |
| Mean (range) | 3.2 (2, 5) | 3 (2, 6) | 3.2 (2, 7) | 5.4 (3, 18) | 2.8 (2, 7) | 3.5 (2, 10) | 3.7 (2, 12) | 4.3 (3, 6) | 2.8 (2, 7) | 4.7 (3, 14) | 5.8 (4, 16) | 3.8 (2, 18) |
| ≤3 | 40 | 78 | 46 | 24 | 127 | 85 | 140 | 2 | 117 | 13 | 0 | 672 |
| 4-5 | 14 | 19 | 18 | 96 | 28 | 35 | 87 | 6 | 24 | 26 | 60 | 413 |
| >5 | 0 | 1 | 1 | 62 | 3 | 6 | 21 | 2 | 2 | 11 | 40 | 149 |
| HPC | | | | | | | | | | | | |
| Yes | 38 | 62 | 45 | 182 | 49 | 81 | 195 | 10 | 48 | 48 | 78 | 836 |
| No | 16 | 36 | 20 | 0 | 109 | 45 | 53 | 0 | 95 | 2 | 22 | 398 |
| Paternal transmission | | | | | | | | | | | | |
| Yes | 23 | 45 | 28 | 115 | 38 | 80 | 99 | 6 | 49 | 13 | 91 | 587 |
| No ^a | 31 | 53 | 37 | 67 | 120 | 46 | 149 | 4 | 94 | 37 | 9 | 647 |
| Race | | | | | | | | | | | | |
| Caucasian | 54 | 83 | 63 | 147 | 157 | 114 | 235 | 10 | 143 | 50 | 100 | 1,156 |
| African | 0 | 7 | 2 | 14 | 0 | 10 | 7 | 0 | 0 | 0 | 0 | 40 |
| Other | 0 | 8 | 0 | 21 | 1 | 2 | 6 | 0 | 0 | 0 | 0 | 38 |

^aPedigrees with unknown transmission status were grouped with the "no" paternal transmission.

