

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

Genome-wide association studies (GWAS) and fine-mapping efforts to date have identified more than 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 ($P < 5.0 \times 10^{-8}$) with PrCa and one locus significantly associated with early-onset PrCa (≤ 55 years). Our findings include missense variants rs1800057 (odds ratio (OR) = 1.16; $P = 8.2 \times 10^{-9}$; G>C, p.Pro1054Arg) in *ATM* and rs2066827 (OR = 1.06; $P = 2.3 \times 10^{-9}$; T>G, p.Val109Gly) in *CDKN1B*. The combination of all loci captured 28.4% of the PrCa familial relative risk, and a polygenic risk score conferred an elevated PrCa risk for men in the ninetieth to ninety-ninth percentiles (relative risk = 2.69; 95% confidence interval (CI): 2.55–2.82) and first percentile (relative risk = 5.71; 95% CI: 5.04–6.48) risk stratum compared with the population average. These findings improve risk prediction, enhance fine-mapping, and provide insight into the underlying biology of PrCa¹.

Although PrCa is the most common noncutaneous cancer among men in the Western world, and one in seven men will be diagnosed during their lifetime², very few modifiable risk factors have been established³. Epidemiological studies have identified age, positive family history, and ancestry as the most prominent risk factors for PrCa^{4–7}. PrCa incidence is highest among men of African ancestry, followed by men of European and Asian ancestries. These observations of ancestral differences in PrCa risk, in conjunction with studies demonstrating the influence of family history^{8,9}, highlight the contribution of genetics to PrCa etiology¹⁰. Our previous work, using a multiplicative model, has estimated that more than 1,800 common SNPs independently contribute to PrCa risk among populations of European ancestry¹¹. GWAS have reported more than 100 of these PrCa variants across multiethnic populations, most of which were identified in populations of European ancestry^{12–29}.

To facilitate additional discovery of PrCa genetic risk factors, we developed a custom high-density genotyping array, the OncoArray, including a 260,000-SNP backbone designed to adequately tag most common genetic variants (minor allele frequency (MAF) >5% in Europeans), and 310,000 SNPs from meta-analyses of five cancers (breast, colorectal, lung, ovarian, and prostate)³⁰. Approximately 80,000 PrCa-specific markers derived from our previous multiethnic 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 and 2). After application of rigorous quality control (QC) criteria and removal of overlapping samples from previous studies, our OncoArray sample yielded 46,939 PrCa cases and 27,910 controls without a known diagnosis of PrCa and of European ancestry for analysis (Methods and Supplementary Table 3). Genotypes were

phased and imputed to the cosmopolitan panel of the 1000 Genomes Project (1KGP; June 2014 release) in SHAPEIT³¹ and IMPUTEv2 (ref.³²) software (Methods and 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 the 1KGP. The final meta-analysis included 79,194 PrCa cases and 61,112 controls without a known diagnosis of PrCa (Fig. 1).

We performed study- and consortia-specific meta-analyses to identify novel PrCa risk loci. We established a P -value threshold of 5.0×10^{-8} to determine genome-wide significance. Our large sample size enabled several stratified meta-analyses focusing on key clinical and biological parameters (Methods and Supplementary Tables 4 and 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 the Gleason score, for which linear regression was used. The genotype doses were incorporated in an allelic genetic model. The average λ_{1000} , an inflation statistic calibrated to a sample size of 1,000 cases and 1,000 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 risk loci (Supplementary Table 7).

After the exclusion of all known susceptibility regions (fine-mapping coordinates provided in Supplementary Table 7 and Supplementary Note), we identified 64 loci associated with overall PrCa susceptibility and 1 locus associated with early-onset PrCa ($P < 5.0 \times 10^{-8}$) in the meta-analysis (Supplementary Fig. 1), of which 53 were imputed, and 12 were genotyped with the OncoArray. The cluster plots for the genotyped markers are presented in Supplementary Fig. 2. Although most of the imputed markers were of high quality, with an average imputed $r^2 > 0.80$ for 61 of the 65 loci across all contributing GWAS (Supplementary Table 8), we closely examined four variants with a poor imputation quality score ($r^2 < 0.80$) in the OncoArray samples by inspecting linkage disequilibrium (LD) plots including only genotyped SNPs from the OncoArray and performing an imputation QC assessment (Methods). After reviewing the LD plots and the imputation QC, we determined that loci rs6602880 and rs144166867 were probably false positives due to imputation artifacts (Supplementary Fig. 3 and Supplementary Table 9). Overall, we identified 62 novel loci associated with overall PrCa risk and one novel locus associated with early-onset PrCa (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, which was significantly associated with early-onset disease (Table 1) but was only nominally significant for overall PrCa risk ($P = 0.02$). In addition, we detected four markers significantly associated ($P < 5 \times 10^{-8}$) with advanced PrCa and two markers associated with early-onset PrCa (Supplementary Table 11). However, the case-only

