**The American Journal of Human Genetics, Volume *110***

## Supplemental information

# Combined CRISPRi and proteomics screening reveal a cohesin-CTCF-bound allele contributing to increased expression of *RUVBL1* and prostate cancer progression

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## Supplementary Figures

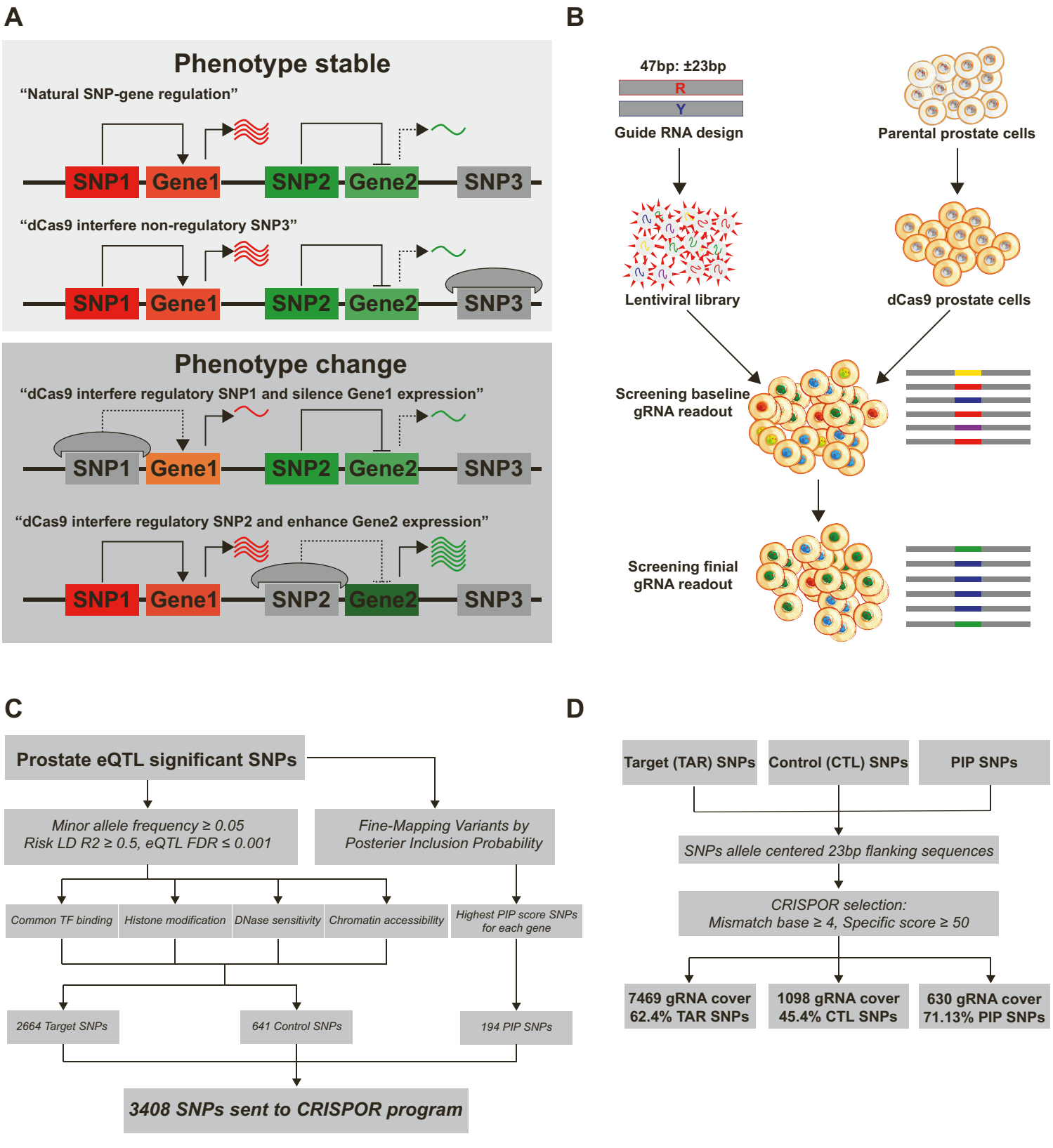
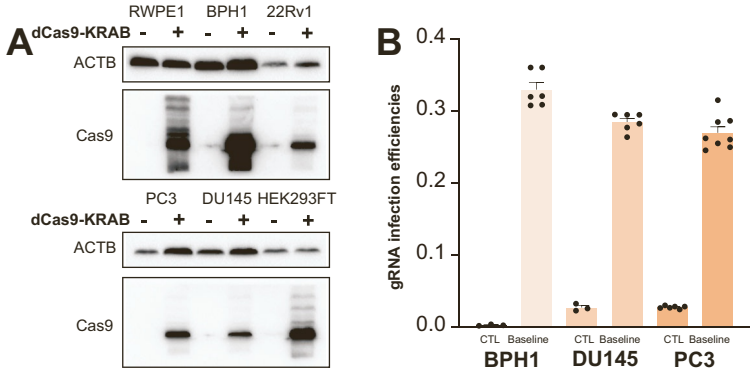
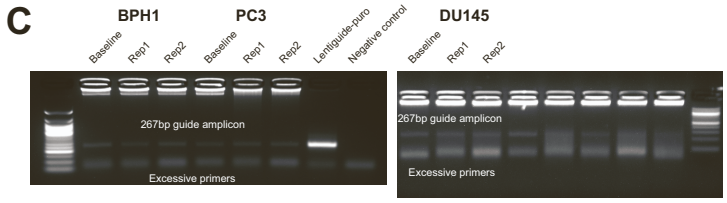



**Figure S1. Overall CRISPRi screening projection and design. A.** Rationale for phenotype oriented CRISPRi-SNPs-seq screening. **B.** CRISPRi screening procedures in dCas9 stable prostate cell lines. **C.** Candidate eQTL risk SNPs selection before gRNA design. **D.** gRNA searching details within candidate SNPs by CRISPOR program.



