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Supplemental information

Large-scale cross-cancer fine-mapping of the 5p15.33 region reveals multiple independent signals

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	Breast, Overall	Breast, ER-neg	Breast, ER-pos	Colorectal	Endometrial	Esophageal	Glioma	Head/Neck	Lung	Melanoma	Ovarian	Pancreatic	Prostate	Renal
Breast, Overall	1													
Breast, ER-negative	**NA**	1												
Breast, ER-positive	**NA**	**NA**	1											
Colorectal	0.009	0.013	0.001	1										
Endometrial	**0.084**	0.044	**0.064**	0.014	1									
Esophageal	0.020	0.007	0.004	0.009	0.016	1								
Glioma	0.017	0.015	0.010	0.012	0.004	0.010	1							
Head/Neck	0.013	0.005	0.012	0.007	0.002	0.002	0.007	1						
Lung	0.031	0.019	0.021	0.025	0.021	0.023	0.024	**0.072**	1					
Melanoma	0.027	0.012	0.010	0.003	0.025	**0.081**	0.039	-0.004	0.032	1				
Ovarian	**0.051**	0.030	0.048	0.007	0.040	0.001	0.008	-0.001	0.013	0.012	1			
Pancreatic	0.001	-0.001	-0.001	0.011	0.009	0.003	0.016	0.015	0.023	-0.002	0.003	1		
Prostate	0.004	0.002	0.004	0.001	0.002	0.003	0.009	0.013	-0.005	0.009	-0.005	0.009	1	
Renal	0.027	0.015	0.010	0.013	0.033	0.023	0.021	0.004	**0.071**	0.047	0.011	0.044	0.033	1

Table S1. Correlation between 14 cancer-specific GWAS summary statistics due to sample overlaps, using the tetrachoric correlation between binary-transformed GWAS summary z-scores. Correlations higher than 0.05 are annotated in bold.

Cancer Type	Signal Index	SNP	Position	Ref/Eff	Unconditioned P-value	Conditioned P-value
ER-negative Breast	1	rs10069690	1279790	C/T	1.34E-35	1.34E-35
	2	rs2736107	1297854	C/T	1.23E-20	2.22E-16
Colorectal	1	rs2735940	1296486	A/G	1.17E-24	1.17E-24
	2	rs34156553	1243245	C/T	1.60E-11	2.90E-09
Glioma	1	rs10069690	1279790	C/T	2.32E-66	2.32E-66
	2	rs2853677	1287194	G/A	1.08E-28	2.87E-14
Lung	1	rs380286	1320247	G/A	1.51E-32	1.51E-32
	2	rs7705526	1285974	C/A	1.01E-18	3.38E-16
Melanoma	1	rs380286	1320247	G/A	1.66E-17	1.66E-17
Ovarian	1	rs4449583	1284135	C/T	5.93E-12	5.93E-12
Pancreatic	1	rs31490	1344458	G/A	1.02E-17	1.02E-17
	2	rs2735940	1296486	A/G	2.67E-15	4.59E-09
Prostate	1	rs2242652	1280028	G/A	3.46E-52	3.46E-52
	2	rs34785213	1284149	AC/A	3.31E-21	5.74E-15
	3	rs71595003	1292118	G/A	1.78E-16	3.75E-13
	4	rs74682426	1289975	A/C	7.59E-46	2.41E-09
	5	rs2853677	1287194	G/A	1.53E-02	1.97E-09

Table S2. Conditional analysis identified independent signals of individual cancer at the 5p15.33 region.

Cancer 1	Cancer 2	# of SNP	PP.H0.abf	PP.H1.abf	PP.H2.abf	PP.H3.abf	PP.H4.abf
ERnegBreast	Colorectal	4,427	0.353	0.220	0.249	0.155	0.023
ERnegBreast	Glioma	4,500	0.046	0.029	0.540	0.341	0.043
ERnegBreast	Lung	4,588	0.160	0.101	0.367	0.233	0.140
ERnegBreast	Melanoma	4,112	0.285	0.134	0.371	0.174	0.036
ERnegBreast	Ovarian	5,916	0.247	0.208	0.266	0.224	0.056
ERnegBreast	Pancreatic	5,806	0.385	0.320	0.149	0.123	0.022
ERnegBreast	Prostate	5,914	0.069	0.056	0.252	0.206	0.417
Colorectal	Glioma	4,171	0.046	0.031	0.532	0.363	0.028
Colorectal	Lung	4,166	0.149	0.095	0.310	0.197	0.249
Colorectal	Melanoma	3,831	0.259	0.163	0.332	0.208	0.038
Colorectal	Ovarian	4,415	0.393	0.276	0.182	0.128	0.022
Colorectal	Pancreatic	4,312	0.431	0.301	0.127	0.088	0.052
Colorectal	Prostate	4,417	0.129	0.091	0.324	0.228	0.228
Glioma	Lung	4,200	0.032	0.272	0.072	0.604	0.020
Glioma	Melanoma	3,879	0.024	0.188	0.030	0.238	**0.519**
Glioma	Ovarian	4,491	0.051	0.598	0.026	0.300	0.025
Glioma	Pancreatic	4,414	0.063	0.691	0.018	0.202	0.025
Glioma	Prostate	4,491	0.020	0.236	0.050	0.587	0.106
Lung	Melanoma	3,947	0.181	0.378	0.124	0.260	0.057
Lung	Ovarian	4,578	0.153	0.351	0.140	0.322	0.033
Lung	Pancreatic	4,502	0.233	0.534	0.064	0.146	0.022
Lung	Prostate	4,578	0.074	0.169	0.159	0.365	0.233
Melanoma	Ovarian	4,113	0.296	0.385	0.131	0.171	0.017
Melanoma	Pancreatic	4,031	0.471	0.332	0.108	0.076	0.014
Melanoma	Prostate	4,106	0.239	0.305	0.173	0.221	0.063
Ovarian	Pancreatic	5,797	0.344	0.368	0.131	0.140	0.017
Ovarian	Prostate	5,907	0.102	0.110	0.368	0.396	0.024
Pancreatic	Prostate	5,793	0.112	0.043	0.410	0.156	0.279

H0 through H4 reflects the assumptions as: H0: neither cancer has a genetic association in the region; H1/H2: only cancer 1/cancer 2 has a genetic association in the region; H3: both cancers are associated, but with different causal variants; H4: both cancers are associated and share a single causal variant.