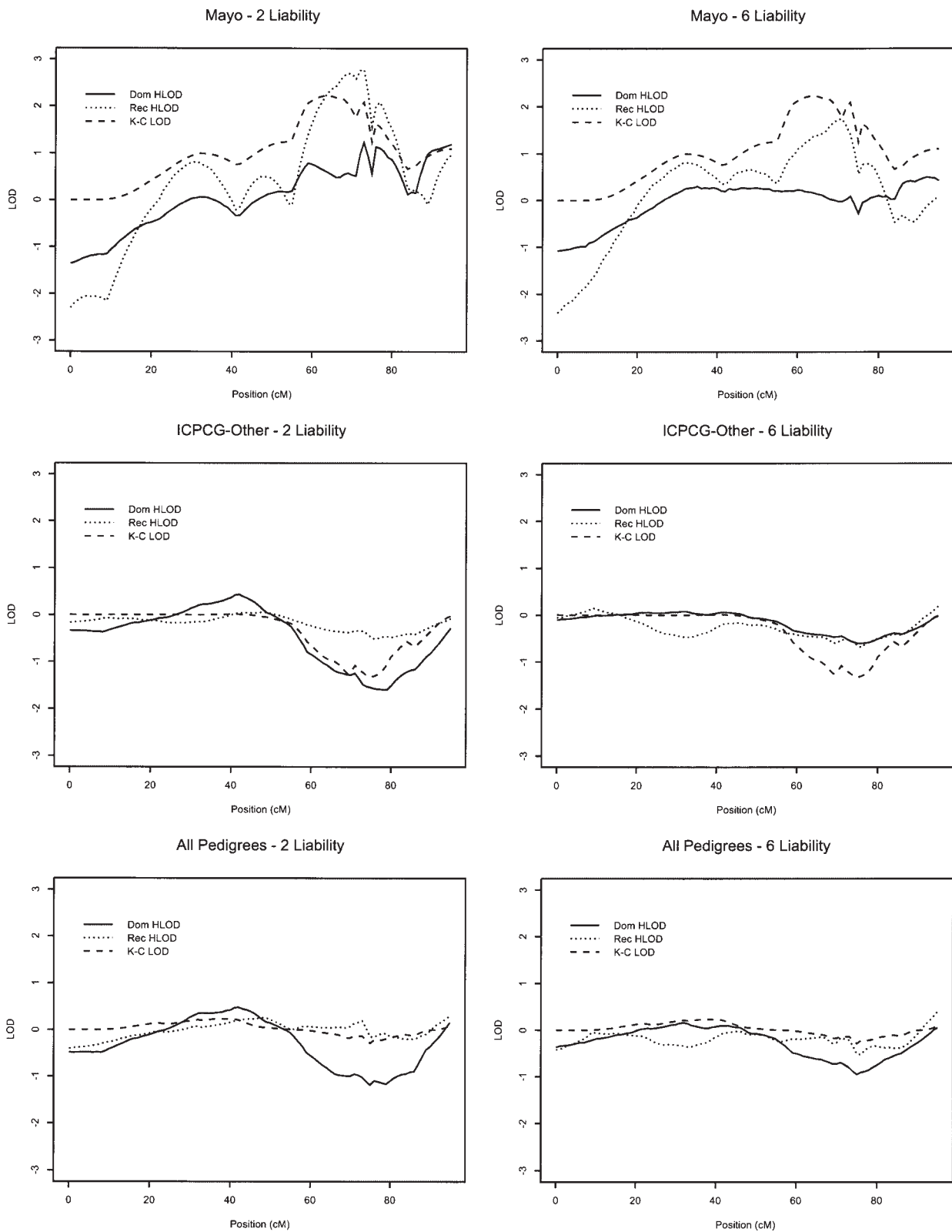


Fig. 1. Multipoint parametric and model-free LOD scores for the Mayo pedigrees and the International Consortium for Prostate Cancer Genetics (ICPCG)-other pedigrees. Parametric models are for two- and six-liability class models; Dom-heterogeneity LOD (HLOD) and Rec-HLOD. Model-free LOD score is the Kong and Cox (KC) LOD score.

men (<5 men with PC), or no male-to-male transmission of PC. We reanalyzed the Mayo pedigrees, using the more refined strata in this report. The linkage results for our chosen strata are presented in Table III for the Mayo pedigrees, the ICPCG-Other pedigrees, and both combined. For the Mayo pedigrees, the largest linkage signals (based on the recessive HLOD and the KC-LOD) were for pedigrees with an average age at diagnosis of 60–70 years (although the pedigrees with an average age >70 years had similar LOD scores), with fewer affected (strongest for pedigrees with ≤ 3 affected men, but some signal for pedigrees with 4–5 affected men), with HPC by Carter criteria, and with no paternal transmission. For the ICPCG-Other pedigrees, the largest LOD scores were for the recessive HLOD, with values of 1.53 for “other” race, and 1.45 for 4–5 affected men per pedigree. Because the Mayo pedigrees showed the largest LOD scores for pedigrees that had either a greater average age at PC diagnosis, fewer affected, and no paternal transmission, we evaluated linkage among the subset of pedigrees that met all three characteristics: average age at diagnosis >60 years, ≤ 3 affected men, and no paternal transmission. There were 87 Mayo pedigrees that met all three criteria, and the maximum LOD scores ranged from 2.01 to 2.34 for the different analysis models. In contrast, among the 274 ICPCG-Other pedigrees that met all three criteria, no LOD scores were greater than zero.

Because there could be linkage heterogeneity across the various groups comprising the ICPCG, we present in Table IV the LOD scores for each of the 11 ICPCG groups. The only other group, besides Mayo, that shows some linkage signal for chromosome 20 was JHU, with a recessive HLOD of 1.41 (KC-LOD of 1.32). To evaluate whether the linkage information content varied across the groups, we computed the mean information content—averaged over pedigrees; this entropy information content is described elsewhere [23]. The last column of Table IV illustrates the mean information content over chromosome 20 from 60 to 80 cM. Within this interval, the average information for the Mayo pedigrees did not differ dramatically from that for many of the other groups. Given the body of evidence from the other studies, particularly other studies in the USA that have similar compositions as the Mayo study (e.g., Michigan and PROGRESS), there is little evidence of replication of linkage for chromosome 20.

