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TITLE: Locating a prostate cancer susceptibility gene on the X chromosome by linkage disequilibrium mapping using three founder populations in Quebec and Switzerland

PRINCIPAL INVESTIGATOR: Dr. William Foulkes

CONTRACTING ORGANIZATION: Montreal General Hospital Institute  
McGill University  
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# REPORT DOCUMENTATION PAGE

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<b>13. SUPPLEMENTARY NOTES</b>						
<b>14. ABSTRACT</b> At the Montreal site, 240 participants (195 cases) have consented to participate and 230 participants (185 cases) had their blood drawn. The pedigrees for cases and some controls have been drawn. Ishihara charts were shown to all cases and controls and the results were recorded. At the Switzerland site, case ascertainment is complete and 250 patients have been contacted; 185 have had a consultation with a DNA sampling. As the X chromosome gene has proved to be elusive, we have focused our attention on candidate genes and have studied CHEK2, PALB2, BRCA1, BRCA2 as well as other candidate genes in this series of cases. We have identified several novel mutations in CHEK2 and PALB2, but none of these mutations appear to be thus far associated with prostate cancer risk. Other known mutations, such as BRCA1: 187delAG and BRCA2: 6174delT do not appear to be more frequent in men with prostate cancer. Our work did not support the initial suggestion that some Ashkenazi Jewish men with prostate cancer carried a prostate cancer-associated allele on chromosome 7q. Prostate cancer genetics remains a difficult area of research; our work has mainly eliminated various candidate genes rather than identify causative mutations in prostate cancer susceptibility genes.						
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**Task 1: Case ascertainment, contact, consent, interview, DNA extraction and pathology confirmation.**

- Obtain approval for this study from relevant IRBs.

As discussed in our previous report, we did not pursue ethical approval at the Chicoutimi site and limited ethics approval to McGill University Hospital sites and Sion and affiliated hospitals and clinics, Le Valais, Switzerland.

- Identify all prevalent cases of prostate cancer at hospitals serving the three populations under study: Chicoutimi, McGill University Hospitals (Quebec) and Sion and affiliated regional hospitals, Valais, Switzerland. This will be carried out by contacting medical records, out-patient charts and cancer registries, confirming that the patient is living and then seeking permission from treating physicians (who are collaborators on this proposal) to contact their patients by letter.

**Montreal:** This goal was achieved at the McGill University Hospitals last year and has been on-going this year. One hundred and eighty-five cases were ascertained in total.

**Valais:** The head of the *Registre Valaisan des Tumeurs* has established a list of all patients diagnosed with prostate cancer since 1997 and who are residents in the *canton du Valais* (n = 730). Only patients whose surnames indicate an origin from the *canton du Valais* (based on the data from the *Association Valaisanne d'Etude Généalogique*) were conserved and thus considered as eligible for the study (n = 558). At the end of February 2004, a mailing was sent to the private physicians in charge of the living patients. We proposed that they send an information sheet about the research project to their patients with the phone number of the research nurse to be contacted. This mode of recruitment turned out to be not efficient (<40 patients recruited).

- Identify incident cases through urology clinics at the three centres (Chicoutimi, McGill University, Sion). Method of contact as for prevalent cases: also, eligible individuals will be approached directly in the clinic.

**Montreal:** This goal has been achieved at the Montreal site. McGill Urology Associates are helping to identify new cases of prostate cancer.

**Chicoutimi:** As stated above, we have abandoned our efforts at this site.

**Valais:** With the collaboration of the Service of Radio-oncology at the Hospital of Sion, the Institute of pathology of the *Institut Central des Hôpitaux Valaisans* and 5 urologists in private practice in the canton du Valais, a series of prevalent cases eligible for this research study were recruited.

- Contact relatives via case

**Montreal:** 42 controls have been recruited into the study at this site

**Valais:** There have been no controls recruited to date at this site (see below)

- Consent all eligible participants (case n~640)

**Montreal:** A total of 195 patients at the McGill University Hospital sites have given their consent to participate. We have DNA from 185 men. We have appointments to meet another 15 men that wish to participate in this study over the next few months. We have purchased DNA from Ashkenazi Jewish controls from Israel, as recruitment of controls was very slow in Montreal. A total of 18 affected men have refused to participate and we have found 7 of the ascertained are deceased.

**Valais:** A total of 190 patients at the Sion Hospital site have given their consent to participate. 1 person was excluded. So far, 185 DNA samples have been collected. The Sion research team has found getting access to familial controls quite difficult and, in agreement with the PI, Dr William Foulkes, the Sion team has started to collect non-familial age- and ethnically-matched male controls from the blood donors' clinic in the Hospital of Sion and from a local familial medicine clinic. Currently, we have DNA from 51 controls and we expect to collect 140 DNA samples in the next 2 months, to reach a total of at least 190 controls.

- Interview and construct three-generation pedigree for each case and control

**Montreal:** A total of 195 pedigrees have been drawn for cases for McGill University Hospital site since the commencement of the study. We have also drawn 42 pedigrees for the controls that have participated in the study.

**Valais:** A total of 185 pedigrees have been drawn for cases at the Sion site.

- Show Ishihara charts to cases

Ishihara charts have been shown to all participants and controls at all sites where the study is being conducted (McGill and Valais).

- Draw blood from all consenting participants

Blood has been drawn from >95% of participants that have been consented at all sites (Montreal and Valais)

- Extract DNA locally at each participating centre, transfer aliquots of DNA to PI laboratory for quality check and storage

DNA has been extracted at the McGill University Hospital and the Switzerland

site. An aliquot of DNA from the Sion site will be transferred to the PI laboratory.

- Transfer representative slides and blocks to Montreal for central pathology review

Slides and blocks from patients ascertained at the McGill University Hospital site have been transferred to a central pathologist for his review. The pathologist has completed his review of the material from 178 of the participating patients. We now have a standard Gleason Score for all cases where we have been able to locate a pathology block. Cases at the Sion site will be reviewed both in Switzerland and in Montreal

- Create central database at the Montreal General Hospital Research Institute

We have developed a database at the McGill University Hospital sites and it is continually updated as more cases and controls are recruited.

### ***Tasks 2 and 3: Genotyping of DNA from cases and controls, followed by statistical analysis***

#### **Specific Aims for this reporting period:**

1. To study *CHEK2* and its contribution to prostate cancer in the AJ population.
2. To study the recently identified breast cancer susceptibility gene *PALB2* in selected familial cases of prostate cancer.

#### **Studies and Results:**

##### **Project 1: *CHEK2* in the Ashkenazi Jewish Population**

To investigate whether *CHEK2* plays an important role in the development of prostate cancer (PRCA) in the Ashkenazi Jewish (AJ) population, we re-sequenced all exons and intron-exon boundaries of *CHEK2* in 75 AJ individuals with prostate, breast or no cancer (n = 25 each). We identified seven coding SNPs (five are novel) that changed the amino acid sequence, resulting in R3W, E394F, Y424H, S428F, D438Y, P509S and P509L. We determined their frequency in probands from 76 AJ families collected by members of the International Consortium for Prostate Cancer Genetics (ICPCG) where  $\geq 2$  men were affected by PRCA and  $\geq 1$  affected man provided a DNA sample. Only one variant, Y424H was identified in more than two families with an affected proband. Exon 11 was screened in nine additional families for a total of 85 families with at least one affected genotyped. The Y424H variant occurred in nine affected cases from four different families. In one family, all three affected cases had the variant. In another, four of the five affected cases carried the Y424H variant. For the other two families, only one affected case out of two or three had this variant. Bioinformatic analysis showed that Y424H is a radical missense substitution that falls at a position that is invariant in vertebrate *CHEK2* orthologs. Both SIFT and

Align/GV-GD predict that this is a loss of function mutation. However, Y424H frequency was 8/702 in prevalent cases and 5/545 in controls (OR 1.23, 95%CI: 0.35-4.82, P =.79). Functional studies suggested that Y424H behaves like wt CHEK2. These results suggest that while the Y424H variant may have a subtle influence on PRCA risk, *CHEK2* has a minor overall role in PRCA susceptibility in the AJ population.

### **Project 2: PALB2 and prostate cancer**

**PALB2 (Partner And Localiser of BRCA2)** is a new breast cancer susceptibility gene. Because BRCA2 is also a prostate cancer susceptibility gene, we screened 35 prostate cancer cases (14 Ashkenazi Jewish (AJ) and 21 French Canadian (FC) males) who had a family history of cancer defined as two or more affected cases and that were previously screened for the AJ or FC *BRCA1/BRCA2* founder mutations as well as *CHEK2:1100delC* and were found not to carry these mutations. We also analysed breast cancer cases at the same time. One mutation was found in a family without prostate cancer, but no clearly pathogenic mutations were identified in any of the other 67 strong family history breast cancer probands sequenced (average BRCAPRO score 0.58), in the FC moderate family history series or in the familial prostate cancer cases. A number of *PALB2* sequence variants were identified, all of which have been previously reported. The variant frequencies were similar to those already reported and common variants (frequency greater than 1%) such as Q559R, E672Q, G998E and T1100T were present in all three groups tested, with the exception of L337S, which was not seen in the FC population. These data reduce the likelihood that a significant fraction of non-*BRCA1/BRCA2* familial breast/ovarian/prostate cancer in the AJ and FC populations is due to common founder mutations in *PALB2*.

### **Significance:**

Identification of variants in candidate genes in founder populations is an important step for validating their candidacy as prostate cancer susceptibility genes.

### ***Task 4: Manuscript preparation***

- Report major findings (2005-2006)

Published papers:

### Full papers

1. Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Bishop T, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Hsieh CL, Halpern J, Balise RN, Oakley-Girvan I, Whittemore AS, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Thibodeau SN, McDonnell SK, Cunningham JM, Zarfes KE, Hebbbring S, Schaid DJ, Friedrichsen DM, Deutsch K, Kolb S,

- Badzioch M, Jarvik GP, Janer M, Hood L, Ostrander EA, Stanford JL, Lange EM, Beebe-Dimmer JL, Mohai CE, Cooney KA, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela TLJ, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson BA, Gronberg H, Camp NJ, Farnham J, Cannon-Albright LA, Seminara D; ACTANE Consortium. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet* 77(2):219-29, 2005.
2. Schaid DJ, McDonnell SK, Zarfes KE, Cunningham JM, Hebring S, Thibodeau SN, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Badzioch M, Bishop DT, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Guy M, Hsieh C-L, Halpern J, Balise RR, Oakley-Girvan I, Whittemore AS, Xu J, Dimitrov L, Chang B-L, Adams TS, Turner AR, Meyers DA, Friedrichsen DM, Deutsch K, Kolb S, Janer M, Hood L, Ostrander EA, Stanford JL, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Lange EM, Ho LA, Beebe-Dimmer JL, Wood DP, Cooney KA, Seminara D, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela T LJ, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson B-A, Grönberg H, Camp NJ, Farnham J, Cannon-Albright LA, Catalona WJ, Suarez BK, Roehl KA. Pooled genome linkage scan of aggressive prostate cancer: results from the International Consortium for Prostate Cancer Genetics. *Human Genetics* 120(4):471-85, 2006.
  3. Tischkowitz MD, Xia B, Sabbaghian N, Reis-Filho JS, Hamel N, Li G, van Beers E, Li L, Khalil T, Quenneville L, Omeroglu A, Poll A, Lepage P, Wong N, Nederlof PM, Ashworth A, Tonin PN, Narod SA, Livingston DM, Foulkes WD. Analysis of PALB2/FANCN-associated breast cancer families. To be submitted February 2007.
  4. Tischkowitz MD, Chen LQ, Friedrichsen-Karyadi DM, Kirchhoff T, Hamel N, Tavtigian SV, Kolb S, Nelson PS, Hood L, Narod SA, White KA, Ostrander EA, Isaacs WB, Offit K, Cooney KA, Stanford JL, Foulkes WD. Identification and characterization of novel SNPs in CHEK2 in Ashkenazi Jewish men with prostate cancer. To be submitted March 2007



## **CURRICULUM VITAE**

### **WILLIAM DAVID FOULKES**

#### **BIRTHPLACE**

Penarth, Wales, UK.

#### **ADDRESS BUSINESS**

Division of Medical Genetics

Montreal General Hospital  
1650 Cedar Avenue, Room L10-116  
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#### **HOME**

45 Elmwood  
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H9X 1T6  
Tel: (514) 457-6669

#### **CITIZENSHIP**

Canadian, British

**EDUCATION & TRAINING**

1980	B.Sc. - Upper second class honours, Anatomy University of London
1984	MB.BS University of London
1984 -1985	House officer in Medicine and Surgery, Hackney and St. Bartholomew's Hospital, London
1985-1986	Senior House Officer Emergency Medicine, Whittington Hospital, London
1986 - 1987	Rotating Senior House Officer Department of Medicine St. Mary's and St. Charles Hospitals, London
1987 - 1988	Senior House Officer Departments of Medicine and Radiotherapy Royal Marsden Hospital, London
1988 - 1989	Registrar in General and Respiratory Medicine Ealing Hospital, Middlesex
1989 - 1990	Registrar in Gastroenterology Hammersmith Hospital, London
1990 – 1994	Ph.D. <i>A molecular genetic analysis of ovarian cancer</i> Completed as an external student of the University of London, at the Imperial Cancer Research Fund (Internal: Galton Laboratory, UCL)

**FELLOWSHIPS**

1990 - 1994	Clinical Research Fellow Human Immunogenetics Laboratory Imperial Cancer Research Fund London and Honorary Research Fellow, Family Cancer Clinic - St. Mark's Hospital, London
-------------	---

(affiliated with the Division of Medical and Molecular Genetics, KGT Medical School, University of London)

## **APPOINTMENTS**

1994 -	Medical Scientist, Montreal General Hospital
1996- 2002	Assistant Professor, Department of Medicine, McGill University, Montreal.
1996-2002	Assistant Professor, Department of Human Genetics, McGill University, Montreal
1996-	Senior Research Associate, Epidemiology Research Centre, Pavillon Hotel Dieu, Centre Hospitalier Université de Montréal (CHUM).
1996-	Project Director, Lady Davis Institute, Sir Mortimer B. Davis-Jewish General Hospital, Montreal
1996-	Assistant Physician, Montreal General Hospital
1996-	Assistant Physician, Royal Victoria Hospital, Montreal
1996-	Assistant Physician, Sir Mortimer B. Davis-Jewish General Hospital, Montreal
1998-2002	Assistant Professor, Department of Oncology, McGill University, Montreal
2001-	Principal Investigator, Canadian Genetic Diseases Network
2001-	Director, Program in Cancer Genetics, Departments of Oncology and Human Genetics, McGill University
2001-	Vice-Chair, Genetic VRC, Canadian Cancer Etiology Research Network
2002-	Associate Professor (tenure), Departments of Medicine, Human Genetics and Oncology, McGill University, Montreal

## **AWARDS RECEIVED**

1979: Junior Scholarship in Anatomy, Physiology and Biochemistry, St Bartholomew's Hospital.

1983: Health Education Council Elective Scholarship "Diabetes in China".

1990-1994: Clinical Research Fellow Bursary, Imperial Cancer Research Fund, London.

1994-1997: Fast Foundation Award of the Montreal General Hospital Research Institute.

1997-1999: Fonds de la recherche en Santé du Québec: Chercheur-boursier clinicien. Junior 1

1997-2000: 175th Anniversary Bursary, Montreal General Hospital Research Institute.

1999-2002: Fonds de la recherche en Santé du Québec: Chercheur-boursier clinicien. Junior 2

2002-2007 : Fonds de la recherche en Santé du Québec: Chercheur-boursier clinicien. Senior

2003-2008: William Dawson Scholar, McGill University (equivalent Canada Research Chair, tier 2)

## **CURRENT COMPETITIVE GRANTS**

### Principal Investigator

Principal applicant: Foulkes, WD

CBCRA-IDEA: *BRCA1* splice variants and breast cancer risk: novel approaches using nanobiology.

(\$ one year, 2006-2007)

Principal applicant: Foulkes, WD

Co-investigators: Bismar, T; Aloyz, R; Ghadirian, P

CBCRA: Toward the biological treatment of BRCA1-related breast cancer: EGF, EGFR and tyrosine kinase inhibitors

(\$ over 3 years, 2006-2009)

Principal applicant: Foulkes, WD

Co-investigators: Nielsen, T; Mai, S

CBCRA: BRCA1, CDC4, Cyclin E, and chromosomal instability in breast cancer

(\$ over 3 years, 2005-2008)

### Co-investigator

Principal applicant: Mai, S

Co-investigators: Foulkes, WD; Watson, P

Susan G Komen Breast Cancer Foundation

The three-dimensional telomeric signature(s) of DCIS

(US \$ over three years 2006-2009)

## Appendices

Principal applicant: Isaacs, W

Co-applicants: Foulkes, WD; Epstein, J; Partin, A; Easton, D; Eeles, R; Maehle, L; Giles, G; Hopper, J; Whittemore, AS; Halpern, J; Hsieh, CL; Cussenot, O; Cancel, G; Jarvik, G; Bdzioch, M; Stanford, J; Ostrander, E; Schaid, D; Thibodeau, S; Gronberg, H; Cooney, K; Lange, E; Schleutker, J; Vogel, W; Cannon-Albright, L; Camp, N; Jianfeng Xu, Meyers, D.

NIH (USA): *Prostate cancer susceptibility: the ICPCG study.*

(\$ as personal award over 4 years, 2002-2006)

Principal applicant: Batista, R

Co-applicants: Foulkes, WD; Blancquaert, I; Cleret de Langavant, G; Gaudet, D; Godard, B; Laflamme, N; Marcoux, A; Rousseau, F

CIHR: *Programme de recherche en appui aux politiques de santé en génétique dans un souci de qualité, d'efficience et de bien-être social.*

(\$ over 4 years, 2003-2007, no financial award to WDF)

Principal applicant: Bismar, T

Co-applicants: Foulkes, WD; Rubin, M.A

Prostate Cancer Research Foundation of Canada (PCRFC): *Defining aggressive phenotype of prostate cancer using a multiplex of 12 gene model*

(\$ over 2 years, 2005-2007)

Principal applicant: Narod, S

Co-applicants: Foulkes WD

CBCRI(Canada): *Risk factor analysis of hereditary breast and ovarian cancer*

(\$ over 5 years, 2004-2009)

## CLINICAL RESEARCH FELLOWS

**Pierre Chappuis MD (1998-2001)**

Research: Cancer Genetics: in particular, treatment and outcome in hereditary breast cancer

Current position: Head, Hereditary cancer clinics, Divisions of Oncology and Medicine, University Hospital of Geneva, Switzerland.

**Zhi Qi Yuan MD (1998-2000)**

Research: Genetics of Colorectal Cancer

Current position: Instructor, Albert Einstein College of Medicine, Bronx, New York.

**David Farber MD (2001-2002)**

Research: Genetics of Colorectal Cancer

Current position: Staff Gastroenterologist, Cité de la Santé, Laval, Québec

**John Goffin MD (2001-2002)**

Research : Survival following breast cancer in *BRCA1/2* mutation carriers

Current position: Instructor, Tufts University Medical Center, Boston, MA

**Rami Younan MD (2003)**

Research: Genomic deletions in *MLH1* and *MSH2*

Current position: Staff surgeon, Université de Montréal

**Polymnia Galiatsatos (2005)**

Research: Genetics of Colorectal Cancer

Current Position: Staff gastroenterologist, SMBD-Jewish General Hospital

**STUDENTS**

**Sophie Sun**, MSc. Title: *CDKN2A/p16 and familial cancer*. FCAR scholar, 1995-1996.

Current position: Oncology Fellow, University of British Columbia.

