Germline Variation at 8q24 and Prostate Cancer Risk in Men of European Ancestry

Matejcić et al.
**Supplementary Figure 1. LocusExplorer plots of the 12 independent signals at 8q24 by subregion.** Plots are shown for all 12 hits combined and divided into five subregions (a-e) to provide greater resolution of the context of individual association signals. ‘Marginal’ and ‘Conditional’ Manhattan plot panels show marginal and conditional association results respectively. Variant positions (x-axis) and -log_{10} P-values from Wald test (y-axis) are shown, with the red line indicating the threshold for genome-wide significant association with PCa risk (P≤5x10^{-8}) and blue peaks local estimates of recombination rates. The position of the 12 independent variants within the positional boundaries is labeled in each plot. Clusters of correlated variants for each independent signal are distinguished using different colors and also depicted on the ‘LD r^2 Hits’ track. Stronger shading indicates greater correlation with the lead variant, with variants not correlated at r^2≥0.2 with any lead variant uncolored. Pairwise correlations are based on the European ancestry (EUR) panel from the 1000 Genomes Project (1KGP) Phase 3. The relative position of RefSeq genes and biological annotations are shown in the ‘Genes’ and ‘Biofeatures’ panels respectively. Genes on the positive strand are denoted in green and those on the negative strand in purple. Annotations displayed are: histone modifications in ENCODE tier 1 cell lines (Histone track), the positions of any variants that were eQTLs with prostate tumor expression in TCGA prostate adenocarcinoma samples and the respective genes for which expression is altered (eQTL track), chromatin state categorizations in the PrEC cell-line by ChromHMM (ChromHMM track), the position of conserved element peaks (Conserved track) and the position of DNasel hypersensitivity site peaks in ENCODE prostate cell-lines (DNasel track). The data displayed in this plot may be explored interactively through the LocusExplorer application (http://www.oncogenetics.icr.ac.uk/8q24/).
Supplementary Figure 2. Linkage disequilibrium plot of the 12 independent signals and previously published PCa risk variants within the 8q24 region. The upper panel shows variants plotted by position (x-axis) and -log10 P-value from Wald test (y-axis). The blue peaks indicate local estimates of recombination rates. The 12 independent risk variants are labeled in the plot. The lower panel shows the LD plot of the 8q24 region bounded by rs1914295 and rs12549761 (chr8:127910317-128540776). The 12 independent variants are surrounded by squares. D clusters and correlation coefficients ($r^2$ and $D'$) were inferred based on recombination hotspots using Haploview 4.2. Pairwise correlations were based on the European ancestry (EUR) panel from the 1000 Genomes Project (1KGP) Phase 3. Colors represent $D'$ values while numbers represent $r^2$ values. Triangles define major LD blocks across the 8q24 region.
<table>
<thead>
<tr>
<th>Haplotype blocks¹</th>
<th>Frequency</th>
<th>OR (95% CI)²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1914295 - rs1487240</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C - G</td>
<td>0.019</td>
<td>1.00 (Ref)</td>
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<tr>
<td>C - A</td>
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<td>T - A</td>
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<td>1.32 (1.21-1.45)</td>
<td>1.10x10⁻⁹</td>
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<tr>
<td>rs77541621 - rs190257175 - rs72725879 - rs5013678 - rs183373024 - rs78511380</td>
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<tr>
<td>G - T - C - C - A - T</td>
<td>0.197</td>
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<td>G - T - C - T - A - T</td>
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<td>1.11 (1.08-1.14)</td>
<td>7.85x10⁻¹⁷</td>
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<tr>
<td>G - T - C - T - G - T</td>
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<td>G - T - T - T - A - A</td>
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<td>G - T - T - T - A - T</td>
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<td>1.44 (1.39-1.49)</td>
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<tr>
<td>A - T - C - T - A - T</td>
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<td>G - C - T - T - A - T</td>
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<td>0.84 (0.73-0.95)</td>
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<td>rs7812894 - rs12549761</td>
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<td>A - C</td>
<td>0.122</td>
<td>1.76 (1.69-1.83)</td>
<td>3.10x10⁻⁶²</td>
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</tbody>
</table>

¹Haplotypes were constructed using the 12 variants from the final stepwise model.
²Letters separated by hyphens correspond to the nucleotide of each variant in the corresponding sequence with risk alleles highlighted in bold.
³Estimated effect of each haplotype relative to the reference haplotype (the one with the highest number of non-risk alleles) adjusted for country and 7 principal components from the OncoArray dataset.
<table>
<thead>
<tr>
<th>Variant ID</th>
<th>Position ×10^9</th>
<th>Allele</th>
<th>RAF (%)</th>
<th>LD cluster</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>Source study</th>
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<td>6.70x10^-54</td>
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<td>rs7837688</td>
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<td>1.42 (1.38-1.45)</td>
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<tr>
<td>rs12549761</td>
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<td>0.89</td>
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<td>1.28 (1.25-1.31)</td>
<td>1.38x10^-78</td>
<td>Conti et al, 2017 (JNCI)</td>
</tr>
</tbody>
</table>

1Risk estimates were derived from a meta-analysis of marginal results of OncoArray and iCOGS data.
2Chromosome 8 co-ordinates based on human genome build 37 (GRCh37).
3Risk allele/reference allele.
4LD clusters were inferred based on recombinant hotspots using Haploview 4.2.
5Per-allele odds ratio and 95% confidence interval adjusted for country and 7 (OncoArray)/8 (iCOGS) principal components.
6Author, year (Journal) of original study reporting a genome-wide significant association between the genetic marker and PCa risk.
Supplementary Note 1. Funding & Acknowledgements. Information and acknowledgements for consortia contributing to the meta-analysis and for individual study groups within the PRACTICAL Consortium.

GWAS Studies in the Meta-Analysis Dataset

The authors wish to pay tribute to Brian Henderson, who was a driving force behind the OncoArray project, for his vision and leadership, and sadly passed away before seeing its fruition.

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Information regarding the PRACTICAL consortium can be found at [http://practical.icr.ac.uk](http://practical.icr.ac.uk)

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The ATBC Study is supported by the Intramural Research Program of the U.S. National Cancer Institute, National Institutes of Health, and by U.S. Public Health Service contract HHSN261201500005C from the National Cancer Institute, Department of Health and Human Services.

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This work was awarded by Prostate Cancer Canada and is proudly funded by the Movember Foundation - Grant # D2013-36.

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COH
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COSM
The Swedish Research Council, the Swedish Cancer Foundation

CPCS1 & CPCS2
Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark

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We thank the CPS-II participants and Study Management Group for their invaluable contributions to this research. We would also like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program.

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The EPICAP study was supported by grants from Ligue Nationale Contre le Cancer, Ligue départementale du Val de Marne; Fondation de France; Agence Nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail (ANSES)

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**IMPACT**
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