DISCUSSION

The ICPCG has assembled a very large collection of well-characterized families with multiple cases of PC. This collection provides the basis for rapid follow-up of reported linkage findings, allowing stratification on important pedigree features that are likely to help

resolve the complex heterogeneity of this disease. Furthermore, this collaborative effort provides a forum of scientific interaction, which may lead to new approaches to evaluate the complex genetics of PC. As demonstrated in this report, the ability to follow-up reported linkage findings for PC in a large number of pedigrees is critical, given the disparate linkage findings reported to date.

This study of linkage to chromosome 20 failed to replicate linkage to *HPC20*. Although, this may be viewed as a negative result, it is an important finding, because the reported linkage to *HPC20* for the Mayo pedigrees is one of the strongest linkage results in the literature. This pattern is reminiscent of that for *HPC1*, where initially strong linkage [42] has proved difficult to replicate in a much larger set of families [47]. The simplest explanation is that the initial linkage report for *HPC20* by Berry et al. [3] was a false-positive finding. However, there remains the possibility that there is something particularly unusual about the Mayo pedigrees. Comparing the characteristics of the Mayo pedigrees to the pool of all ICPCG pedigrees, there are some differences. On average, the Mayo pedigrees tend to have fewer men with confirmed PC than the pool of ICPCG pedigrees; 80% of Mayo pedigrees had three or fewer men with confirmed PC, whereas the pool of all ICPCG pedigrees had 54% in this category. Also, 31% of the Mayo pedigrees met the Carter criteria for HPC, in contrast to 68% of all ICPCG pedigrees. However, even after stratifying the ICPCG pedigrees to control for some of these differences, we could not replicate linkage in the ICPCG-Other pedigrees in any of the strata. There remains the possibility that the discrepant results represent population differences. A large fraction of pedigrees in the Mayo study have Scandinavian ancestry, a population that is not strongly represented in the rest of the ICPCG.