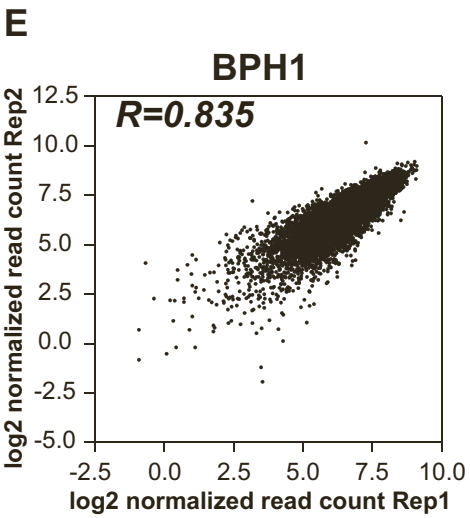


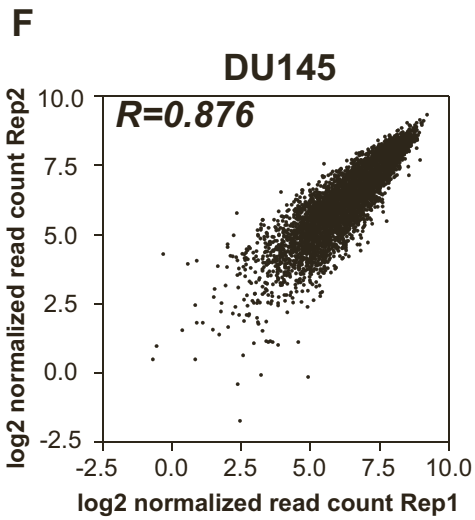





D

| | Total read count | Perfect guide count | Skew ratio |
|---|---|---|---|
| Lentiguide puro | 24.9M | 17.8M | 5.32 |
| BPH1-Baseline | 24.5M | 17.3M | 5.40 |
| BPH1-Rep1 | 28.6M | 20.7M | 6.85 |
| BPH1-Rep2 | 32.2M | 22.9M | 7.17 |
| DU145-Baseline | 37.9M | 27.7M | 5.93 |
| DU145-Rep1 | 32.5M | 22.6M | 6.71 |
| DU145-Rep2 | 62.7M | 43.9M | 6.82 |
| PC3-Baseline | 42.6M | 29.5M | 5.47 |
| PC3-Rep1 | 31.7M | 22.6M | 7.27 |
| PC3-Rep2 | 33.6M | 26.8M | 6.98 |



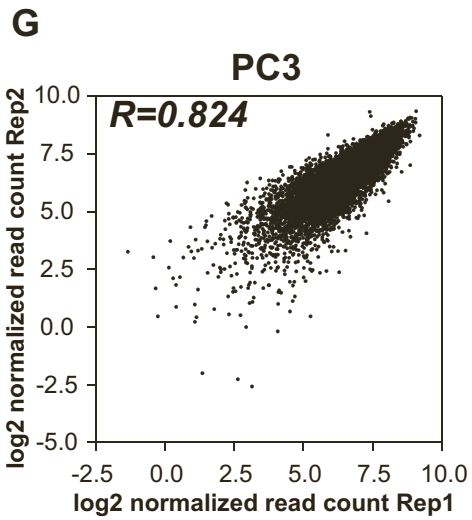




**Figure S2. CRISPRi screening quality control. A.** Western blots of Cas9 protein in dCas9 stable cell lines. **B.** Functional titration of lentiGuide-Puro virus to ensure low MOI integration. Each dot represents a titration technical replicate and the error bar represent the standard error across all measurement. **C.** Gel image of gRNA readout amplicon from each screening after PCR. The template gDNA amount for each sample is equivalent to extraction from at least 5 million cells. **D.** gRNA read count summary after count_spacers.py quantification. **E-G.** Reproducibility of technical replicates in BPH1 (**E**), DU145 (**F**), and PC3 (**G**) cells.

