**TITLE:**

**Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci**

**AUTHOR LIST & AFFILIATIONS:**

Fredrick R. Schumacher1,2,142, Ali Amin Al Olama3,4,142, Sonja I. Berndt5,142, Sara Benlloch3,6, Mahbubl Ahmed6, Edward J. Saunders6, Tokhir Dadaev6, Daniel Leongamornlert6, Ezequiel Anokian6, Clara Cieza-Borrella6, Chee Goh6, Mark N. Brook6, Xin Sheng7, Laura Fachal8,9, Joe Dennis3, Jonathan Tyrer3, Kenneth Muir10,11, Artitaya Lophatananon10,11, Victoria L. Stevens12, Susan M. Gapstur12, Brian D. Carter12, Catherine M. Tangen13, Phyllis J. Goodman13, Ian M. Thompson Jr.14, Jyotsna Batra15,16, Suzanne Chambers17,18, Leire Moya15,16, Judith Clements15,16, Lisa Horvath19,20, Wayne Tilley21, Gail P. Risbridger22,23, Henrik Gronberg24, Markus Aly25,26, Tobias Nordström24,27, Paul Pharoah3,9, Nora Pashayan9,28, Johanna Schleutker29,30, Teuvo L.J. Tammela31, Csilla Sipeky29, Anssi Auvinen32, Demetrius Albanes5, Stephanie Weinstein5, Alicja Wolk33,34, Niclas Håkansson33, Catharine M.L. West35, Alison M. Dunning9, Neil Burnet36, Lorelei A. Mucci37, Edward Giovannucci37, Gerald L. Andriole38, Olivier Cussenot39,40, Géraldine Cancel-Tassin39,40, Stella Koutros5, Laura E. Beane Freeman5, Karina Dalsgaard Sorensen41,42, Torben Falck Orntoft41,42, Michael Borre42,43, Lovise Maehle44, Eli Marie Grindedal44, David E. Neal45-47, Jenny L. Donovan48, Freddie C. Hamdy47, Richard M. Martin48, Ruth C. Travis49, Tim J. Key49, Robert J. Hamilton50, Neil E. Fleshner50, Antonio Finelli51, Sue Ann Ingles7, Mariana C. Stern7, Barry S. Rosenstein52,53, Sarah L. Kerns54, Harry Ostrer55, Yong-Jie Lu56, Hong-Wei Zhang57, Ninghan Feng58, Xueying Mao56, Xin Guo59, Guomin Wang60, Zan Sun61, Graham G. Giles62,63, Melissa C. Southey64, Robert J. MacInnis62,63, Liesel M. FitzGerald62,65, Adam S. Kibel66, Bettina F. Drake38, Ana Vega67, Antonio Gómez-Caamaño68, Robert Szulkin69,70, Martin Eklund24, Manolis Kogevinas71-74, Javier Llorca72,75, Gemma Castaño-Vinyals71-74, Kathryn L. Penney76, Meir Stampfer76, Jong Y. Park77, Thomas A. Sellers77, Hui-Yi Lin78, Janet L. Stanford79,80, Cezary Cybulski81, Dominika Wokolorczyk81, Jan Lubinski81, Elaine A. Ostrander82, Milan S. Geybels79, Børge G. Nordestgaard83,84, Sune F. Nielsen83,84, Maren Weischer84, Rasmus Bisbjerg85, Martin Andreas Røder86, Peter Iversen86, Hermann Brenner87-89, Katarina Cuk87, Bernd Holleczek90, Christiane Maier91, Manuel Luedeke91, Thomas Schnoeller92, Jeri Kim93, Christopher J. Logothetis93, Esther M. John94,95, Manuel R. Teixeira96,97, Paula Paulo96, Marta Cardoso96, Susan L. Neuhausen98, Linda Steele98, Yuan Chun Ding98, Kim De Ruyck99, Gert De Meerleer99, Piet Ost100, Azad Razack101, Jasmine Lim101, Soo-Hwang Teo102, Daniel W. Lin79,103, Lisa F. Newcomb79,103, Davor Lessel104, Marija Gamulin105, Tomislav Kulis106, Radka Kaneva107, Nawaid Usmani108,109, Sandeep Singhal108,109, Chavdar Slavov110, Vanio Mitev107, Matthew Parliament108,109, Frank Claessens111, Steven Joniau112, Thomas Van den Broeck111,112, Samantha Larkin113, Paul A. Townsend114, Claire Aukim-Hastie115, Manuela Gago Dominguez116,117, Jose Esteban Castelao118, Maria Elena Martinez119, Monique J. Roobol120, Guido Jenster120, Ron H.N. van Schaik121, Florence Menegaux122, Thérèse Truong122, Yves Akoli Koudou122, The Profile Study Steering Committee123, Jianfeng Xu124, Kay-Tee Khaw125, Lisa Cannon-Albright126,127, Hardev Pandha115, Agnieszka Michael115, Stephen N. Thibodeau128, Shannon K. McDonnell129, Daniel J. Schaid129, Sara Lindstrom130, Constance Turman131, Jing Ma76, David J. Hunter131, Elio Riboli132, Afshan Siddiq133, Federico Canzian134, Laurence N. Kolonel135, Loic Le Marchand135, Robert N. Hoover5, Mitchell J. Machiela5, Zuxi Cui1, Peter Kraft131, Australian Prostate Cancer BioResource136, The IMPACT Study Steering Committee136, Canary PASS Investigators136, BPC3 (Breast and Prostate Cancer Cohort Consortium)136, The PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium136, CAPS (Cancer of the Prostate in Sweden)136, PEGASUS (Prostate Cancer Genome-wide Association Study of Uncommon Susceptibility Loci)136, The GAME-ON/ELLIPSE Consortium136, Christopher I. Amos137-139, David V. Conti7,143, Douglas F. Easton3,9,143, Fredrik Wiklund24,143, Stephen J. Chanock5,143, Brian E. Henderson7,141,143, ZSofia Kote-Jarai6,143, Christopher A. Haiman7,143, Rosalind A. Eeles6,140,143

1 Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, Ohio, USA

2 Seidman Cancer Center, University Hospitals, Cleveland, Ohio, USA

3 Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK.

4 University of Cambridge, Department of Clinical Neurosciences, Cambridge, UK

5 Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland, USA

6 The Institute of Cancer Research, London, UK

7 Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California, USA

8 Fundación Pública Galega de Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica, CIBERER, IDIS, Santiago de Compostela, Spain

9 Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Cambridge, UK

10 Division of Population Health, Health Services Research and Primary Care, University of Manchester, Manchester, UK

11 Warwick Medical School, University of Warwick, Coventry, UK

12 Epidemiology Research Program, American Cancer Society, Atlanta, Georgia, USA

13 SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

14 CHRISTUS Santa Rosa Hospital - Medical Center, San Antonio, Texas, USA

15 Institute of Health and Biomedical Innovation and School of Biomedical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia

16 Australian Prostate Cancer Research Centre-Qld, Translational Research Institute, Brisbane, Queensland, Australia

17 Menzies Health Institute of Queensland, Griffith University, Queensland, Australia

18 Cancer Council Queensland, Fortitude Valley, QLD, Australia

19 Chris O'Brien Lifehouse (COBLH), Camperdown, NSW, Australia

20 Garvan Institute of Medical Research, Sydney, NSW, Australia

21 Dame Roma Mitchell Cancer Research Centre, University of Adelaide, Adelaide, South Australia, Australia

22 Monash Biomedicine Discovery Institute Cancer Program, Prostate Cancer Research Program, Department of Anatomy and Developmental Biology, Monash University, Victoria, Australia

23 Cancer Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia

24 Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

25 Department of Urology, Karolinska University Hospital, Stockholm, Sweden

26 Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

27 Department of Clinical Sciences at Danderyds Hospital, Karolinska Institutet, Stockholm, Sweden

28 Department of Applied Health Research, University College London, London, UK

29 Institute of Biomedicine, University of Turku, Finland

30 Tyks Microbiology and Genetics, Department of Medical Genetics, Turku University Hospital, Finland

31 Department of Urology, Tampere University Hospital and Faculty of Medicine and Life Sciences, University of Tampere, Finland

32 Department of Epidemiology, School of Health Sciences, University of Tampere, Tampere, Finland

33 Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Sweden

34 Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

35 Division of Cancer Sciences, University of Manchester, Manchester Cancer Research Centre, Manchester Academic Health Science Centre, and The Christie NHS Foundation Trust, Manchester, UK