Finally, unraveling the genetics of PC may be particularly challenging because it is such a common disease, and many pedigrees (if not most) will likely contain phenocopies. One phenocopy in a relatively small pedigree can eliminate the linkage signal. Thus, the current difficulty in replicating many of the reported linkage studies, including that for *HPC20*, may be due to a high frequency of phenocopies. Currently, there are no known tumor or clinical features that help to distinguish hereditary versus non-hereditary PC. As a result, the phenocopy rate is unknown, making it difficult to account for phenocopies when performing linkage analysis. Unfortunately, this issue will continue to cause problems with data analysis until it is understood in more detail. Future linkage studies for PC may benefit by considering only the most extremely aggressive cases, or even use of pathology information as quantitative traits, as exemplified by the linkage

TABLE III. Maximum Multipoint LOD Scores* for the Initial Mayo Pedigrees, the Independent Set of ICPCG Pedigrees, and for all Pedigrees Combined, According to Subsets of Pedigree Characteristics

| Pedigree characteristics | Mayo pedigrees | | | ICPCG-other pedigrees | | | All pedigrees | | | | | |
|--------------------------|----------------|----------|----------|-----------------------|-------|----------|---------------|---------|-------|----------|----------|---------|
| | N | Dom-HLOD | Rec-HLOD | K-C LOD | N | Dom-HLOD | Rec-HLOD | K-C LOD | N | Dom-HLOD | Rec-HLOD | K-C LOD |
| Total | 158 | 1.24 | 2.78 | 2.22 | 1,076 | 0.44 | 0.06 | 0.01 | 1,234 | 0.48 | 0.29 | 0.23 |
| Age | | | | | | | | | | | | |
| ≤60 | 22 | 0.20 | 0.58 | 0.47 | 199 | 0.22 | 0.33 | 0.51 | 221 | 0.29 | 0.30 | 0.58 |
| 60-70 | 108 | 0.90 | 1.93 | 1.38 | 684 | 1.20 | 0.44 | 0.42 | 792 | 1.05 | 0.61 | 0.62 |
| >70 | 28 | 1.26 | 1.67 | 1.28 | 193 | 0.00 | 0.00 | 0.09 | 221 | 0.02 | 0.00 | 0.17 |
| Number affected | | | | | | | | | | | | |
| ≤3 | 127 | 1.91 | 2.66 | 2.72 | 545 | 0.00 | 0.00 | -0.07 | 672 | 0.00 | 0.00 | -0.01 |
| 4-5 | 28 | 1.33 | 1.77 | 1.62 | 385 | 0.99 | 1.45 | 1.00 | 413 | 0.91 | 1.38 | 1.23 |
| ≥6 | 3 | 0.31 | 0.30 | 0.71 | 146 | 0.33 | 0.62 | 0.18 | 149 | 0.32 | 0.68 | 0.19 |
| HPC | | | | | | | | | | | | |
| Yes | 49 | 1.33 | 2.23 | 1.55 | 787 | 0.13 | 0.19 | 0.28 | 836 | 0.43 | 0.72 | 0.31 |
| No | 109 | 0.62 | 1.89 | 1.98 | 289 | 0.38 | 0.04 | 0.03 | 398 | 0.73 | 0.58 | 0.56 |
| Paternal transmission | | | | | | | | | | | | |
| Yes | 38 | 0.13 | 0.75 | 0.73 | 549 | 0.04 | 0.20 | 0.24 | 587 | 0.07 | 0.23 | 0.44 |
| No ^a | 120 | 2.43 | 2.48 | 2.62 | 527 | 0.72 | 0.01 | 0.04 | 647 | 1.13 | 0.15 | 0.34 |
| Race | | | | | | | | | | | | |
| Caucasian | 157 | 1.20 | 2.62 | 2.07 | 999 | 0.40 | 0.03 | 0.00 | 1,156 | 0.43 | 0.28 | 0.19 |
| African | 0 | — | — | — | 40 | 0.44 | 0.35 | 0.47 | 40 | 0.44 | 0.35 | 0.47 |
| Other | 1 | 0.31 | 0.49 | 0.60 | 37 | 1.06 | 1.53 | 0.92 | 38 | 1.18 | 1.35 | 1.10 |
| Combination of: | 87 | 2.01 | 2.34 | 2.34 | 274 | 0.0 | 0.0 | -0.27 | 361 | 0.06 | 0.0 | 0.0 |
| Age >60, | | | | | | | | | | | | |
| Number affected | | | | | | | | | | | | |
| ≤3, Paternal | | | | | | | | | | | | |
| transmission = no | | | | | | | | | | | | |

*Dom and Rec HLODs are based on the two-liability-class model.

^aPedigrees with unknown transmission status were grouped with the “no” paternal transmission.