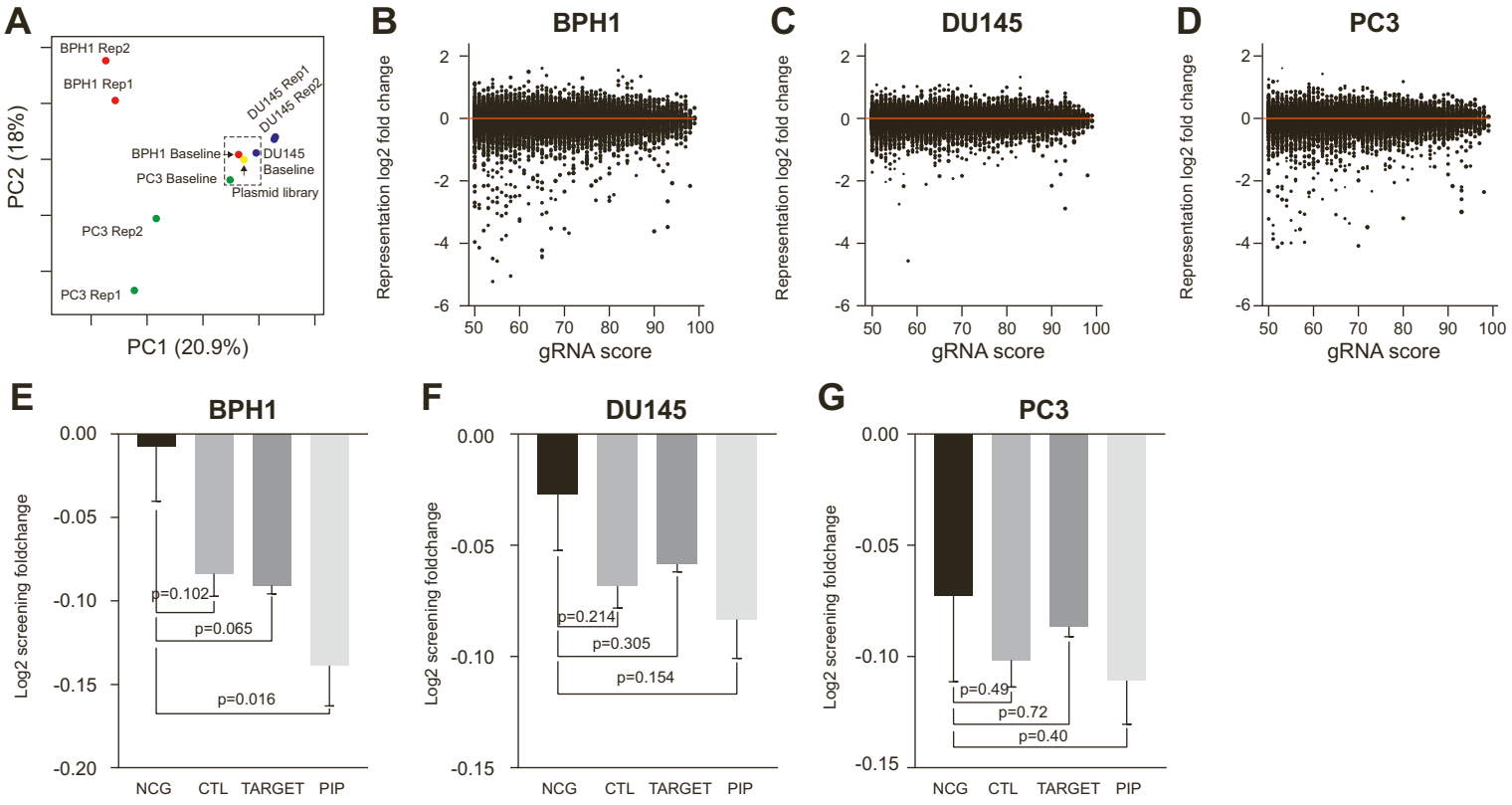



**Figure S3. Screening hit characterization. A.** PCA analysis of raw gRNA count in lentiGuide-Puro plasmid and each screening sample. **B-D.** Correlation between average gRNA foldchange and specificity score in BPH1 (**B**), DU145 (**C**), and PC3 (**D**) cells. **E-G.** gRNA foldchange comparison between predefined categories in BPH1 (**E**), DU145 (**F**), and PC3 (**G**) cells. The gRNA foldchange was calculated by averaging between the 2 biological replicates. The error bar represented the standard error of gRNA foldchange within each category.

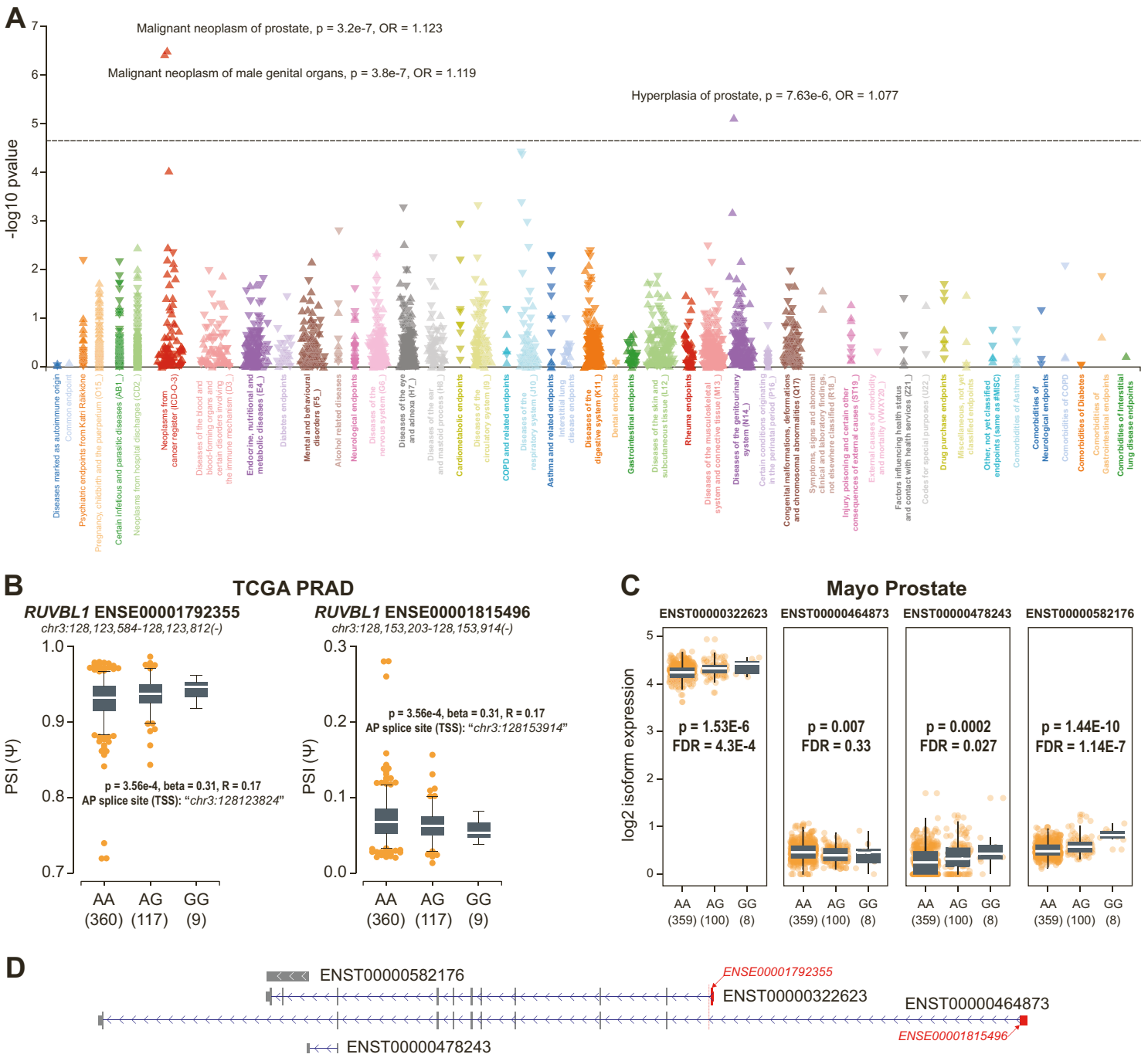



**Figure S4. Prostate cancer risk and *RUVBL1* splicing associations with rs60464856 in existing GWAS and RNA-seq cohorts. A.** PheWAS results between rs60464856 and 2,202 endpoints in the FinnGen study (n = 342,499). **B.** Associations between *RUVBL1* alternative promoter (AP) percent Spliced In (PSI, Ψ) values and rs60464856 genotype. The ENSEMBL id indicated the first exon used by the corresponding AP event. The Ψ values were obtained from TCGA SpliceSeq databases. The pvalues were retrieved from the TCGA Pan-Cancer Splicing QTL databases. **C.** Associations between *RUVBL1* isoform expression and rs60464856 genotype in Mayo prostate cohort. The pvalue and FDR were calculated by MatrixEQTL package. **D.** Demonstration of *RUVBL1* gene structure in relation to the exons and isoforms discussed in the above plots.