Table S3. Colocalization analysis assessing the posterior probability (PP) of the existence of shared causal variant between cancer pairs at the 5p15.33 region, after controlling cancer-specific signals (listed in Table S2). PP.H4.abf, representing the PP of both cancers sharing a single causal variant, is annotated in **bold** if the value is larger than 0.5.

Cancer Type	**Origin of sample**	**Sample Type**	**Assay**	**ENCODE Index**	**Detail**
Glioma	Brain	Tissue	DNase-seq	ENCSR595CSH	*Homo sapiens* brain tissue, embryo (56 days) and male embryo (58 days)
Breast	Breast	Tissue (Epithelial)	DNase-seq	ENCSR600KUR	*Homo sapiens* breast epithelium tissue, female adult (51 years)
Colorectal	Sigmoid Colon	Tissue	DNase-seq	ENCSR276ITP	*Homo sapiens* sigmoid colon tissue, female adult (53 years)
Lung	Lung	Tissue	DNase-seq	ENCFF794QIS	*Homo sapiens* lung tissue, female embryo (76 days)
Ovarian	Ovary	Tissue	DNase-seq	ENCFF173CIO	*Homo sapiens* ovary tissue, female adult (53 years)
Pancreatic	Body of Pancreas	Tissue	DNase-seq	ENCFF706BCL	*Homo sapiens* body of pancreas tissue, female adult (51 years)
Prostate	Prostate	Epithelial Cells	DNase-seq	ENCSR000EPU	*Homo sapiens* epithelial cell of prostate
Melanoma	Lower Leg of Skin	Tissue	DNase-seq	ENCFF129WMG	*Homo sapiens* lower leg skin tissue, female adult (51 years)

Table S4. Tissue-specific open narrow peaks of normal tissues or primary cell lines for the relevant organs, used in the cross-cancer fine-mapping analysis, from the ENCODE project.