TABLE IV. Maximum Multipoint LOD Scores* Scores According to ICPCG Group

| Group | N | Dom-HLOD | Rec-HLOD | KC-LOD | Average information content |
|----------|-----|----------|----------|--------|-----------------------------|
| ACTANE | 54 | 0.17 | 0.28 | 0.53 | 0.38 |
| BC/CA/HI | 98 | 0.17 | 0.12 | 0.06 | 0.46 |
| CeRePP | 65 | 0.02 | 0.09 | -0.01 | 0.47 |
| JHU | 182 | 0.77 | 1.41 | 1.32 | 0.70 |
| Mayo | 158 | 1.24 | 2.78 | 2.22 | 0.59 |
| Michigan | 126 | 0.29 | 0.20 | 0.23 | 0.59 |
| PROGRESS | 248 | 0.16 | 0.00 | -0.01 | 0.35 |
| Tampere | 10 | 0.0 | 0.07 | 0.01 | 0.58 |
| Ulm | 143 | 0.06 | 0.0 | -0.01 | 0.38 |
| Umeå | 50 | 0.27 | 0.25 | 0.22 | 0.44 |
| Utah | 100 | 0.01 | 0.40 | 0.10 | 0.44 |

*Dom and Rec HLODs are based on the two-liability-class model.

Information content from Genehunter within the interval 60–80 cM, averaged over pedigrees.

signals provided by Gleason's grade of PC aggressiveness [28,29,41,46].

In summary, given our current state of knowledge, a combined linkage analysis of marker data from over 1,200 PC families collected by the ICPCG suggests little evidence for the existence of an HPC gene at 20q13. The ICPCG family collection represents a valuable resource to evaluate reported linkages in PC, and should prove critical in efforts to define regions for further study.

THE MEMBERS OF THE INTERNATIONAL CONSORTIUM FOR PROSTATE CANCER GENETICS

Members are as follows:

- *ACTANE Group* (+Principal Investigators): UK, *Sutton*: Steve Edwards, Julia Meitz, Questa Hope, Sarah Bullock, Rifat Hamoudi, Audrey Ardern-Jones, Christine Southgate, Anna Dowe, Kim Coleman, David Dearnaley, The Cancer Research UK/British Prostate Group UK Familial Prostate Cancer Study Collaborators, British Association of Urological Surgeons' Section of Oncology, Ros Eeles⁺ (Institute of Cancer Research and Royal Marsden NHS Trust Hospital). UK, *Cambridge*: Chris Evans, M. Dawn Teare, Doug Easton⁺ (Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Labs, Cambridge). Australia: John Hopper⁺, Graham Giles⁺, Dallas English, Melissa Southey, (Cancer Epidemiology Centre, University of Melbourne, Carlton, Australia). Canada: William D. Foulkes⁺, Nancy Hamel, Steven Narod, Jaques Simard⁺ (Division of Medical Genetics, McGill University, Montreal, Que.; Oncology and Molecular Endocrinology Research Center, CHUL Research Center; Laval University, Quebec City, and Center for Research in Women's Health, University of Toronto). Texas: Mike Badzioch⁺, Chris Amos (M.D. Anderson Cancer Centre, Houston, TX and Division of Medical Genetics, University of Washington Medical Centre, Seattle, WA). Norway, *Oslo*: Ketil Heimdal, Lovise Mahle, Pal Moller⁺ (Unit of Medical Genetics, Norwegian Radium Hospital, Oslo). Norway, *Ullevaal*: Nicolai Wessel, Tone Andersen⁺ (Department of Oncology, Ullevaal University Hospital, Oslo). EU Biomed: Tim Bishop⁺, The EU Biomed Prostate Cancer Linkage Consortium; (Cancer Research UK Genetic Epidemiology Laboratory, St. James' University Hospital, Leeds, UK).
- *BC/CA/HI Group*: Raymond N. Balise¹, Richard Gallagher², Jerry Halpern¹, Chih-lin Hsieh³, Laurence Kolonel⁴, Ingrid Oakley⁵, Dee West^{1,5}, Alice S. Whittemore¹, and Anna Wu³ (¹Stanford University School of Medicine, Stanford, CA; ²British Columbia Cancer Center, Vancouver; ³University of Southern California, Los Angeles, CA; ⁴University of Hawaii, Honolulu, HI; ⁵Northern California Cancer Center, Union City, CA, Stanford, CA).
- *CeRePP Group*: Géraldine Cancel-Tassin, Antoine Valéri, Philippe Mangin, Olivier Cussenot (Centre de Recherche pour les Pathologies Prostatiques, Paris, France).
- *JHU Group*: Kathleen E. Wiley, Sarah D. Isaacs, Marta Gielzak, Charles M. Ewing, Patrick C. Walsh, William B. Isaacs (Johns Hopkins Medical Institutions, Baltimore, MD).
- *Mayo Group*: Daniel J. Schaid, Shannon K. McDonnell, Gerald B. Christensen, Julie M. Cunningham,

Scott Hebbing, Jennifer C. Guenther, Stephen N. Thibodeau (Mayo Clinic, Rochester, MN).

