

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

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Genome-wide association studies (GWAS) and fine-mapping efforts to date 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 ($P < 5.0 \times 10^{-8}$) with PrCa, and one locus significantly associated with early-onset PrCa (≤ 55 years). Our findings include missense variants rs1800057 (OR = 1.16; $P = 8.2 \times 10^{-9}$; G>C, Pro1054Arg) in *ATM* and rs2066827 (OR = 1.06; $P = 2.3 \times 10^{-9}$; 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% percentile (RR = 2.69; 95%CI: 2.55-2.82) and 1% percentile (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.

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 history^{8,9}, highlight the contribution of genetics in PrCa etiology¹⁰. Our previous work, utilizing a multiplicative model, estimated that 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 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 and 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** and **Supplementary Table 3**). Genotypes were phased and imputed to the cosmopolitan panel of the 1000 Genomes Project (1KGP; June 2014 release) using SHAPEIT³¹ and IMPUTEv2³² software (Online 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 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 (Online 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 Gleason score where linear regression was utilized. The genotype dosages 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 one with early-onset ($P < 5.0 \times 10^{-8}$) in the meta-analysis (**Supplementary Fig. 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 $r^2 > 0.80$ 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 quality control assessment (Online Methods). After reviewing the LD plots and the imputation QC, we determined that loci rs6602880 and rs144166867 are likely 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 (**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 ($P < 5 \times 10^{-8}$) 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 ($P < 1.0 \times 10^{-3}$). 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 ($r^2 = 0.54$) associated with overall disease. The early-onset marker rs77777548 is independent of novel and known PrCa risk loci. However, the marker is relatively rare (EAF < 0.02), indicated as monomorphic in 1KGP, and has 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 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 that we assessed co-localization 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 ($P = 5.0 \times 10^{-4}$; **Supplementary Table 13**) after correcting for multiple testing ($P = 0.05/48 = 1.0 \times 10^{-3}$). 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 are 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 to PrCa susceptibility and progression, particularly aggressive PrCa^{34,35}. The index variant within this region is the missense variant rs1800057, exerting a modest increased risk of PrCa (OR = 1.16; $P = 8.15 \times 10^{-9}$; G>C, Pro1054Arg; **Fig. 2a**). 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 at 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* (**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 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.

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 induce apoptosis through the p53 pathway³⁹. A PrCa risk locus, ~100 kb away, within the *RASSF6* family member was previously identified¹¹. However, rs7968403 was also an eQTL for the distant *WIF1* (WNT inhibitory factor 1) gene (**Fig. 2c**). *WIF1* inhibits Wnt signaling and is frequently down regulated in PrCa⁴⁰, while 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 (**Fig. 2d**). *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 manner^{43,44}. 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 hydroperoxides. 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 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 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 that our large sample size minimizes the “winner’s curse” bias (Online Methods and **Supplementary Fig. 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 PrCa^{47,48}, we demonstrate that our 147 loci capture 28.4% of the FRR (**Supplementary Table 17**). The 62 newly 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% percentile 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 warrant further investigation. 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.

URLs. The Profile Study Steering Committee, <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>

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COMPETING INTERESTS

The authors declare no competing 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, where 23 novel variants were identified¹². 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 newly identified prostate cancer risk loci ($n = 74,849$ biologically independent samples). (a-d) Top panels depict Manhattan plots of variant $-\log_{10} P$ 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, $r^2 > 0.8$; 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 panels depict the 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 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 *ATM*. (b) rs1048160 (chr9:18556000-19557000). The index variant is located within the 3'UTR of *HAUS6* and is an eQTL for *HAUS6*. (c) rs7968403 (chr12:64513000-65514000). The signal is centered on *RASSF3*, 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 on *CHD3*. The index SNP is also an eQTL for three other more distantly located genes.