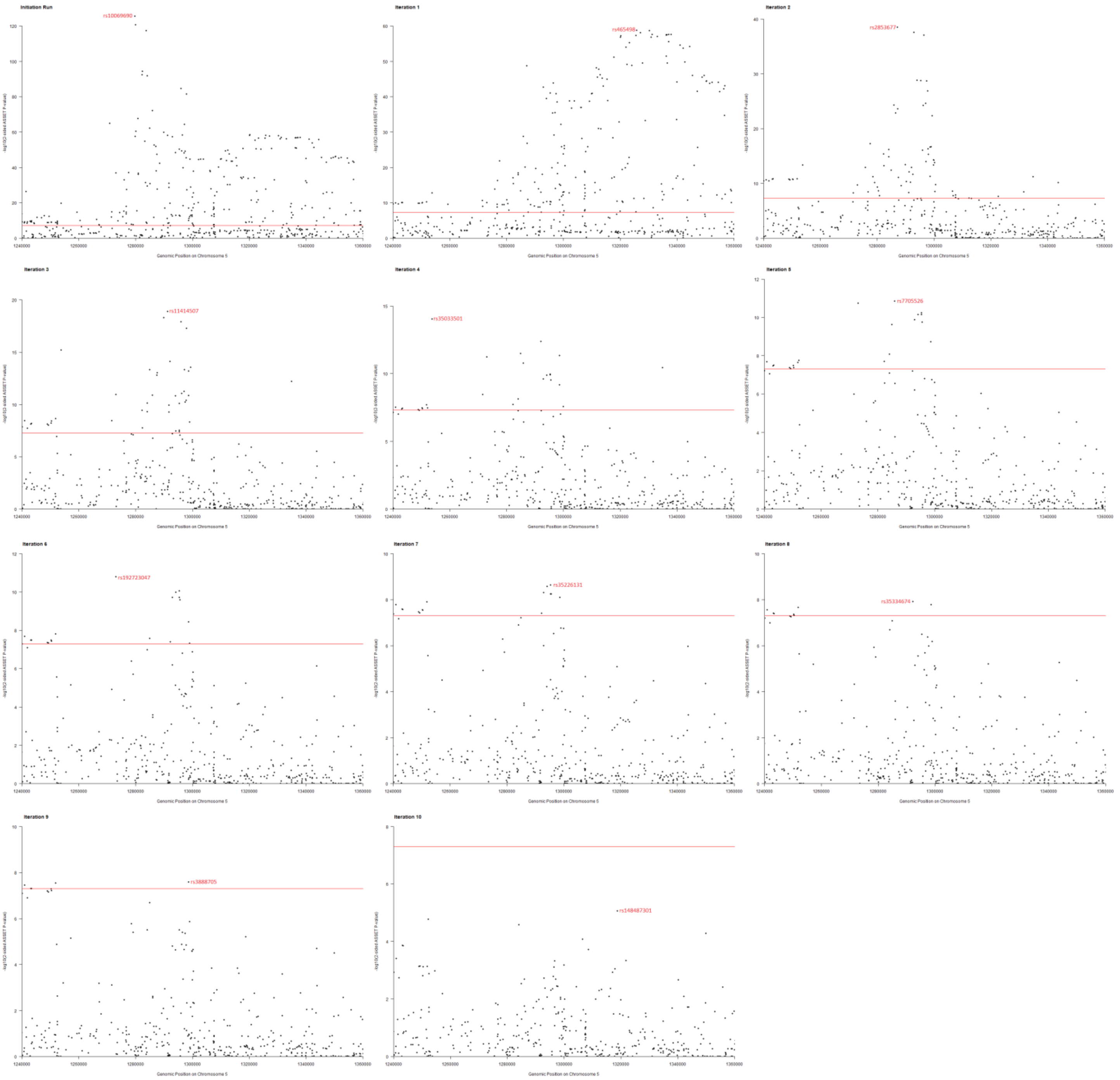
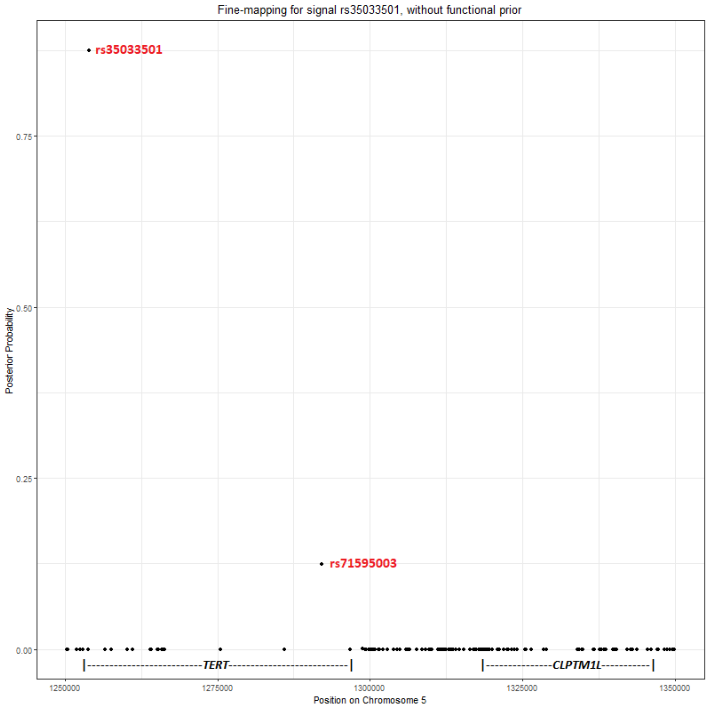
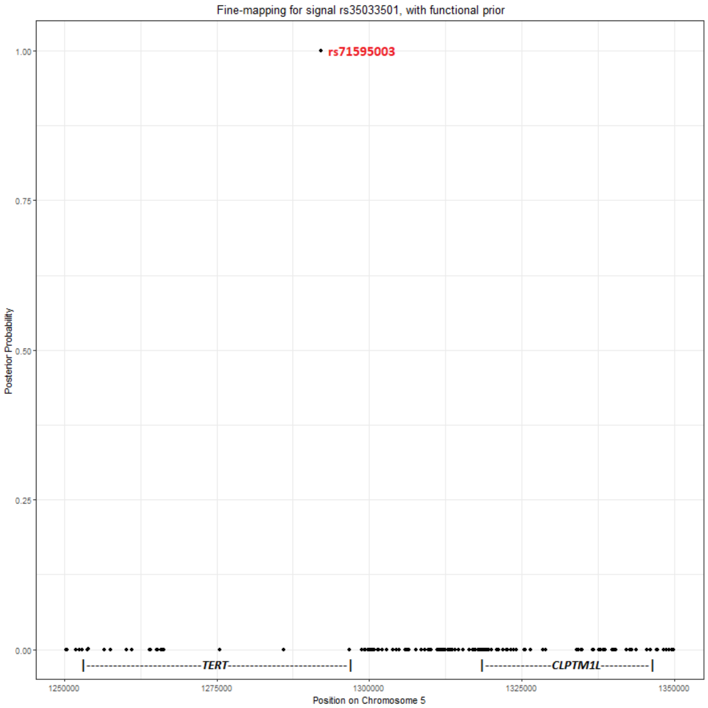


Figure S1. Distribution of two-sided subset-based meta-analysis p-values across eight cancer types at the 5p15.33 region, in each ASSET analysis run. The variant with the smallest p-value in each run (annotated in red) was identified as the index variant of the candidate independent signal, which was further adjusted in the following conditional analysis. The iteration ended when no variant reached genome-wide significant level at p-value = $5x10^{-8}$ (marked with red line in each plot).