- *Michigan Group*: Ethan M. Lange¹, Cralen C. Davis¹, W. Mark Brown¹, Cathryn H. Bock², Kathleen A. Cooney² (¹Wake Forest University, Winston-Salem, NC; ²University of Michigan, Ann Arbor, MI).
- *PROGRESS Group*: Kerry Deutsch¹, Danielle M. Friedrichsen², Suzanne Kolb³, Marta Janer¹, Michael D. Badzioch⁴, Elaine A. Ostrander², Gail P. Jarvik⁴, Lee Hood¹, Janet L. Stanford³ (¹Institute for Systems Biology, Seattle, WA; ²Divisions of Clinical Research and Human Biology and ³Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA; ⁴Division of Medical Genetics, University of Washington, Seattle, WA).
- *Tampere Group*: Annika Rökman¹, Agnes Baffoe-Bonnie^{2,3}, Henna Fredriksson¹, Tarja Ikonen¹, Pasi A. Koivisto¹, Mika P. Matikainen¹, Teuvo L.J. Tammela¹, Joan Bailey-Wilson³, Johanna Schleutker¹ (¹University of Tampere and Tampere University Hospital, Tampere, Finland; ²Fox Chase Cancer Center, Division of Population Science, Philadelphia, PA; ³Inherited Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Baltimore, MD).
- *Ulm Group*: Thomas Paiss¹, Josef Hoegel², Florian Kurtz², Michaela Schedel², Kathleen Herkommer¹, Christiane Maier², Walther Vogel² (¹Urologische Universitätsklinik und Poliklinik, Ulm, Germany; ²Abteilung Humangenetik, Universität, Ulm, Germany).
- *Umeå Group*: Fredrik Wiklund, Anders Bergh, Monica Emanuelsson, Ingela Göransson, Björn-Anders Jonsson, Fredrik Lindmark, Elisabeth Stenman, Henrik Grönberg (Umeå University, Umeå, Sweden).
- *Utah Group*: Lisa A. Cannon-Albright, Nicola J. Camp, James M. Farnham (University of Utah, Salt Lake City, UT).
- *Data Coordinating Center*: Jianfeng Xu, Deborah A. Meyers, Bao-Li Chang, Aubrey R. Turner, Latchezar Dimitrov, Tamara S. Adams (Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, NC).
- *Daniella Seminara* (National Cancer Institute, Division of Cancer Control and Population Sciences, Bethesda, MD).

ELECTRONIC DATABASES

- Goldenpath (<http://genome.ucsc.edu/index.html>),
- deCode map (<http://www.nature.com/ng/journal/v31/n3/supinfo>).

ACKNOWLEDGMENTS

We would like to express our gratitude to the many men who participated in this study and to the many urologists who kindly assisted us by providing information and access to their patients. The ICPCG was supported by the U.S. Public Health Service (USPHS), National Institutes of Health (CA89600). Additional support to participating groups, or members within groups, is as follows: *ACTANE Group*: Genotyping and statistical analysis for this study, and recruitment of U.K. families, was supported by Cancer Research U.K. Additional support was provided by The Prostate Cancer Charitable Trust, The Times Christmas Appeal and the Institute of Cancer Research. Genotyping was conducted in the 'Jean Rook Gene Cloning Laboratory' which is supported by BREAKTHROUGH Breast Cancer—Charity No. 328323. The funds for the ABI 377 used in this study were generously provided by the legacy of the late Marion Silcock. We thank Mrs. Sheila Seal and Mrs. Anita Hall for kindly storing and logging the samples that were provided. DFE is a Principal Research Fellow of Cancer Research UK. Recruitment of Australian prostate cancer families was funded by a grant from the NHMRC (940934) and was further supported by Tattersall's and the Whitten Foundation and infrastructure provided by the Cancer Council Victoria. We would like to acknowledge the work of the study coordinator Margaret Staples and the Research Team Bernadette McCudden, John Connal, Richard Thorowgood, Chris Costa, Melodie Kevan, and Sue Palmer, and to Jolanta Karpowicz for DNA extractions. The Texas study of familial prostate cancer was initiated by the Department of Epidemiology, M.D. Anderson Cancer Center. M. Badzioch was supported by an NCI Post-doctoral Fellowship in Cancer Prevention (R25). *BC/CA/HI Group*: USPHS CA67044. *Mayo Clinic Group*: USPHS CA72818. *Michigan Group*: USPHS CA079596. *PROGRESS Group*: USPHS CA78835 (EAO), CA080122 (JLS), and from the CaP CURE Foundation and the Fred Hutchinson Cancer Research Center, University of Washington Markey Center. *Tampere Group*: Medical Research Fund of Tampere University Hospital, Reino Lahtikari Foundation, Finnish Cancer Organizations, Sigrid Juselius Foundation and Academy of Finland (grant no. 201480). *Ulm Group*: Deutsche Krebshilfe (grant no. 70-3111-V03). *Umeå Group*: Grants from the Swedish Cancer Society (Cancerfonden) and Stiftelsen för Strategisk Forskning. *Utah Group*: USPHS CA90752, CA89600, and M01-RR00064. Data collected for Utah was with assistance from the Utah Cancer Registry supported by NIH contract N01-PC67000 (and PC 35141), with additional support from the Utah Department of Health and the

University of Utah. Partial support for all datasets within the Utah Population Database is provided by the University of Utah Huntsman Cancer Institute. Genotyping was provided by Myriad Genetics, under a previous contract. Additional support was provided to A.B.B-B by USPHS CA06927 and an appropriation from the Commonwealth of Pennsylvania.