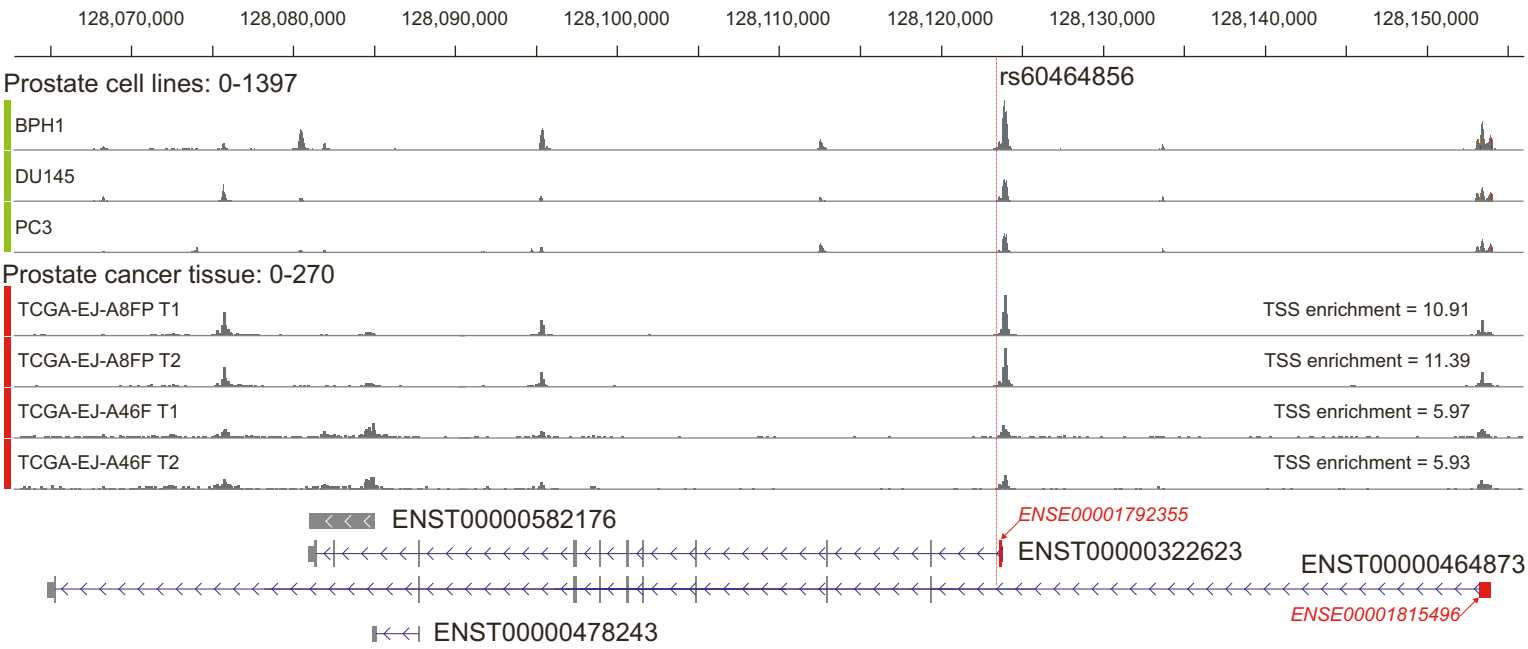
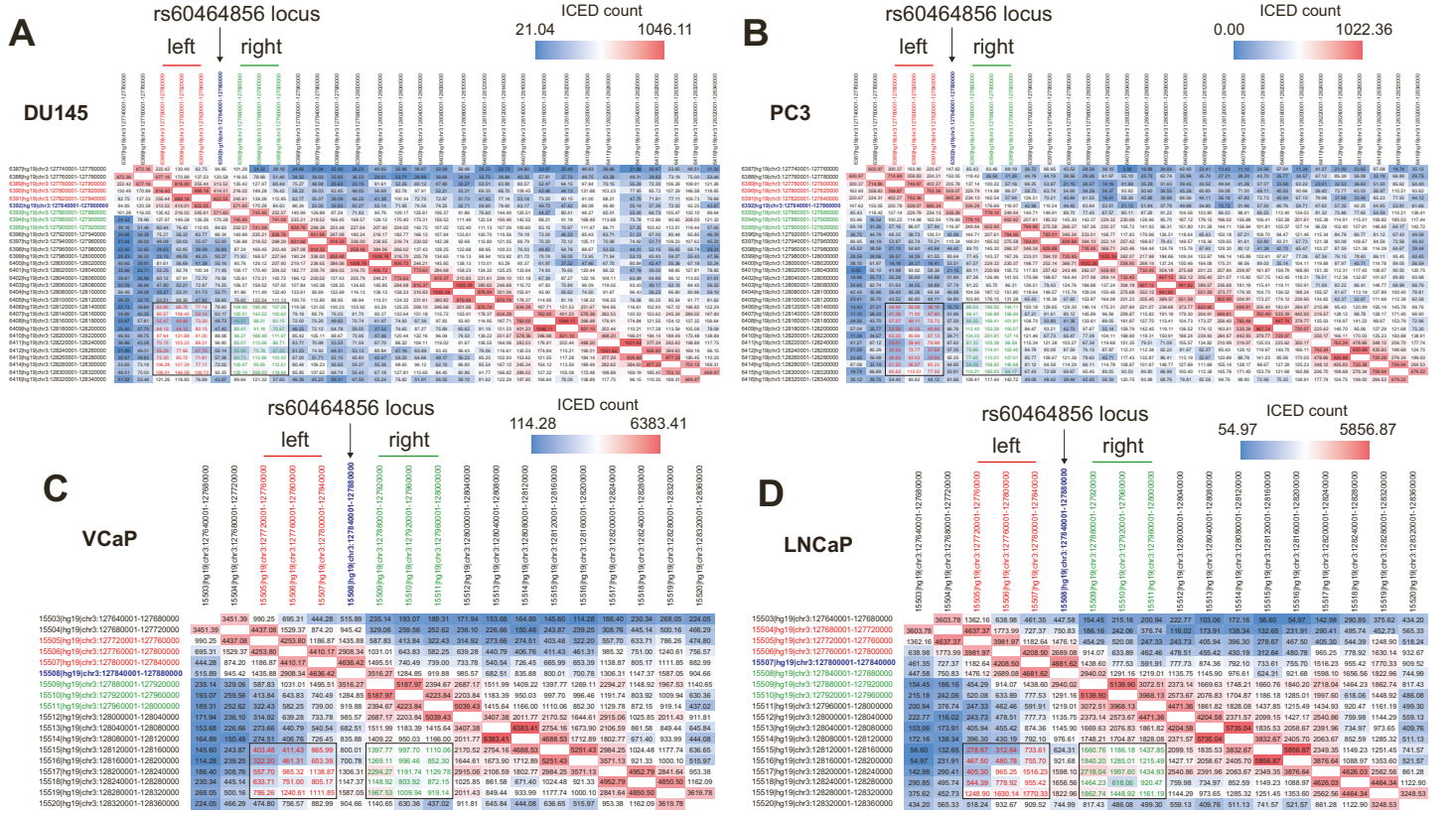