Fine-mapping for signal rs35033501, without functional prior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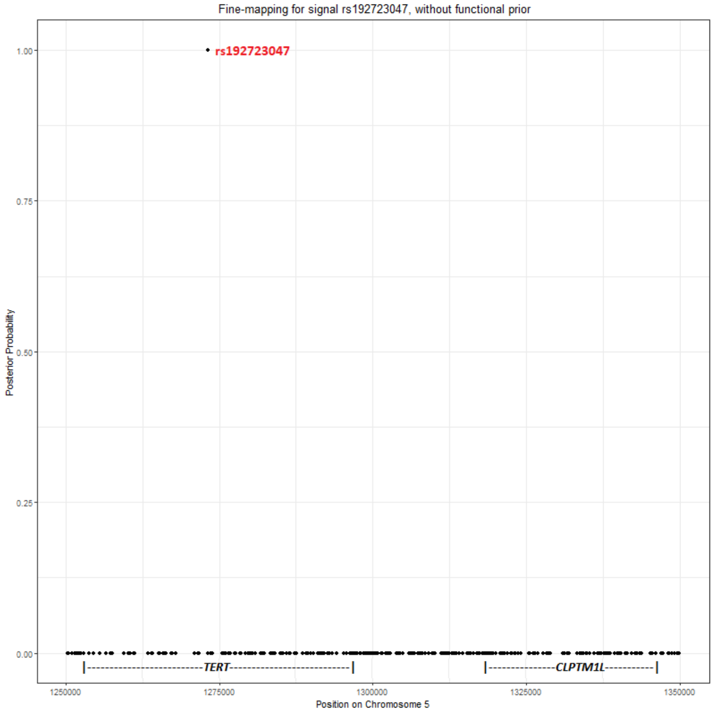
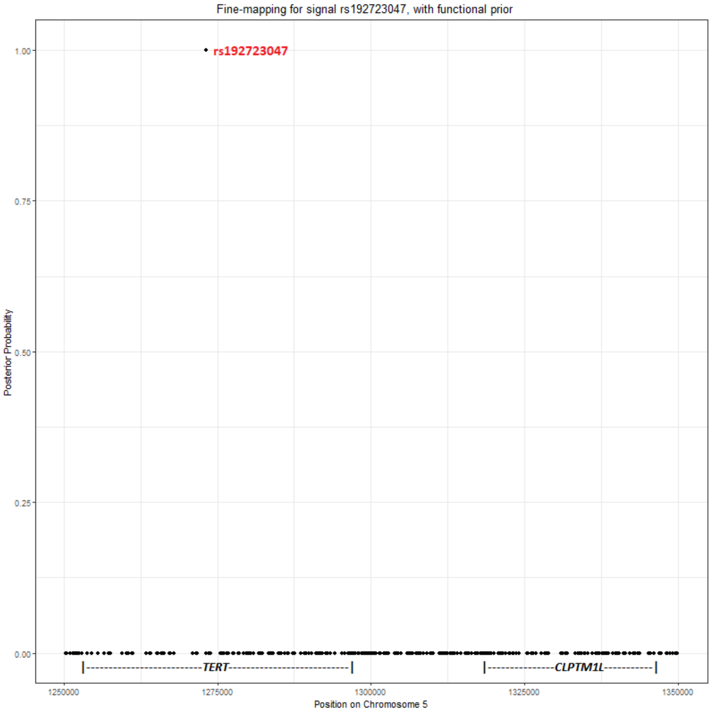