36 University of Cambridge, Department of Oncology, Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

37 Department of Epidemiology, Harvard T.H. Chan School of Pubic Health, Boston, Massachusetts, USA

38 Washington University School of Medicine, St. Louis, Missouri, USA

39 UPMC Sorbonne Universites, GRC N°5 ONCOTYPE-URO, Tenon Hospital, Paris, France

40 CeRePP, Tenon Hospital, Paris, France

41 Department of Molecular Medicine, Aarhus University Hospital, Denmark

42 Department of Clinical Medicine, Aarhus University, Denmark

43 Department of Urology, Aarhus University Hospital, Denmark

44 Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

45 University of Cambridge, Department of Oncology, Addenbrooke's Hospital, Cambridge, UK

46 Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Cambridge, UK

47 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK

48 School of Social and Community Medicine, University of Bristol, Bristol, UK

49 Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

50 Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, Canada

51 Division of Urology, Princess Margaret Cancer Centre, Toronto, Canada

52 Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

53 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA

54 Department of Radiation Oncology, University of Rochester Medical Center, Rochester, New York, USA

55 Professor of Pathology and Pediatrics, Albert Einstein College of Medicine, Bronx, New York, USA

56 Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary University of London, John Vane Science Centre, London, UK

57 Second Military Medical University, Shanghai, China

58 Wuxi Second Hospital, Nanjing Medical University, Wuxi, Jiangzhu Province, China

59 Department of Urology, The First Affiliated Hospital, Chongqing Medical University, Chongqing, China

60 Department of Urology, Zhongshan Hospital, Fudan University Medical College, Shanghai, China

61 The People’s Hospital of Liaoning Province, The People's Hospital of China Medical University, Shenyang, China

62 Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, Victoria, Australia

63 Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

64 Precision Medicine, School and Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia

65 Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

66 Division of Urologic Surgery, Brigham and Womens Hospital, Boston, Massachusetts, USA

67 Fundación Pública Galega de Medicina Xenómica-SERGAS, Grupo de Medicina Xenómica, CIBERER, IDIS, Santiago de Compostela, Spain

68 Department of Radiation Oncology, Complexo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain

69 Division of Famly Medicine, Department of Neurobiology, Care Science and Society, Karolinska, Institutet, Huddinge, Sweden

70 Scandinavian Development Services, Danderyd, Sweden

71 ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

72 CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

73 IMIM (Hospital del Mar Research Institute), Barcelona, Spain

74 Universitat Pompeu Fabra (UPF), Barcelona, Spain

75 University of Cantabria-IDIVAL, Santander, Spain

76 Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, USA

77 Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, Florida, USA

78 Biostatistics Program, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA

79 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

80 Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA

81 International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

82 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA

83 Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

84 Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

85 Department of Urology, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

86 Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

87 Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

88 German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

89 Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

90 Saarland Cancer Registry, Saarbrücken, Germany

91 Institute for Human Genetics, University Hospital Ulm, Ulm, Germany

92 Department of Urology, University Hospital Ulm, Germany

93 The University of Texas - MD Anderson Cancer Center, Department of Genitourinary Medical Oncology, Houston, Texas, USA

94 Cancer Prevention Institute of California, Fremont, California, USA

95 Department of Health Research & Policy (Epidemiology) and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, California , USA

96 Department of Genetics, Portuguese Oncology Institute of Porto, Porto, Portugal

97 Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal

98 Department of Population Sciences, Beckman Research Institute of the City of Hope, Duarte, California, USA

99 Ghent University, Faculty of Medicine and Health Sciences, Basic Medical Sciences, Ghent, Belgium

100 Ghent University Hospital, Department of Radiotherapy, Ghent, Belgium

101 Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

102 Cancer Research Malaysia (CRM), Outpatient Centre, Subang Jaya Medical Centre, Selangor, Malaysia

103 Department of Urology, University of Washington, Seattle, Washington, USA

104 Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

105 Division of Medical Oncology, Urogenital Unit, Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia

106 Department of Urology, University Hospital Center Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia

107 Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, Bulgaria

108 Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada

109 Division of Radiation Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada

110 Department of Urology and Alexandrovska University Hospital, Medical University of Sofia, Sofia, Bulgaria

111 Molecular Endocrinology Laboratory, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium

112 Department of Urology, University Hospitals Leuven, Leuven, Belgium

113 The University of Southampton, Southampton General Hospital, Southampton, UK

114 Division of Cancer Sciences, Manchester Cancer Research Centre, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Center, NIHR Manchester Biomedical Research Centre, Health Innovation Manchester, University of Manchester, Manchester, UK

115 The University of Surrey, Guildford, Surrey, UK

116 Genomic Medicine Group, Galician Foundation Genomic Medicine, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, Servicio Galego de Saúde, SERGAS, Santiago De Compostela, Spain

117 University of California San Diego, Moores Cancer Center, La Jolla, California, USA

118 Genetic Oncology Unit, CHUVI Hospital, Complexo  Hospitalario Universitario de Vigo, Instituto de Investigación Biomédica Galicia Sur (IISGS), Vigo SERGAS, Spain

119 University of California San Diego, Moores Cancer Center, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California, USA

120 Department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands

121 Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, the Netherlands

122 Cancer & Environment Group, Center for Research in Epidemiology and Population Health (CESP), INSERM, University Paris-Sud, University Paris-Saclay, Villejuif, France

123 <http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-find-out-looking-gene-changes-would-be-useful-in-screening-for-prostate-cancer-profile-pilot>

124 Program for Personalized Cancer Care, NorthShore University HealthSystem, Evanston, Illinois, USA

125 Clinical Gerontology Unit, University of Cambridge, Cambridge, UK

126 Division of Genetic Epidemiology, Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA

127 George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah, USA

128 Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

129 Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA

130 Department of Epidemiology, Health Sciences Building, University of Washington, Seattle, Washington, USA

131 Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard T.H. Chan School of Pubic Health, Boston, Massachusetts, USA

132 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

133 Genomics England, Queen Mary University of London, Dawson Hall, Charterhouse Square, London, UK

134 Genomic Epidemiology Group, German Cancer Research Center, (DKFZ), Heidelberg, Germany

135 Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii, USA

136 A list of members and affiliations appears in the Supplementary Note

137 Department of Biomedical Data Science, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire, USA

138 Department of Molecular and Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA

139 Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire, USA

140 Royal Marsden NHS Foundation Trust, London, UK

141 In memorium

142 These authors contributed equally to this work

143 These authors jointly directed this work

Correspondence should be addressed to F.R.S. ([frs2@case.edu](mailto:frs2@case.edu)), A. Al Olama ([aa461@medschl.cam.ac.uk](mailto:aa461@medschl.cam.ac.uk)) and R.A.E. (ros.eeles@icr.ac.uk)

**ABSTRACT:**

**Currently genome-wide association studies (GWAS) and fine-mapping efforts have identified over 100 prostate cancer (PrCa) susceptibility loci. We meta-analyzed genotype data from a custom high-density array of 46,939 PrCa cases and 27,910 controls of European ancestry with previously genotyped data of 32,255 PrCa cases and 33,202 controls of European ancestry. Our analysis identified 62 novel loci associated (*P<5.0x10-*8) with PrCa, and a locus significantly associated with early-onset PrCa (≤ 55 years**)**. Our findings include missense variants rs1800057 (OR=1.16; *P=8.2x10-9*; G>C [Pro1054Arg]) in *ATM* and rs2066827 (OR=1.06; *P=2.3x10-9;* T>G [Val109Gly]) in *CDKN1B*. The combination of all loci captures 28.4% of the PrCa familial relative risk and a polygenic risk score confers an elevated PrCa risk for men in the 90-99%-ile (RR=2.69; 95%CI: 2.55-2.82) and 1%-ile (RR=5.71; 95%CI: 5.04-6.48) risk stratum compared to the population average. These findings improve risk prediction, enhance fine-mapping, and provide insight into the underlying biology of PrCa1.**

**MAIN TEXT:**

Although prostate cancer (PrCa) is the most common non-cutaneous cancer among men in the Western world and 1 in 7 men will be diagnosed during their lifetime2, very few modifiable risk factors have been established3. Epidemiological studies have identified age, a positive family history and race/ethnicity as the most prominent risk factors for PrCa4-7. PrCa incidence is highest among men of African ancestry, followed by men of European and Asian ancestry. These ancestral differences of PrCa risk, in conjunction with studies demonstrating the influence of family history8,9, highlight the contribution of genetics in PrCa etiology10. Our previous work, utilizing a multiplicative model, estimated over 1,800 common single nucleotide polymorphisms (SNPs) independently contribute to PrCa risk among populations of European ancestry11. Genome-wide association studies (GWAS) have reported over 100 of these PrCa variants across multi-ethnic populations, with the vast majority being identified in populations of European ancestry12-29.