**Lucie Dupuis**, MSc. Title: The incidence of cancer in the first degree relatives of women diagnosed with endometrial cancer before age 55. Genetic counselling Master's project (Brandeis University, MA, USA, 1998. *NB* Ms. Dupuis obtained permission to work with me while at Brandeis).

Current position: Genetic Counsellor, Hospital for Sick Children, Toronto, Ontario.

**Isabelle Thiffault**, MSc student, 2002-2004: Towards a molecular understanding of proteus syndrome.

Current Position: PhD student, Université de Montréal.

**Susan McVety**, MSc student, 2003- 2005: Characterisation of cDNA deletions in *MLH1* and *MSH2*.

Current Position: Laboratory Technician.

**Ioli Makriyianni**, MSc student, 2003-2005: Mitochondrial and somatic mutations in hereditary breast cancer.

**Tayma Khalil**, MSc student 2005-: *CDC4*, cyclin E and hereditary breast cancer.

**McGILL UNIVERSITY SUMMER STUDENTS**

(2 month projects)

**Tamar Flanders** 1996. Project: Familial studies of colorectal and endometrial cancer\*

**Kevin Sanders** 1996. Project: Familial risks of Thyroid Cancer and Breast/Thyroid cancer\*

**Nathalie Ng Cheong** 1997. Project: *PTEN* mutations in familial cancer\*

**Marie-Noelle Hébert-Blouin** 1998. Project: *GSTT1* and risk of head and neck cancer\*

**Nicola Matthews** 1998. Project: Lobular breast cancer and familial cancer risk\*

**Karen Buzaglo** 2000. Project: Familial factors in fallopian tube cancer\*

**Maral Ouzounian** 2000. Project: Germ-line mutations in hereditary breast cancer

**Annick Wong** 2002. Project: Claudins and cancer\*

\*work published as a result of their project

## **McGILL UNIVERSITY INDEPENDENT STUDIES STUDENTS**

(3—4 credits)

**Kiersten Henderson** 1999 Project: Association studies in thyroid cancer\*

**Ayesha Islam** 1999 Project: BRCA1/2 mutations in pancreas cancer among French-Canadians

**Elsa Lanke** 1999 Project: Thyroid cancer/Gastric Cancer genetics\*

**Vanessa Rossigny** 2003 Project: CHEK2 and breast cancer in the Ashkenazim

**David Novak** 2005 Project: CHEK2 and breast cancer in French Canadians

\*work published as a result of their project

## **COMPLETED POST DOCTORAL FELLOWSHIPS**

**Ala-Eddin Moustafa PhD** (1999-2002)

Research: Genetic factors in squamous cell carcinoma of the head and neck

Current position: Assistant Professor, Department of Oncology, McGill University

**Long Qi Chen MD PhD** (2004-2005)

Research: SNP Discovery in CHEK2

Current position: Professor of Cardiothoracic Surgery, Szechuan Province, China.

## **MEMBERSHIPS**

1984            General Medical Council: registration number 2921080

1987            Royal College of Physicians (UK)

1996            Collège des Médecins du Québec, licence number 96-449

2000            Association of Medical Geneticists of Québec (by examination)

## **PROFESSIONAL SOCIETIES**

British Medical Association

British Society of Human Genetics

American Society of Human Genetics

## **McGILL UNIVERSITY DEPARTMENTAL COMMITTEES**

2001-            Member, Curriculum Committee, Department of Human Genetics

2001-            Member, Fellowship Committee, Department of Human Genetics

2001-            Member, Standing Committee, Department of Human Genetics

2001-            Member, Management Committee, Department of Oncology

**Ph.D. DEFENCE /M.Sc. REFEREE**

PhD, McGill Dept. Biology  
**Ronald Lafreniere**, June 17, 1997.

MSc, McGill Dept. Epidemiology and Statistics  
**Hela Makni**, April 2000

MSc, McGill Dept. Biology  
**Sahar Sibani**, January 2001

MSc, McGill Dept Epidemiology and Statistics  
**Nooshin Ahmadi Pour**, January 2003

PhD, University of Toronto Faculty of Medicine  
**Alexander Liede**, February 2003

PhD, McGill Dept. Experimental Medicine  
**Kevin Little**, November 2004

MSc, University of Toronto, Faculty of Medicine  
**Sean Cleary**, December 2004

**INTERNATIONAL CONFERENCE ORGANISER**

First International Symposium on Hereditary Breast and Ovarian Cancer, Montreal Oct 19-21, 2005. ([www.odon.ca/brca/](http://www.odon.ca/brca/)). Co-sponsored by the Program in Cancer Genetics and the Hereditary Breast and Ovarian Cancer Foundation ([www.hboc.ca](http://www.hboc.ca)). Role: Scientific Director of Conference.

**INTERNATIONAL COMMITTEES etc**

Cancer Genetics Abstract Referee, ASHG meeting, San Francisco, CA, 1999.

Co-Chair, Breast Cancer Genetics Session, ASHG, Denver, CO, 1998.

Member, Steering Committee, International Prostate Cancer Genetics Collaborative Group (representing Eastern Canada) 1997-

Writing committee, Cancer Genetics Certification Examination, Institute for Clinical Evaluation, American Board of Internal Medicine, Philadelphia, PA 1999-2000

Scientific Organising Committee, UICC International Conference on Familial Cancer, Oklahoma City, OK, June 4-6, 2003.

**NATIONAL and INTERNATIONAL PEER-REVIEW GRANT COMMITTEE etc**

National Cancer Institute of Cancer, Epidemiology panel, 1997-2000

Canadian Breast Cancer Research Initiative, IDEA grant panel, 2002-2003



## Appendices

Canadian Institute for Health Research, Genetics Panel, 2003-  
*ad hoc* external reviewer of grants for MRC (Canada) (6), Alberta Heritage Fund for Medical Research (1), Cancer Research Campaign (UK) (5) Research Grants Council of Hong Kong (3), Yorkshire Cancer Research (1).

Tenure review, Independent Investigator, National Human Genome Research Institute, January 2001.

Promotion review (to Assistant Professor) Memorial Sloan-Kettering Cancer Center, June 2001.

Tenure review (to Associate Professor), University of Vermont, September 2002

Tenure review (to Full Professor) Memorial Sloan-Kettering Cancer Center, January 2003

Tenure review (to Full Professor) Sloan Kettering Institute and Memorial Sloan-Kettering Cancer Center, January 2003

Promotion review (to Clinical Assistant Professor), Ohio State University, July 2003

Promotion review (to Reader), University of London, May 2004

Promotion review (to Clinical Assistant Professor), Ohio State University, August 2004

Promotion review (to Clinical Assistant Professor), Ohio State University, August 2004

Promotion review (to Clinical Associate Professor), Ohio State University, April 2005

Promotion review (to Professor), University of London, April 2005

### **PROVINCIAL EXPERT COMMITTEE**

Member, Advisory Board, Conseil d'Évaluation des technologies de la santé du Québec, 1999-

### **NIH CANCER WORKSHOP**

Invited attendee, NCI/NIDCFR/NIDCD Head and Neck Cancer Workshop, Bethesda, Maryland, February 21-23, 1999

### **VISITING LECTURESHIP**

Samuel Riven Lectureship, Vanderbilt University, Tennessee, USA, September 1-3, 1999.

### **TEACHING**

#### **a) NATIONAL**

Workshop on the Genetics of Cancer, Royal College of Physicians of Canada, Montreal, September 23, 1999.

#### **b) MCGILL UNIVERSITY**

- 1) Environmental Carcinogenesis (516-614B MSc program) 1996-1999, 2003, 2005  
(One two-hour session)
- 2) Unit 8 small group teaching in medical genetics (medical students) 1997-

## Appendices

- (One 2 hour lecture and 4 small group sessions, 3 hours each)
- 3) Genetics course (biology BSc students) 1998-1999  
(Six one hour lectures and one 2 hour pre-exam session)
  - 4) Unit 1 teaching (medical students) 2001-  
(one two hour seminar)
  - 5) Special Topics in Epidemiology and Biostatistics: Introduction to genetic epidemiology and statistical methods for human genetics (513-670A, Department of Epidemiology and Biostatistics) (2001-2, one 1 hour seminar)
  - 6) ICM whole class oncology teaching: Three lectures on the prevention of Colorectal cancer (2002-2004)
  - 7) Experimental and Clinical Oncology #5160635D: Cancer Genetics-1.5 hour seminar (2002-)
  - 8) Inherited Cancer Syndromes, 521-690B, Department of Human Genetics: Four 2 hour lectures (2003-)

### **c) HOSPITAL**

- 1) Genetics in Oncology Lecture (Residents) 1998-1999  
(1.5 hour teaching session residents, SMBD-Jewish General Hospital)
- 2) Hereditary Breast Cancer (Surgical Residents) November 2005  
(1 hour teaching session surgical residents, RVH)
- 3) Hereditary Breast Cancer (Surgical Residents) October 2006  
(1 hour teaching session surgical residents, RVH)

### **HOSPITAL COMMITTEE**

Montreal General Hospital Research Ethics Committee member, 1998-2004

### **PUBLICATIONS** (\* denotes WF corresponding author if more than one author)

#### **a) Peer Reviewed Articles**

1. Levi S, Beardshall K, Swift I, Foulkes WD, Playford R, Ghosh P and Calam, J: Antral *Helicobacter pylori*, hypergastrinaemia, and duodenal ulcers: effect of eradicating the organism. *Br Med J*, 299: 1504-5, 1989.
2. Campbell IG, Jones T, Foulkes WD, and Trowsdale J: Folate Binding Protein is a marker for ovarian cancer. *Cancer Res*, 51: 5529-5538, 1991.

3. Campbell IG, Freemont PS, Foulkes WD, and Trowsdale J: An ovarian tumour marker with homology to vaccinia virus contains an IgV-like region and multiple transmembrane domains. *Cancer Res*, 52: 5416-5420, 1992.
4. Foulkes WD, Campbell IG, Stamp GWH and Trowsdale J: Loss of heterozygosity and amplification of chromosome 11 in human ovarian cancer. *Br J Cancer*, 67: 268-273, 1993.
5. Foulkes WD, Ragoussis J, Stamp GWH, Allan GJ and Trowsdale J: Frequent loss of heterozygosity on chromosome 6 in human ovarian carcinoma. *Br J Cancer*, 67: 551-559, 1993.
6. Foulkes WD, Black DM, Stamp GWH, Solomon E and Trowsdale J: Very frequent loss of heterozygosity on chromosome 17 in ovarian carcinoma. *Int J Cancer*, 54: 220-225, 1993.
7. Naylor MS, Stamp GWH, Foulkes WD, Eccles DM and Balkwill FR: Tumor Necrosis Factor and its receptors in human ovarian cancer-potential role in disease progression. *J Clin Invest*, 91: 2194-2206, 1993.
8. Allan GJ, Cottrell S, Trowsdale J and Foulkes WD: Loss of heterozygosity on chromosome 5 in sporadic ovarian carcinoma is a late event and is not associated with mutations in APC at 5q21-22. *Human Mutation*, 3: 283-291, 1994.
9. Foulkes WD, Englefield P and Campbell IG: Mutation analysis of RASK and the 'FLR exon' of NF1 in sporadic ovarian carcinoma. *Eur J Cancer*, 30A: 528-530, 1994.
10. Campbell IG, Nicolai HM, Foulkes WD, Stamp GWH, Senger G, Allan GJ, Boyer CM, Jones K, Bast RC Jr, Solomon E, Trowsdale J and Black DM: A novel gene encoding a B-Box protein within the BRCA1 region at 17q21.1. *Hum Mol Genet*, 3: 589-594, 1994.
11. Campbell IG, Foulkes WD, Senger G, Trowsdale J, Garin-Chesa P and Rettig WJ: Molecular cloning of the B-CAM cell surface glycoprotein of epithelial cancers: a novel member of the immunoglobulin super-family. *Cancer Res*, 54: 5761-5765, 1994.
12. Englefield P, Foulkes WD and Campbell IG: Loss of heterozygosity on chromosome 22q in ovarian carcinoma is distal to and is not accompanied by mutations in NF2 at 22q12. *Br J Cancer*, 70: 905-907, 1994.
13. Foulkes WD, Stamp GWH, Afzal S, Lalani N, McFarlane C, Trowsdale J and Campbell IG: MDM2 amplification is uncommon in ovarian carcinoma irrespective of TP53 status. *Br J Cancer*, 72: 883-8, 1995.
14. Foulkes WD, Brunet J-S, Kowalski LP, Narod SA and Franco EL: Family history is a risk factor for squamous carcinoma of the head and neck in Brazil: a case-control study. *Int J Cancer*, 63: 769-773, 1995.
15. Campbell, Foulkes WD, Beynon G, Davis M and Englefield P: LOH and mutation analysis of CDKN2 in primary human ovarian cancers. *Int J Cancer*, 63: 222-225, 1995.
16. Phelan CM, Lancaster JM, Tonin P, Gumbs C, Carter R, Ghadirian P, Perret C, Moslehi R, Dion F, Faucher M-C, Dole K, Karimi S, Foulkes WD, Lounis H, Warner E, Goss P,

- Anderson D, Larsson C, Narod SA and Futreal PA: Mutation analysis of the BRCA2 gene in 49 site-specific breast cancer families. *Nature Genetics*, 13:121-123, 1996.
17. Afzal S, Lalani EN, Foulkes WD, Boyce B, Tickle S, Cardillo MR, Baker T, Pignatelli M and Stamp GWH: Matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 expression and synthetic matrix metalloproteinase-2 inhibitor binding in ovarian carcinomas and tumour cell lines. *Laboratory Invest*, 74: 406-421, 1996.
  18. Bryan EJ, Watson RH, Davis M, Hitchcock A, Foulkes WD and Campbell IG: Localization of an ovarian cancer tumor suppressor gene to a 0.5cM region between D22S284 and CYP2D, on chromosome 22q. *Cancer Res*, 56: 719-721, 1996.
  19. Davis M, Hitchcock A, Foulkes WD and Campbell IG: Refinement of two chromosome 11q regions of heterozygosity in ovarian cancer. *Cancer Res*, 56: 741-744, 1996.
  20. Foulkes WD, Bolduc N, Lambert D, Ginsburg O, Yandell DW, Tonin P and Narod SA: Increased incidence of cancer in first degree relatives of women with double primary carcinomas of the breast and colon. *J Med Genet*, 33: 534-539, 1996.
  21. Foulkes WD, Brunet J-S, Sieh W, Shenouda G, Black MJ and Narod SA: Familial risks of squamous cell carcinoma of the head and neck. *Br Med J*, 313: 716-721, 1996.
  22. Tonin P, Weber B, Offit K, Couch F, Rebbeck TR, Neuhausen S, Godwin AK, Daly M, Wagner-Costalos J, Berman D, Grana G, Fox E, Kane MF, Kolodner RD, Krainer M, Haber DA, Struewing JP, Warner E, Rosen B, Lerman C, Peshkin B, Norton L, Serova O, Foulkes WD, Lynch HT, Lenoir GM, Narod SA and Garber JE: Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. *Nature Med*, 2:1179 -1183, 1996.
  23. Milner BJ, Hosking L, Sun S, Haites NE, Foulkes WD: Polymorphisms in P21<sup>CIP1/WAF1</sup> are not correlated with TP53 status in sporadic ovarian tumours. *Eur J Cancer*, 32A: 2360-2363, 1996.
  24. Cutler C, Foulkes WD, Brunet J-S, Flanders T, Shibata H and Narod SA: Cutaneous malignant melanoma is uncommonly associated with a family history of melanoma. *Melanoma Res*, 6: 435-440, 1996.
  25. Foulkes WD, Buu PN, Filiatrault D, Leclerc J-M and Narod SA: An excess of congenital abnormalities in French-Canadian children with neuroblastoma: A case series study from Montreal. *Med Pediatr Oncol*, 29: 272-79, 1997
  26. Karp SE, Tonin PN, Bégin LR, Martinez JJ, Zhang JC, Pollak MN and Foulkes WD: Influence of BRCA1 mutations on nuclear grade and estrogen receptor status on breast carcinoma in Ashkenazi Jewish women. *Cancer*, 80: 435-441, 1997.
  27. Foulkes WD, Wong N, Brunet J-S, Narod SA, Bégin LR, Zhang JC, Martinez JJ, Tonin PN, Karp SE, Pollak MN. Germ-line BRCA1 mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. *Clin Cancer Res*, 3: 2465-2470, 1997
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- FAMMM kindred with cancers at multiple sites results in a functionally abnormal protein. *Int J Cancer*, 73: 531-536, 1997.
29. Bignell GR, Canzian F, Shayeghi M, Stark M, Shugart YY, Biggs P, Mangion J, Hamoudi R, Rosenblatt J, Buu P, Sun S, Stoffer SS, Goldgar DE, Romeo G, Houlston RS, Narod SA, Stratton MR and Foulkes WD: A familial non-toxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial non-medullary thyroid cancer. *Am J Hum Genet*, 61: 1123-1130, 1997.
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  32. Pollock PM, Spurr N, Bishop DT, Newton-Bishop J, Gruis N, Goldstein AM, Tucker MA, Foulkes WD, Barnhill R, Haber D, Fountain J and Hayward NK: Haplotype analysis of 2 recurrent CDKN2A mutations in 10 melanoma families from three continents-evidence for common founders. *Hum Mutation*, 11: 424-431, 1998.
  33. Godard B, Foulkes WD, Provencher D, Brunet J-S, Tonin PN, Mes-Masson, A-M, Narod SA and Ghadirian P: Risk factors for familial and sporadic ovarian cancer among French-Canadians: a case-control study. *Am J Obs Gyne*, 179: 403-410, 1998.
  34. Kerr B, Foulkes WD, Cade D, Hadfield L, Hopwood P, Serruya C, Hoare F, Narod SA and Evans DG: False family history of breast cancer in the family cancer clinic. *Eur J Surg Oncol*, 24: 275-279, 1998.
  35. Tonin PN, Mes-Masson A-M, Futreal PA, Morgan K, Mahon M, Foulkes WD, Cole DEC, Provencher D, Ghadirian P and Narod SA: Founder BRCA1 and BRCA2 mutations in French Canadian breast and ovarian cancer families. *Am J Hum Genet*, 63: 1341-1351, 1998.
  36. Pal T, Flanders T, Lehman M, McMillan A, Brunet J-S, Narod SA and Foulkes, WD: Genetic implications of double primary cancers of the colorectum and endometrium. *J Med Genet*, 35: 978-984, 1998.
  37. de Andrade M, Amos, CI and Foulkes WD: Segregation analysis of squamous cell carcinoma of the head and neck: evidence for a major gene determining risk. *Ann Hum Genet*, 62: 505-510, 1998.
  38. Wang Z-J, Churchman M, Campbell IG, Xu W-H, Yan Z-Y, McCluggage WG, Foulkes WD and Tomlinson IPM: Allele loss and mutation screen at the Peutz-Jeghers (LKB1) locus (19p13.3) in sporadic ovarian tumours. *Br J Cancer*, 80: 70-72, 1999.

