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Supplemental Data

Constrained Score Statistics

Identify Genetic Variants Interacting

with Multiple Risk Factors in Barrett's Esophagus

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Supplementary Materials

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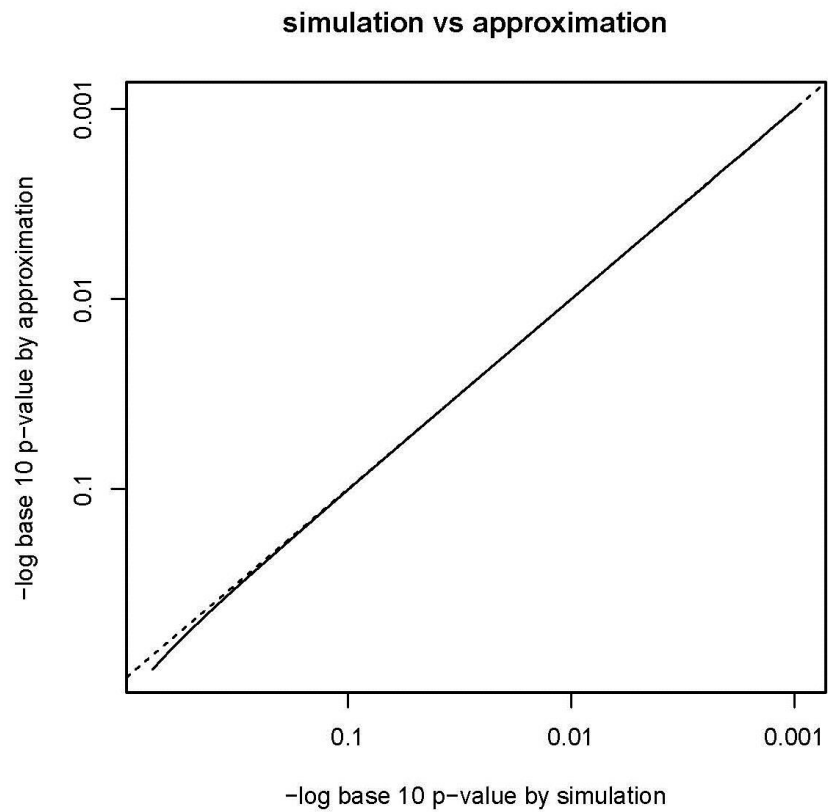


Figure S1. Comparison of the simulation-based p-value and the approximation based p-values for the score statistic for the bidirectional test. The p-value is computed for $p=3$, the 3-dimensional standard multivariate normal distribution.

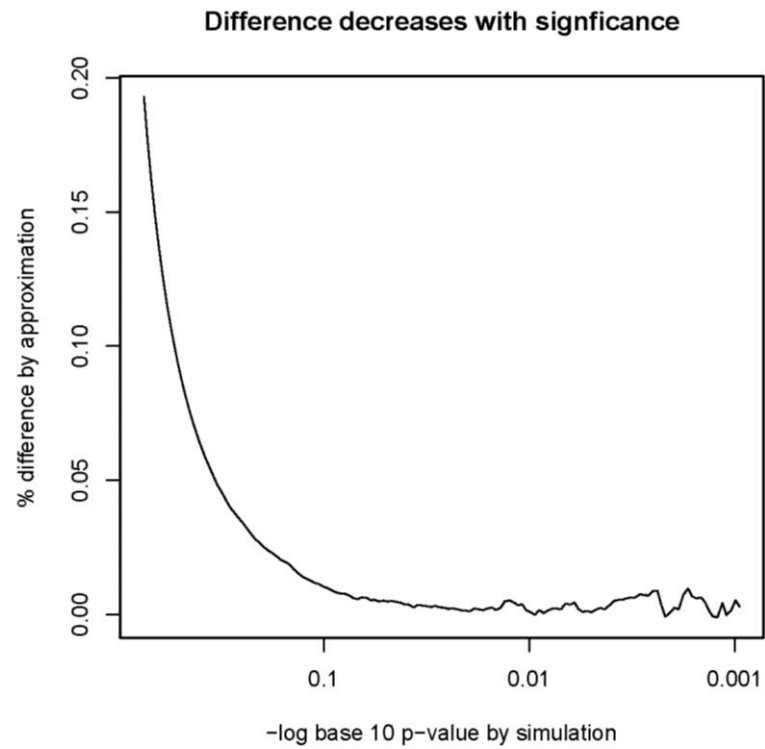


Figure S2. The percentage difference between the simulation-based p-value and the approximation based p-values decreases with the size of p-value. The p-value is computed for bidirectional test with $p=3$, the 3-dimensional standard multivariate normal distribution.