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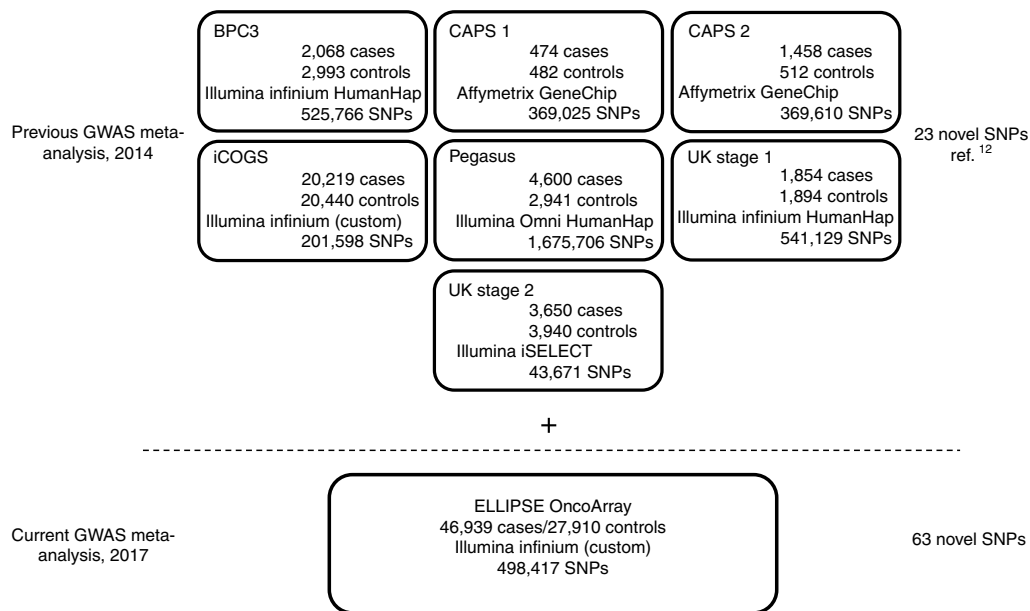


Fig. 1 | ELLIPSE/PRACTICAL study overview of PrCa GWAS meta-analysis. The top section describes the PrCa GWAS meta-analysis published in 2014, in which 23 novel variants were identified¹². The current PrCa GWAS meta-analysis incorporated an additional 46,939 PrCa cases and 27,910 controls independent 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.

Table 1 | Prostate cancer OncoArray and GWAS meta-analysis for 63 novel regions

SNP	Reference RAF ^a	Band	Position	Nearest gene	Alleles ^b	RAF	OR	95% CI	P ^c
Novel loci associated with overall prostate cancer									
rs56391074	0.329	1p22.3	88210715	<i>RP11-60A14.1</i>	A/T	0.38	1.05	1.03–1.06	1.7×10^{-8}
rs34579442	0.316	1q21.3	153899900	<i>DENND4B</i>	C/CT	0.34	1.07	1.05–1.09	4.5×10^{-14}
rs62106670	0.400	2p25.1	8597123	<i>AC011747.3</i>	T/C	0.38	1.05	1.04–1.07	7.1×10^{-9}
rs74702681	0.024	2p14	66652885	<i>MEIS1-AS3</i>	T/C	0.02	1.17	1.11–1.23	2.0×10^{-9}
rs11691517	0.750	2q13	111893096	<i>BCL2L1</i>	T/G	0.74	1.07	1.05–1.08	3.5×10^{-12}
rs34925593	0.481	2q31.1	174234547	<i>CDCA7</i>	C/T	0.48	1.05	1.03–1.07	2.8×10^{-8}
rs59308963	0.726	2q33.1	202123479	<i>CASP8</i>	T/TATTCTGTC	0.73	1.05	1.03–1.07	2.4×10^{-8}
rs1283104	0.407	3q13.12	106962521	<i>DUBR</i>	G/C	0.38	1.05	1.03–1.07	8.8×10^{-9}
rs182314334	0.888	3q25.1	152004202	<i>MBNL1</i>	T/C	0.90	1.09	1.06–1.12	4.1×10^{-11}
rs142436749	0.012	3q26.2	169093100	<i>MECOM</i>	G/A	0.01	1.25	1.16–1.34	4.7×10^{-9}
rs10793821	0.580	5q31.1	133836209	<i>RNU6-456P</i>	T/C	0.57	1.05	1.04–1.07	5.4×10^{-11}
rs76551843	0.991	5q35.1	169172133	<i>DOCK2</i>	A/G	0.99	1.31	1.19–1.44	1.7×10^{-8}
rs4976790	0.096	5q35.3	177968915	<i>COL23A1</i>	T/G	0.11	1.08	1.05–1.10	6.7×10^{-9}
rs12665339	0.148	6p21.33	30601232	<i>ATAT1</i>	G/A	0.17	1.06	1.04–1.08	5.6×10^{-9}
rs9296068	0.645	6p21.32	32988695	<i>HLA-DOA</i>	T/G	0.65	1.05	1.03–1.07	1.3×10^{-8}
rs9469899	0.356	6p21.31	34793124	<i>UHRF1BP1</i>	A/G	0.36	1.05	1.03–1.07	5.3×10^{-9}
rs4711748	0.232	6p21.1	43694598	<i>RP1-261G23.5</i>	T/C	0.23	1.05	1.03–1.07	3.4×10^{-8}
rs527510716	0.251	7p22.3	1944537	<i>MAD1L1</i>	C/G	0.24	1.06	1.04–1.08	4.9×10^{-8}
rs11452686	0.567	7p21.1	20414110	<i>ITGB8</i>	T/TA	0.56	1.05	1.03–1.07	7.8×10^{-9}
rs17621345	0.758	7p14.1	40875192	<i>SUGCT</i>	A/C	0.74	1.07	1.05–1.09	6.7×10^{-14}
rs1048169	0.367	9p22.1	19055965	<i>HAUS6</i>	C/T	0.38	1.06	1.05–1.08	6.5×10^{-14}
rs10122495	0.296	9p13.3	34049779	<i>RN7SKP114</i>	T/A	0.31	1.05	1.03–1.07	1.3×10^{-8}
rs1182	0.258	9q34.11	132576060	<i>TOR1A</i>	A/C	0.22	1.06	1.04–1.08	1.1×10^{-9}
rs141536087	0.166	10p15.3	854691	<i>LARP4B</i>	GCGCA/G	0.15	1.08	1.06–1.11	9.0×10^{-13}