To facilitate additional novel discovery of PrCa genetic risk factors we developed a custom high-density genotyping array, the OncoArray, including a 260K SNP backbone designed to adequately tag most common genetic variants (MAF>5% in Europeans), and 310K SNPs from the meta-analyses of five cancers (breast, colorectal, lung, ovarian, and prostate)30. Approximately 80,000 PrCa-specific markers derived from our previous multi-ethnic meta-analysis12 (including populations of European, African American, Japanese, and Latino ancestry), fine-mapping of known PrCa loci, and candidate SNPs nominated by study collaborators were included on the OncoArray. We assembled a new PrCa sample series from 52 studies to genotype with the OncoArray (**Supplementary Tables 1 & 2**). After applying rigorous quality control criteria and removing overlapping samples from previous studies, our OncoArray sample yielded 46,939 PrCa cases and 27,910 controls without a known diagnosis of PrCa of European ancestry for analysis (see **Online Methods, Supplementary Table 3**). Genotypes were phased and imputed to the cosmopolitan panel of the 1000 Genomes Project (1KGP; 2014 June release) using SHAPEIT31 and IMPUTEv232 software (**Online Methods**, **Supplementary Table 3**). We performed a fixed-effects meta-analysis combining the summary statistics from our OncoArray analysis, and seven previous PrCa GWAS or high-density SNP panels of European ancestry imputed to 1KGP. The final meta-analysis included 79,194PrCa cases and 61,112 controls without a known diagnosis of PrCa (**Figure 1**).

Study- and consortia-specific meta-analyses were performed to identify novel PrCa loci. We established a *P*-value threshold of 5.0x10-8 to determine genome-wide significance. Our large sample size enabled several stratified meta-analyses focusing on key clinical and biological parameters (**Online Methods, Supplementary Tables 4 & 5)**. All analyses used a likelihood ratio test to minimize bias from rare variants and a logistic regression framework was used for all analyses, except for Gleason score where linear regression was utilized. The genotype dosages were incorporated in an allelic genetic model. The average λ1000, an inflation statistic calibrated to a sample size of 1000 cases and 1000 controls33, across the eight GWAS studies was 1.02 (range: 0.98-1.09) and 1.00 for the overall meta-analysis (**Supplementary Table 6**). Our novel findings excluded variants within defined fine-mapped regions of previously reported PrCa loci (**Supplementary Table 7**).

After the exclusion of all known susceptibility regions (fine-mapping coordinates provided in **Supplementary Table 7 & Supplementary Note**) we identified 64 loci associated with overall PrCa susceptibility and one with early-onset (*P<*5.0x10-8) in the meta-analysis (**Supplementary Figure 1**), where 53 were imputed and 12 were genotyped using the OncoArray . The cluster plots for the genotyped makers are presented in **Supplementary Figure 2**. Although a majority of the imputed markers were of high quality with an average imputed r2 greater than 0.80 for 61 of the 65 loci across all contributing GWAS (**Supplementary Table 8**), we closely examined four variants with a poor imputation quality score (r2 <0.80) in the OncoArray samples by inspecting linkage disequilibrium (LD) plots including only genotyped SNPs from the OncoArray and performing an imputation quality control assessment (**Online Methods**). After reviewing the LD plots and the imputation QC, we determined loci rs6602880 and rs144166867 are likely false positives due to imputation artifacts (**Supplementary Figure 3; Supplementary Table 9**). Overall, we identified 62 novel loci associated with overall PrCa risk and one novel loci associated with early-onset (**Table 1**). The consortia specific associations were consistent across the eight contributing GWAS studies (**Supplementary Table 10**).

We performed several stratified analyses defined by clinical and population parameters. We detected a novel variant, rs138004030, significantly associated with early-onset disease (**Table 1**), but only nominally significant for overall PrCa risk (*P=0.02*). In addition, we detected four markers significantly associated (*P*<5x10-8) with advanced PrCa and two markers associated with early-onset PrCa (**Supplementary Table 11**). However, the case-only analyses of these markers indicated marginal statistical significance (*P<1.0x10-3*). Additionally, these markers were in LD with nearby index markers associated with overall PrCa and not significantly associated with overall aggressive disease after adjusting for the index marker (**Supplementary Table 11**). A similar association pattern was observed for rs111599055, which was in LD with marker rs7295014 (r2=0.54) associated with overall disease. The early-onset marker rs77777548 is independent of novel and known PrCa loci. However, the marker is relatively rare (EAF<0.02), indicated as monomorphic in 1KGP, and has a moderate imputation quality score (average r2=0.57) hence we did not include it in further analyses.

Among the 63 novel associations, 38 variants are located within gene-rich regions (**Supplementary Table 12**): intronic (32 SNPs), missense (4 SNPs), and 3’-UTR (2 SNPs). eQTL analyses of the TCGA database identified statistically significant associations (*P<0.05*; **Supplementary Table 12**) in normal PrCa tissue for 17 of the novel associations, including both 3’UTR SNPs and 11 of the 32 intronic SNPs. *Cis* eQTL associations were identified for 3’UTR variant rs1048169 with *HAUS6* (3’UTR) and intronic variants rs182314334 with *MBNL1*, rs4976790 with *COL23A1*, rs9469899 with *UHRF1BP1*, rs878987 with *B3GAT1*, rs11629412 with *PAX9*, and rs11666569 with *MYO9B*. The eQTL associations are consistent with the observed PrCa-SNP associations, given we assessed colocalization between the GWAS and eQTL SNPs. The TCGA data analysis failed to identify an eQTL association with any of the four missense SNPs.

We assessed the association of our newly discovered loci with prostate-specific antigen (PSA) levels using a series of disease-free controls (N=9,090; see **Online Methods**). Among the 48 available loci we observed a significant association for rs8093601 (*P=5.0x10-4*; **Supplementary Table 13**) after correcting for multiple testing (*P=0.05/48=1.0x10-3*). This marker lies near *MBD2*, methyl-CpG binding domain protein 2, and has not been previously associated with either PrCa risk or PSA levels. The effect estimates of PrCa clinical features and overall PrCa did not differ (**Supplementary Table 14**). LD plots incorporating several functional annotation features for each of the 63 novel markers is presented in **Supplementary Figure 4**.

Several strong candidate genes were identified among the PrCa susceptibility loci, including *ATM,* a key gene within the DNA damage response pathway, in which truncating variants contribute towards PrCa susceptibility and progression, particularly aggressive PrCa34,35. The index variant within this region is the missense variant rs1800057, exerting a modest increased risk of PrCa (OR=1.16; *P*=*8.15x10-9*; G>C [Pro1054Arg]; **Figure 2, Panel A**). Although rs1800057 is designated ‘benign’ by ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), it was previously suggested to be associated with a two-fold increased risk of early-onset PrCa in a small clinical series and was unassociated with morbidity following treatment36. In addition to the *ATM* region, we identified missense variants in three separate loci: rs2066827 within the cyclin-dependent kinase inhibitor *CDKN1B*, which controls cell cycle progression; rs33984059 within the transcription factor *RFX7*; and rs2277283 within *INCENP*, which encodes a centromere-interacting protein.

rs1048169 at 9p22 is located in the 3’UTR of *HAUS6* (**Figure 2, Panel B**), a gene that encodes a subunit of augmin, a protein complex required for proper microtubule formation and chromosome segregation during cell division37. rs1048169 is also an eQTL for *HAUS6* expression. Interestingly, an additional lead SNP identified in this study, rs11666569 at 19p13, was an eQTL for two genes including *HAUS8*, which is another member of the augmin complex. These discoveries may implicate a potential role for augmin in PrCa susceptibility.