39. Pereira P, Stanton V, Jothy S, Tomlinson IPM, Foulkes WD and Rozen R: Loss of heterozygosity of methylenetetrahydrofolate reductase in colon carcinomas. *Oncology Reports*, 6: 597-599, 1999.
40. Warner E, Foulkes WD, Goodwin P, Meschino W, Blondal J, Patterson C, Ozcelik H, Goss P, Allingham-Hawkins D, Hamel N, Di Prospero L, Contiga V, Serruya C, Klein M, Moslehi R, Honeyford J, Liede A, Glendon G, Brunet J-S and Narod S: Prevalence and penetrance of BRCA1 and BRCA2 mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst*, 91: 1241-1247, 1999.
41. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. *J. Natl Cancer Instit*, 91: 1310-1316, 1999 (WDF was one of the many who contributed data to this publication).
42. Yuan ZQ, Bégin LR, Wong N, Brunet J-S, Trifiro M, Gordon PH, Pinsky L and Foulkes WD: The effect of the I1307K APC polymorphism on the clinicopathological features and natural history of breast cancer. *Br J Cancer*, 81: 850-854, 1999.
43. Jernström H, Lerman C, Ghadirian P, Lynch H, Weber B, Garber J, Daly M, Olopade O, Foulkes WD, Warner E, Brunet J-S and Narod SA. Pregnancy increases the risk of early breast cancer in BRCA1 and BRCA2 carriers. *Lancet*, 354:1846-1850, 1999.
44. Hamel N, Black MJ, Ghadirian P and Foulkes WD: No association between p53 codon 72 polymorphism and risk of squamous cell carcinoma of the head and neck. *Br J Cancer*, 82: 757-759, 2000.
45. Xu JF and International Consortium for Prostate Cancer Genetics (ICPCG). 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*, 66: 945-957, 2000 (WDF is a member of the ICPCG writing committee for this paper).
46. Foulkes WD, Chappuis PO, Wong N, Brunet J-S, Vesprini D, Rozen F, Yuan ZQ, Pollak MN, Kuperstein G, Narod SA and Bégin LR. Primary node negative breast cancer in BRCA1 mutation carriers has a poor outcome. *Ann Oncol*, 11: 307-313, 2000.
47. Rahman N, Arbour L, Houlston R, Bonaïti-Pellié C, Abidi F, Tranchemontagne J, Ford D, Narod SA, Pritchard-Jones K, Foulkes WD, Schwartz C and Stratton MR. Penetrance of mutations in the familial Wilms tumor gene, FWT1. *J Natl Cancer Inst*, 92: 650-652, 2000.
48. Liu G, Ghadirian P, Vesprini, D, Hamel N, Paradis A-J, Lal G, Gallinger S, Narod SA and Foulkes WD. Polymorphisms in GSTM1, GSTT1 and CYP1A1 and risk of pancreatic cancer. *Br J Cancer*, 82: 1646-9, 2000.
49. Kuperstein G, Foulkes WD, Ghadirian P, Hakimi J and Narod SA. A rapid fluorescent multiplexed-PCR analysis (FMPA) for founder mutations in the BRCA1 and BRCA2 genes. *Clin Genet*, 57: 213-220, 2000.
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- familial Wilms tumour in addition to WT1, FWT1 and FWT2. *Br J Cancer*, 83: 177-83, 2000.
51. Yuan ZQ, Chong GL, Thompson-May S, Trifiro M, Khandjian EW, Rousseau F, Yandell D, McNamara E, Gordon PH and Foulkes WD. Analysis of the hMLH1 and hMSH2 genes in three Quebec families with Hereditary Non-Polyposis Colorectal Cancer. *Ann Roy Coll Phys Surg Canada*, 33: 287-291, 2000.
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  53. Chappuis PO, Kapusta L, Bégin LR, Wong N, Brunet J-S, Narod SA, Slingerland J and Foulkes WD: Germline BRCA1/2 mutations and p27<sup>Kip1</sup> protein levels independently predict outcome after breast cancer. *J Clin Oncol*, 18: 4045-4052, 2000.
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  55. Tonin PN, Perret C, Lambert J, Paradis A-J, Kantemiroff T, Benoit M-H, Martin B, Foulkes WD, Ghadirian P. Founder BRCA1 and BRCA2 mutations in early-onset French Canadian breast cancer cases unselected for family history. *Int. J Cancer*, 95: 189-193, 2001.
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- mutations in unselected French Canadian women with breast cancer. *Clin Genet*, 59: 418-423, 2001.
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*Authorship criteria:*

Foulkes WD and Neylon N: Redefining authorship. *Br. Med. J.* **312**: 1423, 1996.

*Book review:*

Foulkes W. *Hidden Histories of Science* Edited by Robert B Silvers. New York Review Books. *Br. Med. J.* **311**:1101, 1995.

**JOURNAL REFEREE**

***Ad hoc*-more than 10 reviews**

Journal of Medical Genetics  
International Journal of Cancer  
British Journal of Cancer

**Between 5 and 10 reviews**

Nature Genetics  
Lancet  
Journal of the National Cancer Institute  
Cancer Research  
Clinical Cancer Research  
European Journal of Cancer

**Between 1 and 5 reviews**

American Journal of Human Genetics  
Lancet Oncology  
Human Mutation  
Oncogene  
Gastroenterology  
Prostate  
Journal of Clinical Pathology  
Oncology Research  
Molecular and Cellular Probes  
Canadian Journal of Oncology

**BOOK REFEREE**

Cambridge University Press

## **THESIS DEFENCE/REFEREE/COMMITTEE**

PhD, McGill Dept. Biology  
Ronald Lafreniere, June 17, 1997.

Ph.D, McGill Dept Biology  
Adriana Diaz Anzaluda,  
April 1999-current

PhD, McGill Dept Oncology  
David Hamilton  
May 2000-current

MSc, McGill Dept. Epidemiology and Statistics  
Hela Makni, April 2000

MSc, McGill Dept. Biology  
Sahar Sibani, January 2001

MSc, McGill Dept. Human Genetics  
Andrea Karin Lawrance  
May 2001-current

## **INVITED TALKS and SEMINARS, 1995-2006**

### **Scientific Audience**

#### **a) International**

September 19, 1995

**Title:** *Increased risk of squamous cell carcinoma of the head and neck in association with a family history of this cancer.*

Vermont Cancer Center  
Burlington, Vermont

May 9, 1996

**Title:** *Genetics of head and neck cancer*

Epidemiology of head and neck cancer meeting  
IARC, Lyon, France

December 9, 1996

**Title:** *Resolving uncertainty in hereditary breast and ovarian cancer*

Beatson Institute for Cancer Research  
Glasgow, Scotland

Appendices

December 10, 1996

**Title:** *Developing a Cancer Genetics Service*

Department of Medical Genetics, University of Glasgow,  
Yorkhill Hospital  
Glasgow, Scotland

February 13, 1998

**Title:** *Epidemiological and clinical studies of cancer genetics in the Ashkenazi Jewish population.*

Department of Human Genetics Seminar  
Schwartz Building, Memorial Sloan-Kettering Cancer Center,  
New York, New York.

March 12, 1998

**Title:** *The genetics of breast cancer in the Ashkenazi Jewish population*

Department of Epidemiology,  
MD Anderson Cancer Center,  
Houston, Texas.

March 12, 1998

**Title:** *Familial multinodular goitre and hereditary non-medullary thyroid cancer*

Department of Endocrinology,  
MD Anderson Cancer Center,  
Houston, Texas.

May 1, 1998

**Title:** *Endocrine cancers*

Department of Human Genetics  
A “genetics of human cancer” course lecture  
Memorial Sloan-Kettering Cancer Center,  
New York, New York.

September 15, 1998

**Title:** *Overview of studies of prognosis in familial and hereditary breast cancer*

Breast Cancer Linkage Consortium,  
Dublin, Ireland.

September 17, 1998

**Title:** *Genetics of Breast Cancer*

Division of Investigative Sciences,  
Imperial College of Science and Medicine,  
Hammersmith Hospital, London

September 18, 1998

**Title:** *Cancer Genetics: Much Ado about Nothing?*

Appendices

GlaxoWellcome Medicines Research Centre,  
Gunnels Wood Lane  
Stevenage, Herts, UK.

October 5, 1998

**Title:** *Research in progress*

Vermont Cancer Center retreat,  
Baldwin's Creek,  
Bristol, VT, USA

May 26, 1999

**Title:** *The influence of familial and hereditary factors on the clinicopathological features and prognosis of breast cancer*

Department of Epidemiology  
Fred Hutchinson Cancer Research Center  
Seattle, WA, USA

September 2, 1999

**Title:** *Recent advances in cancer genetics*

Division of Genetic Medicine, Department of Medicine,  
Vanderbilt University  
Nashville, TN, USA.

December 3, 1999

**Title:** *Clinicopathological features and prognosis of hereditary breast cancer*

Netherlands Cancer Institute  
Antoni van Leeuwenhoek Huis,  
Amsterdam, Netherlands

December 16, 1999

**Title:** *Clinical, Pathological and Survival studies in hereditary breast cancer*

Duke University Medical Center  
Duke University  
North Carolina, USA

September 25, 2000

**Title:** Hereditary breast cancer: genes, risks and outcome

University of Newcastle Medical School  
University of Newcastle,  
Northumberland, UK

November 28, 2001

**Title:** Clinicopathological studies of hereditary breast cancer

CHUV,  
University of Lausanne  
Lausanne, Switzerland

Appendices

March 27, 2003

**Title:** Founder populations and cancer genetics: a view from just north of here  
NHGRI, Division of Intramural Research Seminar Series,  
NIH,  
Bethesda, MD, USA

September 22, 2003

**Title:** *Clinico-pathological features of BRCA1-related breast cancer*  
Division of Medical and Molecular Genetics  
Guy's Hospital,  
London, UK

September 23, 2003

**Title:** *Five things I learnt about BRCA1-related breast cancer in the last year*  
Gjesteforelesning,  
Gades Institute,  
Haukeland University Hospital  
Bergen, Norway

September 24, 2003

**Title:** *Five things I learnt about BRCA1-related breast cancer in the last year*  
Netherlands Cancer Institute  
Amsterdam, Netherlands

February 2, 2006

**Title:** *Genetic Risk Assessment*  
5<sup>th</sup> International "From Gene to Cure" Congress  
Vrije Universiteit Amsterdam  
Amsterdam, Netherlands

February 2, 2006

**Title:** *Prevention of Hereditary Breast Cancer*  
5<sup>th</sup> International "From Gene to Cure" Congress  
Vrije Universiteit Amsterdam  
Amsterdam, Netherlands

April 20, 2006

**Title:** *Clinico-pathological features of basal-like/BRCA1 tumors*  
"Basal-like and BRCA1-associated Breast Cancer" meeting  
Harvard Club  
Boston, MA, USA

August 16, 2006

**Title:** *Recent advances in understanding of the inherited susceptibility to cancers of the prostate, pancreas, stomach and colorectum*



Appendices

Australian Ovarian Cancer Study and the Family Cancer Clinics of Australia  
Couran Cove Island Resort  
Stradbroke Island, Australia

August 18, 2006

**Title:** *Hereditary breast cancer: from pathology to treatment and beyond*  
Australian Ovarian Cancer Study and the Family Cancer Clinics of Australia  
Couran Cove Island Resort  
Stradbroke Island, Australia

October 28, 2006

**Title:** Breakthrough treatments for BRCA1 and BRCA2 mutation carriers  
10<sup>th</sup> Annual Cincinnati Comprehensive Breast Cancer Conference  
Cutting Edge Strategies in Breast Cancer: The next decade  
Cincinnati, OH, USA

November 9, 2006

**Title:** Hereditary breast cancer: from pathology to treatment and beyond  
Cancer Colloquia IV: Cell and Molecular Biology of Breast Cancer  
University of St-Andrews  
St-Andrews, Scotland

**b) National**

April 26, 1996

**Title:** *Genetics of head and neck cancer*  
Cancer Genetic Epidemiology Workshop  
Environmental Health Centre  
Ottawa, Ontario

February 24, 1999

**Title:** *Genetics of Breast Cancer: some observations from the study of founder populations in Quebec*  
Division of Cancer Biology Research Seminar,  
Sunnybrook and Women's College Hospital Health Sciences Centre,  
Toronto, ON, Canada

May 19, 1999

**Title:** *Genetics of Breast and Ovarian Cancer*  
"New Developments in prenatal diagnosis and medical genetics"  
University of Toronto CME course  
Toronto, ON, Canada

June 20, 1999

**Title:** *Node negative breast cancer in Ashkenazi Jewish women has a very good prognosis if the tumor is both HER2 and BRCA1 germ-line mutation negative*

Appendices

Reasons for Hope: NCIC/CBCRI conference  
Toronto, ON, Canada

June 21, 2001

**Title:** *Treatment issues in hereditary breast cancer*

Theme: The genetic basis of disease

Canadian Federation of Biological Societies, 44<sup>th</sup> annual meeting.

Ottawa Congress Centre

Ottawa, ON, Canada

October 7, 2004

**Title:** *Exons, Introns, Enhancers, Deletions and Founders: an overview of HNPCC in Quebec*

Oncogenetics: Achievements and Challenges,

17ieme entretiens du Centre Jacques Cartier

Crowne Plaza Hotel, Montreal, Quebec

June 15, 2006

**Title:** *Genetics and Breast Cancer: An update*

Toronto Breast Cancer Symposium 2006

Metro Toronto Convention Center, Toronto, Ontario

**c) Local/Provincial**

September 28, 1995

**Title:** *Familial Risks of Squamous Cell Carcinoma of the Head and Neck*

Annual Meeting of Quebec ORL Society

Montibello, Quebec

March 26, 1996

**Title:** *p16 and Familial Cancer*

Institut de Cancer de Montreal - Hopital Notre Dame

Montreal, Quebec

June 19, 1996

**Title:** *A p16 mutation in a family with multiple cancers*

Les Journées de Génétique Humaine - Réseau de Médecine Génétique Appliqués du FRSQ

Montreal, Quebec

October 24, 1997

**Title:** *A gene for familial multinodular goitre maps to chromosome 14q*

Annual Congress of the Quebec ORL Association,

Chateau Frontenac,

Quebec City, Quebec

November 20, 1997

**Title:** *The genetics of breast cancer*

Appendices

Annual Scientific Meeting of Clinical Biochemists of Quebec,  
Hotel Vogue,  
Montreal, Quebec

May 29, 1999

**Title:** *Hereditary predisposition to breast and ovarian cancer*  
Annual Congress of the Quebec Obstetrics and Gynecology Association (AOGQ)  
Hotel Delta Sherbrooke,  
Sherbrooke, Quebec

September 20, 2002

**Title:** *Genetic testing for colorectal cancer*  
3<sup>rd</sup> Annual Montreal Colon and GI cancers conference  
Queen Elizabeth Hotel  
Montreal, Quebec

October 24, 2002

**Title:** *Genetics of Skin Cancer*  
247<sup>th</sup> Scientific meeting of the Montreal Dermatological Society  
Royal Victoria Hospital  
Montreal, Quebec

October 4, 2002

**Title:** *Screening or Risk Reduction?*  
1<sup>st</sup> International Cancer Prevention Symposium-Chagnon Foundation  
Ritz Carlton Hotel,  
Montreal, Quebec

November 13, 2002

**Title:** *Genetics of Breast Cancer*  
Cit  de la Sant  Hematology/Oncology Group  
Laval, Quebec

June 25, 2004

**Title:** *Screening of High Risk Patients*  
23<sup>rd</sup> International Congress of Radiology of the International Society of Radiology  
Palais des Congr s, Montreal, Quebec

October 7, 2004

**Title:** *Exons, Introns, Enhancers, Deletions and Founders: an overview of HNPCC in Quebec*  
Oncogenetics: Achievements and Challenges,  
17ieme entretiens du Centre Jacques Cartier  
Crowne Plaza Hotel, Montreal, Quebec

November 25, 2004

**Title:** *Survola sur la g n tique et la prise en charge du cancer colorectal h r ditaire*

Appendices

Centre intégré de lutte contre le cancer de la Montérégie, Réseau Cancer Montérégie  
Hôtel Gouverneur Île Charron, 2405 Île Charron,  
Longueuil, Quebec

December 15, 2004

**Title:** *Genetic diseases in the adult: New opportunities*  
Hôtel Vogue, Montreal, Quebec

September 28, 2005

**Title:** *Genetics of colorectal cancer: What's new?*  
CCMG 2005 Annual Meeting  
Château Bromont  
Bromont, Quebec

October 12, 2005

**Title:** *Genetic influence of breast and gynecological cancers in pre-menopausal women*  
10<sup>th</sup> McGill International Symposium on Reproductive Endocrinology & Infertility and  
Women's Health  
Centre Mont-Royal, Montreal, Quebec

October 20, 2005

**Title:** *Overview - 10 years of BRCA1 and BRCA2*  
BRCA: Today & Tomorrow  
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility  
Genes  
Marriott Château Champlain, Montreal, Quebec

October 20, 2005

**Title:** *Outcome following BRCA1/2 related breast cancer*  
BRCA: Today & Tomorrow  
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility  
Genes  
Marriott Château Champlain, Montreal, Quebec

**d) Institutional**

January 11, 1996

**Title:** *Breast Cancer Syndromes*  
Endocrinology Research Seminar - Royal Victoria Hospital  
Montreal, Quebec

February 28, 1996

**Title:** *Familial Breast Cancer*  
Oncology Rounds - Royal Victoria Hospital  
Montreal, Quebec

Appendices

February 29, 1996

**Title:** *Preventive Surgery and the High-risk Patient*

Surgical Grand Rounds - Royal Victoria Hospital

Montreal, Quebec

March 29, 1996

**Title:** *Germline mutations in p16 and the risk of cancer*

McGill Genetics rounds: Case presentations-Royal Victoria Hospital

Montreal, Quebec

November 8, 1996

**Title:** *Controversies Surrounding New Genetic Testing* (Panel Discussion)

47th McGill University Annual Refresher Course for Family Physicians

Montreal, Quebec

November 14, 1996

**Title:** *The role of Preventive Surgery in the High-risk Individual*

Surgical Grand Rounds - Sir M.B. Davis Jewish General Hospital

Montreal, Quebec

November 22, 1996

**Title:** *Resolving uncertainty in hereditary breast and ovarian cancer*

McGill Genetics Rounds - Montreal Children's Hospital

Montreal, Quebec

November 25, 1996

**Title:** *Familial Cancer* (with Dr. Patricia Tonin)

Grand Medical Rounds - Sir M.B. Davis Jewish General Hospital

Montreal, Quebec

February 20, 1997

**Title:** *Genetics and epidemiology of non-medullary thyroid cancer*

Endocrinology rounds,

Montreal General Hospital

Montreal, Quebec.

March 20, 1997

**Title:** *Methods and recent results in the genetics of cancer susceptibility*

Montreal Cancer Research Group,

McGill Cancer Centre,

Montreal, Quebec.

November 13, 1997

**Title:** *The genetics of breast cancer*

Department of Epidemiology and Biostatistics,

Fall Seminar Series,

Appendices

McGill University, Montreal

November 24, 1997

**Title:** *Female cancer and genetics*

Department of Obstetrics and Gynaecology Grand Rounds  
Primrose Amphitheatre, Royal Victoria Hospital,  
Montreal, Quebec.

December 5, 1997

**Title:** *Female cancers and genetics*

Department of Obstetrics and Gynaecology Grand Rounds  
Block Amphitheatre, SMBD-Jewish General Hospital,  
Montreal, Quebec.

December 10, 1997

**Title:** *Recent advances in cancer genetics*

Department of Medicine Grand Rounds  
JSL Browne Amphitheatre, Royal Victoria Hospital,  
Montreal, Quebec.

December 15, 1997

**Title:** *Breast cancer: endocrine and genetic factors* (with Professors M. Pollak and L. Pinsky)

Department of Medicine Grand Rounds  
Block Amphitheatre, SMBD-Jewish General Hospital,  
Montreal, Quebec.

February 5, 1998

**Title:** *Genetics of breast and colorectal cancer*

Department of Surgery Grand Rounds  
Osler Amphitheatre, Montreal General Hospital,  
Montreal, Quebec.

February 17, 1998

**Title:** *Cancer genetics: an introduction*

Department of Medicine Grand Rounds  
Osler Amphitheatre, Montreal General Hospital,  
Montreal, Quebec.