REFERENCES

- Bar-Shira A, Pinthus JH, Rozovsky U, Goldstein M, Sellers WR, Yaron Y, Eshhar Z, Orr-Urtreger A. Multiple genes in human 20q13 chromosomal region are involved in an advanced prostate cancer xenograft. *Cancer Res* 2002;62:6803–6807.
- Berry R, Schaid DJ, Smith JR, French AJ, Schroeder JJ, McDonnell SK, Peterson BJ, Wang ZY, Carpten JD, Roberts SG, Tester DJ, Blute ML, Trent JM, Thibodeau SN. Linkage analyses at the chromosome 1 loci 1q24-25 (HPC1), 1q42.2-43 (PCAP), and 1p36 (CAPB) in families with hereditary prostate cancer. *Am J Hum Genet* 2000a;66:539–546.
- Berry R, Schroeder J, French A, McDonnell S, Peterson B, Cunningham J, Thibodeau S, Schaid D. Evidence for a prostate cancer-susceptibility locus on chromosome 20. *Am J Hum Genet* 2000b;67:82–91.
- Berthon P, Valeri A, Cohen-Akenine A, Drelon E, Paiss T, Wöhr G, Latil A, Millasseau P, Mellah I, Cohen N, Blanche H, Bellane-Chantelot C, Demenais F, Teillac P, Le Duc A, de Petriconi R, Hautmann R, Chumakov I, Bachner L, Maitland NJ, Lindereau R, Vogel W, Fournier G, Mangin P, Cussenot O. Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2-43. *Am J Hum Genet* 1998;62:1416–1424.
- Bock CH, Cunningham JM, McDonnell SK, Schaid DJ, Peterson BJ, Pavlic RJ, Schroeder JJ, Klein J, French AJ, Marks A, Thibodeau SN, Lange EM, Cooney KA. Analysis of the prostate cancer-susceptibility locus HPC20 in 172 families affected by prostate cancer. *Am J Hum Genet* 2001;68:795–801.
- Boehnke M, Cox NJ. Accurate inference of relationships in sib-pair linkage studies. *Am J Hum Genet* 1997;61:423–429.
- Cancel-Tassin G, Latil A, Valeri A, Guillaume E, Mangin P, Fournier G, Berthon P, Cussenot O. No evidence of linkage to HPC20 on chromosome 20q13 in hereditary prostate cancer. *Int J Cancer* 2001a;93:455–456.
- Cancel-Tassin G, Latil A, Valeri A, Mangin P, Fournier G, Gerthon P, Cussenot O. PCAP is the major known prostate cancer predisposing locus in families from south and west Europe. *Eur J Hum Genet* 2001b;9:135–142.
- Carter B, Bova G, Beaty T, Steinberg G, Childs B, Isaacs W, Walsh P. Hereditary prostate cancer: Epidemiologic and clinical features. *J Urol* 1993;150:797–802.
- Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci USA* 1992;89:3367–3371.
- Cui J, Staples MP, Hopper JL, English DR, McCredie MR, Giles GG. Segregation analyses of 1,476 population-based Australian families affected by prostate cancer. *Am J Hum Genet* 2001;68:1207–1218.
- Cunningham JM, McDonnell SK, Marks A, Hebbing S, Anderson SA, Peterson BJ, Slager S, French A, Blute ML, Schaid DJ, Thibodeau SN. Genome linkage screen for prostate cancer susceptibility loci: Results from the Mayo Clinic Familial Prostate Cancer Study. *Prostate* 2003;57:335–346.
- Easton DF, Schaid DJ, Whittemore AS, Isaacs WJ. Where are the prostate cancer genes? A summary of eight genome wide searches. *Prostate* 2003;57:261–269.
- Edwards S, Meitz J, Eles R, Evans C, Easton D, Hopper J, Giles G, Foulkes WD, Narod S, Simard J, Badzioch M, Mahle L. Results of a genome-wide linkage analysis in prostate cancer families ascertained through the ACTANE consortium. *Prostate* 2003;57:270–279.
- Friedrichsen DM, Stanford JL, Isaacs SD, Janer M, Chang B-L, Deutsch K, Gillanders E, Kolb S, Wiley KE, Badzioch MD, Zheng SL, Walsh PC, Jarvik GP, Hood L, Trent JM, Isaacs WB, Ostrander EA, Xu J. Identification of a prostate cancer susceptibility locus on chromosome 7q11-21 in Jewish families. *PNAS* 2004;101:1939–1944.
- Gibbs M, Stanford JL, McIndoe RA, Jarvik GP, Kolb S, Goode EL, Chakrabarti L, Schuster EF, Buckley VA, Miller EL, Brandzel S, Li S, Hood L, Ostrander EA. Evidence for a rare prostate cancer-susceptibility locus at chromosome 1p36. *Am J Hum Genet* 1999;64:776–787.
- Grönberg H. Prostate cancer epidemiology. *Lancet* 2003;361:859–864.
- Hsieh C-L, Oakley-Girvan I, Balise RR, Halpern J, Gallagher RP, Wu AH, Kolonel LN, O'Brien LE, Lin IG, Van Den Berg DJ, Teh CZ, West DW, Whittemore AS. A genome screen of families with multiple cases of prostate cancer: Evidence of genetic heterogeneity. *Am J Hum Genet* 2001;69:148–158.
- Janer M, Friedrichsen DM, Stanford JL, Badzioch MD, Kolb S, Deutsch K, Peters MA, Goode EL, Welti R, De France HB, Iwasaki L, Li S, Hood L, Ostrander EA, Jarvik GP. Genomic scan of 254 hereditary prostate cancer families. *Prostate* 2003;57:309–319.
- Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. *BJU Int* 2003;91:789–794.
- Kong A, Cox NJ. Allele-sharing models: LOD scores and accurate linkage tests. *Am J Hum Genet* 1997;61:1179–1188.
- Kong A, Gudbjartsson D, Sainz J, Jonsson G, Gudjonsson S, Richardsson B, Sigurdardottir S, Barnard B, Hallbeck B, Masson M, Shlien A, Palsson S, Frigge M, Thorgeirsson T, Gulcher J, Stefansson K. A high-resolution recombination map of the human genome. *Nat Genet* 2002;31:241–247.
- Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and nonparametric linkage analysis: A unified multipoint approach. *Am J Hum Genet* 1996;58:1347–1363.
- Lange EM, Gillanders EM, Davis CC, Brown WM, Campbell JK, Jones M, Gildea D, Riedesel E, Albertus J, Freas-Lutz D, Markey C, Giri V, Dimmer JB, Montie JE, Trent JM, Cooney KA. Genome-wide scan for prostate cancer susceptibility genes using families from the University of Michigan prostate cancer genetics project finds evidence for linkage on chromosome 17 near BRCA1. *Prostate* 2003;57:326–334.
- Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer: Analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78–85.
- McIndoe RA, Stanford JL, Gibbs M, Jarvik GP, Brandzel S, Neal CL, Li S, Gammack JT, Gay AA, Goode EL, Hood L, Ostrander EA. Linkage analysis of 49 high-risk families does not support a common familial prostate cancer-susceptibility gene at 1q24-25. *Am J Hum Genet* 1997;61:347–353.
- Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. *N Engl J Med* 2003;349:366–381.