Continued

Table 1 | Prostate cancer OncoArray and GWAS meta-analysis for 63 novel regions (Continued)

SNP	Reference RAF ^a	Band	Position	Nearest gene	Alleles ^b	RAF	OR	95% CI	P ^c
rs1935581	0.605	10q23.31	90195149	<i>RNLS</i>	C/T	0.63	1.05	1.03–1.07	6.5 × 10 ⁻⁹
rs7094871	0.540	10q25.2	114712154	<i>TCF7L2</i>	G/C	0.54	1.04	1.03–1.06	4.8 × 10 ⁻⁸
rs1881502	0.193	11p15.5	1507512	<i>MOB2</i>	T/C	0.19	1.06	1.04–1.08	7.4 × 10 ⁻⁹
rs61890184 ^d	0.088	11p15.4	7547587	<i>PPFIBP2</i>	A/G	0.12	1.07	1.05–1.10	6.6 × 10 ⁻⁹
rs547171081	0.468	11p11.2	47421962	<i>RP11-750H9.5</i>	CGG/C	0.47	1.05	1.03–1.07	3.4 × 10 ⁻⁸
rs2277283	0.300	11q12.3	61908440	<i>INCENP</i>	C/T	0.31	1.06	1.04–1.08	3.0 × 10 ⁻¹⁰
rs12785905	0.051	11q13.2	66951965	<i>KDM2A</i>	C/G	0.05	1.12	1.08–1.17	7.8 × 10 ⁻⁹
rs11290954	0.688	11q13.5	76260543	<i>C11orf30</i>	AC/A	0.68	1.06	1.05–1.08	7.4 × 10 ⁻¹³
rs1800057	0.031	11q22.3	108143456	<i>ATM</i>	G/C	0.02	1.16	1.10–1.22	8.1 × 10 ⁻⁹
rs138466039	0.009	11q24.2	125054793	<i>PKNOX2</i>	T/C	0.01	1.32	1.22–1.44	2.0 × 10 ⁻¹¹
rs878987	0.143	11q25	134266372	<i>B3GAT1</i>	G/A	0.15	1.07	1.04–1.09	4.8 × 10 ⁻⁸
rs2066827	0.757	12p13.1	12871099	<i>CDKN1B</i>	T/G	0.76	1.06	1.04–1.08	2.3 × 10 ⁻⁹
rs10845938	0.554	12p13.1	14416918	<i>RNU6-491P</i>	G/A	0.55	1.06	1.04–1.08	9.8 × 10 ⁻¹³
rs7968403	0.655	12q14.2	65012824	<i>RASSF3</i>	T/C	0.64	1.06	1.04–1.08	3.4 × 10 ⁻¹²
rs5799921	0.697	12q21.33	90160530	<i>RNU6-148P</i>	GA/G	0.68	1.06	1.04–1.08	7.0 × 10 ⁻¹²
rs7295014	0.342	12q24.33	133067989	<i>FBRSL1</i>	G/A	0.35	1.05	1.04–1.07	9.5 × 10 ⁻¹⁰
rs1004030	0.581	14q11.2	23305649	<i>MMP14</i>	T/C	0.58	1.05	1.03–1.06	1.5 × 10 ⁻⁸
rs11629412	0.582	14q13.3	37138294	<i>PAX9</i>	C/G	0.58	1.06	1.04–1.08	2.3 × 10 ⁻¹²
rs4924487	0.836	15q15.1	40922915	<i>CASC5</i>	C/G	0.81	1.06	1.04–1.09	1.3 × 10 ⁻⁸
rs33984059	0.982	15q21.3	56385868	<i>RFX7</i>	A/G	0.98	1.19	1.12–1.27	1.1 × 10 ⁻⁸
rs112293876	0.280	15q22.31	66764641	<i>MAP2K1</i>	C/CA	0.29	1.06	1.04–1.08	3.5 × 10 ⁻¹⁰
rs11863709	0.945	16q21	57654576	<i>GPR56</i>	C/T	0.96	1.16	1.11–1.21	1.8 × 10 ⁻¹¹
rs201158093	0.435	16q23.3	82178893	<i>RP11-510J16.5</i>	TAA/TA	0.44	1.05	1.03–1.07	9.1 × 10 ⁻⁹
rs28441558	0.050	17p13.1	7803118	<i>CHD3</i>	C/T	0.05	1.16	1.12–1.20	1.0 × 10 ⁻¹⁶
rs142444269	0.798	17q11.2	30098749	<i>RP11-805L22.3</i>	C/T	0.78	1.07	1.05–1.09	3.2 × 10 ⁻¹⁰
rs2680708	0.623	17q22	56456120	<i>RNF43</i>	G/A	0.61	1.05	1.03–1.06	1.6 × 10 ⁻⁸
rs8093601	0.459	18q21.2	51772473	<i>MBD2</i>	C/G	0.44	1.05	1.03–1.06	2.3 × 10 ⁻⁸
rs28607662	0.085	18q21.2	53230859	<i>TCF4</i>	C/T	0.10	1.08	1.05–1.11	2.8 × 10 ⁻⁸
rs12956892	0.300	18q21.32	56746315	<i>OACYP</i>	T/G	0.30	1.05	1.03–1.07	7.7 × 10 ⁻⁹
rs533722308	0.390	18q21.33	60961193	<i>BCL2</i>	CT/C	0.42	1.05	1.03–1.07	1.2 × 10 ⁻⁸
rs10460109	0.414	18q22.3	73036165	<i>TSHZ1</i>	T/C	0.42	1.05	1.03–1.06	3.5 × 10 ⁻⁸
rs11666569	0.728	19p13.11	17214073	<i>MYO9B</i>	C/T	0.71	1.05	1.03–1.07	8.2 × 10 ⁻⁹
rs118005503	0.912	19q12	32167803	<i>THEG5</i>	G/C	0.91	1.09	1.06–1.13	7.3 × 10 ⁻⁹
rs61088131	0.848	19q13.2	42700947	<i>POU2F2</i>	T/C	0.82	1.06	1.04–1.09	8.8 × 10 ⁻⁹
rs11480453	0.641	20q11.21	31347512	<i>DNMT3B</i>	C/CA	0.60	1.05	1.03–1.06	3.2 × 10 ⁻⁸
rs6091758	0.465	20q13.2	52455205	<i>BCAS1</i>	G/A	0.47	1.07	1.06–1.09	6.4 × 10 ⁻¹⁸
rs9625483	0.026	22q12.1	28888939	<i>TTC28</i>	A/G	0.03	1.14	1.09–1.20	2.4 × 10 ⁻⁸
rs17321482	0.873	23p22.2	11482634	<i>ARHGAP6</i>	C/T	0.87	1.07	1.05–1.09	2.1 × 10 ⁻¹³
Novel locus associated with early-onset prostate cancer									
rs138004030	0.920	6q27	170475879	<i>LOC154449</i>	G/A	0.91	1.27	1.17–1.38	2.9 × 10 ⁻⁸