**Figure S5. Chromatin accessibility surrounding rs60464856 locus in prostate cell lines and prostate cancer tissue.** The ATAC-seq data for prostate cell lines and TCGA prostate cancer cohorts were visualized in the IGV browser. The TSS enrichment scores were obtained from the TCGA chromatin accessibility landscape: https://gdc.cancer.gov/about-data/publications/ATACseq-AW. Two prostate cancer samples with minimal (TCGA-EJ-A46F) and maximum (TCGA-EJ-A8FP) enrichment scores were chosen to bona fide present the consistent accessible profiling surrounding the rs60464856 locus in prostate cancer genome.




**E**

| Bin count on either side | PC3(L/R)/DU145(L/R) One | Two | Three | Four | | VCaP(L/R)/LNCaP(L/R) One | Two | Three | Four |
|---|---|---|---|---|---|---|---|---|---|
| chr3:128100001-128120000 | 0.68 | 0.64 | 0.66 | 0.78 | chr3:128080001-128120000 | 1.14 | 1.36 | 1.30 | 1.23 |
| chr3:128120001-128140000 | 0.79 | 0.78 | 0.72 | 0.67 | chr3:128120001-128160000 | 1.08 | 1.22 | 1.37 | 1.33 |
| chr3:128140001-128160000 | 1.10 | 0.76 | 0.58 | 0.62 | | | | | |
| chr3:128160001-128180000 | 0.66 | 0.80 | 0.83 | 0.74 | chr3:128160001-128200000 | 1.25 | 1.24 | 1.17 | 1.05 |
| chr3:128180001-128200000 | 0.37 | 0.43 | 0.37 | 0.36 | | | | | |
| chr3:128200001-128220000 | 0.54 | 0.56 | 0.56 | 0.55 | chr3:128200001-128240000 | 0.89 | 1.16 | 1.24 | 1.09 |
| chr3:128220001-128240000 | 0.95 | 0.77 | 0.63 | 0.66 | | | | | |
| chr3:128240001-128260000 | 0.57 | 0.60 | 0.51 | 0.63 | chr3:128240001-128280000 | 1.07 | 0.96 | 1.02 | 0.93 |
| chr3:128260001-128280000 | 0.39 | 0.57 | 0.54 | 0.64 | | | | | |
| chr3:128280001-128300000 | 2.14 | 0.71 | 0.57 | 0.55 | chr3:128280001-128320000 | 0.59 | 0.77 | 0.77 | 0.68 |
| chr3:128300001-128320000 | 0.87 | 0.87 | 0.98 | 1.01 | | | | | |
| chr3:128320001-128340000 | 0.37 | 0.58 | 0.41 | 0.42 | chr3:128320001-128360000 | 0.70 | 0.66 | 0.73 | 0.67 |

**Figure S6. Detail HiC analysis in prostate cell lines to calculate left-to-right (L/R) ratio. A-D.** ICED count matrix surrounding the hotspot centering on rs60464856 in the HiC heatmap of DU145 (**A**), PC3 (**B**), VCaP (**C**) and LNCaP (**D**). The ICED count in the hotspot was aggregated for the left (red numbers) and the right (green numbers), and further divided from left to right to obtain the L/R ratio in each cell line. **E.** Additional L/R ratios calculated based on various other options, including ratios calculated from different bin numbers on each side, and ratios calculated from individual bin in the distant regions.

