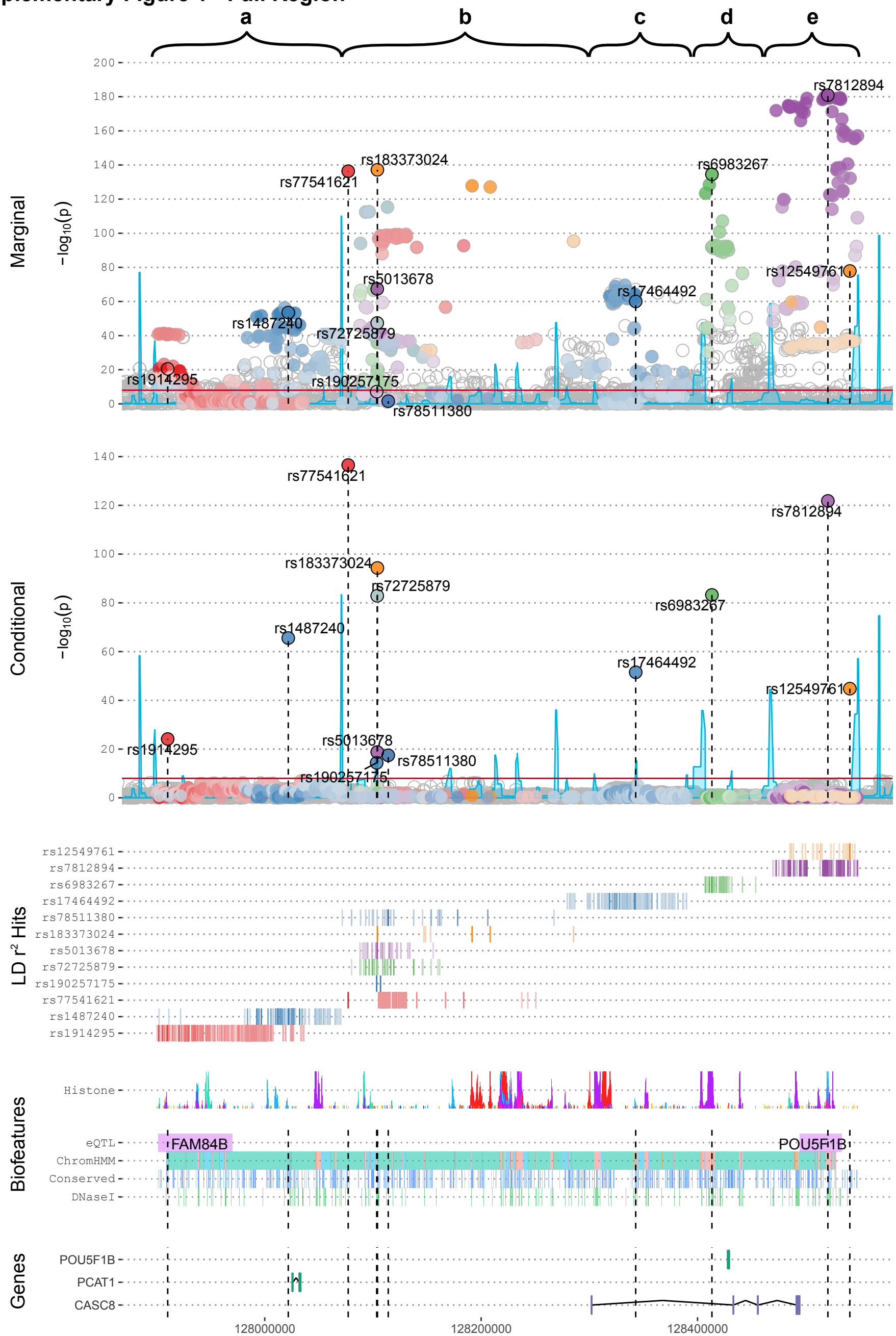
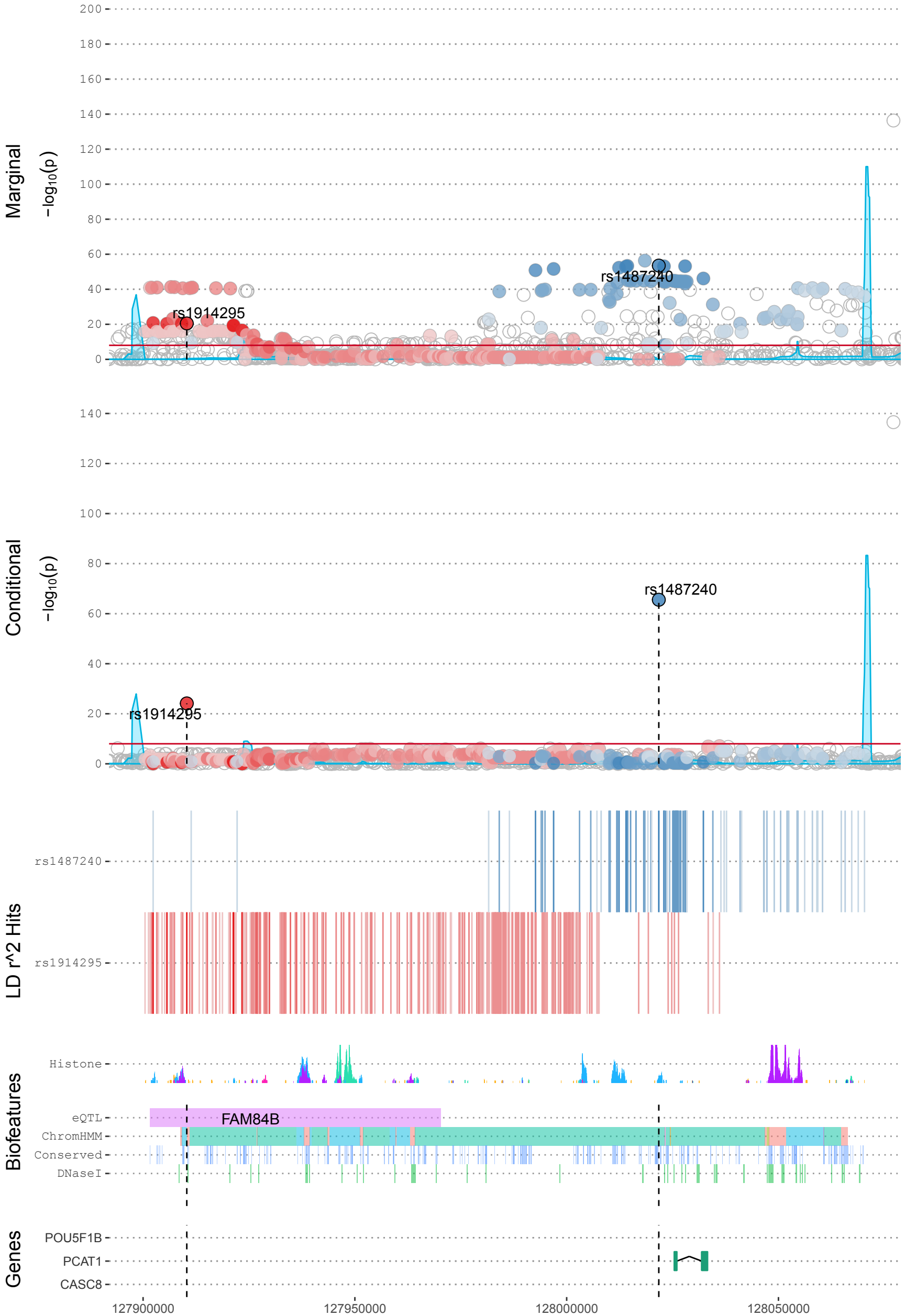
Germline Variation at 8q24 and Prostate Cancer Risk in Men of European Ancestry