^aRisk-allele frequency (RAF) in 1KGP Europeans. ^bRisk allele/reference allele. ^cP values generated from likelihood-ratio tests. ^dRegion previously reported by Wang et al.⁴⁹; rs12791447; rs61890184–rs12791447 r^2 (EUR) = 0.41.

analyses of these markers indicated marginal statistical significance ($P < 1.0 \times 10^{-3}$). Additionally, these markers were in LD with nearby index markers associated with overall PrCa and were not significantly associated with overall aggressive disease after adjustment for the index marker (Supplementary Table 11). A similar association pattern was observed for rs111599055, which was in LD with rs7295014 ($r^2 = 0.54$), a marker associated with overall disease. The early-onset marker rs7777548 was independent of novel and known PrCa-risk loci. However, the marker was relatively rare

(effect-allele frequency <0.02), was indicated as monomorphic in the 1KGP, and had a moderate imputation quality score (average $r^2 = 0.57$); hence, we did not include it in further analyses.

Among the 63 novel associations, 38 variants were found to be located within gene-rich regions (Supplementary Table 12): intronic (32 SNPs), missense (4 SNPs), and 3' untranslated region (UTR) (2 SNPs). Analyses of expression quantitative trait loci (eQTL) in The Cancer Genome Atlas (TCGA) database identified statistically significant associations ($P < 0.05$; Supplementary Table 12) in