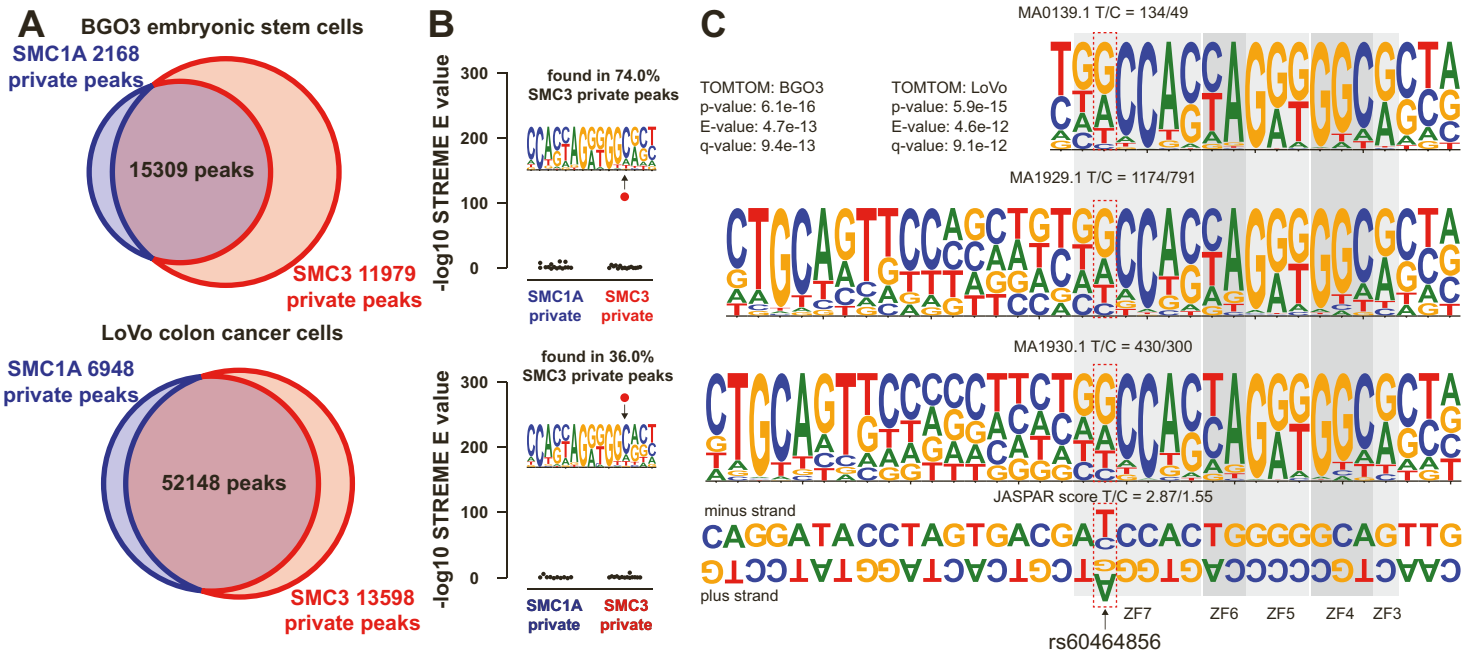



**Figure S7. Motif analysis for SMC1A and SMC3 in human cell lines. A.** Proportional Venn diagram of SMC1A and SMC3 ChIP-seq peak overlapping in BGO3 and LoVo cell lines. The private peak was highlighted with color strokes in the pie chart. We defined the private peak regions as those merely showed in SMC1A or SMC3 ChIP-seq capturing. **B.** STREME motif scan in BGO3 and LoVo cell lines. **C.** TOMTOM comparison of SMC3 private motif to CTCF(MA0139.1) and base composition on SNP location in different CTCF motifs. The shaded blocks highlighted DNA binding sites interacting with CTCF zinc finger (ZF) domains.

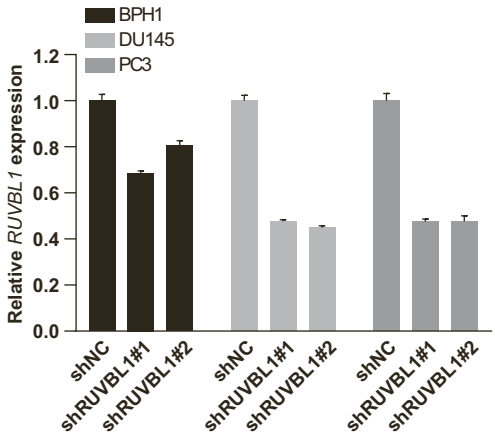



**Figure S8. qPCR results of lentiviral shRNA knockdown in BPH1, DU145 and PC3 cells.** The The error bar represented standard error across three technical replicates for each shRNA clone.

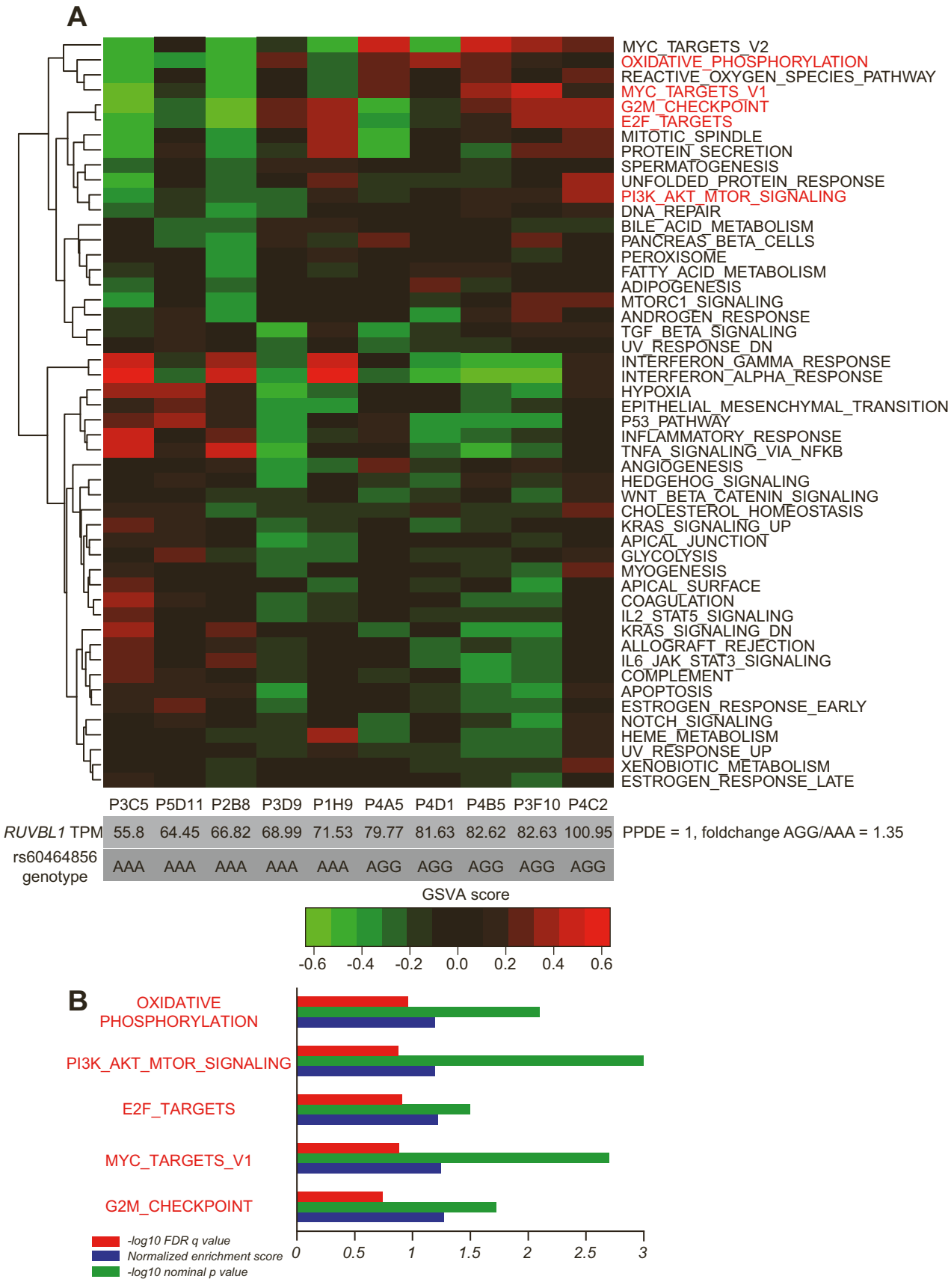



**Figure S9. RNA-seq profiling of base edited BPH1 clones A.** GSVA score heatmap of the HALLMARK gene set collections. Pathways enriched with the top 5 normalized enrichment scores were highlighted. **B.** Top 5 enriched HALLMARK pathways with detailed GSEA metrics, including nominal pvalue, FDR qvalue and normalized enrichment score.