April 24, 1999

**Title:** *Hereditary ovarian cancer*

4<sup>th</sup> McGill International Symposium on reproductive endocrinology and infertility  
Jeanne Timmins Amphitheatre,  
McGill University, Montreal.

May 12, 1999

**Title:** *Recent advances in breast and ovarian cancer genetics*

Appendices

Surgical Grand Rounds,  
Royal Victoria Hospital,  
McGill University, Montreal

August 25, 1999

**Title:** *The role of BRCA1 and BRCA2 in breast and ovarian cancer*

Obstetrics and Gynecology Rounds

Royal Victoria Hospital,  
McGill University, Montreal

December 13, 1999

**Title:** *Genetics and Adult Onset diseases: A changing role for medical genetics.* (with Prof. D. Rosenblatt)

Medical Grand Rounds,  
Sir M.B. Davis-Jewish General Hospital,  
McGill University, Montreal

January 12, 2000

**Title:** *Genetic predisposition and outcome from cancer*

Montreal Cancer Research Group,  
McGill Cancer Centre,  
Montreal, Quebec.

February 24, 2000

**Title:** *Non-medullary thyroid cancer*

Endocrinology Grand Rounds  
Sir MB Davis-Jewish General Hospital  
Montreal, Quebec.

March 15, 2000 (with Ms. Lidia Kasprzak and Dr. Georges Chong)

**Title:** *Genetics and Cancer: How mutation analysis affects clinical management*

Medical Grand Rounds  
Royal Victoria Hospital  
MUHC, Montreal, Quebec

April 4, 2000 (with Ms. Lidia Kasprzak)

**Title:** *Colorectal Cancer Genetics: How mutation analysis affects clinical management*

Medical Grand Rounds  
Montreal General Hospital  
MUHC, Montreal, Quebec

November 7, 2000

**Title:** *Management of Hereditary Breast and Ovarian Cancer*

Medical Grand Rounds  
Montreal General Hospital  
MUHC, Montreal, Quebec

Appendices

November 8, 2000

**Title:** *Management of Hereditary Breast and Ovarian Cancer*

Medical Grand Rounds

Royal Victoria Hospital

MUHC, Montreal, Quebec

October 22, 2001

**Title:** *Management of Hereditary Breast and Ovarian Cancer: Prevention, Early Detection and Treatment*

Medical Grand Rounds

Sir M.B. Davis-Jewish General Hospital,

McGill University, Montreal

November 17, 2001

**Title:** *McGill Program in Cancer Genetics: Bringing together human genetics and oncology*

McGill Oncology Research Retreat,

November 16-17,

Hotel Days Inn,

Montreal

December 16, 2002

**Title:** *Genetics of Cancer: an update*

MUHC Radiation Oncology Group

Montreal General Hospital

November 23, 2004

**Title:** *Clinicopathological features of Hereditary Breast Cancer: Ten years on*

MUHC Clinical and Research Seminar

Meakins Auditorium

McIntyre Building

McGill University

December 15, 2004

**Title:** *Genetics of Colorectal cancer*

GI residents

Montreal General Hospital

Lectures to Interested Groups and/or the General Public

October 26, 1996

**Title:** *Risk factors, prevention and early diagnosis in prostate cancer*

First Patient Advocates for Advanced Cancer Treatment (PAACT) Prostate Cancer Conference,

Grand Rapids, MI, USA



Appendices

May 22, 2001

**Title:** *Genetics and Cancer: Prevention, Early Diagnosis and Treatment*  
Research Governor's Society First Lecture Series  
Lady Davis Institute for Medical Research,  
Montreal, Quebec.

October 24, 2001

**Title:** *Genetic Testing for Cancer Susceptibility*  
38<sup>th</sup> Annual André Aisenstadt Clinical Day  
The Use of Genetic tests in Medical Diagnosis and Treatment  
Sir M.B. Davis-Jewish General Hospital,  
**McGill University, Montreal**

September 18, 2002

**Title:** *Genetic testing for colorectal cancer*  
3<sup>rd</sup> Annual Montreal Colon and GI cancers pre-conference lay workshop  
Queen Elizabeth Hotel  
Montreal, Quebec

October 1, 2002

**Title:** *Genetics of Breast Cancer*  
CanSupport Public Lecture  
Omni Hotel,  
Montreal, Quebec

September 27, 2004

**Title:** *The Why, Where and How of genes and diseases in the Jewish population*  
National Council of Jewish Women of Canada  
The power of genealogy  
Gelber Conference Center Montreal, Quebec

September 19, 2005

**Title:** *Role of genetic factors in cancer & familial diseases*  
National Council of Jewish Women of Canada  
Gelber Conference Centre  
Montreal, Quebec

## A Combined Genomewide Linkage Scan of 1,233 Families for Prostate Cancer–Susceptibility Genes Conducted by the International Consortium for Prostate Cancer Genetics

Jianfeng Xu,<sup>1</sup> Latchezar Dimitrov,<sup>1</sup> Bao-Li Chang,<sup>1</sup> Tamara S. Adams,<sup>1</sup> Aubrey R. Turner,<sup>1</sup> Deborah A. Meyers,<sup>1</sup> Rosalind A. Eeles,<sup>2</sup> Douglas F. Easton,<sup>2</sup> William D. Foulkes,<sup>2</sup> Jacques Simard,<sup>2</sup> Graham G. Giles,<sup>2</sup> John L. Hopper,<sup>2</sup> Lovise Mahle,<sup>2</sup> Pal Moller,<sup>2</sup> Tim Bishop,<sup>2</sup> Chris Evans,<sup>2</sup> Steve Edwards,<sup>2</sup> Julia Meitz,<sup>2</sup> Sarah Bullock,<sup>2</sup> Questa Hope,<sup>2</sup> The ACTANE Consortium,<sup>2</sup> Chih-lin Hsieh,<sup>3</sup> Jerry Halpern,<sup>3</sup> Raymond N. Balise,<sup>3</sup> Ingrid Oakley-Girvan,<sup>3</sup> Alice S. Whittemore,<sup>3</sup> Charles M. Ewing,<sup>4</sup> Marta Gielzak,<sup>4</sup> Sarah D. Isaacs,<sup>4</sup> Patrick C. Walsh,<sup>4</sup> Kathleen E. Wiley,<sup>4</sup> William B. Isaacs,<sup>4</sup> Stephen N. Thibodeau,<sup>5</sup> Shannon K. McDonnell,<sup>5</sup> Julie M. Cunningham,<sup>5</sup> Katherine E. Zarfes,<sup>5</sup> Scott Hebbing,<sup>5</sup> Daniel J. Schaid,<sup>5</sup> Danielle M. Friedrichsen,<sup>6</sup> Kerry Deutsch,<sup>6</sup> Suzanne Kolb,<sup>6</sup> Michael Badzioch,<sup>2,6</sup> Gail P. Jarvik,<sup>6</sup> Marta Janer,<sup>6</sup> Leroy Hood,<sup>6</sup> Elaine A. Ostrander,<sup>6</sup> Janet L. Stanford,<sup>6</sup> Ethan M. Lange,<sup>7</sup> Jennifer L. Beebe-Dimmer,<sup>7</sup> Caroline E. Mohai,<sup>7</sup> Kathleen A. Cooney,<sup>7</sup> Tarja Ikonen,<sup>8</sup> Agnes Baffoe-Bonnie,<sup>8</sup> Henna Fredriksson,<sup>8</sup> Mika P. Matikainen,<sup>8</sup> Teuvo L.J. Tammela,<sup>8</sup> Joan Bailey-Wilson,<sup>8</sup> Johanna Schleutker,<sup>8</sup> Christiane Maier,<sup>9</sup> Kathleen Herkommer,<sup>9</sup> Josef J. Hoegel,<sup>9</sup> Walther Vogel,<sup>9</sup> Thomas Paiss,<sup>9</sup> Fredrik Wiklund,<sup>10</sup> Monica Emanuelsson,<sup>10</sup> Elisabeth Stenman,<sup>10</sup> Björn-Anders Jonsson,<sup>10</sup> Henrik Grönberg,<sup>10</sup> Nicola J. Camp,<sup>11</sup> James Farnham,<sup>11</sup> Lisa A. Cannon-Albright,<sup>11</sup> and Daniela Seminara<sup>12,\*</sup>

<sup>1</sup>Data Coordinating Center, <sup>2</sup>ACTANE, <sup>3</sup>BC/CA/HI, <sup>4</sup>Johns Hopkins University, <sup>5</sup>Mayo Clinic, <sup>6</sup>PROGRESS, <sup>7</sup>University of Michigan, <sup>8</sup>University of Tampere and Tampere University Hospital, <sup>9</sup>University of Ulm, <sup>10</sup>University of Umeå, <sup>11</sup>University of Utah, and <sup>12</sup>National Cancer Institute

Evidence of the existence of major prostate cancer (PC)–susceptibility genes has been provided by multiple segregation analyses. Although genomewide screens have been performed in over a dozen independent studies, few chromosomal regions have been consistently identified as regions of interest. One of the major difficulties is genetic heterogeneity, possibly due to multiple, incompletely penetrant PC–susceptibility genes. In this study, we explored two approaches to overcome this difficulty, in an analysis of a large number of families with PC in the International Consortium for Prostate Cancer Genetics (ICPCG). One approach was to combine linkage data from a total of 1,233 families to increase the statistical power for detecting linkage. Using parametric (dominant and recessive) and nonparametric analyses, we identified five regions with “suggestive” linkage (LOD score >1.86): 5q12, 8p21, 15q11, 17q21, and 22q12. The second approach was to focus on subsets of families that are more likely to segregate highly penetrant mutations, including families with large numbers of affected individuals or early age at diagnosis. Stronger evidence of linkage in several regions was identified, including a “significant” linkage at 22q12, with a LOD score of 3.57, and five suggestive linkages (1q25, 8q13, 13q14, 16p13, and 17q21) in 269 families with at least five affected members. In addition, four additional suggestive linkages (3p24, 5q35, 11q22, and Xq12) were found in 606 families with mean age at diagnosis of  $\approx$ 65 years. Although it is difficult to determine the true statistical significance of these findings, a conservative interpretation of these results would be that if major PC–susceptibility genes do exist, they are most likely located in the regions generating suggestive or significant linkage signals in this large study.

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### Introduction

Familial clustering of prostate cancer (PC [MIM 176807]) has been consistently recognized for many years (reviewed by Isaacs and Xu [2002]). Segregation analyses and twin studies strongly suggest that genetic factors ex-

plain at least some of the familial aggregation of PC (reviewed by Schaid [2004]). Research groups worldwide have recruited families with multiple members with PC and have performed linkage analyses to search for PC-susceptibility genes. More than a dozen genomewide screens have been performed (Easton et al. 2003), and numerous regions have been suggested as harboring hereditary PC (HPC) genes. Furthermore, several genes in regions linked to PC have been proposed as candidate HPC genes, notably *ELAC2* (MIM 605367), *RNASEL* (MIM 180435), and *MSR1* (MIM 153622) (Tavtigian et al. 2001; Carpten et al. 2002; Xu et al. 2002).

Despite these extensive efforts, linkage findings suggested by individual groups and proposed associations with variants in candidate genes have not been reproducibly replicated by other groups. The difficulties in mapping PC genes have been widely discussed (Isaacs and Xu 2002; Edwards and Eccles 2004; Ostrander et al. 2004; Schaid 2004). Briefly, it is likely that multiple genes predispose to PC and that no single gene is sufficiently important to provide a reliable linkage signal when a small number of families are analyzed. PC linkage may be further complicated by phenocopies, particularly given the high prevalence of the disease and widespread use of prostate-specific antigen screening. These difficulties are inherent to PC-linkage studies, and, although they cannot be completely overcome, several approaches can be used to reduce their impact. One approach is to study a much larger number of families, which should improve the statistical power to detect regions containing genes that are mutated in a small proportion of families. Another approach is to study subsets of families with PC that are more likely both to segregate mutations in genes conferring a strong PC risk and to have a reduced number of phenocopies, such as those with a large number of affected members and/or affected members with early ages at diagnosis.

The International Consortium for Prostate Cancer Genetics (ICPCG) was formed to facilitate the task of PC-susceptibility gene identification through the combined analyses of linkage data from families with PC. In the present study, we describe the results from a combined genomewide screen for PC-susceptibility genes among 1,233 PC-affected families within the ICPCG, the largest study of its kind to date.

## Methods

### *Ascertainment of Families*

The overall ICPCG study population was described in detail elsewhere (Schaid et al. 2005). All members of the ICPCG recruited their study population, supported through their own research funding. Ten ICPCG groups participated in this combined genomewide screen, AC-

TANE (Anglo/Canadian/Texan/Australian/Norwegian/European Union Biomed), BC/CA/HI (British Columbia, California, and Hawaii), Johns Hopkins University (JHU), Mayo Clinic, University of Michigan, PROGRESS (Prostate Cancer Genetic Research Study, Fred Hutchinson Cancer Research Center), University of Tampere in Finland, University of Ulm in Germany, University of Umeå in Sweden, and University of Utah. There were 1,233 PC pedigrees in this combined analysis. The research protocols and informed consent procedures were approved by each group's institutional review board.

### *Definition of Affection Status and Classification of Pedigrees*

Affected individuals were defined as "those men affected with PC who had been confirmed by either medical records or death certificates." Affected individuals without either medical records or death-certificate confirmation were considered as having unknown affection status (hence, instances of self-reported PC and of PC status that was based solely on family-history interviews were considered of unknown status). Because of this restricted definition, some pedigrees had fewer affected men than were previously reported in publications by the respective groups. All men without a diagnosis of PC were coded as having unknown affection status, regardless of whether they had undergone screening for PC. Hence, all analyses were based on the sharing of marker genotypes among affected individuals, with no consideration of the phenotype for the remaining subjects. Although such an approach may result in some loss of power, it provided a uniform approach across all participating groups.

### *Genotyping and Consensus Genetic Map*

Various methods were used by different groups to genotype microsatellite markers in their respective genomewide screen, as described in detail elsewhere (Hsieh et al. 2001; Cunningham et al. 2003; International AC-TANE Consortium 2003; Janer et al. 2003; Lange et al. 2003; Schleutker et al. 2003; Wiklund et al. 2003; Xu et al. 2003; Maier et al. 2005; Camp et al., in press). Different sets of genomewide-screen markers were used by these 10 groups (see individual references for complete description of markers), with a range of information contents of 0.38–0.57 across the various groups and a total of 1,322 markers. To facilitate a combined linkage analysis, we generated a consensus map by aligning all these markers to the draft human reference sequence (physical position) on the basis of the Human hg13 assembly (released November 14, 2002). Ten of these markers could not be uniquely located in the human reference sequence and were dropped from the combined analysis. The genetic position of the aligned markers was pri-

marily determined on the basis of the deCode map (Kong et al. 2002). Among the 1,312 mapped markers, we were able to find the deCode genetic position for 964 markers. For the remaining 348 markers, for which only physical position was available, we estimated their genetic positions by interpolation based on the flanking markers for which both physical positions and deCode positions are available.

#### Linkage-Analysis Methods

The combined linkage analysis was performed in two stages. In the first stage, the linkage analyses were performed by each of the 10 groups, by use of the same definition of affection status and parametric model and the same linkage programs and options. All linkage results were based on multipoint calculations implemented in the Genhunter-Plus software (Kruglyak et al. 1996; Kong and Cox 1997). Because of their large size, the Utah pedigrees were selected from the larger set of all Utah pedigrees with at least four subjects with PC with no more than two meioses separating them (Camp et al. 2005); these pedigrees were then further trimmed to allow analysis by Genhunter-Plus. The analysis performed by each group was implemented by scripts provided by the ICPCG Data Coordinating Center (DCC), to facilitate consistency and automation. Although different genomewide screen markers were used among groups, the marker position was determined on the basis of the consensus map described above; therefore, the length of each chromosome was the same across all the groups. The linkage was evaluated at a resolution of 1 cM for each chromosome. The output files containing pedigree-specific linkage information at every cM across the genome were sent to the DCC. In the second stage, a combined analysis was performed at the DCC. For

nonparametric linkage analysis, the combined allele-sharing LOD score was evaluated for each chromosome on the basis of the family-specific allele sharing at each centimorgan by use of the computer program ASM (Kong and Cox 1997). For the parametric linkage analysis, the combined LOD score with the assumption of heterogeneity (HLOD) was evaluated for each chromosome, on the basis of the family-specific LOD score at each centimorgan, by use of the computer program HOMOG (Ott 1999). Throughout the present study, we used LOD scores to describe HLODs for the results of parametric analyses and allele sharing LODs for nonparametric analyses.

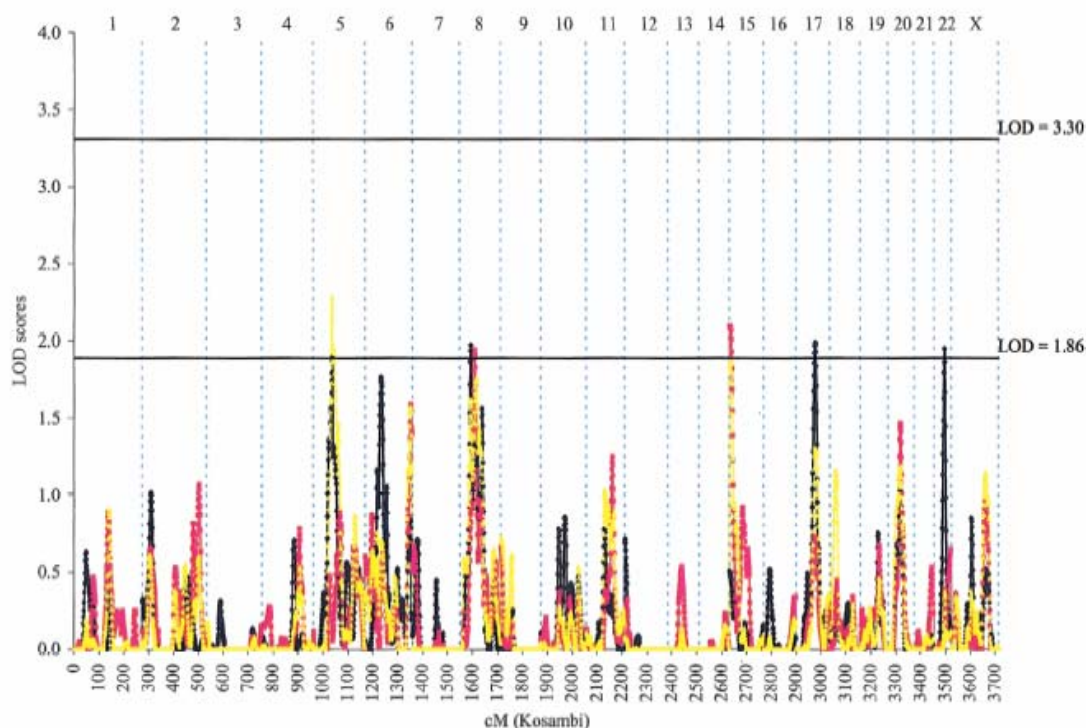
The allele frequencies used were population specific; that is, for each marker, allele frequencies were estimated by counting alleles across all families within each individual group, without consideration of genetic relationships. Although not fully efficient, this provides straightforward, unbiased allele-frequency estimates. Because few families within any participating group had a known non-white racial background, allele frequencies were estimated from the pool of all data within a group, without consideration of race. Both nonparametric and parametric linkage analyses were performed. Allele-sharing nonparametric linkage analysis was performed, because that did not require specification of a model and would be expected to have good power against a wide range of alternative models. The linear allele-sharing model was implemented using ASM (Kong and Cox 1997). Families were weighted equally, and the score function "all" was used, which provides more evidence of linkage than does the "pairs" option whenever most affected individuals in a pedigree share the same allele that is identical by descent. For the parametric linkage analyses, a dominant model and a recessive model were used. The dominant

**Table 1**  
Characteristics of Families

ICPCG MEMBER	MEAN AGE AT DIAGNOSIS <sup>a</sup> (YEARS)		NO. OF AFFECTED MEMBERS				RACE <sup>b</sup>		TOTAL NO. OF FAMILIES
	≤65	>65	2	3	4	≥5	White	Black	
ACTANE	41	21	18	32	11	3	64	0	64
BC/CA/HI	41	57	24	54	16	4	83	7	98
JHU	95	93	2	26	47	113	169	17	188
Mayo Clinic	72	87	70	58	21	10	158	0	159
PROGRESS	141	113	38	107	66	43	240	8	254
University of Michigan	103	73	55	76	29	16	158	16	176
University of Tampere	3	7	0	2	5	3	10	0	10
University of Ulm	84	55	60	42	29	8	139	0	139
University of Umeå	10	40	0	13	17	20	50	0	50
University of Utah	16	79	18	14	14	49	95	0	95
Total	606	625	285	424	255	269	1,166	48	1,233

<sup>a</sup> Information about family mean age at diagnosis was not available for two families.