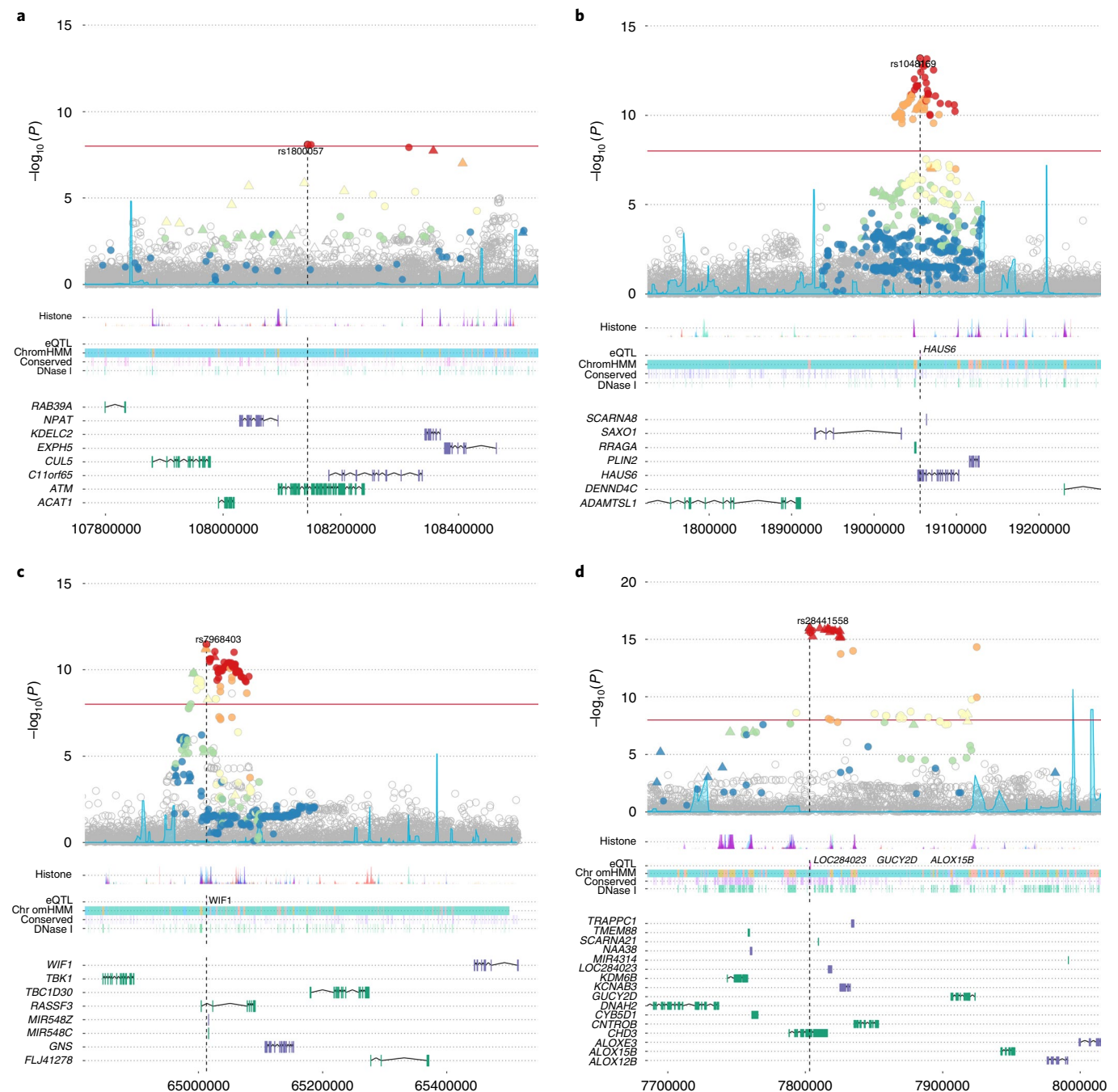


Fig. 2 | Locus Explorer plots depicting the statistical association with PrCa and biological context of variants from four of the newly identified PrCa-risk loci ($n = 74,849$ biologically independent samples). **a–d, Top, Manhattan plots of variant $-\log_{10} P$ values (y axis), with the index SNP labeled. Variants that were directly genotyped with the OncoArray are represented as triangles, and imputed variants are represented as circles. Variants in LD with the index SNP are denoted by color (red, $r^2 > 0.8$; orange, $0.6 < r^2 < 0.8$; yellow, $0.4 < r^2 < 0.6$; green, $0.2 < r^2 < 0.4$; blue, $r^2 \leq 0.2$). Middle, relative locations of selected biological annotations: histone marks within seven cell lines from the ENCODE project; genes for which the index SNP is an eQTL in TCGA prostate adenocarcinoma dataset; chromatin state annotation by ChromHMM in PrEC cells; conserved elements within the genome; and DNase I-hypersensitivity sites in ENCODE prostate cell lines. Bottom, positions of genes within the region, with genes on the positive and negative strands marked in green and purple, respectively. The horizontal axis represents genomic coordinates in the hg19 reference genome. **a**, rs1800057 (chromosome (chr) 11: 107643000–108644000). The index variant is a nonsynonymous SNP in *ATM*. **b**, rs1048169 (chr 9: 18556000–19557000). The index variant is located within the 3' UTR of *HAUS6* and is an eQTL for *HAUS6*. **c**, rs7968403 (chr 12: 64513000–65514000). The signal is centered on *RASSF3*, and the index variant is 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 (chr 17: 7303000–8304000). The signal implicates a cluster of highly correlated variants centered on *CHD3*. The index SNP is also an eQTL for three other more distantly located genes.**