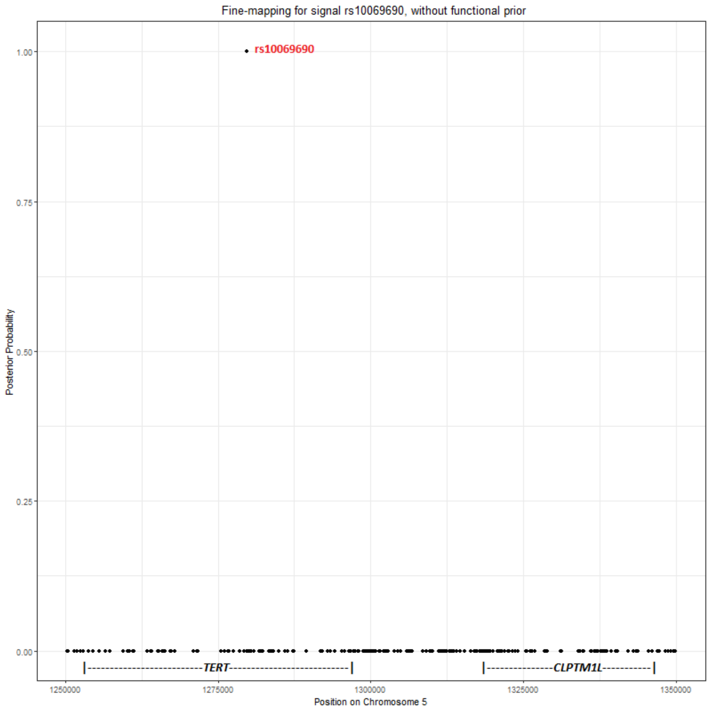
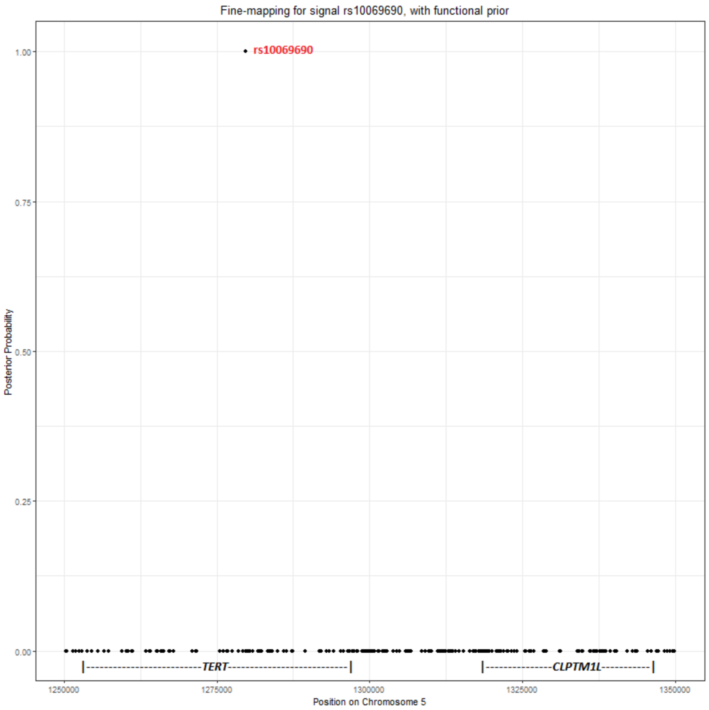
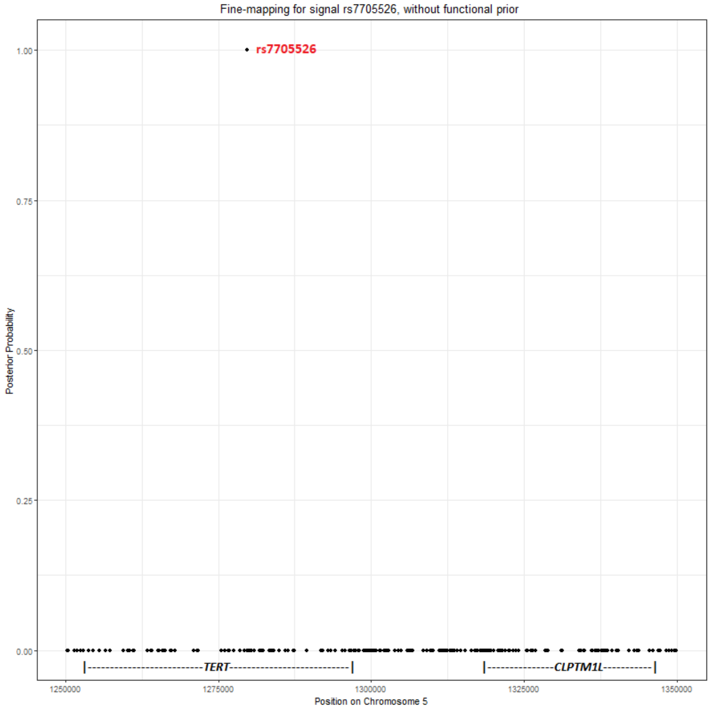
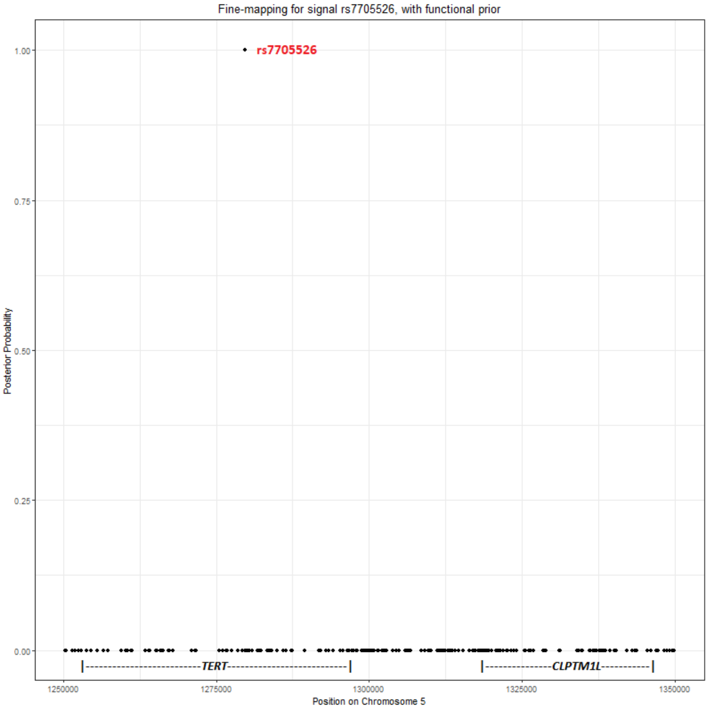