Variant rs7968403 (OR=1.06; *P=3.38x10-12*; **Figure 2, Panel C**) is situated within the first intron of *RASSF3.* Members of the Ras association domain family (RASSF) are putative tumor suppressors implicated in a range of biological processes38. *RASSF3* is ubiquitously expressed across tissue types and has been observed to arrest the cell cycle in the G1 phase and induce apoptosis through the p53 pathway39. A previously identified PrCa risk locus, ~100kb away, within the *RASSF6* family member was previously identified11. However, rs7968403 was also an eQTL for the distant *WIF1* (WNT inhibitory factor 1) gene (**Figure 2, Panel C**). *WIF1* inhibits Wnt signaling and is frequently down regulated in PrCa40, whilst aberrant activation of Wnt signaling is common in many solid tumor types. Restoration of *WIF1* expression has also been demonstrated to decrease cell motility and invasiveness in a metastatic PrCa cell-line and reduce tumor growth in a mouse xenograft model41. Both *RASSF3* and *WIF1* therefore represent plausible mechanisms for the modulation of PrCa risk at this locus.

rs28441558 at 17p13 is the lead variant for a cluster of highly correlated SNPs centered on the *CHD3* gene (**Figure 2, Panel D**). *CHD3* is an ATPase that forms a component of the NuRD (nucleosome remodeling and deacetylase) histone deacetylase complex, involved in chromatin remodeling. NuRD plays an important role in regulating gene expression, both as a silencer and activator of transcription, in addition to maintenance of genomic integrity and the DNA damage response42. Alterations to NuRD function have been implicated in several cancer types in a highly complex manner43,44. Additionally however, rs28441558 was observed to be an eQTL for three genes; *LOC284023*, a currently uncharacterized non-coding RNA transcript, *GUCY2D*, a guanylate cyclase enzyme expressed predominantly in the retina and *ALOX15B*, a member of the lipoxygenase family of enzymes that produce fatty acid hyperoxides. Although *CHD3* appears to represent the most biologically plausible candidate gene for this locus, we cannot exclude a role for any of these genes.

Our pathway analysis based on mapping each SNP to the nearest gene (**see Online Methods**) using the meta-analysis summary association statistic identified several pathways implicated in PrCa susceptibility. The top 53 pathways detected (enrichment score, ES>0.50) are provided (**Supplementary Table 15**). The most significant pathway detected was PD-1 signaling (ID: 389948), ES=0.74, as defined by the REACTOME database (**Supplementary Figure 5**). This pathway is intriguing given the therapeutic potential of several checkpoint inhibitors focusing on the PD-1 signaling pathway to enhance immune responses45.

In summary, we have identified 63 novel PrCa susceptibility variants, including strong candidate loci highlighting the DNA repair and cell cycle pathways. Previous studies likely overestimated the effect estimates of PrCa loci due to the “winner’s curse”, thus yielding a biased FRR and polygenic risk score (PRS). Here, we apply a weighted Bayesian correction approach and demonstrate our large sample size minimizes the “winner’s curse” bias (**Online Methods; Supplementary Figure 6**)46. We applied the beta estimates calculated in our overall meta-analysis to the OncoArray sample set to calculate the FRR and PRS risk models (**Supplementary Table 16**). Our prediction models included 85 previously reported PrCa loci replicating in our overall meta-analysis and our 62 novel loci associated with overall PrCa risk. Assuming a familial risk estimate of 2.5 for PrCa47,48, we demonstrate our 147 loci captures 28.4% of the FRR (**Supplementary Table 17**). The newly 62 identified PrCa loci increase the FRR by 4.4%. On the assumption of a log-additive model, the estimated RR for PrCa relative to men in the 25-75% PRS percentile (baseline group) was 5.71 (95%CI: 5.04-6.48) for men in the top 1% of the polygenic risk score (PRS) distribution and 2.69 (95%CI: 2.55-2.82) for individuals in the 90-99%-ile of the PRS (**Table 2**). The PRS score was positively associated with overall PrCa compared to all controls (OR=1.86; 95%CI: 1.83-1.89; **Supplementary Table 18**). Our novel associations highlight several biological pathways that suggest further investigation is warranted. The increased PRS can be used to improve the identification of men at high risk of PrCa and therefore inform PSA guidelines for screening and management to reduce the burden of over testing.

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**AUTHOR CONTRIBUTIONS:**

Writing group: F.R.S., C.A.H., D.V.C., A. Al Olama, S.I.B., M.A, Z.K.J., R.A.E. Conception and coordination of OncoArray synthesis: F.R.S., C.I.A., D.F.E., S.J.C., C.A.H., B.E.H., F.W. Database management: S.B., M.N.B., X.S., K.M., A.L. Bioinformatics support: E.J.S., T.D., D.L., E.A., C.C.B., C.G. Genotyping calling and quality control: L.F., J.D., J.T. Provision of DNA samples and/or phenotypic data: V.L.S., S.M.G, B.D.C., C.M.T., P.J.G., I.M.T., J.B., S.C., L.M., J.C., L.H., W.T., G.P.R., H.G., M.A., T.N., P.P., N.P., J.S., T.L.J.T., C.S., A.A., D.A., S.W., A.W., N.H., C.M.L.W., A.M.D., N.B., L.A.M., E.G., G.L.A., O.C.,G.C.T., S.K., L.E.B.F., K.D.S., T.F.O., M.B., L.M., E.M.G., D.E.N, J.L.D., F.C.H., R.M.M, R.C.T, T.J.K., R.J.H., N.E.F., A.F., S.A.I., M.C.S., B.S.R., S.L.K., H.O., Y.L., H.Z., N.F., X.M., X.G., G.W., Z.S., G.G.G., M.C.S., R.J.M., L.M.F., A.S.K., B.M.K., J.L., G.C.V., K.L.P., M.S., J.Y.P., T.A.S., H.L., J.L.S., C.C., D.W., J.L., E.A.O., M.S.G., B.G.N., S.F.N., M.W.,R.B., M.A.R., P.I., H.B., K.C., B.H.,C.M., M.L., T.S., J.K., C.J.L., E.M.J., M.R.T., P.P., M.C., S.L.N., L.S., Y.C.D., K.D.R., G.D.M., P.O., A.R., J.L., S.T., D.W.L., L.F.N., D.L., M.G., T.K., R.K., N.U., S.S., C.S., V.M., M.P., F.C., S.J., T.V.B., S.L., P.A.T., C.A.H., M.G.D., J.E.C., M.E.M., M.J.R., G.J., R.H.N.S, F.M., T.T., Y.A.K., J.X., K.K., L.C.A., H.P., A.M., S.N.T., S.K.M., D.J.S., S.L., C.T., J.M., D.J.H., E.R., A.S., F.C., L.N.K., L.L.M., R.N.H., M.J.M., Z.C., P.K., F.W., S.J.C., B.E.H., C.A.H., R.A.E. APCB investigators, IMPACT Study, Canary PASS investigators, BPC3, PRACTICAL, CAPS, PEGASUS, GAME-ON/ELLIPSE. All authors read and approved the final version of the manuscript.

**COMPETING FINANCIAL INTERESTS STATEMENT:**

The authors declare no competing financial interests.

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**FIGURE LEGENDS:**

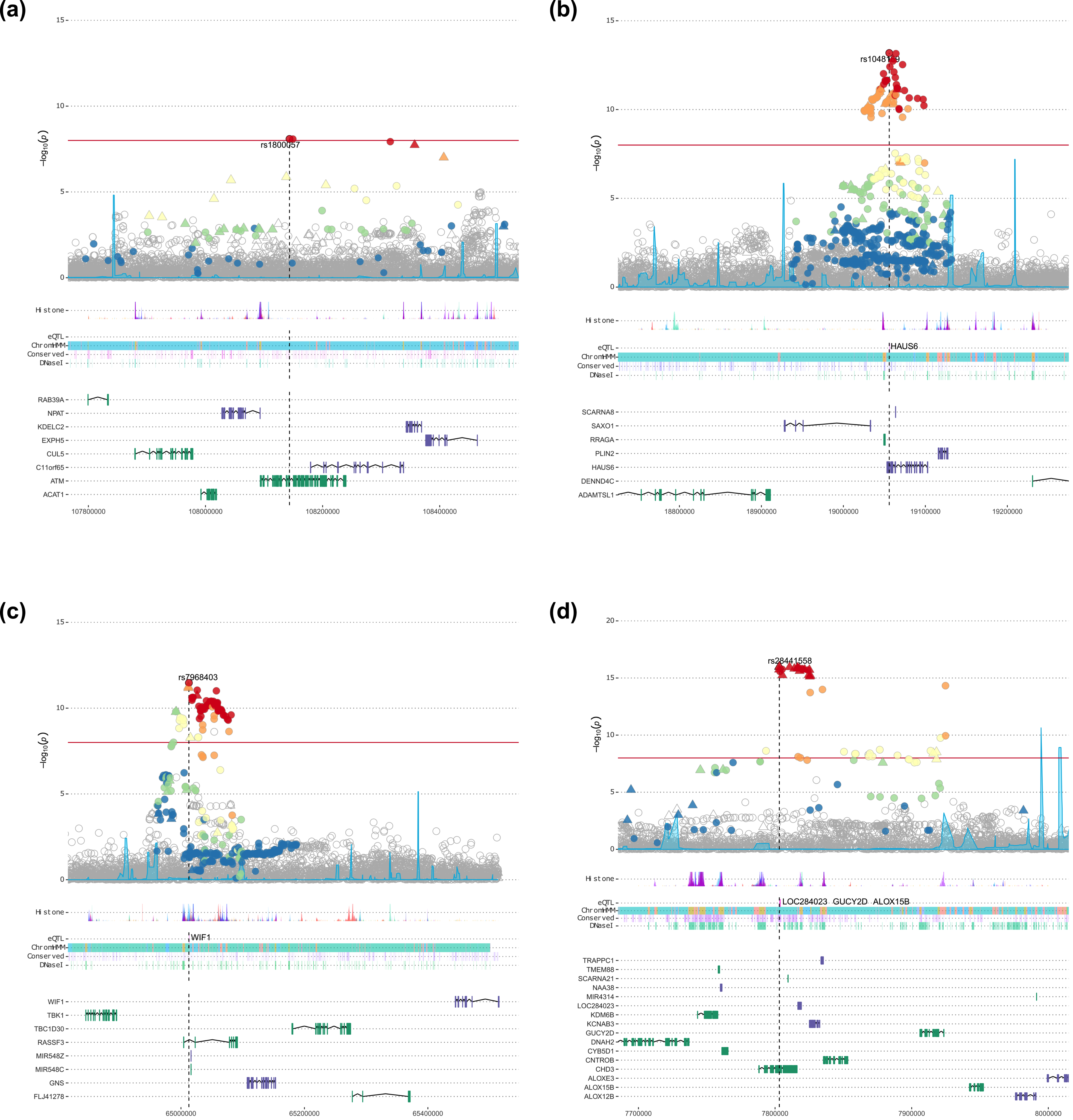
**Figure 1. ELLIPSE/PRACTICAL study overview of prostate cancer (PrCa) GWAS meta-analysis.** The top section describes the PrCa GWAS meta-analysis published in 2014 (AA Olama *et al*, Nature Genetics 201412) where 23 novel variants were identified. The current PrCa GWAS meta-analysis incorporates an additional 46,939 PrCa cases and 27,910 controls independent of the meta-analyses. The current meta-analysis discovered 62 novel variants associated with overall PrCa and 1 novel variant associated with early-onset PrCa.