BE: Score Test for Proportional GxE effects - Without Correction

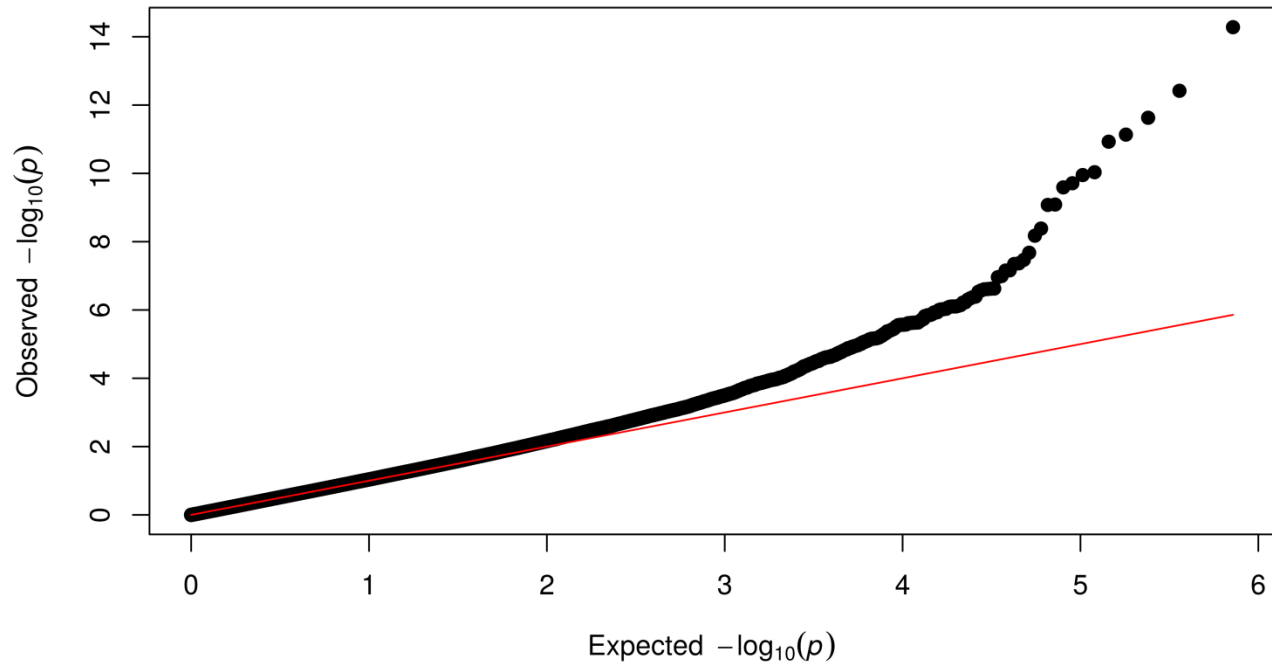


Figure S3. The q-q plot from the score test for 1df proportional interactions on Barrett's esophagus (without correction). The 1-df Chi-square test takes the standard forms of mean and variance for the Rao score statistic.

BE: Tukey test for proportional interactions (Correction 1)