Fine-mapping for signal rs192723047, without functional prior

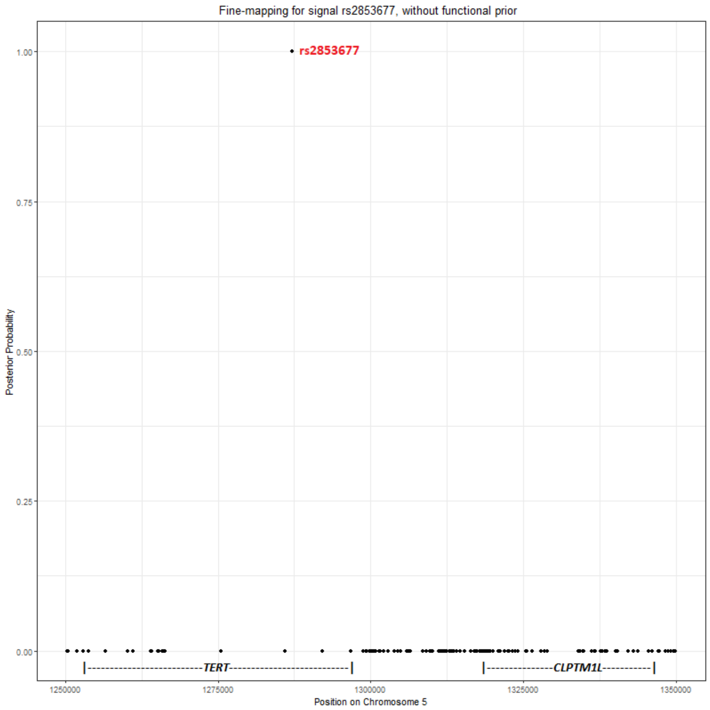

Fine-mapping for signal rs192723047, with functional prior

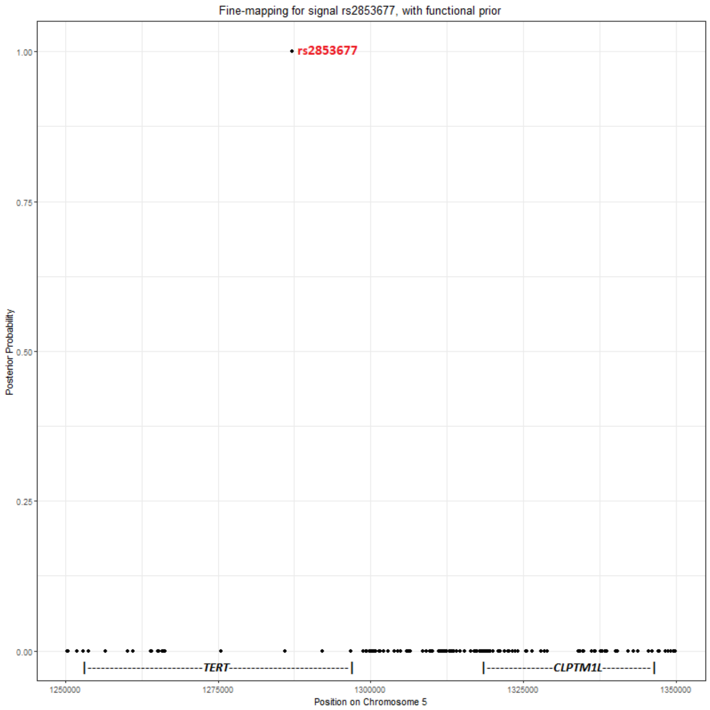

Fine-mapping for signal rs10069690, without functional prior
rs10069690
Posterior Probability
1.00
0.75
0.50
0.25
0.00
|------------------------TERT--------------------------|
|--------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5

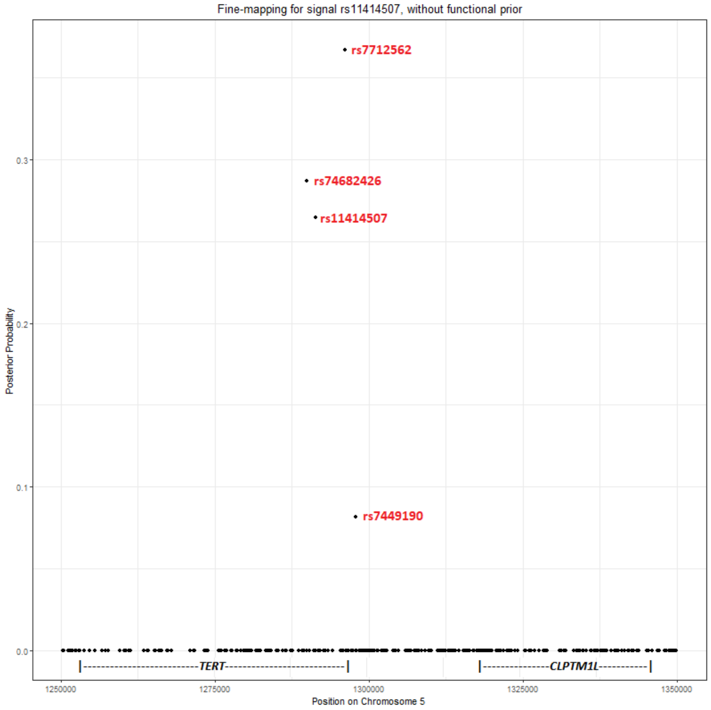

Fine-mapping for signal rs10069690, with functional prior
rs10069690
Posterior Probability
1.00
0.75
0.50
0.25
0.00
|------------------------TERT--------------------------|
|--------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5

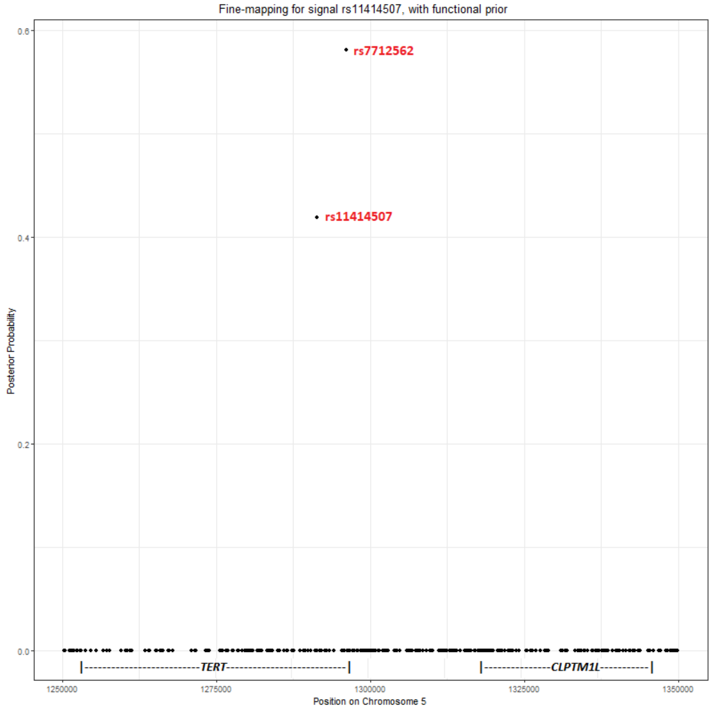

Fine-mapping for signal rs7705526, without functional prior
rs7705526
Posterior Probability
1.00
0.75
0.50
0.25
0.00
|------------------------TERT--------------------------|
|--------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5