**Figure 2.** **Locus Explorer plots depicting the statistical association with PrCa and biological context of variants from four of the novel prostate cancer loci identified (N=74,849 biologically independent samples).** For each panel (**a-d**), top panels depict Manhattan plots of variant -log10 *P* values (y-axis), with the index SNP labeled. Variants that were directly genotyped by the OncoArray are represented as triangles and imputed variants are represented as circles. Variants in linkage disequilibrium with the index SNP are denoted by color (red = *r2* >0.8, orange = *r2* 0.6-0.8, yellow = *r2* 0.4-0.6, green = *r2* 0.2-0.4, blue = *r2* ≤0.2). Middle panels depict the relative locations of selected biological annotations; histone marks within 7 cell lines from the ENCODE project; genes for which the index SNP is an eQTL in the TCGA prostate adenocarcinoma dataset; chromatin state annotation by ChromHMM in PrEC cells; conserved elements within the genome and DNAseI hypersensitivity sites in ENCODE prostate cell lines. The lower panel denotes the position of genes within the region, with genes on the positive and negative strands marked in green and purple, respectively. The horizontal axis represents genomic co-ordinates in the hg19 reference genome. **(a)** rs1800057 (chr11:107643000-108644000) - The index variant is a non-synonymous SNP in the *ATM* gene. **(b)** rs1048160 (chr9:18556000-19557000) - The index variant is located within the 3’UTR of the *HAUS6* gene and is an eQTL for *HAUS6*. **(c)** rs7968403 (chr12:64513000-65514000) - The signal is centered on the *RASSF3* gene, with the index variant located within the first intron. This SNP is also situated within a region annotated for multiple regulatory markers and is an eQTL for the more distant *WIF1* gene. **(d)** rs28441558 (chr17:7303000-8304000) - The signal implicates a cluster of highly correlated variants centered upon the *CHD3* gene. The index SNP is also an eQTL for three other more distantly located genes.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1. Prostate cancer OncoArray and GWAS meta-analysis for 63 novel regions.** | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  |
| SNP | Reference RAF a | Band | Position | Nearest Gene | Alleles b | RAF c | OR d | 95% CI e | P-value f |
| Novel loci associated with overall prostate cancer | | | | | | | | | |
| rs56391074 | 0.329 | 1p22.3 | 88210715 | RP11-60A14.1 | AT/A | 0.38 | 1.05 | 1.03-1.06 | 1.7E-08 |
| rs34579442 | 0.316 | 1q21.3 | 153899900 | DENND4B | C/CT | 0.34 | 1.07 | 1.05-1.09 | 4.5E-14 |
| rs62106670 | 0.400 | 2p25.1 | 8597123 | AC011747.3 | T/C | 0.38 | 1.05 | 1.04-1.07 | 7.1E-09 |
| rs74702681 | 0.024 | 2p14 | 66652885 | MEIS1-AS3 | T/C | 0.02 | 1.17 | 1.11-1.23 | 2.0E-09 |
| rs11691517 | 0.750 | 2q13 | 111893096 | BCL2L11 | T/G | 0.74 | 1.07 | 1.05-1.08 | 3.5E-12 |
| rs34925593 | 0.481 | 2q31.1 | 174234547 | CDCA7 | C/T | 0.48 | 1.05 | 1.03-1.07 | 2.8E-08 |
| rs59308963 | 0.726 | 2q33.1 | 202123479 | CASP8 | T/TATTCTGTC | 0.73 | 1.05 | 1.03-1.07 | 2.4E-08 |
| rs1283104 | 0.407 | 3q13.12 | 106962521 | DUBR | G/C | 0.38 | 1.05 | 1.03-1.07 | 8.8E-09 |
| rs182314334 | 0.888 | 3q25.1 | 152004202 | MBNL1 | T/C | 0.90 | 1.09 | 1.06-1.12 | 4.1E-11 |
| rs142436749 | 0.012 | 3q26.2 | 169093100 | MECOM | G/A | 0.01 | 1.25 | 1.16-1.34 | 4.7E-09 |
| rs10793821 | 0.580 | 5q31.1 | 133836209 | RNU6-456P | T/C | 0.57 | 1.05 | 1.04-1.07 | 5.4E-11 |
| rs76551843 | 0.991 | 5q35.1 | 169172133 | DOCK2 | A/G | 0.99 | 1.31 | 1.19-1.44 | 1.7E-08 |
| rs4976790 | 0.096 | 5q35.3 | 177968915 | COL23A1 | T/G | 0.11 | 1.08 | 1.05-1.10 | 6.7E-09 |
| rs12665339 | 0.148 | 6p21.33 | 30601232 | ATAT1 | G/A | 0.17 | 1.06 | 1.04-1.08 | 5.6E-09 |
| rs9296068 | 0.645 | 6p21.32 | 32988695 | HLA-DOA | T/G | 0.65 | 1.05 | 1.03-1.07 | 1.3E-08 |
| rs9469899 | 0.356 | 6p21.31 | 34793124 | UHRF1BP1 | A/G | 0.36 | 1.05 | 1.03-1.07 | 5.3E-09 |
| rs4711748 | 0.232 | 6p21.1 | 43694598 | RP1-261G23.5 | T/C | 0.23 | 1.05 | 1.03-1.07 | 3.4E-08 |
| rs527510716 | 0.251 | 7p22.3 | 1944537 | MAD1L1 | C/G | 0.24 | 1.06 | 1.04-1.08 | 4.9E-08 |
| rs11452686 | 0.567 | 7p21.1 | 20414110 | ITGB8 | T/TA | 0.56 | 1.05 | 1.03-1.07 | 7.8E-09 |
| rs17621345 | 0.758 | 7p14.1 | 40875192 | SUGCT | A/C | 0.74 | 1.07 | 1.05-1.09 | 6.7E-14 |
| rs1048169 | 0.367 | 9p22.1 | 19055965 | HAUS6 | C/T | 0.38 | 1.06 | 1.05-1.08 | 6.5E-14 |
| rs10122495 | 0.296 | 9p13.3 | 34049779 | RN7SKP114 | T/A | 0.31 | 1.05 | 1.03-1.07 | 1.3E-08 |
| rs1182 | 0.258 | 9q34.11 | 132576060 | TOR1A | A/C | 0.22 | 1.06 | 1.04-1.08 | 1.1E-09 |
| rs141536087 | 0.166 | 10p15.3 | 854691 | LARP4B | GCGCA/G | 0.15 | 1.08 | 1.06-1.11 | 9.0E-13 |
| rs1935581 | 0.605 | 10q23.31 | 90195149 | RNLS | C/T | 0.63 | 1.05 | 1.03-1.07 | 6.5E-09 |
| rs7094871 | 0.540 | 10q25.2 | 114712154 | TCF7L2 | G/C | 0.54 | 1.04 | 1.03-1.06 | 4.8E-08 |
| rs1881502 | 0.193 | 11p15.5 | 1507512 | MOB2 | T/C | 0.19 | 1.06 | 1.04-1.08 | 7.4E-09 |
| rs61890184g | 0.088 | 11p15.4 | 7547587 | PPFIBP2 | A/G | 0.12 | 1.07 | 1.05-1.10 | 6.6E-09 |
| rs547171081 | 0.468 | 11p11.2 | 47421962 | RP11-750H9.5 | CGG/C | 0.47 | 1.05 | 1.03-1.07 | 3.4E-08 |
| rs2277283 | 0.300 | 11q12.3 | 61908440 | INCENP | C/T | 0.31 | 1.06 | 1.04-1.08 | 3.0E-10 |
| rs12785905 | 0.051 | 11q13.2 | 66951965 | KDM2A | C/G | 0.05 | 1.12 | 1.08-1.17 | 7.8E-09 |
| rs11290954 | 0.688 | 11q13.5 | 76260543 | C11orf30 | AC/A | 0.68 | 1.06 | 1.05-1.08 | 7.4E-13 |
| rs1800057 | 0.031 | 11q22.3 | 108143456 | ATM | G/C | 0.02 | 1.16 | 1.10-1.22 | 8.1E-09 |
| rs138466039 | 0.009 | 11q24.2 | 125054793 | PKNOX2 | T/C | 0.01 | 1.32 | 1.22-1.44 | 2.0E-11 |
| rs878987 | 0.143 | 11q25 | 134266372 | B3GAT1 | G/A | 0.15 | 1.07 | 1.04-1.09 | 4.8E-08 |
| rs2066827 | 0.757 | 12p13.1 | 12871099 | CDKN1B | T/G | 0.76 | 1.06 | 1.04-1.08 | 2.3E-09 |
| rs10845938 | 0.554 | 12p13.1 | 14416918 | RNU6-491P | G/A | 0.55 | 1.06 | 1.04-1.08 | 9.8E-13 |
| rs7968403 | 0.655 | 12q14.2 | 65012824 | RASSF3 | T/C | 0.64 | 1.06 | 1.04-1.08 | 3.4E-12 |
| rs5799921 | 0.697 | 12q21.33 | 90160530 | RNU6-148P | GA/G | 0.68 | 1.06 | 1.04-1.08 | 7.0E-12 |
| rs7295014 | 0.342 | 12q24.33 | 133067989 | FBRSL1 | G/A | 0.35 | 1.05 | 1.04-1.07 | 9.5E-10 |
| rs1004030 | 0.581 | 14q11.2 | 23305649 | MMP14 | T/C | 0.58 | 1.05 | 1.03-1.06 | 1.5E-08 |
| rs11629412 | 0.582 | 14q13.3 | 37138294 | PAX9 | C/G | 0.58 | 1.06 | 1.04-1.08 | 2.3E-12 |
| rs4924487 | 0.836 | 15q15.1 | 40922915 | CASC5 | C/G | 0.81 | 1.06 | 1.04-1.09 | 1.3E-08 |
| rs33984059 | 0.982 | 15q21.3 | 56385868 | RFX7 | A/G | 0.98 | 1.19 | 1.12-1.27 | 1.1E-08 |
| rs112293876 | 0.280 | 15q22.31 | 66764641 | MAP2K1 | C/CA | 0.29 | 1.06 | 1.04-1.08 | 3.5E-10 |
| rs11863709 | 0.945 | 16q21 | 57654576 | GPR56 | C/T | 0.96 | 1.16 | 1.11-1.21 | 1.8E-11 |
| rs201158093 | 0.435 | 16q23.3 | 82178893 | RP11-510J16.5 | TAA/TA | 0.44 | 1.05 | 1.03-1.07 | 9.1E-09 |
| rs28441558 | 0.050 | 17p13.1 | 7803118 | CHD3 | C/T | 0.05 | 1.16 | 1.12-1.20 | 1.0E-16 |
| rs142444269 | 0.798 | 17q11.2 | 30098749 | RP11-805L22.3 | C/T | 0.78 | 1.07 | 1.05-1.09 | 3.2E-10 |
| rs2680708 | 0.623 | 17q22 | 56456120 | RNF43 | G/A | 0.61 | 1.05 | 1.03-1.06 | 1.6E-08 |
| rs8093601 | 0.459 | 18q21.2 | 51772473 | MBD2 | C/G | 0.44 | 1.05 | 1.03-1.06 | 2.3E-08 |
| rs28607662 | 0.085 | 18q21.2 | 53230859 | TCF4 | C/T | 0.10 | 1.08 | 1.05-1.11 | 2.8E-08 |
| rs12956892 | 0.300 | 18q21.32 | 56746315 | OACYLP | T/G | 0.30 | 1.05 | 1.03-1.07 | 7.7E-09 |
| rs533722308 | 0.390 | 18q21.33 | 60961193 | BCL2 | CT/C | 0.42 | 1.05 | 1.03-1.07 | 1.2E-08 |
| rs10460109 | 0.414 | 18q22.3 | 73036165 | TSHZ1 | T/C | 0.42 | 1.05 | 1.03-1.06 | 3.5E-08 |
| rs11666569 | 0.728 | 19p13.11 | 17214073 | MYO9B | C/T | 0.71 | 1.05 | 1.03-1.07 | 8.2E-09 |
| rs118005503 | 0.912 | 19q12 | 32167803 | THEG5 | G/C | 0.91 | 1.09 | 1.06-1.13 | 7.3E-09 |
| rs61088131 | 0.848 | 19q13.2 | 42700947 | POU2F2 | T/C | 0.82 | 1.06 | 1.04-1.09 | 8.8E-09 |
| rs11480453 | 0.641 | 20q11.21 | 31347512 | DNMT3B | C/CA | 0.60 | 1.05 | 1.03-1.06 | 3.2E-08 |
| rs6091758 | 0.465 | 20q13.2 | 52455205 | BCAS1 | G/A | 0.47 | 1.07 | 1.06-1.09 | 6.4E-18 |
| rs9625483 | 0.026 | 22q12.1 | 28888939 | TTC28 | A/G | 0.03 | 1.14 | 1.09-1.20 | 2.4E-08 |
| rs17321482 | 0.873 | 23p22.2 | 11482634 | ARHGAP6 | C/T | 0.87 | 1.07 | 1.05-1.09 | 2.1E-13 |
| Novel loci associated with early-onset | | | | | | | | | |
| rs138004030 | 0.920 | 6q27 | 170475879 | LOC154449 | G/A | 0.91 | 1.27 | 1.17-1.38 | 2.9E-08 |
|  |  |  |  |  |  |  |  |  |  |
| a Risk allele frequency - 1000 Genomes Project Europeans | | | | | | | | | |
| b Risk allele/Reference allele | | | | | | | | | |
| c Risk allele frequency | | | | | | | | | |
| d Odds ratio and confidence interval | | | | | | | | | |
| e Confidence interval | | | | | | | | | |
| f P-values are generated from a likelihood ratio test | | | | | | | | | |
| g Region previously reported by Wang et al (Nat Comm 2015), rs12791447; rs61890184-rs12791447 r2 (EUR)=0.41 | | | | | | | | | |