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

Table 2 | Estimation of polygenic risk scores by using 147 prostate cancer-susceptibility variants

Risk category percentile ^a	Relative risk	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

^aPRS percentiles based on the cumulative score distributed among controls. The beta coefficients computed from the European overall meta-analysis were applied to determine the PRS risk among individuals in the OncoArray study.

associations were consistent with the observed PrCa–SNP associations, given that we assessed colocalization between the GWAS and eQTL SNPs. The TCGA data analysis did not 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 by using a series of disease-free controls ($n=9,090$; Methods). Among the 48 available loci, we observed a significant association for rs8093601 ($P=5.0 \times 10^{-4}$; Supplementary Table 13) after correction for multiple testing ($P=0.05/48=1.0 \times 10^{-3}$). This marker lies near *MBD2* (encoding methyl-CpG binding domain protein 2) and has not previously been 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 are presented in Supplementary Fig. 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 to PrCa susceptibility and progression, particularly aggressive PrCa^{34,35}. The index variant within this region is the missense variant rs1800057, exerting a modestly increased risk of PrCa (OR=1.16; $P=8.15 \times 10^{-9}$; G>C, p.Pro1054Arg; Fig. 2a). Although rs1800057 is designated ‘benign’ by ClinVar (see URLs), it has been suggested to be associated with a twofold-increased risk of early-onset PrCa in a small clinical series and has been found to be unassociated with morbidity after treatment³⁶. In addition to the *ATM* region, we identified missense variants at three separate loci: rs2066827 within *CDKN1B*, encoding a cyclin-dependent-kinase inhibitor that controls cell-cycle progression; rs33984059 within *RFX7*, encoding a transcription factor; and rs2277283 within *INCENP*, encoding a centromere-interacting protein.

rs1048169 at 9p22 is located in the 3′ UTR of *HAUS6* (Fig. 2b), which 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 found to be an eQTL for two genes, including *HAUS8*, which encodes another member of the augmin complex. These discoveries may implicate a potential role of augmin in PrCa susceptibility.

rs7968403 (OR=1.06; $P=3.38 \times 10^{-12}$; Fig. 2c) 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 to induce apoptosis through the p53 pathway³⁹. A PrCa-risk locus, ~100 kb away, within *RASSF6* has been

identified in a previous study¹¹. However, rs7968403 was also an eQTL for the distant *WIF1* (encoding WNT-inhibitory factor 1; Fig. 2c). *WIF1* inhibits Wnt signaling and is frequently downregulated in PrCa⁴⁰, whereas 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 to reduce tumor growth in a mouse xenograft model⁴¹. Both *RASSF3* and *WIF1* therefore are plausible mechanisms for the modulation of PrCa risk at this locus.

rs28441558 at 17p13 was the lead variant for a cluster of highly correlated SNPs centered on the *CHD3* gene (Fig. 2d). *CHD3* encodes an ATPase that forms a component of the nucleosome-remodeling and deacetylase (NuRD) histone deacetylase complex, which is involved in chromatin remodeling. NuRD plays an important role in regulating gene expression, as both a silencer and an activator of transcription, in addition to its roles in maintaining genomic integrity and in the DNA-damage response⁴². Alterations in NuRD function have been implicated in several cancer types and found to act in a highly complex manner^{43,44}. However, rs28441558 was also observed to be an eQTL for three genes: *LOC284023*, encoding a currently uncharacterized noncoding RNA transcript; *GUCY2D*, encoding a guanylate cyclase enzyme expressed predominantly in the retina; and *ALOX15B*, encoding a member of the lipoxygenase family of enzymes that produce fatty acid hydroperoxides. Although *CHD3* appears to be the most biologically plausible candidate gene for this locus, we cannot exclude roles of any of these genes.

Our pathway analysis based on mapping each SNP to the nearest gene (Methods) by 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 in Supplementary Table 15. The most significant pathway detected was PD-1 signaling (ID: 389948), ES=0.74, as defined by the REACTOME database (Supplementary Fig. 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 identified 63 novel PrCa-susceptibility variants, including strong candidate loci highlighting the DNA-repair and cell-cycle pathways. Previous studies have probably overestimated the effect estimates of PrCa loci as a result of the ‘winner’s curse’, thus yielding a biased familial relative risk (FRR) and polygenic risk score (PRS). Here, we applied a weighted Bayesian correction approach and demonstrated that our large sample size minimized the winner’s curse bias⁴⁶ (Methods and Supplementary Fig. 6). 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 PrCa^{47,48}, we demonstrated that our 147 loci captured 28.4% of the FRR (Supplementary Table 17). The 62 newly identified PrCa loci increased the FRR by 4.4%. On the basis of the assumption of a log-additive model, the estimated RR for PrCa relative to men in the twenty-fifth to seventy-fifth PRS percentiles (baseline group) was 5.71 (95% CI: 5.04–6.48) for men in the top first percentile of the PRS distribution and 2.69 (95% CI: 2.55–2.82) for individuals in the ninetieth to ninety-ninth percentiles of the PRS distribution (Table 2). The PRS score was positively associated with overall PrCa risk (OR=1.86; 95% CI: 1.83–1.89; Supplementary Table 18). Our novel associations highlight several biological pathways that warrant further investigation. The increased PRS can be used to improve the identification of men at high risk for PrCa and therefore inform PSA guidelines for screening and management to reduce the burden of over-testing.