<sup>b</sup> Nineteen families are from other ethnic groups, such as Asian, Hispanic, or Native American.



**Figure 1** Combined genomewide screen for PC-susceptibility genes with use of nonparametric and parametric multipoint linkage analyses among the entire set of 1,233 PC-affected families recruited from 10 ICPCG members. LOD scores obtained from parametric analysis with use of a dominant model (blue line), a recessive model (red line), and nonparametric analysis (yellow line) are plotted by individual chromosome for the whole genome.

model was similar to the one used to map *HPC1* (MIM 601518) (Smith et al. 1996). The frequency of the susceptibility allele was assumed to be 0.003, with a penetrance of 0.001 for noncarriers and 1.0 for carriers. Unaffected subjects were coded as having noninformative phenotypes. The recessive model was similar to the dominant model, except that the susceptibility-allele frequency was set to 0.15 and the penetrance for heterozygous carriers was set equal to the penetrance for homozygous noncarriers. Stratified linkage analyses were also performed in two predetermined subsets of families: 269 families with at least five affected members, and 606 families with family mean age at diagnosis of  $\leq 65$  years. The planned analyses were developed and approved by members of the ICPCG.

We summarized our linkage results on the basis of the proposed guidelines for reporting linkage results of a genomewide screen: a cutoff LOD score of 3.30 as “significant” evidence of linkage and a cutoff LOD score of 1.86 as “suggestive” evidence of linkage (Lander and Kruglyak 1995). On the basis of asymptotic arguments, a LOD score of 3.30 is expected to occur 0.05 times in

a genome screen that makes use of a fully informative marker set, and a LOD score of 1.86 is expected to occur once by chance.

## Results

### Analyses of All Families

Table 1 summarizes the characteristics of the 1,233 PC-affected families from 10 different ICPCG groups that were included in the analysis. Fifty-one percent of families had a mean age at onset of  $< 65$  years; 22% had five or more affected family members.

We first performed a combined genomewide linkage analysis of the complete set of 1,233 PC-affected families, using parametric and nonparametric approaches. Although no significant evidence of linkage was observed in the genome, evidence of suggestive PC linkage was observed at five chromosomal regions, 5q12, 8p21, 15q11, 17q21, and 22q12 (fig. 1 and table 2). The highest overall LOD score in the genome was 2.28 from the nonparametric analysis, found near marker *D5S2858* on

**Table 2**  
Chromosomal Regions with Suggestive Evidence of Linkage

POPULATION AND REGION	DISTANCE FROM			ANALYSIS TYPE	LOD	1-LOD DROP INTERVAL	
	PTER cM	NEAREST MARKER				Genetic (cM)	Physical (Mb)
Primary analysis: entire set of families ( <i>N</i> = 1,233):							
5q12	77	D5S2858	Nonparametric	2.28	66–96	43–78	
8p21	46	D8S1048	Dominant	1.97	39–52	22–32	
15q11	1	D15S817	Recessive	2.10	0–14	0–25	
17q21	77	D17S1820	Dominant	1.99	66–85	35–54	
22q12	42	D22S283	Dominant	1.95	35–47	29–37	
Secondary analysis: subset of families with at least five affected family members ( <i>n</i> = 269):							
1q25	184	D1S2818	Nonparametric	2.62	170–198	165–196	
8q13	81	D8S543	Recessive	2.41	75–90	66–75	
13q14	56	D13S1807	Recessive	2.27	42–67	39–71	
16p13	34	D16S764	Nonparametric	1.88	19–46	9–23	
17q21	77	D17S1820	Dominant	2.04	66–83	39–53	
22q12	42	D22S283	Dominant	3.57	32–50	27–42	
Secondary analysis: subset of families with mean age at diagnosis of ≤65 years ( <i>n</i> = 606):							
3p24	57	D3S2432	Dominant	2.37	47–69	28–49	
5q35	179	D5S1456	Dominant	2.05	166–193	162–174	
11q22	102	D11S898	Recessive	2.20	89–112	81–111	
Xq12	80	DXS7132	Dominant	2.30	62–90	40–85	

5q12 (77 cM from pter). The linkage results for each individual family collection for each of these five chromosomal regions are shown in table 3. As seen in table 3, with the exception of 17q21, the LOD scores for each of the highlighted regions are higher in the combined analysis than those observed in any individual group, reaching a suggestive level of evidence only in the combined family data.

*Analyses of Subsets of Families*

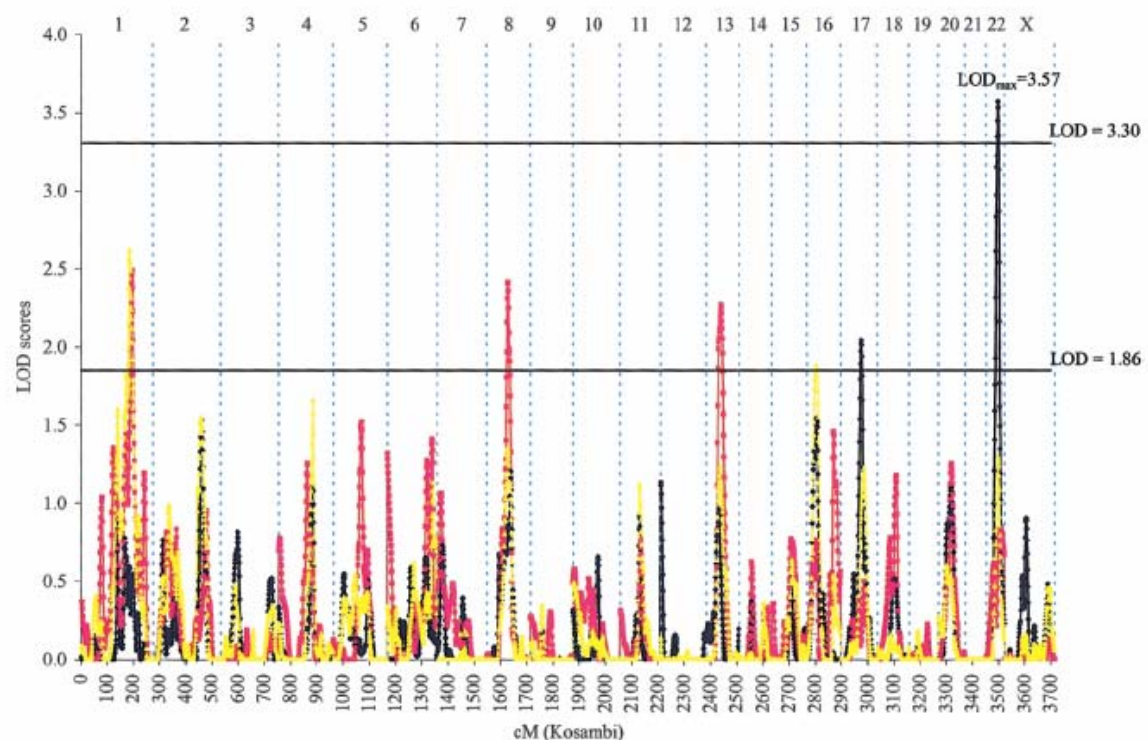
We also performed linkage analyses in subsets of families that might be more likely to segregate genes conferring strong PC risk: families with at least five affected members or with family mean age at diagnosis of ≤65 years. As hypothesized, we found stronger evidence of linkage among 269 families with at least five affected

members—one region with significant evidence of linkage and four additional regions with suggestive evidence of linkage (fig. 2 and table 2). The strongest evidence of linkage in the genome was found at 22q12 with use of the dominant model, with LOD score of 3.57 at 42 cM (near marker D22S283). This LOD score exceeded the criterion of significant evidence of linkage in the genomewide screen. Evidence of linkage at this region was provided by multiple ICPCG groups (fig. 3). Of the 10 groups, 4 had a LOD score >1.0 at this region, including a LOD score of 2.05 from the Mayo group, a LOD score of 1.57 from the Michigan group, a LOD score of 1.31 from the Utah group, and a LOD score of 1.22 from the JHU group. It is noted that linkage evidence at this region was observed in the complete set of 1,233 families (LOD score of 1.95 at 42 cM) and was strengthened

**Table 3**  
Support for Linkage from Each Group at Chromosomal Regions with Suggestive Linkage

POPULATION	LOD SCORE BY CHROMOSOMAL REGION AND MODEL				
	5q12 (77 cM)	8p21 (46 cM)	15q11 (1 cM)	17q21 (77 cM)	22q12 (42 cM)
	Nonparametric	Dominant	Recessive	Dominant	Dominant
All groups ( <i>N</i> = 1,233)	2.28	1.97	2.10	1.99	1.95
ACTANE ( <i>n</i> = 64)	.00	.00	.00	.00	.00
BC/CA/HI ( <i>n</i> = 98)	1.17	.00	.26	.76	.00
JHU ( <i>n</i> = 188)	.29	.16	.95	.72	1.28
Mayo Clinic ( <i>n</i> = 159)	.32	.09	.00	.00	1.10
PROGRESS ( <i>n</i> = 254)	.25	1.64	.64	.01	.00
University of Michigan ( <i>n</i> = 176)	.01	.28	1.06	3.07	.13
University of Tampere ( <i>n</i> = 10)	.00	.19	.00	.42	.02
University of Ulm ( <i>n</i> = 139)	.38	.77	.04	.00	.00
University of Umeå ( <i>n</i> = 50)	1.62	.00	.87	.00	.00
University of Utah ( <i>n</i> = 95)	.27	.17	.00	.03	1.47





**Figure 2** Combined genomewide screen for PC-susceptibility genes with use of nonparametric and parametric multipoint linkage analyses among 269 families with at least five affected members recruited from 10 ICPCG members. LOD scores obtained from parametric analysis with use of a dominant model (blue line), a recessive model (red line), and nonparametric analysis (yellow line) are plotted by individual chromosome for the whole genome.

in this subset. When families with at least five affected family members were removed from the analysis, no evidence of linkage at this region was found in the remaining 964 families. In addition to the 22q12 region, five additional regions reached suggestive evidence of PC linkage in this subset of families with at least five affected family members (fig. 2 and table 2).

For 606 families with family mean age at diagnosis of  $\leq 65$  years, suggestive evidence of PC linkage was found at four chromosomal regions (fig. 4 and table 2), with the highest LOD score of 2.37 near marker *D3S2432* at 3p24 (57 cM). The four PC linkages identified in this subset of families were unique to the early-age-at-diagnosis subset. No evidence of linkage at these four regions was observed in the complete set of 1,233 families.

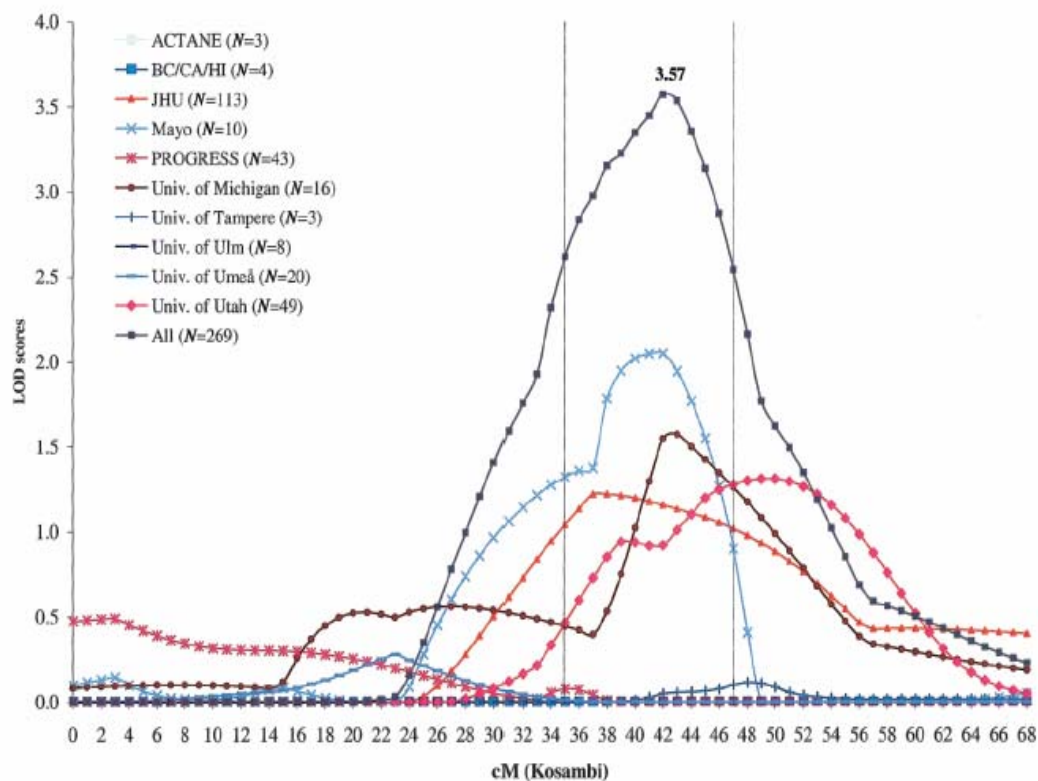
## Discussion

We have described results from the largest PC genomewide screen reported to date, with combined linkage data from 1,233 PC-affected families collected by 10 different groups in the ICPCG. From the primary analysis of the

entire set of the families, we identified five chromosomal regions (5q12, 8p21, 15q11, 17q21, and 22q12) with suggestive evidence of linkage. With one exception (i.e., 17q21), the threshold for suggestive evidence of linkage was reached only in the combined analysis, which emphasizes the advantage of this combined approach.

Importantly, we found significant evidence of linkage at the 22q12 region in 269 families with at least five affected members, a subset of PC-affected families that is more likely to segregate mutations in genes conferring a strong PC risk. Suggestive evidence of linkage at five other regions (1q25, 8q13, 13q14, 16p13, and 17q21) was also observed in this subset of families. In addition, four additional regions (3p24, 5q35, 11q22, and Xq12) were found to have suggestive evidence of PC linkage in 606 families with family mean age at diagnosis of  $\leq 65$  years.

We recognize that many of the regions identified in this study may represent false positive findings due to multiple tests in a genomewide screen and that it is difficult to dissect true linkages from false signals. On the basis of the assumption of a fully informative marker



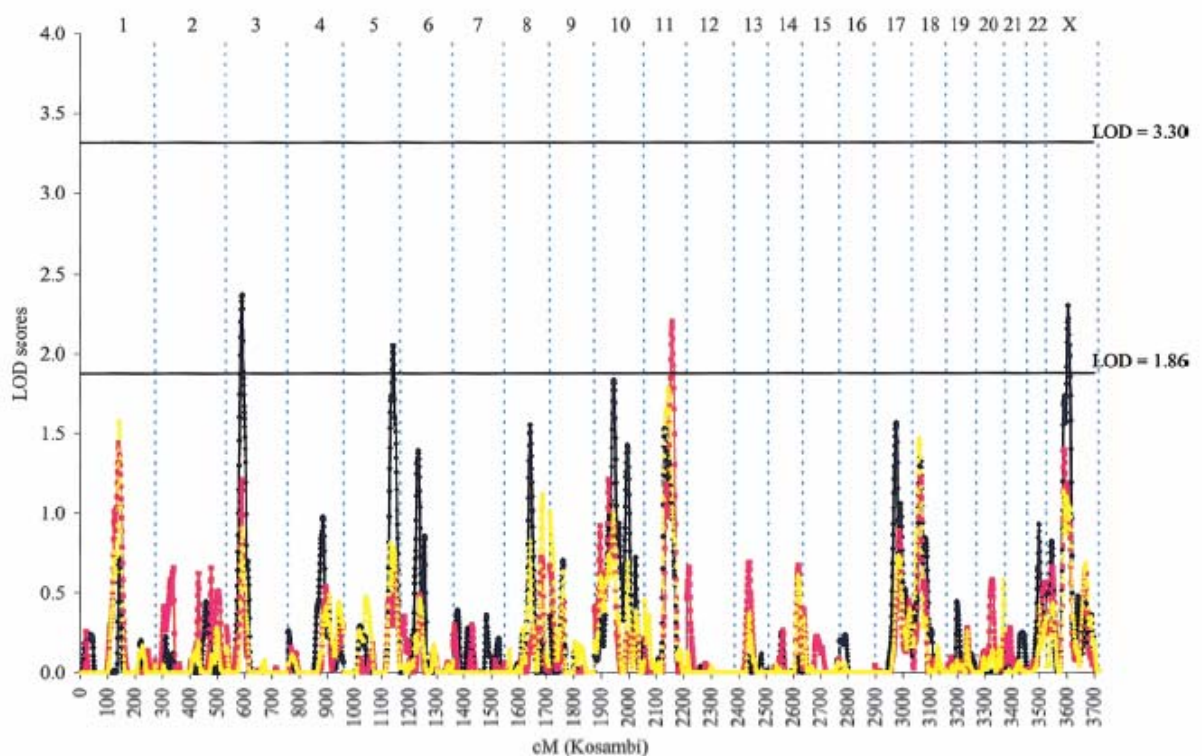
**Figure 3** Parametric linkage analysis of chromosome 22 among families with at least five affected members with use of the dominant model. LOD scores are plotted for each of the 10 ICPCG groups.

map, LOD scores  $>3.30$  or  $1.86$  would have been expected to occur  $0.05$  times and  $1$  time, respectively, in a single genomewide screen. Here, we performed nine genomewide screens (three in the primary analyses and six in the subgroup analyses); this needs to be considered when interpreting the results. However, these nine analyses are not independent. Using the method of Camp and Farnham (2001), we determined that the nine non-independent analyses performed were equivalent to  $\sim 5.2$  independent genomewide screens. We therefore estimate that, after correcting for multiple testing, regions with a LOD score of  $>3.30$  (significant evidence) in at least one analysis would be expected  $0.25$  times in  $5.2$  independent screens and regions with a LOD score of  $>1.86$  (suggestive evidence),  $5.2$  times. Our empirical results (one observed LOD score of  $3.57$  and  $13$  regions with LOD scores  $\geq 1.86$ ) therefore exceeded the expectation under the null hypothesis of no linkage. Furthermore, these thresholds may be unduly conservative for the less-than-informative real data used in these genomewide screens. Although it is difficult to determine the true statistical significance of these findings, a conservative

interpretation of these results would be that if major PC-susceptibility genes do exist, they are most likely to be located in the regions generating suggestive or significant linkage signals. Therefore, results from this analysis are likely to be helpful in prioritizing any efforts to identify PC-susceptibility genes.