|  |  |  |
| --- | --- | --- |
| **Table 2.** Polygenic Risk Score (PRS) estimation using 147 prostate cancer susceptibility variants. | | |
|  |  |  |
| **Risk Category Percentiles a** | **RR** | **95% CI** |
| <1% | 0.15 | 0.11-0.20 |
| 1-10% | 0.35 | 0.32-0.37 |
| 10-25% | 0.54 | 0.51-0.57 |
| 25-75% | 1.00 (Baseline) |  |
| 75-90% | 1.74 | 1.67-1.82 |
| 90-99% | 2.69 | 2.55-2.82 |
| ≥99% | 5.71 | 5.04-6.48 |
| a Polygenetic Risk Score (PRS) percentiles based on the cumulative score distributed among controls. The beta coefficients computed from the European overall meta-analysis was applied to determine the PRS risk among individuals in the OncoArray study. | | |
| b Relative risk and 95% confidence intervals. | | |

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**ONLINE METHODS:**

Study subjects

A brief overview and study details for participating prostate cancer (PrCa) studies in the newly genotyped OncoArray project are provided in **Supplementary Table 1**1 for men of European ancestry. All studies were approved by the appropriate ethics committees and informed consent was obtained from all participants. **Supplementary Table 2** summarizes the PrCa sample series of the Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE) consortia contributing both newly obtained genotyping data for the OncoArray and previous genome-wide association studies (GWAS). The majority of the studies contributing to the OncoArray were case-control studies primarily based in either the United States or Europe. In total 52 new studies provided core data on disease status, age at diagnosis (age at observation or questionnaire for controls), family history of PrCa, and clinical factors for cases (*e.g.* PSA at diagnosis, Gleason score, etc.) for 48,455 PrCa cases and 28,321 disease-free controls. Previous GWAS contributed an additional 32,255 PrCa cases and 33,202 disease-free controls of European ancestry for the overall meta-analysis1. **Supplementary Table 3** provides quality control information by consortia (*i.e.* OncoArray project, UK GWAS, etc) for both samples and SNPs. After removing all overlapping samples the OncoArray contribution for newly genotyped samples was 46,939 PrCa cases and 27,910 disease-free controls.