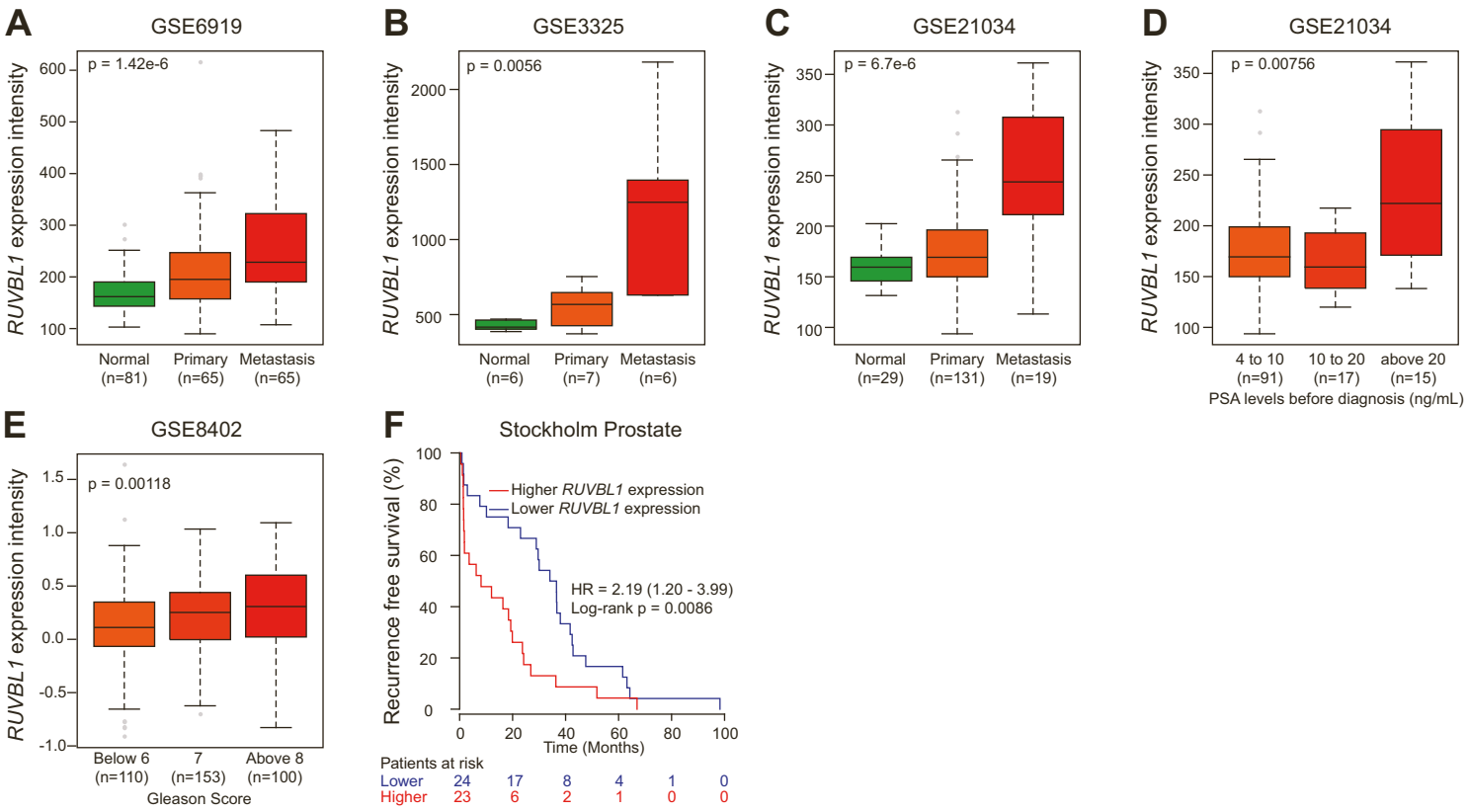



**Figure S10. Associations between *RUVBL1* gene expression and clinicopathological variables in other prostate cancer cohorts. A-C.** Associations between *RUVBL1* gene expression and prostate cancer tissue type in Yu (**A**), Varambally (**B**), and Taylor's (**C**) prostate cancer cohorts. **D.** Associations between *RUVBL1* gene expression and the pre-diagnosis prostate-specific antigen (PSA) levels in Taylor's prostate cancer cohorts. **E.** Associations between *RUVBL1* gene expression and the Gleason score in Setlur's prostate cancer cohorts. **F.** Kaplan-Meier analysis on biochemical recurrence-free survival in Stockholm prostate cohort stratified by *RUVBL1* expression. The Mann-Whitney U test was used to calculate the p-value for A to E. The whiskers are drawn down to the 10th percentile and up to the 90th.

## Supplementary Tables

| | Primer Sequences for QPCR |
|---|---|
| RUVBL1-mRNA-F | AGGTGAAGAGCACTACGAAGA |
| RUVBL1-mRNA-R | CTACTATGACGCCACATGCCT |
| ACTB-mRNA-F | CCAGAGCAAGAGAGGCATCC |
| ACTB-mRNA-R | GTACATGGCTGGGGTGTTGA |

| | Primer Sequences for reporter assay construction |
|---|---|
| RUVBL1_Gibson_F | cggcggccaagcttagacacCACATCTCACGTTGCAAG |
| RUVBL1_Gibson_R | aacagtaccggattgccaagTCTTCATTTTGCAGACGC |

| | shRNA sequences |
|---|---|
| shRUVBL1#1-Sense | GUGGCGUCAUAGUAGAAUUAA |
| shRUVBL1#1-Antisense | UUAAUUCUACUAUGACGCCAC |
| shRUVBL1#2-Sense | CCGGCCAACUUGCUUGCUAAA |
| shRUVBL1#2-Antisense | UUUAGCAAGCAAGUUGGCCGG |
| shNC-Sense | CCUAAGGUUAAGUCGCCCUCG |
| shNC-Antisense | CGAGGGCGACUUAACCUUAGG |

| | Primers for genome editing |
|---|---|
| rs60464856-A2G-gRNA | TGGATCGTCACTAGGTATCC |
| rs60464856-Sanger-F | TAATTCCCGCTGTATCCCAGTGTC |
| rs60464856-Sanger-R | CCCGCCATTATTTCCTCAGGGAAGT |
| ARMS-F-outer | AACCGTCCCATAGCCTGCCACTGCATTC |
| ARMS-R-outer | AGAGGTGTGGCCAGTGGACCAGGGAGTT |
| ARMS-R-inner | GGGGCCGCCCCAGGATACCTAGTGACTAC |

| | Primers for ChIP-qPCR |
|---|---|
| rs60464856-locus-F | TAATTCCCGCTGTATCCCAGTGTC |
| rs60464856-locus-R | CCCGCCATTATTTCCTCAGGGAAGT |
| rs60464856-NC-F | AAGTGAGGCATTCTATGGGACTG |
| rs60464856-NC-R | CCAGGGGATATTCCTCTGTGC |
| AS-rs60464856-R-A | CCAGGATACCTAGTGACGAC |
| AS-rs60464856-R-G | CCAGGATACCTAGTGACGAT |
| AS-rs60464856-F | CAAAGCCCTGCAGTAACTAACC |