Matejcic et al.

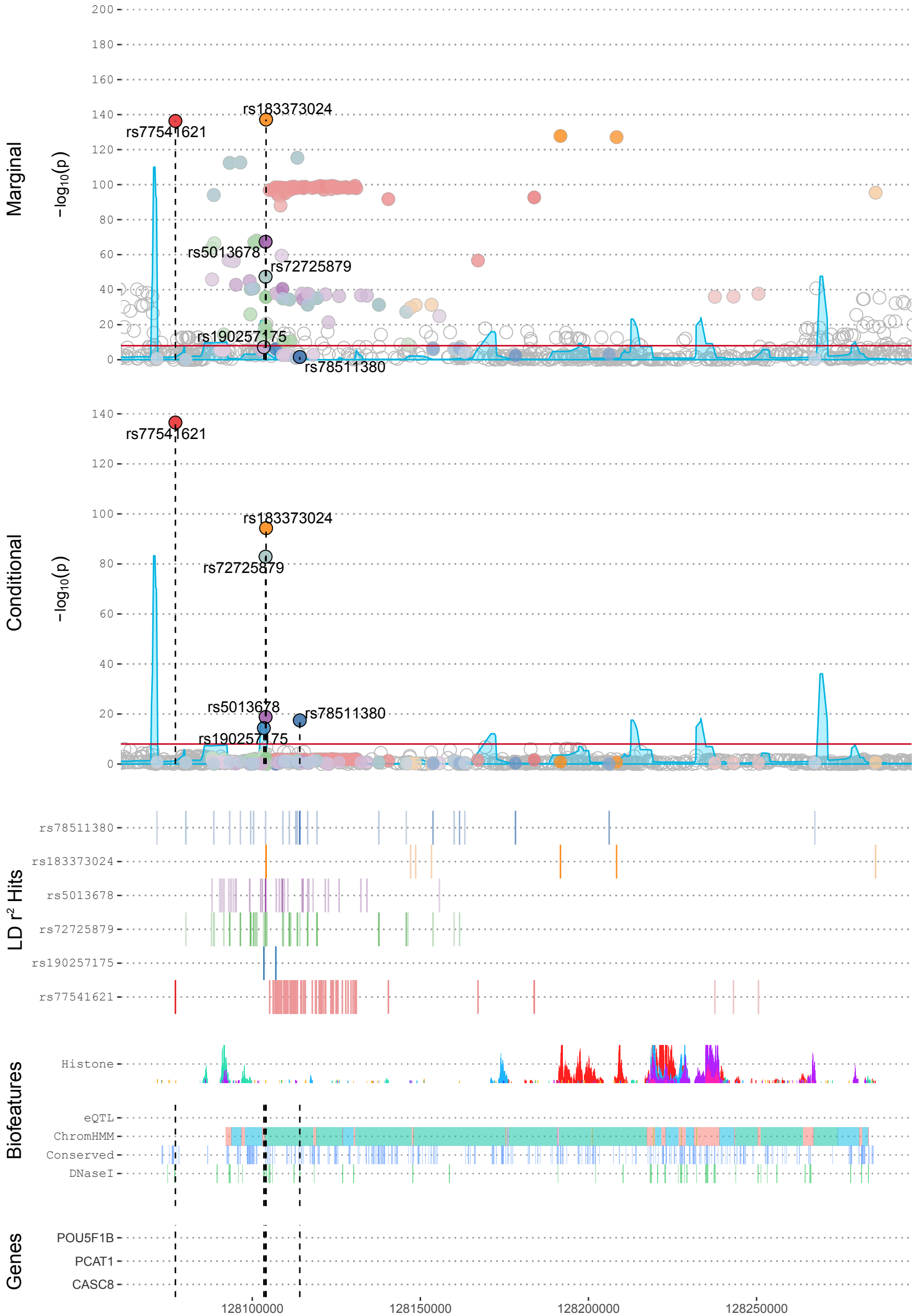
Supplementary Figure 1 - Full Region



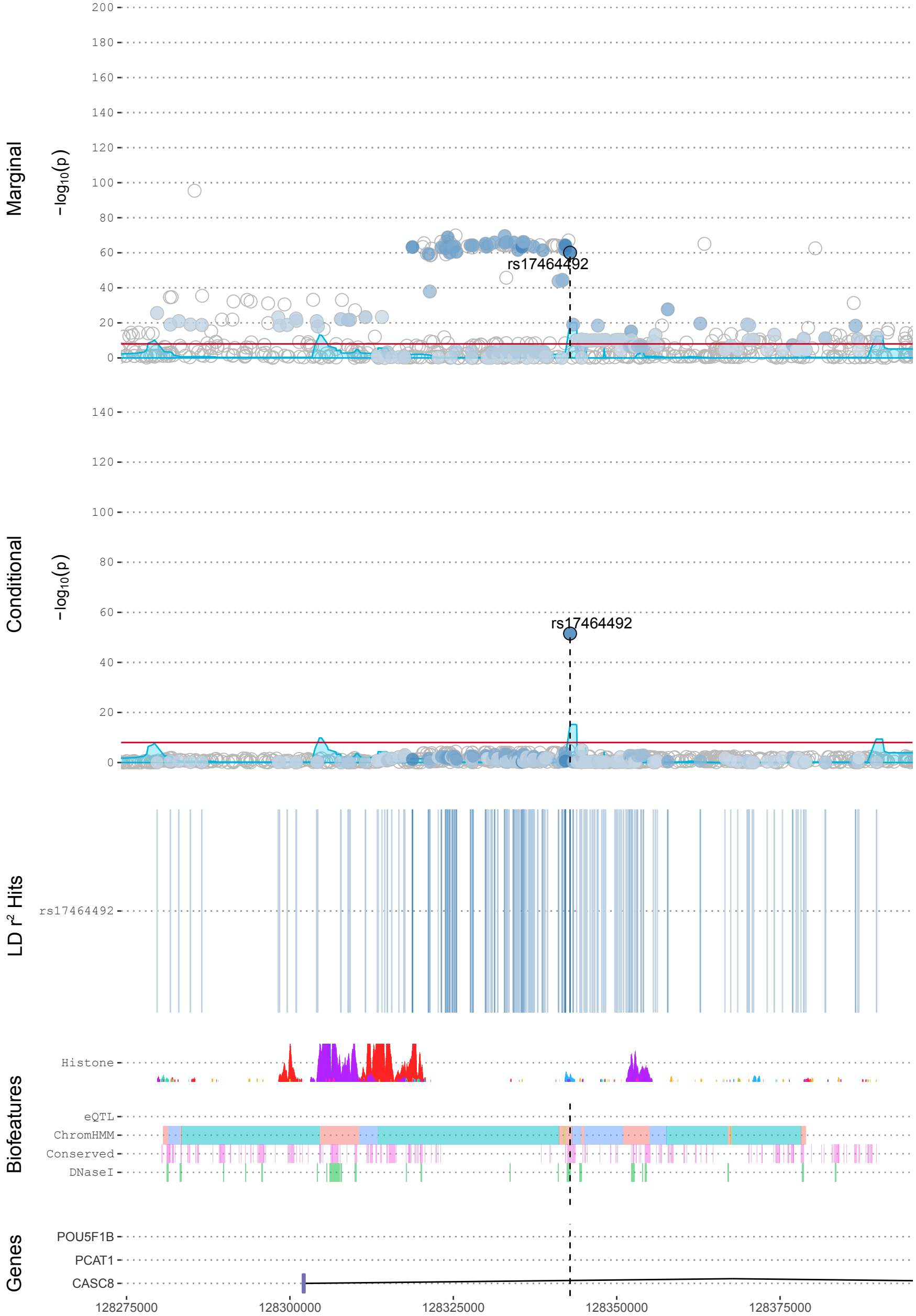
Supplementary Figure 1 - Subregion a



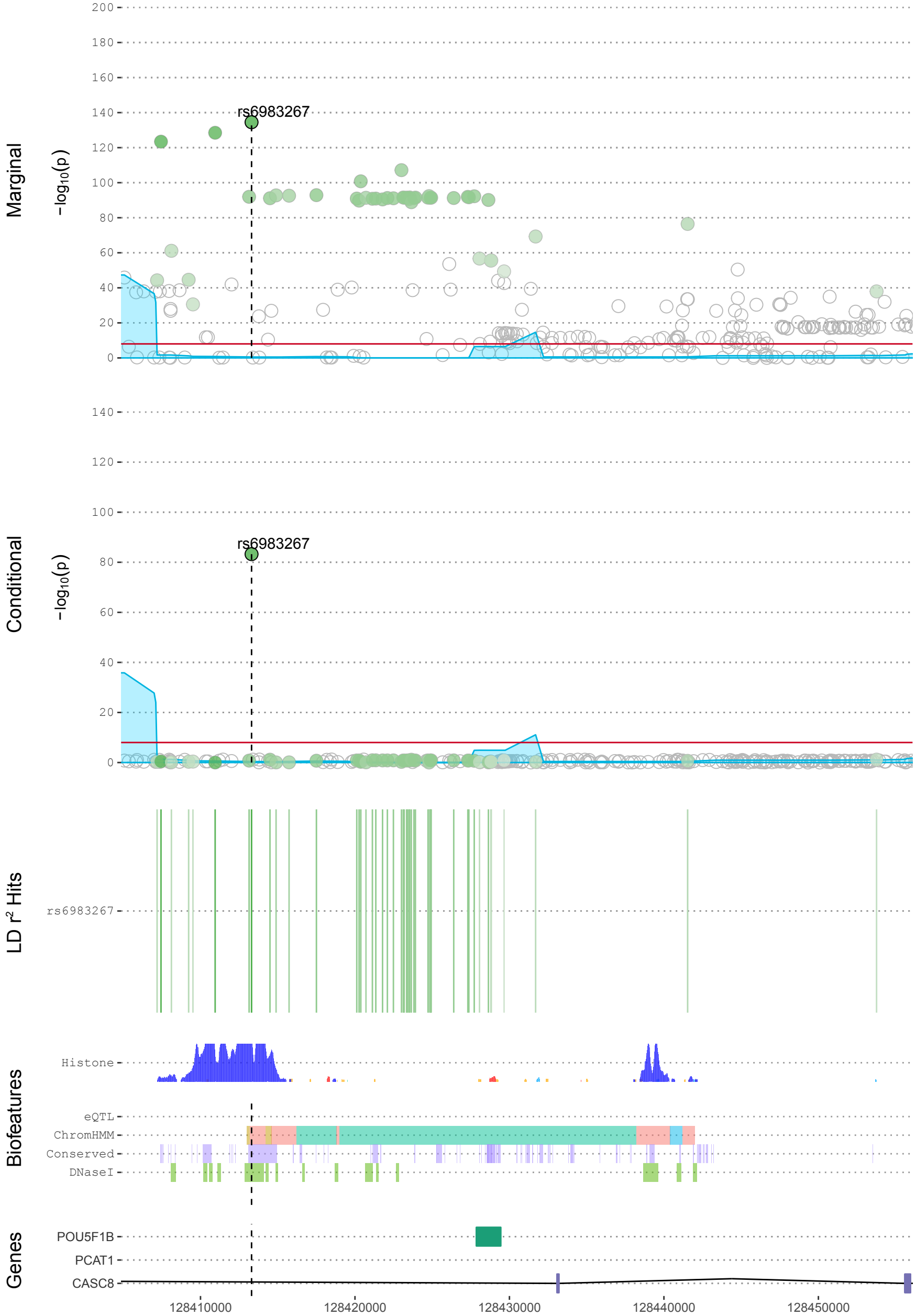
Supplementary Figure 1 - Subregion b



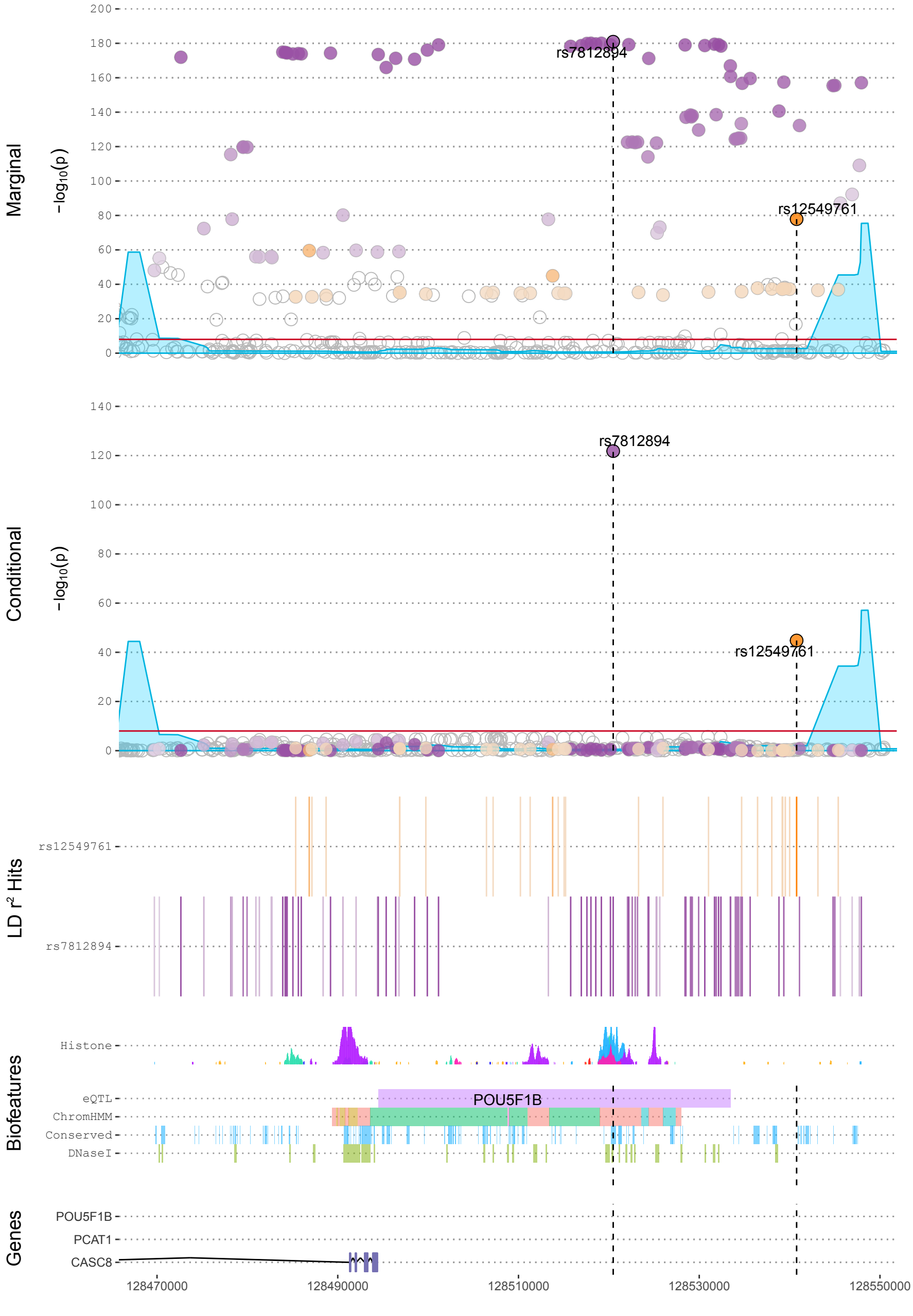
Supplementary Figure 1 - Subregion c



Supplementary Figure 1 - Subregion d

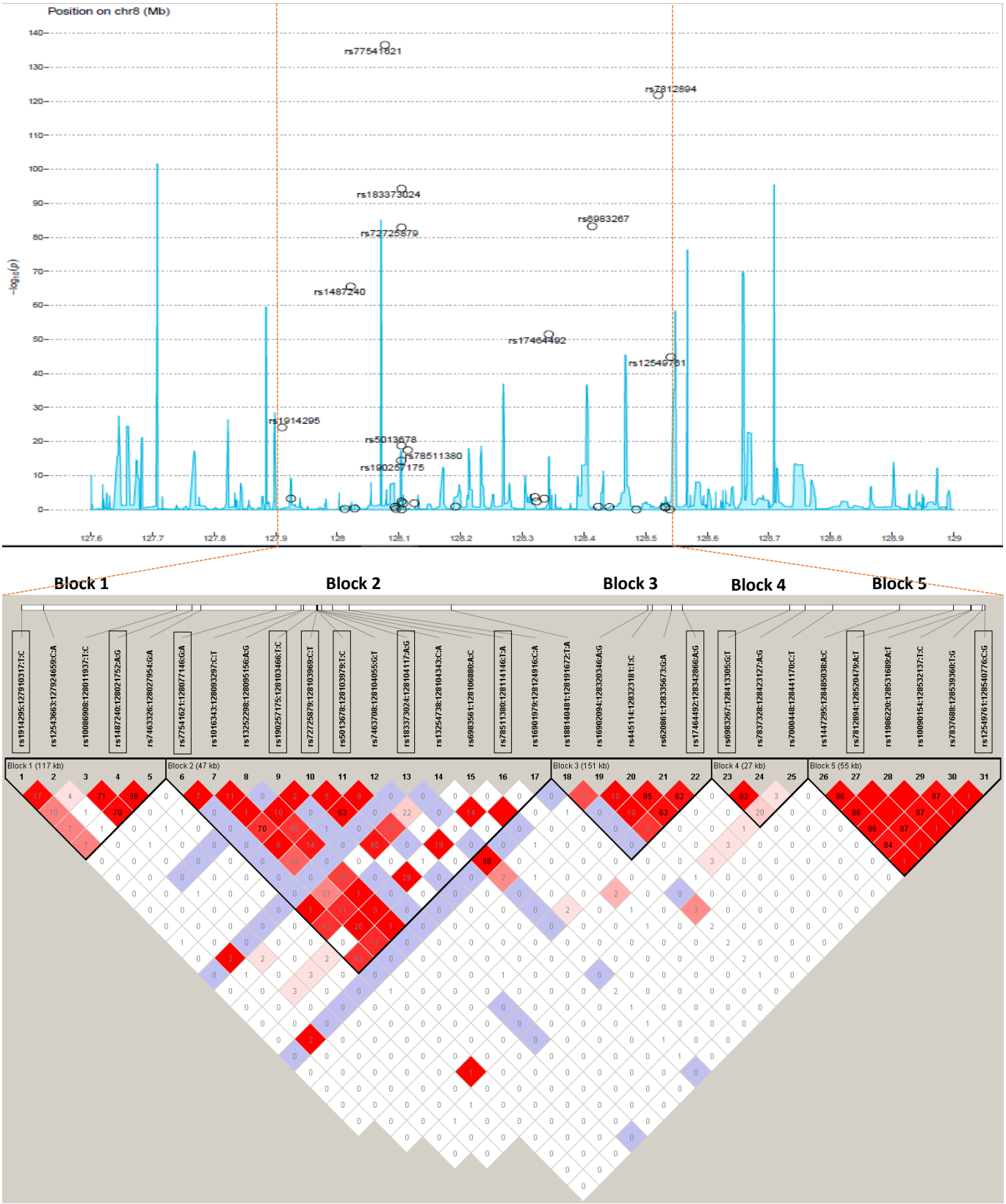


Supplementary Figure 1 - Subregion e