Several strata-specific analyses were implemented to evaluate the impact of genetic variation in PrCa disease aggressiveness. **Supplementary Table 4** describes the analysis title, outcome and reference groups, and the statistical model used. Several classification schemes (*i.e.* low aggressiveness, intermediate aggressiveness, etc.) were implemented to better assess the spectrum of genetic involvement. All classification schemes incorporated the diagnostic clinical features PSA, tumor stage and Gleason score. In order to compare to previous PrCa aggressive analyses1 by our research group, we included the ‘Advanced (plus death due to PrCa)’ classification. Contributing study groups missing clinical features were excluded (**Supplementary Table 2**). Individuals with missing or granular clinical information were excluded. The strata-specific sample sizes by PrCa GWAS consortium are provided in **Supplementary Table 5**. Furthermore we analysed Gleason score as a continuous variable.

OncoArray SNP selection

The NCI Genetic Associations and Mechanisms in Oncology (GAME-ON) consortia (<http://epi.grants.cancer.gov/gameon/)> provided SNPs to be included on the Illumina OncoArray. Approximately 50% of the OncoArray was a compilation of SNP lists by the GAME-ON disease consortia of cancer (breast, colorectal, lung, ovarian, and prostate), a common set of variants for common risk regions, other related traits (*i.e.* BMI, age at menarche, etc), pharmacogenetics, and candidates2. The remaining content of the OncoArray was selected as a “GWAS backbone” (Illumina HumanCore), which aimed to provide high coverage for the majority of common variants through imputation. Approximately 79k SNPs were selected specifically for their relevance to PrCa, based on prior evidence of association with overall or subtype-specific disease, fine-mapping of known PrCa regions, and candidate submissions (*i.e.* survival, exome sequencing, etc). In order to maximize efficiency of the array, cancer-specific candidate lists were merged to remove redundant genetc variation3.

Genotype calling and quality control

Details of the genotype calling and quality control (QC) for the iCOGS and GWAS are described elsewhere4-20.

Of the 568,712 variants selected for genotyping on OncoArray, 533,631 were successfully manufactured on the array (including 778 duplicate probes). OncoArray genotyping of ELLIPSE studies was conducted at five sites (Cambridge [UK], CIDR, Copenhagen, USC, NCI). Details of the genotyping calling for the OncoArray are described in more detail elsewhere3. Briefly, we developed a single calling pipeline that was applied to more than 500,000 samples across the GAME-ON consortia. An initial cluster file was generated using 56,284 samples selected from all major genotyping centers and ethnicities, using the Gentrain2 algorithm. Variants likely to have problematic clusters were selected for manual inspection using the following criteria: call rate below 99%, minor allele frequency (MAF) <0.001, poor Illumina intensity and clustering metrics, deviation from the MAF observed in the 1000 Genomes Project (1KGP) using the criterion: , where *p*0 and *p*1 are the minor frequencies in the 1KGP and OncoArray datasets, respectively, and *C*=0.008. This resulted in manual adjustment of the cluster file for 3,964 variants, and the exclusion of 16,526 variants. The final cluster file was then applied to the full dataset.

Our quality control pipeline for ELLIPSE excluded SNPs with a call rate <95% by study, not in Hardy-Weinberg equilibrium (*P*<10-7 in controls, or *P*<10-12 in cases) or with concordance <98% among 11,260 duplicate pairs. In order to minimize imputation errors, we additionally excluded SNPs with a MAF<1% and a call rate <98% in any study, SNPs that could not be linked to the 1KGP reference, those with MAF for Europeans that differed from that for the 1KGP and a further 16,526 SNPs where the cluster plot was judged to be not ideal. Of the 533,631 manufactured SNPs on the OncoArray, we retained 498,417 SNPs among our samples of European ancestry following QC.

We excluded duplicate samples and first-degree relatives within each study, duplicates across studies, samples with a call rate <95%, and samples with extreme heterozygosity (>4.9 standard deviations from the mean for the reported ethnicity). We excluded duplicated samples as well as first-degree relatives across the GWAS studies CAPS1, CAPS2, UK Stage 1, UK Stage 2, and iCOGS. Duplicate and first-degree related samples were assessed across the BPC3 and Pegasus GWAS studies as well. Ancestry was computed using a principal component analysis using 2,318 informative markers on a subset of ~47,000 samples and projected onto the complete OncoArray dataset. The current analysis was restricted to men of European ancestry, defined as individuals with an estimated proportion of European ancestry >0.8, with reference to the HapMap populations, based on the first two principal components. Of the 78,182 samples genotyped (regardless of race/ethnicity), the final dataset consisted of 74,849 samples, of which 46,939 PrCa cases and 27,910 disease-free controls (**Supplementary Table 3**) after excluding overlap samples, were meta-analysed with previous studies.

Imputation

Genotypes for ~70M SNPs were imputed for all samples using the October 2014 (Phase 3) release of the 1KGP data as the reference panel. The OncoArray and GWAS datasets were imputed using a two-stage imputation approach, using SHAPEIT21 for phasing and IMPUTEv222 for imputation. The imputation was performed in 5Mb non-overlapping intervals. All subjects were split into subsets of ~10,000 samples, with subjects from the same group in the subset. We imputed genotypes for all SNPs that were polymorphic (MAF>0.1%) in European samples. We excluded data for all monomorphic SNPs and those with an imputation r2<0.3 leaving a total of 20,370,935 SNP across chromosomes 1-22 and chromosome X. Of the SNPs imputed, 49.3% had a MAF<1%, 15.2% had a MAF ranging between 1-5%, and 35.5% had a MAF≥5%.

Statistical analyses

Per-allele odds ratios and standard errors were generated for the OncoArray and each GWAS, adjusting for principal components and study relevant covariates using logistic regression. The OncoArray and iCOGS analyses were additionally stratified by country and study, respectively. We used the first seven principal components in our analysis of individuals of European ancestry, as additional components did not further reduce inflation in the test statistics.

Odds ratio (OR) estimates were derived using either SNPTEST (<https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html>) or an in-house C++ program (**Supplementary Table 3**). OR estimates and standard errors were combined by a fixed effects inverse variance meta-analysis using METAL23. All statistical tests conducted were two-sided.

Our analyses included overall PrCa and several clinically relevant strata. These included: 1) high vs low aggressive PrCa; 2) high vs low/intermediate aggressive PrCa; 3) advanced vs non-advanced PrCa; 4) advanced PrCa vs controls; 5) early-onset PrCa (≤55 yrs) vs controls; and 6) Gleason score (**Supplementary Tables 4 & 5**). We defined low aggressive as tumor stage ≤T1 and Gleason ≤6 and PSA <10 ng/mL, intermediate aggressive as tumor stage T2 or Gleason=7 or PSA 10-20 ng/mL, high aggressive as tumor stage T3/T4 or N1 or M1 or Gleason ≥8 or PSA >20 ng/mL, and advanced as either metastatic disease, Gleason ≥8, PSA>100 or PrCa-related deaths (**Supplementary Table 4**).

Definition of new hits

To search for novel loci, we assessed all SNPs excluding those within a known PrCa locus, defined by current fine-mapping assessments (**Supplementary Table 7**). SNPs that were associated with disease risk at *P*<5x10-8 in the meta-analysis (GWAS and OncoArray) were considered novel. The SNP with the lowest p-value in a region was considered the lead SNP. Imputation quality assessed by IMPUTE2 imputation r2 in the OncoArray dataset (**Supplementary Table 8**).