**Table S1. Sequences of primers and oligos used in this project.**

| | Accession number and web link |
|---|---|
| DU145 – H3K4me1 | SRR3624829, SRR3624830 |
| DU145 – H3K4me3 | SRR3624831 |
| DU145 – H3K27ac | SRR5823947 |
| PC-3 – H3K4me1 | ENCSR566UMF |
| PC-3 – H3K4me3 | ENCSR275NCH |
| PC-3 – H3K27ac | ENCSR826UTD |
| PrEC – H3K4me1 | SRR1282226 |
| PrEC – H3K4me3 | SRR1282227 |
| PrEC – H3K27ac | SRR1282224 |
| RWPE-1 – H3K4me1 | SRR1645120, SRR1645121 |
| RWPE-1 – H3K4me3 | SRR1645122, SRR1645123 |
| RWPE-1 – H3K27ac | SRR1645108, SRR1645109, SRR1645110, SRR1645111 |
| BGO-SMC1 | SRR445918 |
| BGO-SMC3 | SRR445917 |
| LoVo-SMC1 | SRR952473 |
| LoVo-SMC3 | SRR952474 |
| Yu's PCa cohort | GSE6919 |
| Varambally's PCa cohort | GSE3325 |
| Taylor's PCa cohort | GSE21034 |
| Setlur's PCa cohort | GSE8402 |
| Stockholm's PCa cohort | GSE70769 |

**Table S4. Published datasets used in this project.**

**Table S2 (Spreadsheet table).** CRISPRi gRNA design and readout quantification.

**Table S3 (Spreadsheet table).** Proliferative essential SNPs identified in the RIGER analysis.

**Table S5 (Spreadsheet table).** DNA pull down profiling in BPH1 SILAC proteomics.

## Supplemental Material and Methods

The motif analysis of SMC1A and SMC3 ChIP-seq data

To identify the SMC1A or SMC3 specific binding motif, we retrieved the ChIP-seq peak BED files (Download: BED Peaks menu) of BGO3 and LoVo cell lines from Cistrome Data Browser (http://cistrome.org/db/#/) and used intervene software (https://intervene.readthedocs.io/en/latest/introduction.html) to determine the private peaks. We defined the SMC1A private peaks as those without any overlap with SMC3 peaks, and verse visa for the SMC3 private peaks. As a result, we obtained 2,168 private peaks for SMC1A and 11,979 private peaks for SMC3 in BGO3 cells, and 6,948 private peaks for SMC1A and 13,598 private peaks for SMC3 in LoVo cells. We then used the STREME module in MEME Suite (https://meme-suite.org/meme/index.html) to scan for motif enrichment with shuffled control sequences under default settings. We plotted all motif discovered with E-value less than 0.05 for each scanning and compared the standing out motif (red dot in Figure S7B) to the HOCOMOCO motif collection with TOMTOM module to identify known DNA motif.

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## Acknowledgements for PRACTICAL Consortium

CRUK and PRACTICAL consortium

This work was supported by the Canadian Institutes of Health Research, European Commission's Seventh Framework Programme grant agreement n° 223175 (HEALTH-F2-2009-223175), Cancer Research UK Grants C5047/A7357, C1287/A10118, C1287/A16563, C5047/A3354, C5047/A10692, C16913/A6135, and The National Institute of Health (NIH) Cancer Post-Cancer GWAS initiative grant: No. 1 U19 CA 148537-01 (the GAME-ON initiative).

We would also like to thank the following for funding support: The Institute of Cancer Research and The Everyman Campaign, The Prostate Cancer Research Foundation, Prostate Research Campaign UK (now PCUK), The Orchid Cancer Appeal, Rosetrees Trust, The National Cancer Research Network UK, The National Cancer Research Institute (NCRI) UK. We are grateful for support of NIHR funding to the NIHR Biomedical Research Centre at The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, and Manchester NIHR Biomedical Research Centre. The Prostate Cancer Program of Cancer Council Victoria also acknowledge grant support from The National Health and Medical Research Council, Australia (126402, 209057, 251533, , 396414, 450104, 504700, 504702, 504715, 623204, 940394, 614296,), VicHealth, Cancer Council Victoria, The Prostate Cancer Foundation of Australia, The Whitten Foundation, PricewaterhouseCoopers, and Tattersall's. EAO, DMK, and EMK acknowledge the Intramural Program of the National Human Genome Research Institute for their support.

Genotyping of the OncoArray was funded by the US National Institutes of Health (NIH) [U19 CA 148537 for ELucidating Loci Involved in Prostate cancer SuscEptibility (ELLIPSE) project and X01HG007492 to the Center for Inherited Disease Research (CIDR) under contract number HHSN268201200008I]. Additional analytic support was provided by NIH NCI U01 CA188392 (PI: Schumacher).

Research reported in this publication also received support from the National Cancer Institute of the National Institutes of Health under Award Numbers U10 CA37429 (CD Blanke), and UM1 CA182883 (CM Tangen/IM Thompson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund.

BPC3
The BPC3 was supported by the U.S. National Institutes of Health, National Cancer Institute (cooperative agreements U01-CA98233 to D.J.H., U01-CA98710 to S.M.G., U01-CA98216 to E.R., and U01-CA98758 to B.E.H., and Intramural Research Program of NIH/National Cancer Institute, Division of Cancer Epidemiology and Genetics).

CAPS
CAPS GWAS study was supported by the Cancer Risk Prediction Center (CRisP; www.crispcenter.org), a Linneus Centre (Contract ID 70867902) financed by the Swedish Research Council, (grant no K2010-70X-20430-04-3), the Swedish Cancer Foundation (grant no 09-0677), the Hedlund Foundation, the Soederberg Foundation, the Enqvist Foundation, ALF funds from the Stockholm County Council. Stiftelsen Johanna Hagstrand och Sigfrid Linner's Minne, Karlsson's Fund for urological and surgical research.

PEGASUS
PEGASUS was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health.