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 ($P \leq 5 \times 10^{-8}$) 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 $r^2 \geq 0.2$ 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 DNaseI hypersensitivity site peaks in ENCODE prostate cell-lines (DNaseI 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



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 [29]. 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.

Supplementary Table 1. Association of common haplotypes at 8q24 with PCa risk under the additive model[1]

Haplotype blocks[1]	Frequency	OR (95% CI)[2]	p-value
rs1914295 - rs1487240			
C - G	0.019	1.00 (Ref)	
C - **A**	0.291	1.16 (1.05-1.27)	2.19×10^{-3}
T - G	0.218	1.10 (0.99-1.21)	5.89×10^{-2}
T - **A**	0.472	1.32 (1.21-1.45)	1.10×10^{-9}
rs77541621 - rs190257175 - rs72725879 - rs5013678 - rs183373024 - rs78511380			
G - **T** - C - C - A - **T**	0.197	1.00 (Ref)	
G - **T** - C - **T** - A - **T**	0.556	1.11 (1.08-1.14)	7.85×10^{-17}
G - **T** - C - **T** - **G** - **T**	0.013	3.41 (3.06-3.80)	1.52×10^{-110}
G - **T** - **T** - **T** - A - A	0.079	1.21 (1.16-1.26)	1.18×10^{-19}
G - **T** - **T** - **T** - A - **T**	0.111	1.44 (1.39-1.49)	4.96×10^{-86}
A - **T** - C - **T** - A - **T**	0.035	2.10 (1.98-2.23)	4.46×10^{-127}
G - C - **T** - **T** - A - **T**	0.005	0.84 (0.73-0.95)	7.34×10^{-3}
rs7812894 - rs12549761			
T - G	0.108	1.00 (Ref)	
T - **C**	0.768	1.22 (1.18-1.26)	1.30×10^{-37}
A - C	0.122	1.76 (1.69-1.83)	3.10×10^{-162}

[1]Haplotypes were constructed using the 12 variants from the final stepwise model.

[2]Letters separated by hyphens correspond to the nucleotide of each variant in the corresponding sequence with risk alleles highlighted in bold.

[3]Estimated 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.

Supplementary Table 2. Marginal estimates for previously reported PCa risk variants at 8q24 in the current study[1]