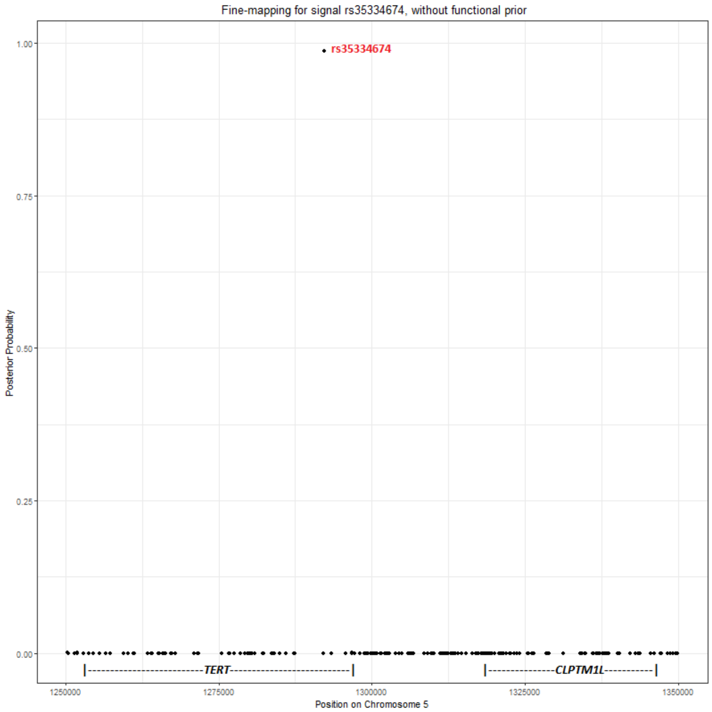

Fine-mapping for signal rs7705526, with functional prior
rs7705526
Posterior Probability
1.00
0.75
0.50
0.25
0.00
|------------------------TERT--------------------------|
|--------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5

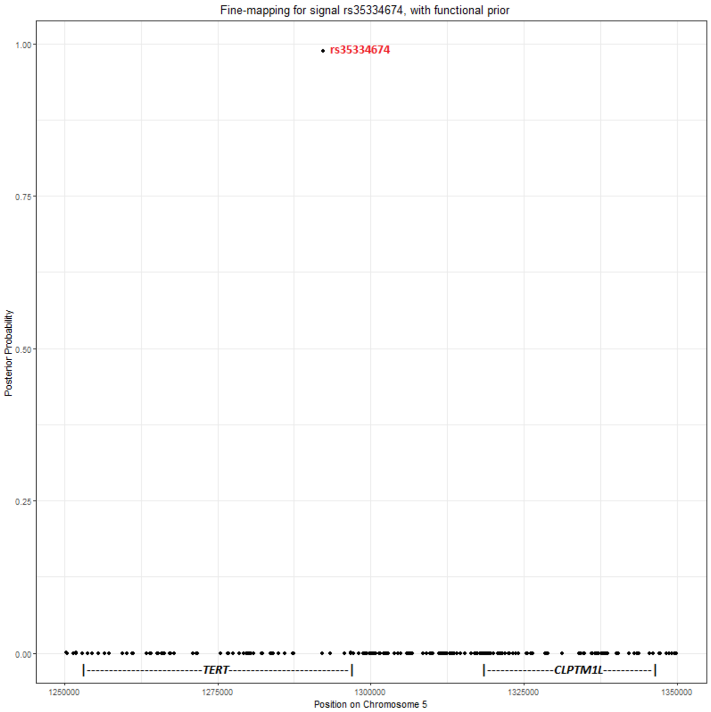

Fine-mapping for signal rs2853677, without functional prior
Posterior Probability
1.00
0.75
0.50
0.25
0.00
rs2853677
|------------------------TERT---------------------------|
|---------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5

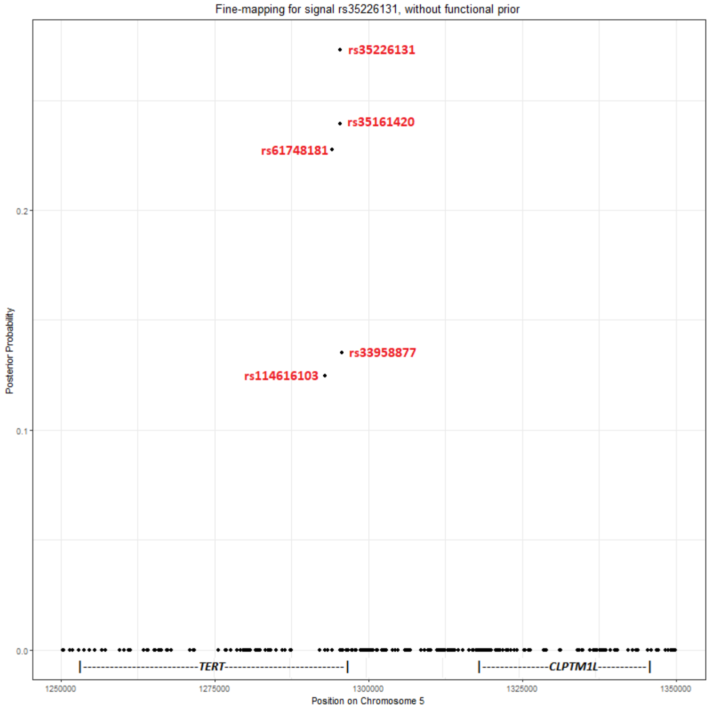

Fine-mapping for signal rs2853677, with functional prior
Posterior Probability
1.00
0.75
0.50
0.25
0.00
rs2853677
|------------------------TERT---------------------------|
|---------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5