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	<i>p</i> ^f
Novel loci associated with overall prostate cancer									
rs56391074	0.329	1p22.3	88210715	<i>RP11-60A14.1</i>	AT/A	0.38	1.05	1.03-1.06	1.7E-08
rs34579442	0.316	1q21.3	153899900	<i>DENND4B</i>	C/CT	0.34	1.07	1.05-1.09	4.5E-14
rs62106670	0.400	2p25.1	8597123	<i>AC011747.3</i>	T/C	0.38	1.05	1.04-1.07	7.1E-09
rs74702681	0.024	2p14	66652885	<i>MEIS1-AS3</i>	T/C	0.02	1.17	1.11-1.23	2.0E-09
rs11691517	0.750	2q13	111893096	<i>BCL2L11</i>	T/G	0.74	1.07	1.05-1.08	3.5E-12
rs34925593	0.481	2q31.1	174234547	<i>CDCA7</i>	C/T	0.48	1.05	1.03-1.07	2.8E-08
rs59308963	0.726	2q33.1	202123479	<i>CASP8</i>	T/TATTCTGTC	0.73	1.05	1.03-1.07	2.4E-08
rs1283104	0.407	3q13.12	106962521	<i>DUBR</i>	G/C	0.38	1.05	1.03-1.07	8.8E-09
rs182314334	0.888	3q25.1	152004202	<i>MBNL1</i>	T/C	0.90	1.09	1.06-1.12	4.1E-11
rs142436749	0.012	3q26.2	169093100	<i>MECOM</i>	G/A	0.01	1.25	1.16-1.34	4.7E-09
rs10793821	0.580	5q31.1	133836209	<i>RNU6-456P</i>	T/C	0.57	1.05	1.04-1.07	5.4E-11
rs76551843	0.991	5q35.1	169172133	<i>DOCK2</i>	A/G	0.99	1.31	1.19-1.44	1.7E-08
rs4976790	0.096	5q35.3	177968915	<i>COL23A1</i>	T/G	0.11	1.08	1.05-1.10	6.7E-09
rs12665339	0.148	6p21.33	30601232	<i>ATAT1</i>	G/A	0.17	1.06	1.04-1.08	5.6E-09
rs9296068	0.645	6p21.32	32988695	<i>HLA-DOA</i>	T/G	0.65	1.05	1.03-1.07	1.3E-08
rs9469899	0.356	6p21.31	34793124	<i>UHRF1BP1</i>	A/G	0.36	1.05	1.03-1.07	5.3E-09
rs4711748	0.232	6p21.1	43694598	<i>RP1-261G23.5</i>	T/C	0.23	1.05	1.03-1.07	3.4E-08
rs527510716	0.251	7p22.3	1944537	<i>MAD1L1</i>	C/G	0.24	1.06	1.04-1.08	4.9E-08
rs11452686	0.567	7p21.1	20414110	<i>ITGB8</i>	T/TA	0.56	1.05	1.03-1.07	7.8E-09
rs17621345	0.758	7p14.1	40875192	<i>SUGCT</i>	A/C	0.74	1.07	1.05-1.09	6.7E-14
rs1048169	0.367	9p22.1	19055965	<i>HAUS6</i>	C/T	0.38	1.06	1.05-1.08	6.5E-14
rs10122495	0.296	9p13.3	34049779	<i>RN7SKP114</i>	T/A	0.31	1.05	1.03-1.07	1.3E-08

rs1182	0.258	9q34.11	132576060	<i>TOR1A</i>	A/C	0.22	1.06	1.04-1.08	1.1E-09
rs141536087	0.166	10p15.3	854691	<i>LARP4B</i>	GCGCA/G	0.15	1.08	1.06-1.11	9.0E-13
rs1935581	0.605	10q23.31	90195149	<i>RNLS</i>	C/T	0.63	1.05	1.03-1.07	6.5E-09
rs7094871	0.540	10q25.2	114712154	<i>TCF7L2</i>	G/C	0.54	1.04	1.03-1.06	4.8E-08
rs1881502	0.193	11p15.5	1507512	<i>MOB2</i>	T/C	0.19	1.06	1.04-1.08	7.4E-09
rs61890184 ^B	0.088	11p15.4	7547587	<i>PPFIBP2</i>	A/G	0.12	1.07	1.05-1.10	6.6E-09
rs547171081	0.468	11p11.2	47421962	<i>RP11-750H9.5</i>	CGG/C	0.47	1.05	1.03-1.07	3.4E-08
rs2277283	0.300	11q12.3	61908440	<i>INCENP</i>	C/T	0.31	1.06	1.04-1.08	3.0E-10
rs12785905	0.051	11q13.2	66951965	<i>KDM2A</i>	C/G	0.05	1.12	1.08-1.17	7.8E-09
rs11290954	0.688	11q13.5	76260543	<i>C11orf30</i>	AC/A	0.68	1.06	1.05-1.08	7.4E-13
rs1800057	0.031	11q22.3	108143456	<i>ATM</i>	G/C	0.02	1.16	1.10-1.22	8.1E-09
rs138466039	0.009	11q24.2	125054793	<i>PKNOX2</i>	T/C	0.01	1.32	1.22-1.44	2.0E-11
rs878987	0.143	11q25	134266372	<i>B3GAT1</i>	G/A	0.15	1.07	1.04-1.09	4.8E-08
rs2066827	0.757	12p13.1	12871099	<i>CDKN1B</i>	T/G	0.76	1.06	1.04-1.08	2.3E-09
rs10845938	0.554	12p13.1	14416918	<i>RNU6-491P</i>	G/A	0.55	1.06	1.04-1.08	9.8E-13
rs7968403	0.655	12q14.2	65012824	<i>RASSF3</i>	T/C	0.64	1.06	1.04-1.08	3.4E-12
rs5799921	0.697	12q21.33	90160530	<i>RNU6-148P</i>	GA/G	0.68	1.06	1.04-1.08	7.0E-12
rs7295014	0.342	12q24.33	133067989	<i>FBRSL1</i>	G/A	0.35	1.05	1.04-1.07	9.5E-10
rs1004030	0.581	14q11.2	23305649	<i>MMP14</i>	T/C	0.58	1.05	1.03-1.06	1.5E-08
rs11629412	0.582	14q13.3	37138294	<i>PAX9</i>	C/G	0.58	1.06	1.04-1.08	2.3E-12
rs4924487	0.836	15q15.1	40922915	<i>CASC5</i>	C/G	0.81	1.06	1.04-1.09	1.3E-08
rs33984059	0.982	15q21.3	56385868	<i>RFX7</i>	A/G	0.98	1.19	1.12-1.27	1.1E-08
rs112293876	0.280	15q22.31	66764641	<i>MAP2K1</i>	C/CA	0.29	1.06	1.04-1.08	3.5E-10
rs11863709	0.945	16q21	57654576	<i>GPR56</i>	C/T	0.96	1.16	1.11-1.21	1.8E-11
rs201158093	0.435	16q23.3	82178893	<i>RP11-510J16.5</i>	TAA/TA	0.44	1.05	1.03-1.07	9.1E-09
rs28441558	0.050	17p13.1	7803118	<i>CHD3</i>	C/T	0.05	1.16	1.12-1.20	1.0E-16
rs142444269	0.798	17q11.2	30098749	<i>RP11-805L22.3</i>	C/T	0.78	1.07	1.05-1.09	3.2E-10