Lack of reproducibility among PC-linkage studies in recent years demonstrates the difficulties faced in the effort to identify PC-susceptibility genes with the linkage approach (Isaacs and Xu 2002; Edwards and Eccles 2004; Ostrander et al. 2004; Schaid 2004). One of the major difficulties is genetic heterogeneity due to multiple but incompletely penetrant PC-susceptibility genes. Each of these genes may be responsible for a small fraction of PC-affected families. In this study, we planned two approaches to address the impact that these difficulties have on identification of PC linkage. One approach was to perform linkage analysis in a large number of PC-affected families, to increase the statistical power to detect linkage. This approach led to the identification of five regions with evidence suggestive of linkage in the complete set of  $1,233$  families. However, the failure to





**Figure 4** Combined genomewide screen for PC-susceptibility genes with use of nonparametric and parametric multipoint linkage analyses among 606 families with family mean age at diagnosis  $\leq 65$  years recruited from 10 ICPCG members. LOD scores obtained from parametric analysis with use of a dominant model (blue line), a recessive model (red line), and nonparametric analysis (yellow line) are plotted by individual chromosome for the whole genome.

identify significant linkage in the genome, even with this large number of families, indicates a substantial degree of genetic heterogeneity and suggests that this approach alone is insufficient to uncover a significant signal if it is present. Our second approach was to focus on subsets of families that are more likely to segregate highly penetrant mutations, including families with large numbers of affected individuals and/or early age at diagnosis. This latter approach appeared to be more effective; stronger evidence of linkage was found in several regions among these subsets of families than from the complete set of families. The most noteworthy finding was the considerable increase in evidence of linkage at 22q12—from a LOD score of 1.95 (suggestive linkage) in the complete set of families to a LOD score of 3.57 (significant linkage) in 269 families with at least five affected members. It is important to note that the large number of families in our combined study makes it possible to analyze sufficient numbers in each subset of families. Linkage studies in families with large numbers of affected individuals and/or early ages at diagnosis

have proved to be effective in identifying breast cancer-susceptibility genes (Hall et al. 1990; Easton et al. 1993).

Three pieces of evidence from our study increase our confidence that the linkage at 22q12 is due to PC-susceptibility gene(s) at this region. First, the LOD score at this region reached the criterion of significant linkage. The chance of observing this magnitude of LOD score in the genome under a null hypothesis of no linkage is  $<0.25$  times in our study. Second, this linkage was identified in the families with at least five affected members, a subset of families that is more likely to segregate mutations in genes conferring strong PC risk. Third, the evidence of linkage at this region was supported by multiple individual groups; of six groups with  $\geq 10$  such large families, four had LOD scores  $>1$  in this interval. The relatively good reproducibility of this linkage finding is an unusual observation in PC-linkage studies (Easton et al. 2003). More than 129 known genes are in the 1-LOD drop interval (29–37 Mb). An important candidate gene, *CHEK2* (MIM 604373), is outside the interval, at  $\sim 27$  Mb.

Because the mode of inheritance for PC is uncertain, we performed linkage analysis using both parametric (dominant or recessive) and nonparametric methods. In general, evidence of PC linkage was consistently provided by both parametric and nonparametric methods, although with different strengths at different regions. Parametric analysis will have better power to detect linkage when an assumed genetic model approximates the underlying mode of inheritance of a disease susceptibility gene (Clerget-Darpoux et al. 1986a, 1986b; Lio and Morton 1997). Nonparametric analysis, by assessment of allele sharing among affected individuals within a pedigree, may have better power when the underlying genetic model cannot be specified with any confidence (Whittemore and Halpern 1994).

Most of the linkage regions identified in the present study are broad. The information content of the marker sets used in these analyses is generally low, particularly since most of our families are small and often do not include genotypes of all parents. Further genotyping at a higher density, with use of either microsatellite markers or SNPs, should improve informativeness. An additional approach currently under way by the ICPCG incorporates clinical and pathological tumor variables in the assignment of affected status, to emphasize clinically aggressive disease in this large data set. Hopefully, these approaches should help to confirm or refute the evidence of linkage and narrow the regions of interest.

During the last decade, tremendous effort has been put forth to identify major susceptibility genes for PC. Linkage studies with smaller numbers of PC-affected families have identified and implicated many chromosomal regions that might harbor PC-susceptibility genes. The large number of different regions that have been implicated—and the general lack of reproducibility among these studies—has provided a tenuous foundation for subsequent PC-gene identification. In this context, results from the current study, with a very large number of families in the overall analysis, provides a strong basis for prioritizing regions for PC-gene identification.

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## Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for PC, *ELAC2*, *RNASEL*, *MSR1*, *HPC1*, and *CHEK2*)

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## Pooled genome linkage scan of aggressive prostate cancer: results from the International Consortium for Prostate Cancer Genetics

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**Abstract** While it is widely appreciated that prostate cancers vary substantially in their propensity to progress to a life-threatening stage, the molecular events responsible for this progression have not been identified. Understanding these molecular mechanisms could provide important prognostic information relevant to more effective clinical management of this heterogeneous cancer. Hence, through genetic linkage analyses, we examined the hypothesis that the tendency to develop *aggressive* prostate cancer may have an important genetic component. Starting with 1,233 familial prostate cancer families with genome scan data available from the International Consortium for Prostate Cancer Genetics, we selected those that had at least three members with the phenotype of clinically aggressive prostate cancer, as defined by either high tumor grade and/or stage, resulting in 166 pedigrees (13%). Genome-wide linkage data were then pooled to perform a combined linkage analysis for these families. Linkage signals reaching a suggestive level of significance were found on chromosomes 6p22.3 (LOD = 3.0), 11q14.1–14.3 (LOD = 2.4), and 20p11.21–q11.21 (LOD = 2.5). For chromosome 11, stronger evidence of linkage (LOD = 3.3) was observed among pedigrees with an average at diagnosis of 65 years or younger. Other chromosomes that showed evidence for

heterogeneity in linkage across strata were chromosome 7, with the strongest linkage signal among pedigrees without male-to-male disease transmission (7q21.11, LOD = 4.1), and chromosome 21, with the strongest linkage signal among pedigrees that had African American ancestry (21q22.13–22.3; LOD = 3.2). Our findings suggest several regions that may contain genes which, when mutated, predispose men to develop a more aggressive prostate cancer phenotype. This provides a basis for attempts to identify these genes, with potential clinical utility for men with aggressive prostate cancer and their relatives.

### Introduction

There is much evidence that prostate cancer, the most frequent of all cancers in men (Jemal et al. 2004), has a familial, if not genetic, etiology. This evidence is supported by a variety of study designs, including case-control, cohort, twin, and family-based studies (Grönberg 2003; Schaid 2004), although linkage studies to find genes associated with high prostate cancer risk have been disappointing. Early linkage results implicated targeted candidate regions for prostate cancer susceptibility loci, including HPC1 on chromosome 1q23–25 (Smith et al. 1996; Xu 2000; Carpten et al. 2002), PCAP on chromosome 1q42–43 (Berthon et al. 1998), CAPB on chromosome 1p36 (Gibbs et al. 1999), chromosome 8p22–23 (Xu et al. 2001), HPC2 on chromosome 17p (Tavtigian et al. 2001), HPC20 on chromosome 20q13 (Berry et al. 2000), and HPCX on chromosome Xq27–28 (Xu et al. 1998). A few of the targeted linkage studies have led to the identification

The names of all authors and their affiliations are listed in the Acknowledgements. The fact that Dr Schaid's name is given here for purposes of correspondence should not be taken to imply that he played the sole leading part in writing this article.

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of candidate susceptibility genes including RNASEL (HPC1) on chromosome 1 (Carpten et al. 2002), ELAC2 (HPC2) on chromosome 17 (Tavtigian et al. 2001), and MSR1 on chromosome 8 (Xu et al. 2002). Despite these promising findings, however, confirmatory studies for these genes have provided mixed results. A number of studies provide strong support, both functional and epidemiological, while other studies suggest that the roles of these genes, in terms of individual risks and/or prevalence of mutations, might be small (Ostrander and Stanford 2000; Schaid 2004).

In addition to targeted linkage analyses, at least 12 genome linkage scans based on microsatellite markers have now been performed (Easton et al. 2003; Matsui et al. 2004; Schaid 2004; Camp et al. 2005). Overall, the cumulative data across all of these studies show some suggestive evidence for linkage to almost every chromosome. Although there is some overlap among studies for chromosomal regions that show suggestive to moderate evidence for linkage, there is no evidence for a single (or a common few) major susceptibility loci. In total, these studies illustrate the difficulty in finding consistent linkage results across different studies and emphasize the likely large amount of genetic heterogeneity of prostate cancer risk. Furthermore, these results suggest that if linkage analysis is to be used successfully to identify prostate cancer susceptibility genes, innovative approaches to address such extensive genetic heterogeneity will be required.

The diagnosis of prostate cancer is common—in the U.S. approximately one in six men is diagnosed with prostate cancer in his lifetime. The *development* of prostate cancer is even more common—estimates from autopsy studies indicate that between 40 and 70% of men over age 70 will have cancer in their prostates, at least in the form of histologically identifiable lesions. It is clear that only a subset of these lesions are detected clinically and that only a subset of these clinically detected cancers will progress to life-threatening disease. A recent study of the use of prostate-specific antigen (PSA) to screen for prostate cancer estimated that 15–37% of men are overdiagnosed with prostate cancer, meaning that they have clinically insignificant prostate cancer that otherwise would not be detected in their lifetime (Etzioni et al. 2002). Correspondingly, identification of genetic factors that affect the aggressiveness of prostate cancers is an important question both mechanistically and clinically. Most previous attempts to identify prostate cancer susceptibility genes using linkage analysis have focused on families with multiple members affected with prostate cancers regardless of clinical-pathologic characteristics. The few studies that focused on families with men

diagnosed with clearly aggressive disease have been hampered by the small number of families available within individual study samples. To overcome these limitations, we used genome-wide linkage to evaluate evidence for linkage in a set of unique families, each with at least three men affected with aggressive prostate cancer.

From a genetic perspective, it is unclear whether so-called clinically insignificant cancers share the same molecular risk factors as their aggressive counterparts. If they do, it is important to understand the molecular determinants of risk for all prostate cancers, although such factors would likely be extremely common, since the disease is so common, at least in most western populations. On the other hand, if genetic susceptibility for more aggressive prostate cancer is mediated through different, or additional, mechanisms, it is important to characterize those specific mechanisms and identify the genes involved. From a clinical perspective, it is important to understand the predisposition to an aggressive form of the disease, because such cancers can cause disability and death if not effectively treated.

Supporting our hypothesis that the more aggressive prostate cancers are more likely to have a genetic cause, several studies have found linkage of Gleason grade to a number of genomic regions. Gleason grade is used to measure prostate tumor differentiation and is considered a measure of cancer aggressiveness. Although the Gleason sum scale ranges from 2 to 10, most tumors are scored in a much more narrow range, most commonly 6 and 7. Using Gleason grade in quantitative trait linkage analyses, the reported linkage regions include chromosomes 5q31–33, 7q32, and 19q12 (Witte et al. 2000; Neville et al. 2002, 2003; Paiss et al. 2003), 9q34 (Neville et al. 2003), 4 (Slager et al. 2003), and 1p13–q21, 5p13–q11, and 6q23 (Slager et al. 2006). Furthermore, two recent studies reported interesting linkage signals from genome linkage scans restricted to men with clinically aggressive prostate cancer. One recent study (Chang et al. 2005) reported suggestive evidence for linkage on chromosome X (HLOD = 2.54) and on chromosome 22 (HLOD = 2.06), while another (Stanford et al. 2006) found suggestive evidence for linkage on chromosome 22 (dominant HLOD = 2.18). Although neither study found a LOD score greater than 3.0, the criterion typically used to define statistically significant linkage, it is intriguing that both studies were consistent for their findings on chromosome 22. Since the above-mentioned studies were carried out on limited numbers of families, the power to detect linkage in restricted subsets of families with aggressive disease was limited.

Because it has not been possible to discover prostate cancer susceptibility genes, and considering our

hypothesis that aggressive prostate cancer may be more genetically homogeneous, we used the International Consortium for Prostate Cancer Genetics (ICPCG) to pool pedigrees that had at least three men with aggressive prostate cancer. Pooling was necessary to obtain a sufficiently large sample size to perform a genome-wide linkage scan. Other pooled analyses by the ICPCG have been used to evaluate linkage for prostate cancer not restricted to the aggressive phenotype on chromosomes 1 (Xu 2000) and 20 (Schaid and Chang 2005), as well as a pooled genome linkage scan (Xu et al. 2005).

## Methods

### Ascertainment of pedigrees

The ICPCG study sample has been described in detail elsewhere (Schaid and Chang 2005; Xu et al. 2005). Eleven research groups participated in this combined linkage analysis of aggressive prostate cancer pedigrees, providing 166 pedigrees. Although the methods of pedigree ascertainment and confirmation of prostate cancer diagnoses differed somewhat across the groups, only men with aggressive prostate cancer diagnosis confirmed by medical records or death certificates were included in this analysis.

### Definition of aggressive disease

Clinical data were used to classify affected men into three groups according to the aggressiveness of their prostate cancer. The classification criteria, presented in Table 1, were developed by the ICPCG Epidemiology subcommittee and are similar to those used in other recent linkage analyses of clinically significant disease

(Chang et al. 2005; Stanford et al. 2006). Men with aggressive prostate cancer were those who had at least one of the following characteristics: regional or distant stage (stage T3, T4, N1, or M1, based on the radical prostatectomy specimen for patients treated with surgery; otherwise, based on clinical stage); tumor Gleason grade at diagnosis  $\geq 7$  (or poorly differentiated grade if no Gleason grade was available); pretreatment PSA at diagnosis  $\geq 20$  ng/ml; death from metastatic prostate cancer before age 65 years (if deceased).

Pedigrees were included in the analyses if they had three or more men with aggressive disease, of whom at least two men had aggressive disease and genotype data. Men with aggressive disease were coded as affected, and all other subjects were coded as unknown phenotype (i.e., men with clinically insignificant and moderate disease did not contribute their phenotypes to the linkage analyses). This approach avoids the complication of unaffected men who have not been screened for prostate cancer, and avoids attempting to model the unknown parameters that might influence the penetrance of less aggressive prostate cancers. Hence, we focused solely on evidence for genetic linkage to aggressive disease.

Each participating group submitted to the Data Coordinating Center (DCC) summary information about each pedigree, including mean age at diagnosis of aggressive disease, number of men with aggressive disease who had genotype data, hereditary prostate cancer (HPC), and male-to-male transmission of prostate cancer. A pedigree was classified as HPC if it met the criteria of Carter et al. (1993). At least one of the following three criteria must have been met: (1) three consecutive generations of prostate cancer along a line of descent; (2) at least three first-degree relatives with a diagnosis of prostate cancer; (3) two or more relatives with a diagnosis of prostate cancer at age  $\leq 55$

**Table 1** Definition of prostate cancer aggressiveness

<p><b>Insignificant:</b> a subject was classified as having had clinically insignificant disease if he had <i>all</i> of the following characteristics:</p> <ul style="list-style-type: none"> <li>• Clinically unapparent tumor at diagnosis (stage A, NOS, T1a, T1b, or T1c)</li> <li>• Tumor in only one lobe if radical prostatectomy was done (T2a)</li> <li>• No evidence of non-localized disease (node negative NX or N0; no metastasis, M0, confined to prostate, T2a)</li> <li>• Tumor Gleason grade at diagnosis <math>&lt; 6</math>; if no Gleason grade, then not moderately or poorly differentiated</li> <li>• Pretreatment PSA at diagnosis <math>&lt; 4</math> ng/ml</li> <li>• If deceased, prostate cancer not listed as primary cause of death on death certificate</li> </ul> <p><b>Aggressive:</b> a subject was classified as having had aggressive disease if he had <i>any</i> of the following characteristics:</p> <ul style="list-style-type: none"> <li>• Regional or distant stage (stage T3, T4, N1, or M1, based on pathology if radical prostatectomy was done; otherwise, clinical stage)</li> <li>• Tumor Gleason grade at diagnosis <math>\geq 7</math></li> <li>• Poorly differentiated grade (if no Gleason grade available)</li> <li>• Pretreatment PSA at diagnosis <math>\geq 20</math> ng/ml</li> <li>• If deceased, death from metastatic prostate cancer before age 65 years</li> </ul> <p><b>Moderate:</b> a subject was classified as having had moderate disease if clinical data were available and he did not meet the criteria for insignificant or aggressive disease</p>
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years. Furthermore, because linkage of prostate cancer susceptibility to chromosome X has been reported (Xu et al. 1998), pedigrees were classified according to male-to-male transmission (yes versus no). Pedigrees classified as “yes” were consistent with autosomal dominant transmission, allowing for incomplete penetrance. For example, pedigrees were classified as “yes” if a father and son both had prostate cancer, or if the father was unaffected, but paternal cousins both had prostate cancer. All other pedigrees were classified as “no”; this means that the “no” group includes pedigrees that have a clear pattern of X-linked transmission and pedigrees that did not have sufficient information to distinguish incomplete penetrance for an autosomal dominant susceptibility allele versus X-linked transmission (e.g., nuclear families with unaffected fathers).

#### Genotyping and consensus genetic map

The participating groups used a total of 1,322 microsatellite markers, although the genotype methods and the sets of markers differed across the groups. Details of the genotype methods and construction of a consensus map are given elsewhere (Xu et al. 2005). Briefly, a consensus map was created by aligning all markers to the draft human reference sequence (physical position) based on the Human hg13 assembly (released November 14, 2002). Ten of these markers could not be uniquely located in the human reference sequence and were dropped from the combined analysis. The genetic positions of the aligned markers were determined from the deCode map (Kong et al. 2002). Among the 1,312 mapped markers, the deCode genetic position was available for 964 markers. The genetic positions for the remaining 348 markers, where only physical positions were available, were estimated by interpolation between the flanking markers where both physical positions and deCode positions were available.

#### Statistical analyses

Linkage analyses were performed by each of the 11 groups using common methods of analysis. Output files from Genehunter-Plus (Kruglyak et al. 1996; Kong and Cox 1997) containing pedigree-specific linkage information at 1 cM intervals across the genome were sent to the ICPCG DCC. The analyses were developed and approved by members of the ICPCG and are described in detail elsewhere (Schaid and Chang 2005). Both parametric and non-parametric linkage analyses were performed. For parametric analyses, dominant and recessive models were used. The dominant model, the

same as that used to map HPC1 (Smith et al. 1996), had two liability classes. Men with aggressive prostate cancer were placed in the first liability class with penetrances of 0.001 and 1.0 for non-carriers and carriers, respectively. All other subjects were placed in a second uninformative liability class, i.e., assigned penetrance of 0.5 for all genotypes. Hence, analyses were for aggressive affecteds only, yet other family members with genotypes helped to infer the missing genotypes among parents. The frequency of the susceptibility allele was set at 0.003. The recessive model was similar to the dominant model, except that the susceptibility allele frequency was set at 0.15, and the penetrances for heterozygous carriers and homozygous non-carriers were assumed to be equivalent. These model-based analyses allowed for a fraction of linked pedigrees by computing heterogeneity LOD scores using the algorithm of HOMOG, estimating a single fraction of linked pedigrees ( $\alpha$ ) for all positions on a chromosome (HLOD-DOM for the dominant model and HLOD-REC for the recessive model). For the non-parametric analyses, Kong and Cox LOD scores for the linear (KCLOD-LIN) and exponential (KCLOD-EXP) allele-sharing models were calculated by the ASM software (Kong and Cox 1997). Pedigrees were weighted equally, and the score function “all” was used. All linkage results were based on multipoint calculations by the Genehunter-Plus software (Kruglyak et al. 1996; Kong and Cox 1997).