For ten regions where the newly identified locus was near a previously known region, we reported a novel association if the pairwise r2 between the new and the previously known SNP was less than 0.2. For novel PrCa associations where the variant was imputed in the OncoArray study samples series and had an imputed quality score less than 0.70, we assessed the quality of the imputation by masking the variant in a subset of the 1KGP European sample and calculating the concordance following re-imputation in the remaining 1KGP samples.

Reliability of Imputation

Novel SNPs with an IMPUTE2 r2<0.80 among the OncoArray sample series (**Supplementary Table 8**) were flagged for further investigation to minimize the probability of a false positive. First, we examined linkage disequilibrium (LD) plots (<http://locuszoom.org/>) for poorly imputed SNPs (+/-500kb) including only genotyped SNPs within the region. The imputed index SNP was included in the plot to determine the strength of LD with nearby signals and assess a pattern of association. Furthermore, we performed an imputation experiment using the 2,504 1KGP Phase 3 samples. We split this sample into two parts: a random sample of 259 individuals of European ancestry (excluding the Finnish) and a mixed-population reference panel of 2,245 individuals. The random sample of 259 individuals of European ancestry was filtered to include only the genetic variants available from the OncoArray following QC. This ensured the same imputation input used in the overall imputation. The 259 individuals were imputed using 2,245 individuals as the reference panel. A 5 MB segment of the genome was selected based on the target SNP (+/- 250 MB). SHAPEIT2 was used for pre-phasing and IMPUTE2 for imputation. Customized imputation settings included an effect size of 20,000, allowance of large region imputation and a random seed of 12345. A weighted linear Kappa statistic was calculated to determine correlation of the imputation with the true genotypes.

We evaluated four SNPs where the IMPUTE2 r2 was less than 0.80 in the OncoArray sample series: rs527510716 (Chr 7), rs6602880 (Chr 10), rs533722308 (Chr 18) and rs144166867 (Chr X). **Supplementary Figure 3** includes the LD plots for three of the poorly imputed SNPs. The variant rs144166867 (Chr X) could not be plotted given no genotype SNPs were available +/-500 KB on the OncoArray. Both LD plots for markers rs527510716 (Chr 7) and rs533722308 (Chr 18) showed significant associations (*P*<1x10-3) for several genotype markers with moderate LD of the index SNP. The Kappa coefficient for markers rs527510716 (Chr 7) and rs533722308 (Chr 18) was 0.911 and 0.931, respectively (**Supplementary Table 9**). The marker rs6602880 (Chr 10) had a Kappa coefficient of 0.812 and was the only significant variant in the LD plot. The Kappa coefficient for marker rs144166867 (Chr X) was 0.665 (**Supplementary Table 9**). The markers rs6602880 (Chr 10) and rs144166867 (Chr X) are most likely false positives due to poor imputation for these regions.

Proportion of familial risk explained

The contribution of the known SNPs to the familial risk of PrCa, under a multiplicative model, was computed using the formula



where is the observed familial risk to first degree relatives of PrCa cases24,25, assumed to be 2.5, and is the familial relative risk due to locus k, given by:



whereis the frequency of the risk allele for locus k,  and is the estimated per-allele odds ratio.

Based on the assumption of a log-additive model, we constructed a polygenic risk score (PRS) from the summed risk allelic dosages weighted by the per-allele log-odds ratios. Thus for each individual *j* we derived:



Where:

: Number of SNPs

: Allele dose at SNPi for individual j

: Per-allele log-odds ratio of SNPi

The risk of PrCa was estimated for the percentile of the distribution of the PRS (<1%, 1-10%, 10-25%, 25-75%, 75-90%, 90-99%, >99% and <10%, 10-25%, 25-75%, 75-90%, >90%) where cumulative score thresholds were determined by the observed distribution among controls. We applied effect sizes and allele frequencies obtained from the overall meta-analysis of Europeans to estimate risk scores for individuals of European ancestry in the OncoArray study26. A standardized PRS score was calculated by dividing the observed PRS score by the standard deviation of the PRS score among controls. A logistic regression framework was used to evaluate the percentile comparisons and determine the risk estimate. The models were adjusted for the first seven principal components to account for population stratification and stratified by country.

The FRR and PRS risk estimation was limited to the variants where our overall meta-analysis observed a statistically significant association. In total, we included 147 PrCa index SNPs in our risk score modelling, including 85 previously published associations and the 62 novel findings reported here. To correct for potential bias in effect estimation of newly discovered variants, we implemented a fully Bayesian version of a weighted correction given in Zhong and Prentice, Eq 3.427. Specifically, we place a normal prior distribution on MLE effect estimates of the form . Here, *βm* is the log odds ratio from the overall meta-analysis; is the bias corrected estimate calculated using the expectation-adjusted estimator from Eq 3.1 in Zhong and Prentice; and τ is a pre-specified variance of the effect distribution reflecting the bias and is defined as .

eQTL analyses

Genotype and gene expression data were downloaded from The Cancer Genome Atlas (TCGA) for 494 samples with PrCa (<https://gdc-portal.nci.nih.gov>). Quality Control (QC) was performed on both these datasets as follows: on the genotype, we filtered out samples with high heterozygosity (mean heterozygosity +/- 2 standard deviation) and missing genotypes, duplicated or related samples. We then performed Principal Component Analysis on the 494 samples plus 2,506 samples from 1KGP to infer the ancestry of the TCGA samples; samples of non-European ancestry were removed. We also filtered out variants with missing call rate > 5%. For the expression data, samples from two plates had, on average, much higher expression values than the remaining samples, and these were excluded. We also filtered genes with mean expression across samples <= 6 counts. Finally, expression values were quantile-normalized by samples and rank-transformed by genes. After QC we used the data from 359 samples. For the eQTL analysis, 35 PEER factors from the top 10,000 expressed genes were used as covariates, plus three genotyping PCs (which explained 18% of total variation). eQTL analysis was performed using FastQTL with 1,000 permutations over the 85 regions. We used a window of 1 Megabases (upstream/downstream) from the transcription start site (TSS) of each gene.

Gene Set Enrichment Analyses

The file Human\_GOBP\_AllPathways\_no\_GO\_iea\_September\_01\_2016\_symbol.gmt (<http://baderlab.org/EM_GeneSets>), from the GeneSets database28, was used for all analyses. This database contains pathways from Reactome29, NCI Pathway Interaction Database30, GO (Gene Ontology) biological process31, HumanCyc32, MSigdb33, NetPath34 and Panther35. We manually corrected several pathways where the *PDPK1* gene was entered as *PDK1.* GO pathways inferred from electronic annotation terms were excluded. The same pathway (e.g. apoptosis) may be defined in two or more databases with potentially different sets of genes, and all versions of these duplicate/overlapping pathways were included. Pathway size was determined by the total number of genes in the pathway to which SNPs in the imputed GWAS dataset could be mapped. To provide more biologically meaningful results, and reduce false positives, only pathways that contained between 10 and 200 geneswere considered.

Gene information (hg19) was downloaded from the ANNOVAR36 website (http://www.openbioinformatics.org/annovar/). SNPs were mapped to the nearest gene within 500kb window; those that were further away from any gene were excluded. Gene significance was calculated by assigning the lowest p-value observed across all SNPs assigned to a gene37,38, based on the combined European meta-analysis (previous GWAS and OncoArray).

The gene set enrichment analysis (GSEA)28 algorithm, as implemented in the GenGen package (http://gengen.openbioinformatics.org/en/latest/)38,39 was used to perform pathway analysis. Briefly, the algorithm calculates an enrichment score (ES) for each pathway based on a weighted Kolmogorov-Smirnov statistic39. To calculate the ES we performed 100 permutations and averaged the final score. Pathways that have most of their genes at the top of the ranked list of genes obtain higher ES values. Only pathways with positive ES and at least one gene with P<5x10-8 were retained for subsequent analysis. An enrichment map was created using the Enrichment Map (EM) v 2.1.0 app28 in Cytoscape v3.4040, applying force directed layout, weighted mode. We restricted our pathway analysis those with an ES≥0.50 to ensure a true positive rate > 0.20 and a false positive rate < 0.15.

**DATA AVAILABILITY:**

The OncoArray genotype data and relevant covariate information (*i.e.* ethnicity, country, principal components, etc.) generated during this study will be deposited into dbGAP for access. In total 47 of the 52 OncoArray studies encompassing nearly 90% of the individual samples will be available (**Supplementary Table 19**). The previous meta-analysis summary results and genotype data currently12 are available in dbGAP (Accession #: phs001081.v1.p1). The complete meta-analysis summary associations statistics is publicly available at the PRACTICAL website (<http://practical.icr.ac.uk/blog/>).

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