rs2680708	0.623	17q22	56456120	<i>RNF43</i>	G/A	0.61	1.05	1.03-1.06	1.6E-08
rs8093601	0.459	18q21.2	51772473	<i>MBD2</i>	C/G	0.44	1.05	1.03-1.06	2.3E-08
rs28607662	0.085	18q21.2	53230859	<i>TCF4</i>	C/T	0.10	1.08	1.05-1.11	2.8E-08
rs12956892	0.300	18q21.32	56746315	<i>OACYLP</i>	T/G	0.30	1.05	1.03-1.07	7.7E-09
rs533722308	0.390	18q21.33	60961193	<i>BCL2</i>	CT/C	0.42	1.05	1.03-1.07	1.2E-08
rs10460109	0.414	18q22.3	73036165	<i>TSHZ1</i>	T/C	0.42	1.05	1.03-1.06	3.5E-08
rs11666569	0.728	19p13.11	17214073	<i>MYO9B</i>	C/T	0.71	1.05	1.03-1.07	8.2E-09
rs118005503	0.912	19q12	32167803	<i>THEG5</i>	G/C	0.91	1.09	1.06-1.13	7.3E-09
rs61088131	0.848	19q13.2	42700947	<i>POU2F2</i>	T/C	0.82	1.06	1.04-1.09	8.8E-09
rs11480453	0.641	20q11.21	31347512	<i>DNMT3B</i>	C/CA	0.60	1.05	1.03-1.06	3.2E-08
rs6091758	0.465	20q13.2	52455205	<i>BCAS1</i>	G/A	0.47	1.07	1.06-1.09	6.4E-18
rs9625483	0.026	22q12.1	28888939	<i>TTC28</i>	A/G	0.03	1.14	1.09-1.20	2.4E-08
rs17321482	0.873	23p22.2	11482634	<i>ARHGAP6</i>	C/T	0.87	1.07	1.05-1.09	2.1E-13
Novel locus associated with early-onset									
rs138004030	0.920	6q27	170475879	<i>LOC154449</i>	G/A	0.91	1.27	1.17-1.38	2.9E-08

^aRisk allele frequency in 1000 Genomes Project Europeans.

^bRisk allele/Reference allele.

^cRisk allele frequency.

^dOdds ratio.

^e95% confidence interval

^f*P*-values are generated from a likelihood ratio test.

^gRegion previously reported by Wang *et al.*⁴⁹, rs12791447; rs61890184-rs12791447 r^2 (EUR) = 0.41.

Table 2 Polygenic Risk Score (PRS) estimation using 147 prostate cancer susceptibility variants

Risk category percentiles^a	RR^b	95% CI^c
<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

^aPolygenic Risk Score (PRS) 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.

^bRelative risk.

^c95% confidence intervals.

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** 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-analysis¹². **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 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 by PrCa GWAS consortium are provided in **Supplementary Table 5**. Furthermore, we analyzed 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 candidates³⁰. 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). To maximize 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 quality control (QC) for the iCOGS and GWAS are described elsewhere¹¹⁻²⁸.