28. Neville PJ, Conti DV, Krumroy LM, Catalona WJ, Suarez BK, Witte JS, Casey G. Prostate cancer aggressiveness locus on chromosome segment 19q12-q13.1 identified by linkage and allelic imbalance studies. *Genes Chromosomes Cancer* 2003;36:332–339.
29. Neville PJ, Conti DV, Paris PL, Levin H, Catalona WJ, Suarez BK, Witte JS, Casey G. Prostate cancer aggressiveness locus on chromosome 7q32-q33 identified by linkage and allelic imbalance studies. *Neoplasia* 2002;4:424–431.
30. Ostrander EA, Stanford JL. Genetics of prostate cancer: Too many loci, too few genes. *Am J Hum Genet* 2000;67:1367–1375.
31. Ott J. Analysis of human genetic linkage. Baltimore: The Johns Hopkins University Press; 1999.
32. Page WF, Braun MM, Partin AW, Caporaso N, Walsh P. Heredity and prostate cancer: A study of World War II veteran twins. *Prostate* 1997;33:140–145.
33. Paiss T, Herkommer K, Chab A, Haussler J, Vogel W, Gschwend JE, Hautmann RE. Familial prostate carcinoma in Germany. *Urologia A* 2002;41:38–43.
34. Paiss T, Worner S, Kurtz F, Haeussler J, Hautmann RE, Gschwend JE, Herkommer K, Vogel W. Linkage of aggressive prostate cancer to chromosome 7q31-33 in German prostate cancer families. *Eur J Hum Genet* 2003;11:17–22.
35. Risch N. The genetic epidemiology of cancer: Interpreting familial and twin studies and their implications for molecular genetic approaches. *Cancer Epidemiol Biomarkers Prev* 2001;10:733–741.
36. Schaid D. The complex genetic epidemiology of prostate cancer. *Hum Mol Genet* 2004;13, Review Issue:R103–R121.
37. Schaid D, McDonnell S, Blute M, Thibodeau S. Evidence for autosomal dominant inheritance of prostate cancer. *Am J Hum Genet* 1998;62:1425–1438.
38. Schleutker J, Baffoe-Bonnie AB, Gillanders E, Kainu T, Jones MP, Freas-Lutz D, Markey C, Gildea D, Riedesel E, Albertus J, Gibbs KD Jr, Matikainen M, Koivisto PA, Tammela T, Bailey-Wilson JE, Trent JM, Kallioniemi OP. Genome-wide scan for linkage in Finnish hereditary prostate cancer (HPC) families identifies novel susceptibility loci at 11q14 and 3p25-26. *Prostate* 2003;57:280–289.
39. Schleutker J, Matikainen M, Smith J, Koivisto P, Baffoe-Bonnie A, Kainu T, Gillanders E, Sankila R, Pukkala E, Carpten J, Stephan D, Tammela T, Brownstein M, Bailey-Wilson J, Trent J, Kallioniemi OP. A genetic epidemiological study of hereditary prostate cancer (HPC) in Finland: Frequent HPCX linkage in families with late-onset disease. *Clin Cancer Res* 2000;6:4810–4815.
40. Skolnick M, Bean L, Dintelman S, Mineau G. A computerized family history data base system. *Sociol Soc Res* 1979;63:506–523.
41. Slager S, Schaid D, Cunningham J, McDonnell S, Marks A, Peterson B, Hebring S, Anderson S, French A, Thibodeau S. Confirmation of Linkage of Prostate Cancer Aggressiveness with Chromosome 19q. *Am J Hum Genet* 2003;72:759–762.
42. Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujinovsky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM, Isaacs WB. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* 1996;274:1371–1374.
43. Tavtigian SV, Simard J, Teng DH, Abtin V, Baumgard M, Beck A, Camp NJ, Carillo AR, Chen Y, Dayananth P, Desrochers M, Dumont M, Farnham JM, Frank D, Frye C, Ghaffari S, Gupta JS, Hu R, Iliev D, Janecki T, Kort EN, Laity KE, Leavitt A, Leblanc G, McArthur-Morris J, Pederson A, Penn B, Peterson KT, Reid JE, Richards S, Schroeder M, Smith R, Snyder SC, Swedlund B, Swensen J, Thomas A, Tranchant M, Woodland AM, Labrie F, Skolnick MH, Neuhausen S, Rommens J, Cannon-Albright LA. A strong candidate prostate cancer susceptibility gene at chromosome 17p. *Nat Genet* 2001;27:172–180.
44. Whittemore AS, Wu AH, Kolonel LN, John EM, Gallagher RP, Howe GR, West DW, Teh CZ, Stamey T. Family history and prostate cancer risk in black, white, and Asian men in the United States and Canada. *Am J Epidemiol* 1995;141:732–740.
45. Wiklund F, Gillanders EM, Albertus JA, Bergh A, Damber JE, Emanuelsson M, Freas-Lutz DL, Gildea DE, Goransson I, Jones MS, Jonsson BA, Lindmark F, Markey CJ, Riedesel EL, Stenman E, Trent JM, Grönberg H. Genome-wide scan of Swedish families with hereditary prostate cancer: Suggestive evidence of linkage at 5q11.2 and 19p13.3. *Prostate* 2003;57:290–297.
46. Witte J, Goddard K, Conti D, Elston R, Lin J, Suarez B, Broman K, Burmester J, Weber J, Catalona W. Genomewide scan for prostate cancer-aggressiveness loci. *Am J Hum Genet* 2000;67:92–99.
47. Xu J. Combined analysis of hereditary prostate cancer linkage to 1q24-25: Results from 772 hereditary prostate cancer families from the International Consortium for Prostate Cancer Genetics. *Am J Hum Genet* 2000;66:945–957.
48. Xu J, Gillanders EM, Isaacs SD, Chang BL, Wiley KE, Zheng SL, Jones M, Gildea D, Riedesel E, Albertus J, Freas-Lutz D, Markey C, Meyers DA, Walsh PC, Trent JM, Isaacs WB. Genome-wide scan for prostate cancer susceptibility genes in the Johns Hopkins hereditary prostate cancer families. *Prostate* 2003;57:320–325.
49. Xu J, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, Ewing C, Wilkens E, Bujinovsky P, Bova GS, Walsh P, Isaacs W, Schleutker J, Matikainen M, Tammela T, Visakorpi T, Kallioniemi O-P, Berry R, Schaid D, French A, McDonnell S, Schroeder J, Blute M, Thibodeau S, Grönberg H, Emanuelsson M, Damber J-E, Bergh A, Jonsson B-A, Smith J, Bailey-Wilson J, Carpten J, Stephan D, Gillanders E, Amundson I, Kainu T, Freas-Lutz D, Baffoe-Bonnie A, Van Aucken A, Sood R, Collins F, Brownstein M, Trent J. Evidence for a prostate cancer susceptibility locus on the X chromosome. *Nat Genet* 1998;20:175–179.
50. Xu J, Zheng SL, Hawkins GA, Faith DA, Kelly B, Isaacs SD, Wiley KE, Chang B, Ewing CM, Bujinovsky P, Carpten JD, Bleecker ER, Walsh PC, Trent JM, Meyers DA, Isaacs WB. Linkage and association studies of prostate cancer susceptibility: Evidence for linkage at 8p22-23. *Am J Hum Genet* 2001;69:341–350.
51. Zheng SL, Xu J, Isaacs SD, Wiley K, Chang B, Bleecker ER, Walsh PC, Trent JM, Meyers DA, Isaacs WB. Evidence for a prostate cancer linkage to chromosome 20 in 159 hereditary prostate cancer families. *Hum Genet* 2001;108:430–435.