URLs. ClinVar, <http://www.ncbi.nlm.nih.gov/clinvar/>.

Methods

Methods, including statements of data availability and any associated accession codes and references, are available at <https://doi.org/10.1038/s41588-018-0142-8>.

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Competing interests

The authors declare no competing interests.

Additional information

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Methods

Study subjects. A brief overview and study details for participating PrCa studies in the newly genotyped OncoArray project are provided in Supplementary Table 1 for men of European ancestry. All studies were approved by the appropriate ethics committees (as described in the references for each study listed in Supplementary Table 1), 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) consortium contributing both newly obtained genotyping data for the OncoArray and previous GWAS. Most 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 (for example, PSA at diagnosis and Gleason score) 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 to the overall meta-analysis¹². Supplementary Table 3 provides QC information by consortia (e.g., OncoArray project, UK GWAS, and so forth) for both samples and SNPs. After removal of 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 effects of genetic variation on PrCa disease aggressiveness. Supplementary Table 4 describes the analysis title, outcome and reference groups, and the statistical model used. Several classification schemes (low aggressiveness, intermediate aggressiveness, and so forth) were implemented to better assess the spectrum of genetic involvement. All classification schemes incorporated the diagnostic clinical features PSA, tumor stage, and Gleason score. To compare the results with those from previous PrCa aggressive analyses¹² 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 from the PrCa GWAS consortium are provided in Supplementary Table 5. Furthermore, we analyzed Gleason score as a continuous variable.

OncoArray SNP selection. The NCI GAME-ON consortium (<http://epi.grants.cancer.gov/gameon/>) provided SNPs to be included in the Illumina OncoArray. Approximately 50% of the OncoArray was a compilation of SNP lists by the GAME-ON disease consortium of cancer (breast, colorectal, lung, ovarian, and prostate), a common set of variants for common risk regions, other related traits (BMI, age at menarche, and so forth), pharmacogenetics, and candidates³⁰. The remaining content of the OncoArray was selected as a 'GWAS backbone' (Illumina HumanCore), which aimed to provide high coverage for most common variants through imputation. Approximately 79,000 SNPs were selected specifically for their relevance to PrCa, on the basis of prior evidence of association with overall or subtype-specific disease, fine-mapping of known PrCa regions, and candidate submissions (survival, exome sequencing, and so forth). To maximize the efficiency of the array, cancer-specific candidate lists were merged to remove redundant genetic variation³⁰.

Genotype calling and quality control. Details of the genotype calling and QC for the iCOGS and GWAS have been described elsewhere^{11–28}.

Of the 568,712 variants selected for genotyping on the OncoArray, 533,631 were successfully manufactured on the array (including 778 duplicate probes). OncoArray genotyping of ELLIPSE studies was conducted at five sites (Cambridge, CIDR, Copenhagen, USC, and NCI). Details of the genotype calling for the OncoArray have been described in more detail elsewhere³⁰. Briefly, we developed a single calling pipeline that was applied to more than 500,000 samples across the GAME-ON consortium. An initial cluster file was generated by using 56,284 samples selected from all major genotyping centers and ancestries, with the Gentrain2 algorithm. Variants likely to have problematic clusters were selected for manual inspection on the basis of the following criteria: call rate <99%, MAF <0.001, poor Illumina intensity and clustering metrics, deviation from the MAF observed in the 1KGP, by using the criterion $\frac{(|p_1 - p_0| - 0.01)^2}{(p_1 + p_0)(2 - p_1 - p_0)} > C$, where p_0 and p_1 are the minor frequencies

in the 1KGP and OncoArray datasets, respectively, and $C = 0.008$. This procedure 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 QC 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. 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 for which 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 after 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 s.d. from the mean for the reported ancestry). 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 through 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, on the basis of the first two principal components. Of the 78,182 samples genotyped (regardless of ancestry), the final dataset consisted of 74,849 samples, of which 46,939 PrCa cases and 27,910 disease-free controls (Supplementary Table 3), after exclusion of overlap samples, were meta-analyzed with previous studies.

Imputation. We imputed genotypes for ~70 million SNPs for all samples by using the October 2014 (Phase 3) release of the 1KGP data as the reference panel. We imputed the OncoArray and GWAS datasets through a two-stage imputation approach, using SHAPEIT³¹ for phasing and IMPUTE2 (ref. ³²) for imputation. The imputation was performed in 5-Mb nonoverlapping 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 $r^2 < 0.3$, thus leaving a total of 20,370,935 SNPs 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% and 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, with adjustment for principal components and study-relevant covariates through 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, because additional components did not further decrease inflation in the test statistics.