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 elsewhere³⁰. 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 < 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: $\frac{(|p_1 - p_0| - 0.01)^2}{((p_1 + p_0)(2 - p_1 - p_0))} > C$, where p_0 and p_1 are the minor frequencies in the 1KGP and OncoArray datasets, respectively, and $C = 0.008$. This 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. 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-analyzed 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 SHAPEIT³¹ for phasing and IMPUTEv2³² for imputation. The imputation was performed in 5-Mb 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 $r^2 < 0.3$, 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 \geq 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 SNPTTEST (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 METAL⁵⁰. All statistical tests conducted were two-sided.

Our analyses included overall PrCa and several clinically relevant strata. These included: (i) high vs. low aggressive PrCa; (ii) high vs. low/intermediate aggressive PrCa; (iii) advanced vs. non-advanced PrCa; (iv) advanced PrCa vs. controls; (v) early-onset PrCa (≤ 55 yrs) vs. controls; and (iv) Gleason score (**Supplementary Tables 4 and 5**). We defined low aggressive as tumor stage $\leq T1$ 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 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 by 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 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 $r^2 < 0.80$ 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 (+/- 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 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 r^2 was < 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 ($P < 1 \times 10^{-3}$) 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

$$\frac{\lambda_k(\log I_k)}{(\log I_0)}$$

where λ_0 is the observed familial risk to first degree relatives of PrCa cases^{47,48}, assumed to be 2.5, and λ_k is the familial relative risk due to locus k, given by:

$$\lambda_k = \frac{p_k r_k^2 + q_k}{(p_k r_k + q_k)^2}$$

where p_k is the frequency of the risk allele for locus k, $q_k = 1 - p_k$ and r_k 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:

$$Score_j = \sum_{i=1}^N \beta_i g_{ij}$$

where N is the number of SNPs, g_{ij} is the allele dose at SNP _{i} for individual j , and β_i is the per-allele log-odds ratio of SNP _{i} .

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 study⁵¹. 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 3.4)⁴⁶. Specifically, we place a normal prior distribution on MLE effect estimates of the form $\beta_m \sim N(\beta_{Cor}, \tau^2)$. Here, β_m is the log odds ratio from the overall meta-analysis; β_{Cor} 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 $\tau = |\hat{\beta}_m - \beta_{Cor}|$.

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 s.d.) 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 Mb (upstream/downstream) from the transcription start site (TSS) of each gene.

Gene Set Enrichment Analyses. The file Human_GOBP_AllPathways_no_GO_iaa_September_01_2016_symbol.gmt (http://baderlab.org/EM_GeneSets), from the GeneSets database⁵², was used for all analyses. This database contains pathways from Reactome⁵³, NCI Pathway Interaction Database⁵⁴, GO (Gene Ontology) biological process⁵⁵, HumanCyc⁵⁶, MSigdb⁵⁷, NetPath⁵⁸ and Panther⁵⁹. 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 genes were considered.

Gene information (hg19) was downloaded from the ANNOVAR⁶⁰ website (<http://www.openbioinformatics.org/annovar/>). SNPs were mapped to the nearest gene within 500-kb 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 gene^{61,62}, based on the combined European meta-analysis (previous GWAS and OncoArray).

The gene set enrichment analysis (GSEA)⁵² algorithm, as implemented in the GenGen package (<http://gengen.openbioinformatics.org/en/latest/>)^{62,63} was used to perform pathway analysis. Briefly, the algorithm calculates an enrichment score (ES) for each pathway based on a weighted Kolmogorov-Smirnov statistic⁶³. 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 $P < 5 \times 10^{-8}$ were retained for subsequent analysis. An enrichment map was created using the Enrichment Map (EM) v 2.1.0 app⁵² in Cytoscape v3.40⁶⁴, applying force directed layout, weighted mode. We restricted our pathway analysis those with an $ES \geq 0.50$ to ensure a true positive rate > 0.20 and a false positive rate < 0.15.

Life Sciences Reporting Summary. Further information on experimental design is available in the **Life Sciences Reporting Summary**.

Data availability. The OncoArray genotype data and relevant covariate information (*i.e.* ethnicity, country, principal components, etc.) generated during this study have been deposited in dbGaP (phs001391.v1.p1). 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 data¹² are available in dbGaP (phs001081.v1.p1). The complete meta-analysis summary associations statistics are publicly available at the PRACTICAL website (<http://practical.icr.ac.uk/blog/>).

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Editorial summary:

A large meta-analysis combining genome-wide and custom high-density genotyping array data identifies 63 new susceptibility loci for prostate cancer, enhancing fine-mapping efforts and providing insights into the underlying biology.