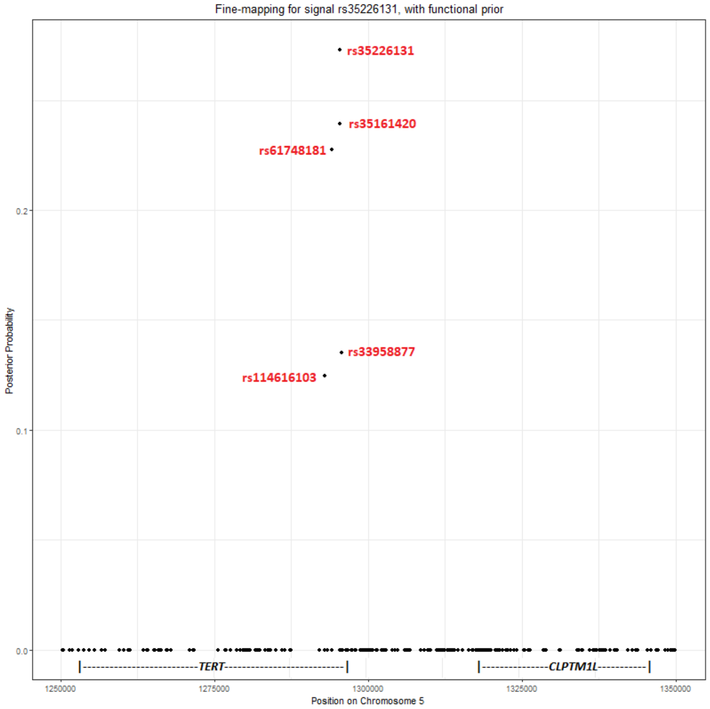

Fine-mapping for signal rs11414507, without functional prior
Posterior Probability
0.3
0.2
0.1
0.0
rs7712562
rs74682426
rs11414507
rs7449190
|------------------------TERT---------------------------|
|---------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5


Fine-mapping for signal rs11414507, with functional prior
Posterior Probability
0.6
0.4
0.2
0.0
rs7712562
rs11414507
|------------------------TERT---------------------------|
|---------------CLPTM1L-----------|
1250000
1275000
1300000
1325000
1350000
Position on Chromosome 5


Fine-mapping for signal rs35334674, without functional prior


Fine-mapping for signal rs35334674, with functional prior


Fine-mapping for signal rs35226131, without functional prior


Fine-mapping for signal rs35226131, with functional prior

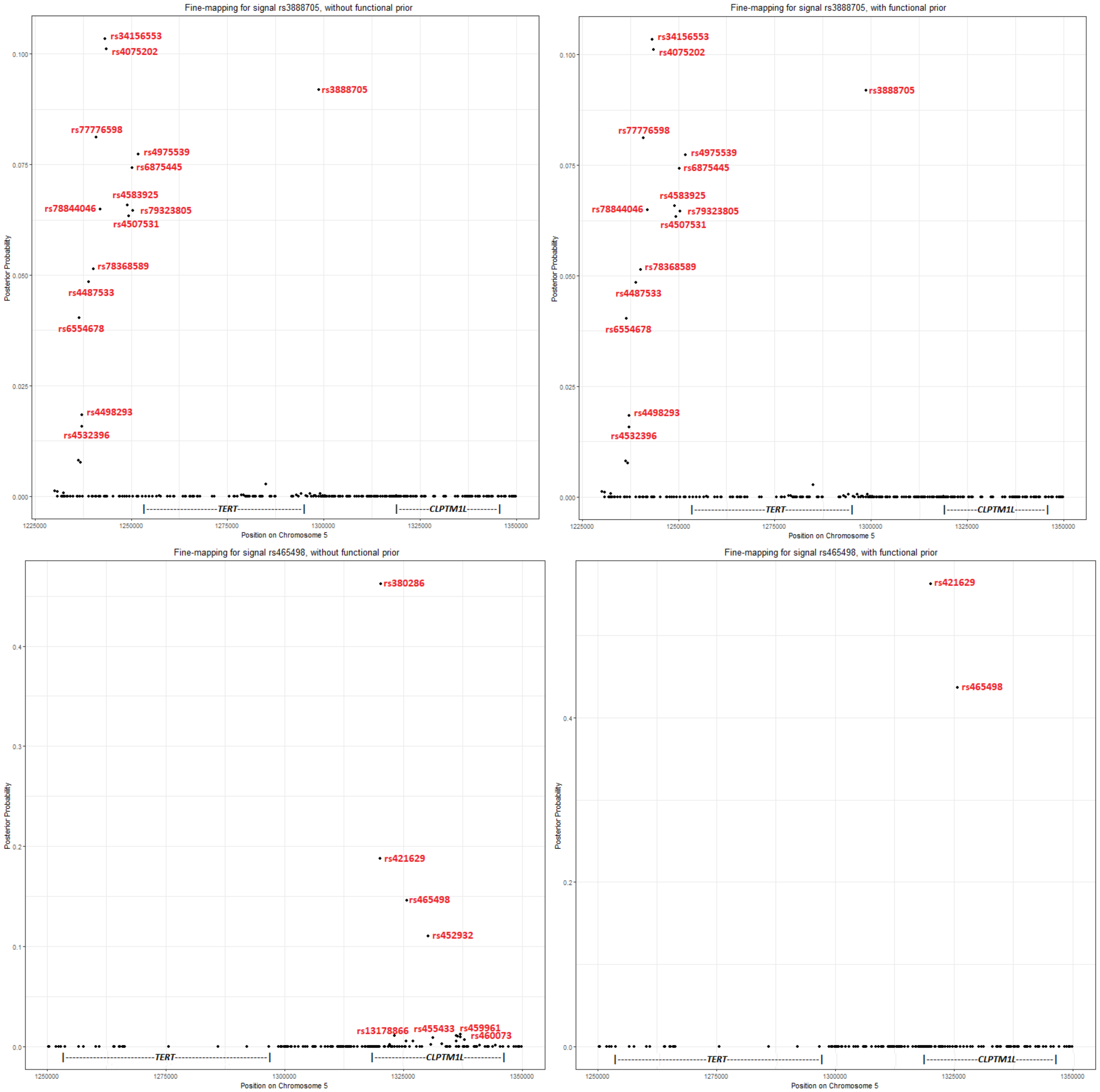


Figure S2. Posterior probability (PP) generated from the fine-mapping analysis for ten independent cross-cancer signals in 5p15.33 region, using PAINTOR V3.0. Each figure shows the fine-mapping results without functional prior (left) or using functional prior (right). Variants included in corresponding 95% PP credible set of each signal were annotated in red

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