Because some studies suggest that early age at prostate cancer diagnosis increases the likelihood of a genetic etiology, and some families fit an autosomal dominant mode of transmission (see reviews by Grönberg 2003; Schaid 2004) we attempted to create genetically homogeneous subsets. To do this, we stratified pedigrees according to mean age at diagnosis of aggressive prostate cancer ( $\leq 65$ ,  $> 65$  years), number of men with both aggressive prostate cancer and genotype data per pedigree ( $< 4$  versus  $4+$ ), evidence of HPC for any type of prostate cancer, as defined elsewhere (Carter et al. 1993), and racial ancestry. Furthermore, pedigrees were classified according to male-to-male transmission of any form of prostate cancer (“yes” versus “no”).

Like others, we computed the maximum LOD scores within subsets. However, using this strategy alone can be misleading. The magnitude of the maximum LOD score depends on the number of pedigrees and their information content. Strata with more informative pedigrees, and a larger number of them, can give larger linkage signals than other less-informative strata. Thus, it would be incorrect to interpret the results to indicate that only the strata with



large linkage signals show evidence for linkage. Furthermore, examining multiple subsets can inflate the false-positive rate. To avoid these problems, there should be significant heterogeneity of the linkage signals across strata, because one would not expect to find heterogeneity in the absence of linkage. Hence, to aid our interpretations, we tested for statistically significant different linkage signals across strata by likelihood ratio statistics, constructed as follows. For the parametric HLOD statistics, we allowed each stratum to have its own parameter representing the fraction of linked pedigrees within the stratum ( $\alpha_k$ ), yet we assumed that all strata share the same position of linkage on a chromosome ( $\theta$ ). For  $K$  strata there were  $(K+1)$  parameters to estimate. Under the null hypothesis of homogeneity across strata, there were only two parameters to estimate, the common value of  $\alpha$  and  $\theta$ . By maximizing the HLOD functions under the null hypothesis ( $\text{HLOD}_{\text{null}}$ ) and under the alternative hypothesis ( $\text{HLOD}_{\text{alt}}$ ), we computed a likelihood ratio statistic,  $2(\text{HLOD}_{\text{alt}} - \text{HLOD}_{\text{null}})$ , and used the  $\chi^2_{K-1}$  distribution to determine probability values. Similar likelihood ratio statistics were computed using the KC LOD scores.

To illustrate the amount of heterogeneity of linkage, we present the estimated  $\alpha$  parameters for each stratum. Statistically significant heterogeneity can arise from differences in the  $\alpha$  parameters. However, the estimated  $\alpha$ 's must be viewed cautiously, because they are most likely biased. Bias can occur when the assumed penetrance is not correct (e.g., when penetrance varies over etiologically relevant genes), when the phenocopy rate is misspecified, and the likelihood used in HOMOG is not correct for estimating  $\alpha$  (Whittemore and Halpern 2001).

We summarized our linkage results based on the proposed guidelines for reporting linkage results of a genome-wide screen: a cutoff of  $\text{LOD} = 3.30$  as “significant” evidence for linkage, and a cutoff of  $\text{LOD} = 1.86$  as “suggestive” evidence for linkage (Lander and Kruglyak 1995). Based on asymptotic arguments, a  $\text{LOD}$  score of 3.30 is expected to occur 0.05 times in a genome screen using a fully informative marker set and a  $\text{LOD}$  score of 1.86 is expected to occur once by chance.

Although computing  $P$ -values for extreme linkage statistics by simulations is an ideal way to evaluate the statistical significance of large  $\text{LOD}$  scores, we could not compute these by the usual methods that rely on the raw genotype and phenotype data. The data were collected during a period of time when informed consents did not request sending data to a central location, and some institutions felt that they would need to

reconsent participants in order to submit their raw data to a central location. To overcome this limitation, we computed empirical  $P$ -values in a limited (i.e., conservative) manner. To compute permutation  $P$ -values, we use the rapid permutation strategy for score statistics proposed by Lin (2005). He showed that under the null hypothesis, and conditional on the data, permutation  $P$ -values can be computed by multiplying an observed score statistic for an observation (in our case, each pedigree is an observation) by a standard normal random variable, and then computing the desired summary statistic. In our application, the NPL scores per pedigree are score statistics for the Kong and Cox allele-sharing models (both linear and exponential) (Kong and Cox 1997). So, for each of 10,000 simulations, we generated a random normal variable per pedigree, multiplied the observed NPL scores by the random variable, computed the summary NPL over all pedigrees, and then determined the maximum summary statistic over all positions on a chromosome. The method by Lin is appropriate when the different statistics (e.g., maximum  $\text{LOD}$  scores per chromosome) have the same null distribution. However, this is not the case, because longer chromosomes are more likely to have larger  $\text{LOD}$  scores than shorter chromosomes, because longer chromosomes have less dependence due to more recombinations. This can be verified by asymptotic approximations given elsewhere (Feingold et al. 1993). Hence, we computed permutation  $P$ -values separately for each chromosome, and then used Benjamini and Hochberg's (Benjamini and Hochberg 1995) step-up method to determine  $P$ -values corrected for testing multiple chromosomes while controlling the false-discovery rate. An advantage of this approach is that by conditioning on the observed NPL scores, it implicitly conditions on the linkage information in a pedigree, in contrast to other approaches that assume fully informative markers for simulations. A limitation, however, is that it is well known that NPL summary statistics have less power than the Kong and Cox  $\text{LOD}$  scores when linkage information is not complete. Hence, our reported permutation  $P$ -values are likely too large, compared to what might be achieved with the raw data.

## Results

The characteristics of the 166 aggressive prostate cancer pedigrees from the 11 groups of the ICPCG are summarized in Table 2. Among these pedigrees, 44% had a mean age at diagnosis of 65 years or younger, 27% had at least four men with aggressive prostate

**Table 2** Characteristics of the ICPG pedigrees used for aggressive prostate cancer linkage

ICPG member	Mean age at aggressive disease diagnosis (years)		No. with aggressive disease and genotype data		Hereditary prostate cancer		Male-to-male		Race			Total no. of pedigrees
	≤ 65	> 65	2–3	4+	No	Yes	Yes	No	African American	Other	Caucasian	
ACTANE		1	1			1		1			1	1
BC/CA/HI	1	2	3		1	2	1	2	2		1	3
JHU	10	13	16	7		23	20	3	2		21	23
Mayo Clinic	8	10	15	3	10	8	10	8			18	18
Fred Hutchinson/ISB	17	20	27	10	7	30	17	20	1	2	34	37
University of Michigan	14	8	17	5	8	14	14	8	3	1	18	22
Washington University	4	4	6	2	1	7	7	1		1	7	8
University of Tampere	2	2		4		4	3	1			4	4
University of Ulm	9	5	13	1	3	11	7	7			14	14
University of Umeå	1	7	7	1	1	7	2	6			8	8
University of Utah	7	21	16	12	17	11	25	3			28	28
All	73	93	121	45	48	118	107	59	8	4	154	166

cancer and genotype data, 71% met the Carter criteria for HPC, and 92% had Caucasian ancestry (8 pedigrees had African American ancestry; 1 pedigree, Asian; 1 pedigree, Hispanic; 2 pedigrees, Native American).

The linkage results for the pool of all 166 pedigrees are summarized in Table 3. Suggestive linkage results (LOD scores > 1.86) were observed on chromosomes 6p, 11q, and 20p. See Fig. 1 for plots of LOD scores for these chromosomes. The largest LOD scores were found at chromosome 6p22.3, with KCLOD-LIN = 3.00 and KCLOD-EXP = 2.63 (42 cM). The recessive model HLOD-REC was 2.20 in this region of chromosome 6 (43 cM). At chromosome 11q14.1–14.3, the recessive model HLOD-REC was 2.40 (89 cM), with weaker evidence provided by the allele-sharing models (KCLOD-LIN = 1.81 and KCLOD-EXP = 1.91 at 88 cM). At chromosome 20p11.21–q11.21, the largest LOD score was an HLOD-DOM of 2.49 (54 cM). The permutation *P*-values are consistent with these findings, with chromosome 6 having the smallest *P*-value ( $P = 0.004$ ; pFDR = 0.08), and chromosomes 11 ( $P = 0.017$ ; pFDR = 0.196) and 20 ( $P = 0.057$ ; pFDR = 0.263) less significant. However, because chromosome 20 showed the largest LOD score by the dominant model, the true level of statistical significance for chromosome 20 is not well approximated by the permutation *P*-values, which are based on the NPL scores.

#### Heterogeneity across strata and subset results

Our results from evaluating heterogeneity across strata suggested that there might be heterogeneity for six

chromosomes: chromosomes 5, 6, 7, 11, 20, and 21. As summarized in Table 4, the linkage results for these chromosomes varied substantially according to the strata analyzed. See also Fig. 1 for the LOD scores plotted within each of the strata for these chromosomes. Three of these six chromosomes were those for which suggestive linkage evidence was found in the pool of all 166 pedigrees: chromosomes 6, 11, and 20. For chromosomes 6 and 20, the stronger linkage signals were found in the subset of pedigrees with an average age at diagnosis greater than 65 years; for chromosome 6, the strongest linkage signal was KCLOD-LIN = 2.74, while for chromosome 20, the strongest linkage signal was HLOD-DOM = 2.65. In contrast, for chromosome 11, the strongest linkage signal was for pedigrees with an average age at diagnosis of 65 years or younger, with HLOD-REC = 3.31.

The three other chromosomes that showed evidence for heterogeneity across strata were chromosomes 5, 7, and 21. Chromosomes 5 and 7 showed the strongest linkage signal among pedigrees without male-to-male disease transmission (5q21.2–22.1, KCLOD-LIN = 2.24; 7q21.11, HLOD-DOM = 4.09). Chromosome 21q22.13–22.3 showed the strongest linkage signal for pedigrees that had African American ancestry (HLOD-DOM = 3.19). Each of these subset linkage signals was located within approximately 5 cM of the maximum LOD score observed in the full set of pedigrees for the corresponding chromosomes (Table 3).

Previous linkage to chromosome 20 has been reported by the Mayo Clinic group (Berry et al. 2000), of which 18 of the original Mayo Clinic pedigrees were

**Table 3** Maximum LOD scores for each chromosome

Chromosome	Allele-sharing exponential model		Allele-sharing linear model		Simulation <i>P</i> -values		Dominant model			Recessive model		
	KCLOD-EXP	cM	KCLOD-LIN	cM	Empiric	FDR	HLOD	cM	$\alpha$	HLOD	cM	$\alpha$
1	0.53	156	0.60	154	0.556	0.765	0.34	158	0.07	0.43	188	0.09
2	0.82	83	0.82	83	0.398	0.765	0.99	67	0.10	0.99	66	0.13
3	0.24	171	0.26	168	0.760	0.832	0.05	34	0.02	0.55	175	0.11
4	1.42	0	1.43	0	0.192	0.568	1.25	0	0.24	1.09	0	0.26
5	1.39	96	1.64	101	0.041	0.233	0.87	85	0.14	1.19	117	0.16
6 <sup>a</sup>	2.63	42	3.00	42	0.004	0.080	1.21	43	0.15	2.20	43	0.25
7	0.47	32	0.45	33	0.484	0.765	0.43	32	0.07	1.02	35	0.14
8	0.89	136	0.78	136	0.242	0.618	1.17	137	0.15	0.79	136	0.15
9	0.21	46	0.26	46	0.714	0.832	0.12	137	0.05	0.57	110	0.10
10	0.34	81	0.23	95	0.667	0.832	0.97	81	0.08	0.75	81	0.10
11 <sup>a</sup>	1.91	88	1.81	88	0.017	0.196	0.71	78	0.11	2.40	89	0.23
12	1.81	21	1.82	21	0.033	0.233	1.61	21	0.19	0.83	22	0.15
13	0.33	123	0.26	123	0.545	0.765	1.00	123	0.13	0.83	123	0.13
14	0.02	91	0.02	91	0.930	0.930	0	0	0	0.08	94	0.03
15	0.25	80	0.30	122	0.566	0.765	0.14	133	0.06	0.50	81	0.11
16	0.49	39	0.48	39	0.341	0.765	0.92	25	0.13	0.77	40	0.14
17	0.32	48	0.27	48	0.539	0.765	0.38	50	0.07	0.48	47	0.10
18	0.74	97	0.84	98	0.196	0.568	0.35	91	0.07	0.51	95	0.11
19	0.11	36	0.10	36	0.732	0.832	0.29	37	0.06	0.10	77	0.05
20 <sup>a</sup>	1.43	52	1.16	52	0.057	0.263	2.49	54	0.18	1.48	52	0.16
21	0.01	79	0.01	79	0.844	0.882	0	0	0	0.14	78	0.09
22	0.20	23	0.14	23	0.490	0.765	0.79	19	0.11	0.61	18	0.13
X	0.94	134	0.93	133	0.198	0.568	1.00	139	0.15	0.94	136	0.24

<sup>a</sup> Chromosomes with LOD scores > 2.0

also included in this analysis. Excluding these 18 Mayo Clinic pedigrees resulted in an HLOD-DOM of 1.85 on chromosome 20, suggesting that the pedigrees with aggressive prostate cancer from the remaining ICPCG members contribute a large fraction to this linkage signal. Furthermore, two of the groups participating in this pooled analysis recently reported their own genome-wide linkage scans for aggressive prostate cancer [Johns Hopkins University (Chang et al. 2005); Fred Hutchinson Cancer Center/Institute of Systems Biology (Stanford et al. 2006)]. To determine whether our findings were influenced by the pedigrees from these prior studies, and to determine the influence from each group, we analyzed the linkage signals for each group that had at least ten pedigrees; all groups with fewer pedigrees were combined into a single “others” group. The heterogeneity results presented in Table 5 illustrate significant heterogeneity across groups for chromosomes 1 and 2, but not for the regions on chromosomes 6, 11, and 20. For chromosome 1, the heterogeneity was most obvious for the dominant model, with pedigrees from Johns Hopkins, Mayo Clinic, and University of Michigan giving the largest LOD scores. For chromosome 2, the recessive model gave the largest heterogeneity, with pedigrees from the

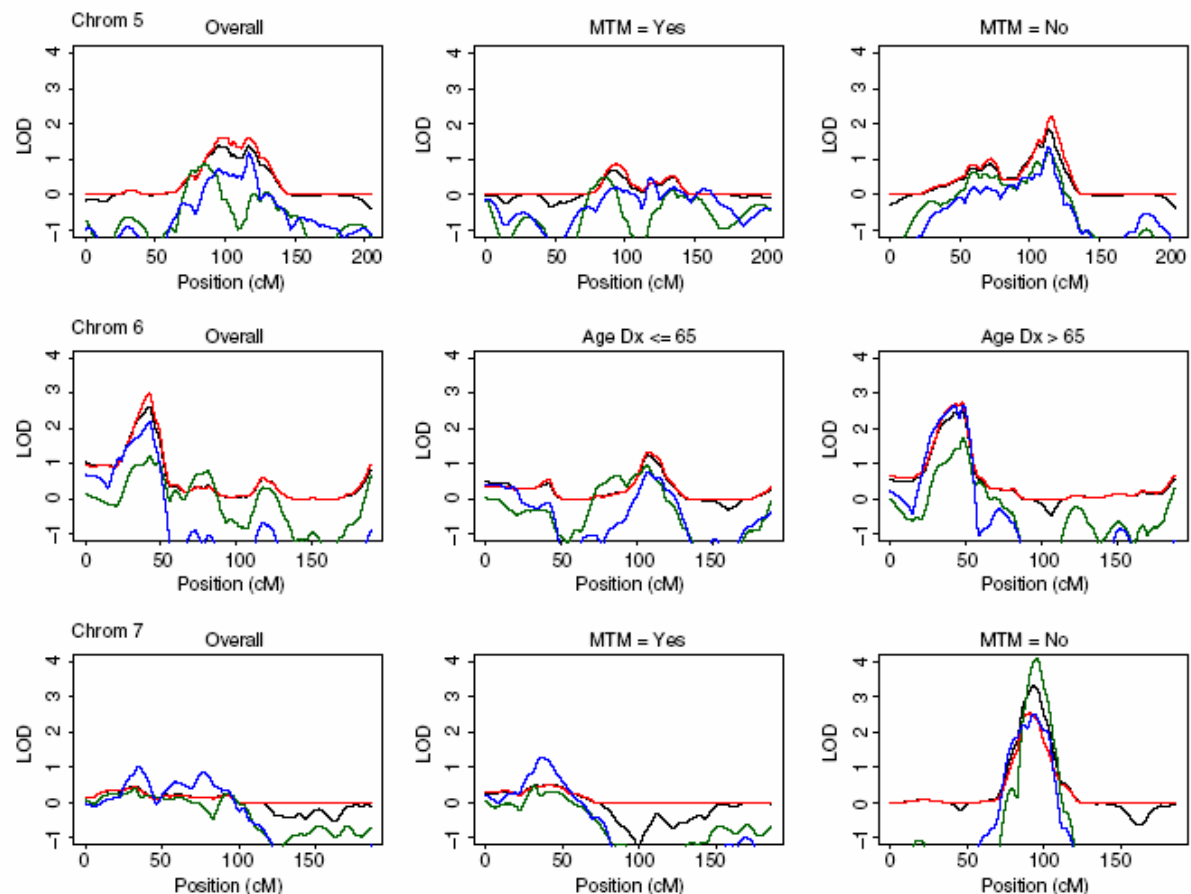
“others” group giving the largest LOD score, followed by pedigrees from the Mayo Clinic.

## Discussion

Our main findings, based on the pool of 166 pedigrees with aggressive prostate cancer, were statistically significant evidence for linkage for chromosome 6 and suggestive linkage signals, with LOD scores at least 2.0, on chromosomes 11, and 20. In the stratified analyses, we found evidence for significantly different linkage signals across strata for these three chromosomes, and in some strata, the linkage signals for chromosomes 11 and 20 increased. In fact, the strongest signal was at chromosome 11q14.1–14.3, from the 73 pedigrees with younger ages at diagnosis. From a genetic perspective, this is enticing: the strength of familial risks for prostate cancer are greater for earlier age at diagnosis (Johns and Houlston 2003). The stratified analyses provided additional interesting linkage signals on chromosomes 5, 7, and 21.

A hallmark of genetically inherited cancer syndromes is the tendency for cancers to begin, or at least become clinically detectable, at an earlier age than





**Fig. 1** LOD scores for chromosomes and strata with statistically significant linkage heterogeneity and LOD scores  $> 2$  in at least one stratum—chromosomes 5, 6, 7, 11, 20, and 21 (*MTM* male-

to-male transmission of prostate cancer, *Age Dx* age at diagnosis). The *line colors* represent different linkage tests (see figure legend)

their non-genetic counterparts (Lindor et al. 1998). For this reason, age at diagnosis is frequently used as a potential indicator of inherited prostate cancers. However, age at diagnosis is a poor surrogate for age at onset of prostate cancer, because age at diagnosis is strongly influenced by screening practices. For example, a man not previously screened for prostate cancer, yet diagnosed at age 70 with metastatic prostate cancer, possibly could have been diagnosed 10–20 years earlier had he been screened for prostate cancer. A man diagnosed at age 55 with a low-volume, low-grade cancer may be just one of the substantial proportion of men of this age in the general population who have within their prostates small amounts of cancerous cells that have minimal clinical significance. On the other hand, if this latter man had such extensive cancer that it was no longer confined to the prostate, it would suggest that the cancer had been present for a number of years, and it was “early-onset” disease. Therefore,

our focus on clinically aggressive prostate cancer not only emphasizes a clinically important phenotype, but also, in the case of aggressive disease at an early age, it increases the likelihood that we are studying truly early-onset disease. Using families that have multiple men affected with aggressive disease provides an opportunity to enrich the study sample for genetic influences that may be detectable by linkage analysis. Our finding of a LOD score greater than 3.3 in families with aggressive disease at an early age is particularly interesting in this respect.