OR estimates were derived with either SNPTEST (https://mathgen.stats.ox.ac.uk/genetics_software/snpstest/snpstest.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 in METAL³⁰. All statistical tests conducted were two sided.

Our analyses included overall PrCa and several clinically relevant strata. These strata comprised: (i) high versus low aggressive PrCa; (ii) high versus low/intermediate aggressive PrCa; (iii) advanced versus nonadvanced PrCa; (iv) advanced PrCa versus controls; (v) early-onset PrCa (≤55 years) versus controls; and (iv) Gleason score (Supplementary Tables 4 and 5). We defined low aggressive as tumor stage ≤T1 and Gleason score ≤6 and PSA <10 ng/mL; intermediate aggressive as tumor stage T2 or Gleason score = 7 or PSA 10–20 ng/mL; high aggressive as tumor stage T3/T4 or N1 or M1, or Gleason score ≥8 or PSA >20 ng/mL; and advanced as either metastatic disease, Gleason score ≥8, PSA >100 or PrCa-related death (Supplementary Table 4).

Definition of newly associated loci. 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 $P < 5 \times 10^{-8}$ 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 was assessed on the basis of IMPUTE2 imputation r^2 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 r^2 between the new and the previously known SNP was <0.2. For novel PrCa associations for which the variant was imputed in the OncoArray study sample series and had an imputed quality score <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 after reimputation in the remaining 1KGP samples.

Reliability of imputation. Novel SNPs with an IMPUTE2 $r^2 < 0.80$ among the OncoArray sample series (Supplementary Table 8) were flagged for further investigation to minimize the probability of false positives. First, we examined LD plots (<http://locuszoom.org/>) for poorly imputed SNPs (±500 kb), 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 to 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 Finnish individuals) 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 after QC. This procedure ensured that the same imputation input was used in the overall imputation. The 259 individuals were imputed by using 2,245 individuals as the reference panel. A 5-Mb segment of the genome was selected on the basis of the target SNP (±250 Mb). SHAPEIT2 was used for prephasing, and IMPUTE2 was used 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 the correlation of the imputation with the true genotypes.

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► Experimental design

1. Sample size

Describe how sample size was determined.

We recruited all available population studies with adequate DNA samples and eligible to deposit data into a public database. Our new sample series genotyped with OncoArray includes over 73,000 samples.

2. Data exclusions

Describe any data exclusions.

We excluded all samples that performed poorly with respect to genotyping. We also limited our analyses to individuals of European ancestry to avoid the potential for spurious associations.

3. Replication

Describe whether the experimental findings were reliably reproduced.

We meta-analyzed our new genotyped samples with previous studies. We set a stringent statistical threshold to minimize false positive results.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

We recruited individuals based on presence or absence of prostate cancer. Covariate information was collected and controlled in the regression models (i.e. age, recruitment center, country, etc.).

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Blinding was not necessary in our study. This was a population-based observation study.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or the Methods section if additional space is needed).

n/a Confirmed

- | | | |
|-------------------------------------|-------------------------------------|--|
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | The <u>exact</u> sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.) |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly. |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | A statement indicating how many times each experiment was replicated |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section) |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as an adjustment for multiple comparisons |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | The test results (e.g. p values) given as exact values whenever possible and with confidence intervals noted |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | A summary of the descriptive statistics, including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range) |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Clearly defined error bars |

See the web collection on [statistics for biologists](#) for further resources and guidance.

► Software

Policy information about [availability of computer code](#)

7. Software

Describe the software used to analyze the data in this study.

All statistical packages used are publicly available and referenced in the manuscript. These include IMPUTE2, SHAPEIT, SNPTEST, and R.

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* [guidance for providing algorithms and software for publication](#) may be useful for any submission.

► Materials and reagents

Policy information about [availability of materials](#)

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

No unique materials were used.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

No antibodies were used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

No eukaryotic cell lines were used.

b. Describe the method of cell line authentication used.

No eukaryotic cell lines were used.

c. Report whether the cell lines were tested for mycoplasma contamination.

No eukaryotic cell lines were used.

d. If any of the cell lines used in the paper are listed in the database of commonly misidentified cell lines maintained by [ICLAC](#), provide a scientific rationale for their use.

No commonly misidentified cell lines were used.

► Animals and human research participants

Policy information about [studies involving animals](#); when reporting animal research, follow the [ARRIVE guidelines](#)

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

No animals were used.

Policy information about [studies involving human research participants](#)

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Our study was limited to males (due to disease). Cases were individuals diagnosed with prostate cancer. Controls were prostate cancer free at time of recruitment. All baseline information such as age, country of residence were collected. Average age and clinical features (where applicable) are reported in the manuscript by epidemiological study. Genotype summaries are reported.

The OncoArray genotype data and relevant covariate information (i.e. ethnicity, country, principal components, etc.) generated during this study are currently being deposited into dbGAP for access (Accession #: phs001391.v1.p1; the submission is still underway). 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 currently 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/>).