Variant ID	Position[2]	Allele[3]	RAF[4]	LD cluster[5]	OR (95%CI)[6]	p-value	Source study[7]
rs12543663	127924659	C/A	0.29	block 1	1.13 (1.11-1.15)	$8.38x10^{-40}$	Al Olama *et al*, 2009 (Nat Genet)
rs10086908	128011937	T/C	0.68	block 1	1.14 (1.12-1.16)	$1.69x10^{-44}$	Al Olama *et al*, 2009 (Nat Genet)
rs7463326	128027954	G/A	0.75	block 1	1.16 (1.14-1.18)	$6.70x10^{-54}$	Conti *et al*, 2017 (JNCI)
rs77541621	128077146	A/G	0.02	block 2	1.83 (1.74-1.92)	$4.33x10^{-137}$	Hoffmann *et al*, 2015 (Cancer Discov)
rs1016343	128093297	T/C	0.22	block 2	1.25 (1.23-1.28)	$3.76x10^{-113}$	Al Olama *et al*, 2009 (Nat Genet)
rs13252298	128095156	A/G	0.71	block 2	1.14 (1.12-1.16)	$1.65x10^{-43}$	Al Olama *et al*, 2009 (Nat Genet)
rs72725879	128103969	T/C	0.2	block 2	1.17 (1.14-1.19)	$3.96x10^{-48}$	Han *et al*, 2016 (JNCI)
rs7463708	128104055	T/G	0.28	block 2	1.13 (1.1-1.15)	$1.58x10^{-36}$	Marzec *et al*, 2016 (Oncotarget)
rs183373024	128104117	G/A	0.01	block 2	3.2 (2.92-3.5)	$6.60x10^{-138}$	Gudmundsson *et al*, 2012 (Nat Genet)
rs13254738	128104343	C/A	0.33	block 2	1.08 (1.06-1.09)	$3.68x10^{-16}$	Haiman *et al*, 2007 (Nat Genet)
rs6983561	128106880	C/A	0.04	block 2	1.59 (1.52-1.66)	$3.44x10^{-99}$	Haiman *et al*, 2007 (Nat Genet)
rs16901979	128124916	A/C	0.04	block 2	1.59 (1.53-1.66)	$1.60x10^{-99}$	Haiman *et al*, 2007 (Nat Genet)
rs188140481	128191672	A/T	0.01	block 3	3.18 (2.89-3.49)	$1.61x10^{-128}$	Gudmundsson *et al*, 2012 (Nat Genet)
rs16902094	128320346	G/A	0.16	block 3	1.22 (1.19-1.24)	$4.95x10^{-64}$	Gudmundsson *et al*, 2009 (Nat Genet)
rs445114	128323181	T/C	0.64	block 3	1.16 (1.14-1.18)	$8.29x10^{-64}$	Gudmundsson *et al*, 2009 (Nat Genet)
rs620861	128335673	G/A	0.64	block 3	1.16 (1.14-1.18)	$7.08x10^{-67}$	Al Olama *et al*, 2009 (Nat Genet)
rs17464492	128342866	A/G	0.72	block 3	1.17 (1.14-1.19)	$9.05x10^{-61}$	Al Olama *et al*, 2009 (Nat Genet)
rs6983267	128413305	G/T	0.5	block 4	1.23 (1.21-1.25)	$3.15x10^{-135}$	Haiman *et al*, 2007 (Nat Genet)
rs7837328	128423127	A/G	0.38	block 4	1.19 (1.17-1.21)	$2.80x10^{-92}$	Yeager *et al*, 2007 (Nat Genet)
rs7000448	128441170	T/C	0.4	block 4	1.08 (1.06-1.1)	$3.55x10^{-19}$	Haiman *et al*, 2007 (Nat Genet)
rs1447295	128485038	A/C	0.1	block 5	1.44 (1.4-1.48)	$1.55x10^{-174}$	Amundadottir *et al*, 2006 (Nat Genet)
rs7812894	128520479	A/T	0.1	block 5	1.45 (1.41-1.49)	$1.20x10^{-181}$	Conti *et al*, 2017 (JNCI)
rs11986220	128531689	A/T	0.1	block 5	1.45 (1.41-1.49)	$3.35x10^{-180}$	Jia *et al*, 2009 (PLoS Genet)
rs10090154	128532137	T/C	0.1	block 5	1.45 (1.41-1.49)	$5.90x10^{-180}$	Haiman *et al*, 2007 (Nat Genet)
rs7837688	128539360	T/G	0.11	block 5	1.42 (1.38-1.45)	$3.56x10^{-158}$	Yeager *et al*, 2007 (Nat Genet)
rs12549761	128540776	C/G	0.89	block 5	1.28 (1.25-1.31)	$1.38x10^{-78}$	Conti *et al*, 2017 (JNCI)

[1]Risk estimates were derived from a meta-analysis of marginal results of OncoArray and iCOGS data.

[2]Chromosome 8 co-ordinates based on human genome build 37 (GRCh37).

[3]Risk allele/reference allele.

[4]Risk allele frequency.

[5]LD clusters were inferred based on recombination hotspots using Haploview 4.2.

[6]Per-allele odds ratio and 95% confidence interval adjusted for country and 7(OncoArray)/8(iCOGS) principal components.

[7]Author, year (Journal) of original study reporting a genome-wide significant association between the genetic marker and PCa risk.

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GWAS Studies in the Meta-Analysis Dataset

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