To assess the strength of evidence for our regions of interest, we reviewed 21 reports that published genome-wide linkage scans for prostate cancer. Two studies, like ours, restricted their analyses to only aggressive prostate cancers (Chang et al. 2005; Stanford et al. 2006). Four studies screened for linkage by using Gleason grade as a quantitative trait (Witte et al. 2000, 2003; Slager et al. 2003, 2006). Finally, the majority of

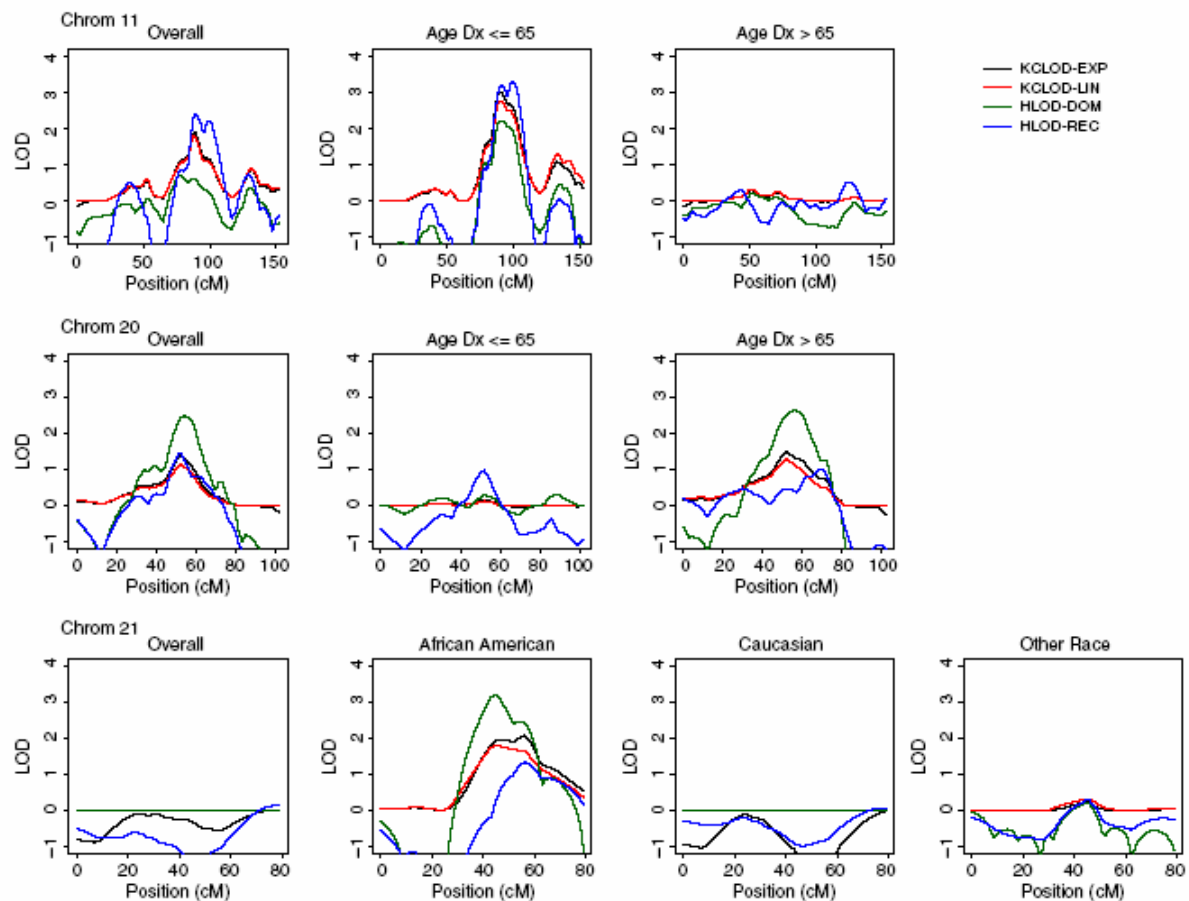


Fig. 1 continued

studies—15—analyzed any type of prostate cancer (Smith et al. 1996; Suarez et al. 2000; Goddard et al. 2001; Hsieh et al. 2001; Cunningham et al. 2003; Edwards et al. 2003; Janer et al. 2003; Lange et al. 2003; Schleutker et al. 2003; Wiklund et al. 2003; Xu et al. 2003; Gillanders et al. 2004; Matsui et al. 2004; Camp et al. 2005; Xu et al. 2005). These studies are not all independent, because some represent expanded accrual over prior studies, and some represent analyses combined over multiple groups. Many of these reports are from members of the ICPCG; the report by Xu et al. (2005) is a pooled analysis of any form of prostate cancer among 1,233 pedigrees from ten groups of the ICPCG. To quantify the linkage evidence as LOD scores, results reported as  $P$ -values were converted to LOD scores for this discussion. This conversion is  $\text{LOD} = \chi_{1,1-2P}^2 \log_{10}(e)/2$  where  $\chi_{1,1-2P}^2$  is the quantile of a chi-square distribution with one degree of freedom, at the percentile  $1-2P$ ,  $P$  is the  $P$ -value, and  $e$  is the base

of the natural logarithm. A summary of chromosomes that had LOD scores at least 2.0 for our chromosomes of interest is given in Table 6.

For chromosome 5, Stanford et al. (2006)—who restricted their analyses to the aggressive disease phenotype—found a suggestive linkage signal among pedigrees classified as not having HPC (following Carter's criteria). A number of studies have found similar evidence for linkage near this same region. Slager et al. (2006) reported a similar linkage signal using Gleason grade as a quantitative trait, Goddard et al. (2001) found similar linkage evidence using Gleason grade as a covariate, and Wiklund et al. (2003) found similar evidence among men from Sweden. It is worth emphasizing that in this Swedish study approximately two-thirds of the men were diagnosed with prostate cancer before 1990 when PSA was introduced as an aid to early detection, and 79% of the men had clinical symptoms at diagnosis. This suggests that the men in the Swedish

**Table 4** Summary of chromosomes and strata with significant heterogeneity over strata and LOD scores >2 in at least one stratum

Chromosome	Strata	No. ped.	KC-EXP		KC-LIN		DOM		REC			
			LOD	cM	LOD	cM	HLOD	$\alpha$	cM	HLOD	$\alpha$	cM
5	MTM <sup>a</sup>											
	Yes	107	0.69	93	0.87	94	0.50	0.13	86	0.51	0.12	118
	No	59	1.85 (0.10)	114	2.24 (0.048)	116	1.20 (0.80)	0.29	114	1.34 (0.47)	0.30	113
6	Dx age											
	≤ 65	73	1.26	107	1.32	108	0.99	0.22	107	0.77	0.23	107
	> 65	93	2.47 (0.28)	48	2.74 (0.30)	48	1.72 (0.039)	0.23	48	2.68 (0.10)	0.36	49
7	MTM											
	Yes	107	0.52	42	0.50	42	0.49	0.08	32	1.29	0.20	37
	No	59	3.31 (0.002)	93	2.54 (0.002)	91	4.09 (0.02)	0.49	96	2.51 (0.61)	0.43	94
11	Dx age											
	≤ 65	73	3.02	90	2.76	90	2.22	0.32	90	3.31	0.44	100
	> 65	93	0.30 (0.022)	53	0.33 (0.035)	53	0.23 (0.10)	0.08	53	0.52 (0.91)	0.15	124
20	Dx age											
	≤ 65	73	0.18	52	0.14	52	0.32	0.08	89	0.99	0.17	52
	> 65	93	1.49 (0.29)	52	1.29 (0.27)	52	2.65 (0.045)	0.26	56	1.01 (0.27)	0.18	69
21	African American	8	2.08	56	1.79	45	3.19	1.0	45	1.35	1.0	56
	Caucasian	154	-0.03	79	0.00	79	0.00	0	79	0.06	0.06	79
	Other	4	0.25 (0.11)	45	0.31 (0.008)	45	0.21 (0.05)	1.0	45	0.30 (0.29)	0.73	45

Maximum LOD scores by chromosome and strata. *P*-values to test heterogeneity over strata are enclosed in parentheses

<sup>a</sup> Male-to-male transmission of prostate cancer

study have more aggressive disease than those in the typical linkage study performed elsewhere.

At approximately 80 cM distant from this region on chromosome 5, Witte et al. (2000) reported suggestive linkage at 5q31–33. It is interesting that in an independent follow-up study, Witte et al. (2003) reported a LOD score of 1.6 at 5p15, approximately 150 cM distant from their initial finding. This large variation in chromosome position of the largest linkage signal is clearly illustrated in Table 6 for most of the chromosomes of interest. Finally, when analyzing any form of

prostate cancer, both Camp et al. (2005) and Xu et al. (2005) reported suggestive linkage signals on chromosome 5 among pedigrees with an earlier age at diagnosis.

For chromosome 6, Stanford et al. (2006), using the aggressive disease phenotype, found a suggestive linkage signal among pedigrees with an earlier age at diagnosis. Slager et al. (2006), using Gleason grade as a quantitative trait, found a similar linkage signal in this same region. The University of Michigan group recently completed a genome scan of their 71 pedigrees

**Table 5** Summary of chromosomes and strata with significant heterogeneity over ICPCG Member Groups and LOD scores > 2 in at least one stratum

Chromosome	Strata	No. ped.	KC-EXP		KC-LIN		DOM		REC			
			LOD	cM	LOD	cM	HLOD	$\alpha$	cM	HLOD	$\alpha$	cM
1	Fred Hutchinson/ISB	37	0.14	159	0.17	159	0.05	0.05	195	0.52	0.21	188
	JHU	23	2.17	150	2.06	72	2.65	0.73	152	2.14	0.75	64
	University of Ulm	14	0.88	247	1.00	247	0.21	0.20	47	0.50	0.46	246
	Mayo Clinic	18	1.53	271	1.31	271	1.86	0.51	271	0.88	0.48	271
	University of Michigan	22	1.33	182	0.92	182	0.96	0.36	183	1.60	0.50	184
	University of Utah	28	0.79	66	0.75	66	0.64	0.24	59	0.30	0.28	28
	Others	24	0.51 (0.26)	187	0.18 (0.13)	188	0.37 (0.05)	0.22	188	0.34 (0.27)	0.23	186
2	Fred Hutchinson/ISB	37	0.39	19	0.33	19	0.87	0.24	25	0.48	0.18	210
	JHU	23	0.08	55	0.08	55	0.28	0.19	89	0.05	0.09	89
	University of Ulm	14	0.39	204	0.35	204	0.42	0.32	171	0.31	0.23	165
	Mayo Clinic	18	0.62	50	0.85	230	0.50	0.29	49	0.96	0.42	67
	University of Michigan	22	0.86	205	0.87	211	1.12	0.42	202	0.34	0.27	204
	University of Utah	28	0.54	96	0.59	94	0.58	0.14	67	0.43	0.34	102
	Others	24	1.70 (0.43)	77	2.13 (0.21)	77	1.47 (0.44)	0.56	77	2.41 (0.05)	0.69	78

Maximum LOD scores by chromosome and strata. *P*-values to test heterogeneity over strata are enclosed in parentheses

**Table 6** Summary of published LOD scores at least 2.0 for chromosomes 5, 6, 7, 11, and 20

Chromosome	Type of PC	LOD	cM	Nearest marker	Stratum or covariate	Reference
5	Aggressive	2.0	69	D5S2500	HPC = no	Stanford et al. (2006)
	Gleason as QTL	2.1	65	D5S407		Slager et al. (2006)
	Gleason as QTL	2.4	147	D5S1480		Witte et al. (2000)
	Any	2.3	56	D5S1457	Gleason as covariate	Goddard et al. (2001)
	Any	2.2	65	D5S407	All pedigrees	Wiklund et al. (2003)
	Any	2.1	110	D5S1503	Dx age ≤ 69	Camp et al. (2005)
	Any	2.3	77	D5S2858	All pedigrees	Xu et al. (2005)
	Any	2.0	179	D5S1456	Dx age ≤ 65	Xu et al. (2005)
	Any	2.0	179	D5S1456	Dx age ≤ 58	Stanford et al. (2006)
6	Aggressive	2.2	125	D6S1040		Stanford et al. (2006)
	Gleason as QTL	2.1	137	D6S292		Slager et al. (2006)
	Any	3.9	185	D6S281	Dx age ≥ 66	Cunningham et al. (2003)
	Any	2.5	25	D6S1281	All pedigrees	Janer et al. (2003)
7	Aggressive	3.2	7	D7S3056	N. affected ≥ 5	Stanford et al. (2006)
	Aggressive	2.1	42	D7S1824	Dx age > 65	Paiss et al. (2003)
	Gleason as QTL	2.2	130	D7S1804		Witte et al. (2000)
	Gleason as QTL	2.1	130	D7S1804	Expansion of above study	Witte et al. (2003)
	Any	2.3	96	D7S2212	All pedigrees	Janer et al. (2003)
11	Any	3.4	88	D11S901	All pedigrees	Schleutker et al. (2003)
	Any	2.2	102	D11S898	All pedigrees	Xu et al. (2005)
	Any	2.1	123	D11S4464	All pedigrees	Witte et al. (2003)
20	Aggressive	2.6	27	ATT013	MTM = no	Stanford et al. (2006)
	Any	4.8	78	D20S196	All pedigrees	Cunningham et al. (2003)

MTM male-to-male transmission of prostate cancer, HPC hereditary prostate cancer

with aggressive prostate cancer. Their inclusion criteria were more liberal than those used in this study, because Lange et al. (2006) included pedigrees with only two men with aggressive disease. They had 49 such pedigrees, while 22 of their pedigrees with at least three men with aggressive disease overlapped with this current pooled analysis. Their strongest signal, on chromosome 15q, was driven entirely by the 49 families with only two men with aggressive prostate cancer, while their second largest linkage signal, on chromosome 6p, was similar for those families included versus those not included in this current pooled analysis. Their 49 excluded pedigrees had a LOD score of approximately 1.2 in the chromosome 6p22–23 region (E.M. Lange, personal communication). When analyzing any form of prostate cancer, the ACTANE group (Edwards et al. 2003) found a LOD score over 1.0 on 6p for a large number of families that did not meet the more strict criteria of this pooled analysis. Furthermore, Janer et al. (2003) found a linkage signal approximately 100 cM distant from these other reports. Cunningham et al. (2003) found a strong linkage signal on 6p among men with an older age at diagnosis. These regions varied from our region at 6p22.3—at approximately 50 cM—that had a LOD score of 3.0. This region is approximately 20 cM distant to HLA, which resides at 6p21.3. Perhaps this ties with the speculation that immunity and inflammatory mechanisms play a critical role in the development of prostate cancer (Nelson et al. 2004).

For chromosome 7, Stanford et al. (2006), using the aggressive disease phenotype, found a suggestive linkage signal among pedigrees with at least five men with prostate cancer. The linkage signal, however, was approximately 90 cM distant from a prior report by this group that found suggestive linkage for chromosome 7 when analyzing any form of prostate cancer (Janer et al. 2003). In contrast, when restricted to men with an aggressive disease and an older age at diagnosis, Paiss et al. (2003) reported a suggestive linkage signal that was only about 35 cM from that reported by Stanford et al. When analyzing Gleason grade as a quantitative trait, Witte et al. found linkage signals at approximately 130 cM (Witte et al. 2000, 2003), much closer to the position of 96 cM reported by Janer et al. Further support for chromosome 7q32 comes from finding an increased allelic imbalance in primary prostate tumors (Neville et al. 2002).

For chromosome 11, both Schleutker et al. (2003) and Witte et al. (2003) reported interesting LOD scores at about the same locations, and an ICPCG pooled analysis confirmed these findings (Xu et al. 2005). Although Schleutker et al. (2003) did not restrict their pedigrees to only men with aggressive disease, they did skew their selected pedigrees to have as many affected men as possible (at least 3 per pedigree), and out of the 13 pedigrees used in their initial findings for chromosome 11, 4 met the present criteria for aggressive prostate cancer to be included in our current



analyses. Furthermore, like the Swedish families, many of the Finnish families were diagnosed prior to the use of PSA screening that started in early 1990s in Finland. Among the original families used for linkage, 32% of the patients were diagnosed before 1990, and 42% had clinical symptoms at diagnosis.

For chromosome 20, Stanford et al. (2006), using the aggressive disease phenotype, found a suggestive linkage signal among pedigrees without male-to-male transmission. The position of this linkage signal was about 30 cM distant from the large linkage signal that Cunningham et al. (2003) reported when analyzing any form of prostate cancer. Unfortunately, the findings by Cunningham et al. could not be replicated by a pooled ICPCG study; a LOD score of 0.06 was found among 1,076 pedigrees not included in the original Mayo Clinic study (Schaid and Chang 2005). These results suggest that focusing on aggressive prostate cancer may reveal linkage that is not apparent among all types of prostate cancers.

Our finding of a linkage signal for chromosome 21 among eight pedigrees with African American ancestry is intriguing, yet no other studies reported LOD scores greater than 2.0 for chromosome 21. This suggests that our finding may be spurious. A possible cause of a spurious finding is that the founders of our pedigrees, typically parent and grand-parent generations, do not have DNA available for genotyping. Hence, our statistical analyses depend on estimated allele frequencies. Because each group had few non-Caucasian pedigrees, each group estimated allele frequencies in the pool of all their pedigrees. If these allele frequencies differed between the majority of the Caucasian pedigrees and the African American pedigrees, then this could lead to bias, and possibly falsely inflated LOD scores in the African American pedigrees.

In contrast to our summary of linkage signals that have been reported for our regions of interest, it is worthwhile to consider reported linkage signals for the aggressive disease phenotype that we did not detect. Using a similarly defined aggressive disease phenotype, Chang et al. found a LOD score of 2.5 for chromosome X and a LOD score of 2.1 for chromosome 22 (Chang et al. 2005). They also found interesting, yet less striking, signals on chromosomes 3 and 9. Stanford et al. also found an interesting signal on chromosome 22, a LOD score of 2.2 (Stanford et al. 2006). The University of Michigan group, that also focused on aggressive prostate cancer, recently found a LOD score of 3.5 at chromosome 15q12 (Lange et al. 2006). Other regions reported to have suggestive linkage signals when analyzing Gleason grade as a quantitative trait are chromosomes 4 and 15 (Slager et al. 2003),

chromosome 9 (Witte et al. 2003) and chromosome 19 (Witte et al. 2000; Neville et al. 2002, 2003).

In summary, our linkage findings for aggressive prostate cancer that seem to be most consistent with prior published studies are chromosomes 5q, 6p, 7q, and 11q. These results suggest that prostate cancer aggressiveness might be controlled by multiple genes. Although the major strength of our study is the large number of pedigrees with aggressive prostate cancer, we recognize that our selection criteria means our conclusions are likely to be relevant more for disease with an earlier age at disease onset; requiring metastatic disease or death from prostate cancer implies an earlier age at onset, because it takes time for metastases and death to occur. Nonetheless, we chose our study design because we believed it would enrich for HPC. Like many genetically complex traits, resolving the genetic basis of prostate cancer is likely to require large studies, much like ours based on the ICPCG, as well as novel experimental designs and analyses. Our findings provide directions for future studies to target candidate genes for aggressive prostate cancer, based on our strongest linkage findings for chromosomes 6 and 11, and possibly 20.

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