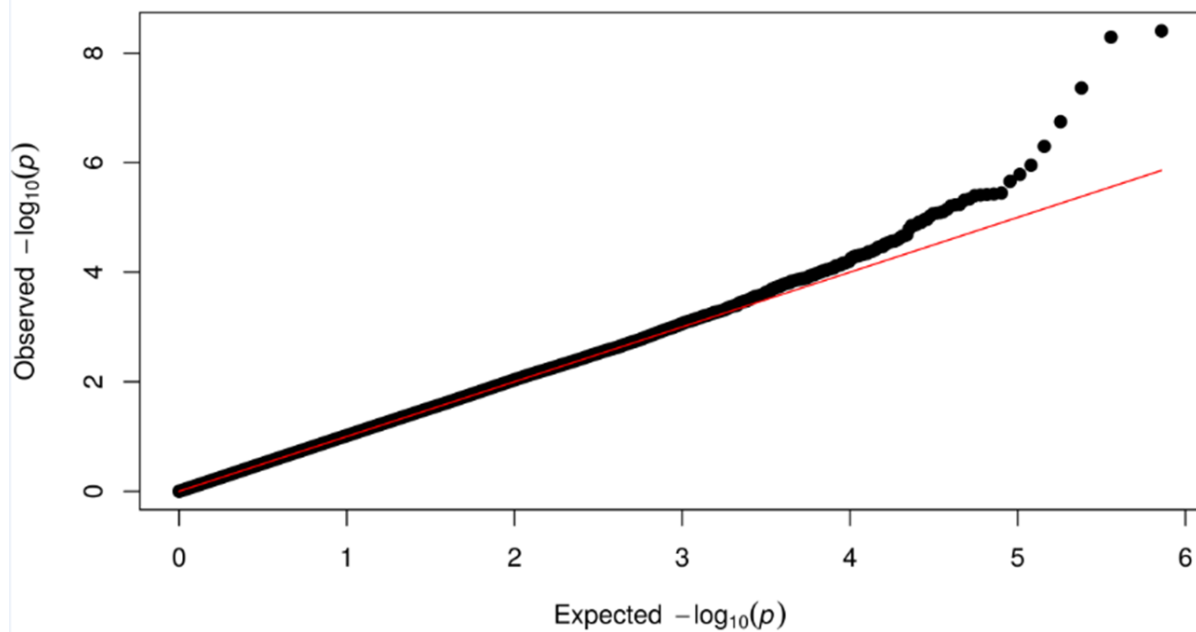


Figure S4. The q-q plot from the score test for 1df proportional interactions on Barrett's esophagus with the first-order correction. The 1-df Chi-square test takes the corrected forms of mean and variance for the Rao score statistic after the first-order Taylor expansion.

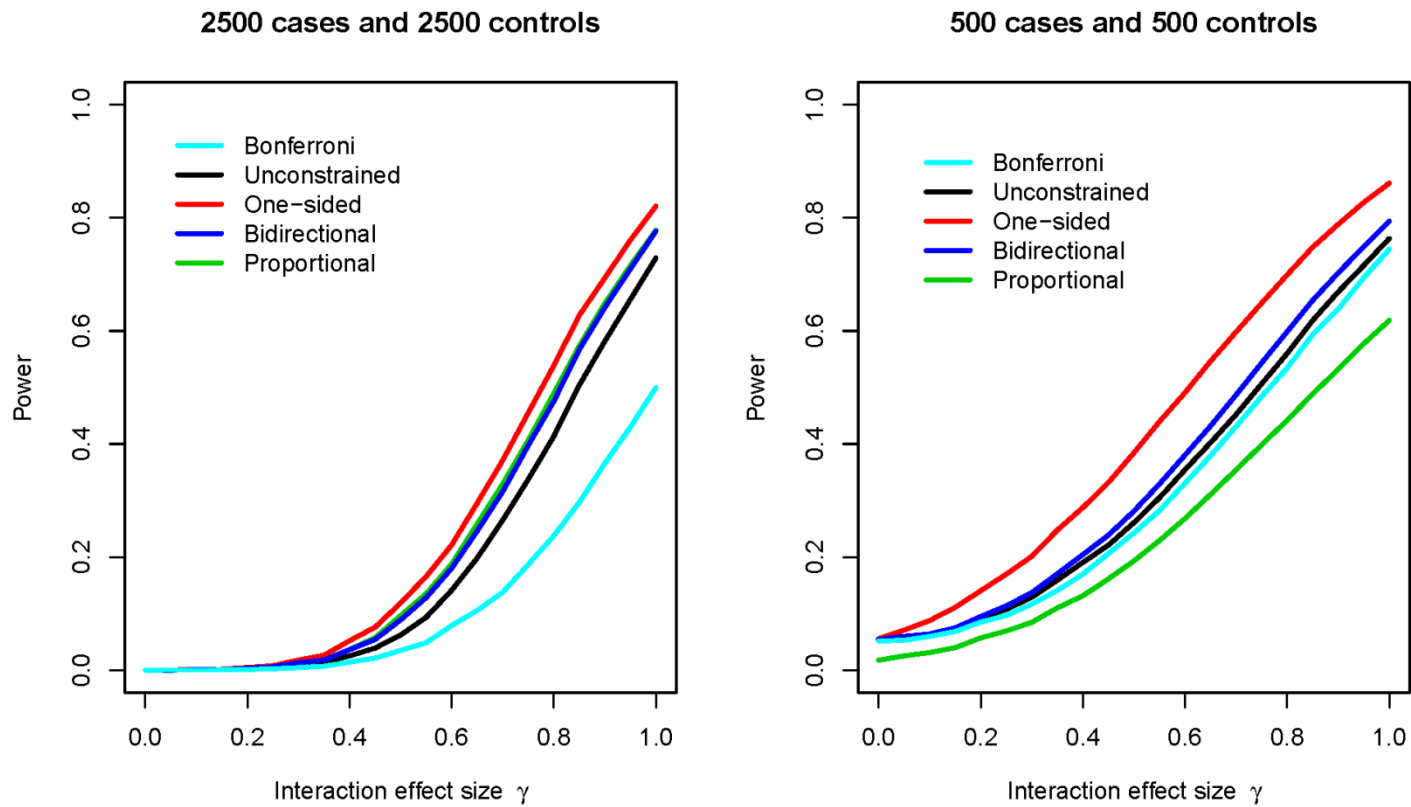


Figure S5. The power of the various test when the main environmental effect is (0.4,0.4,0.4), and all other parameters are the same as Figure 1(a) and Figure 1(b). The left panel shows the scenario with 2500 cases and 2500 controls, the right panel shows the scenario with 500 cases and 500 controls.

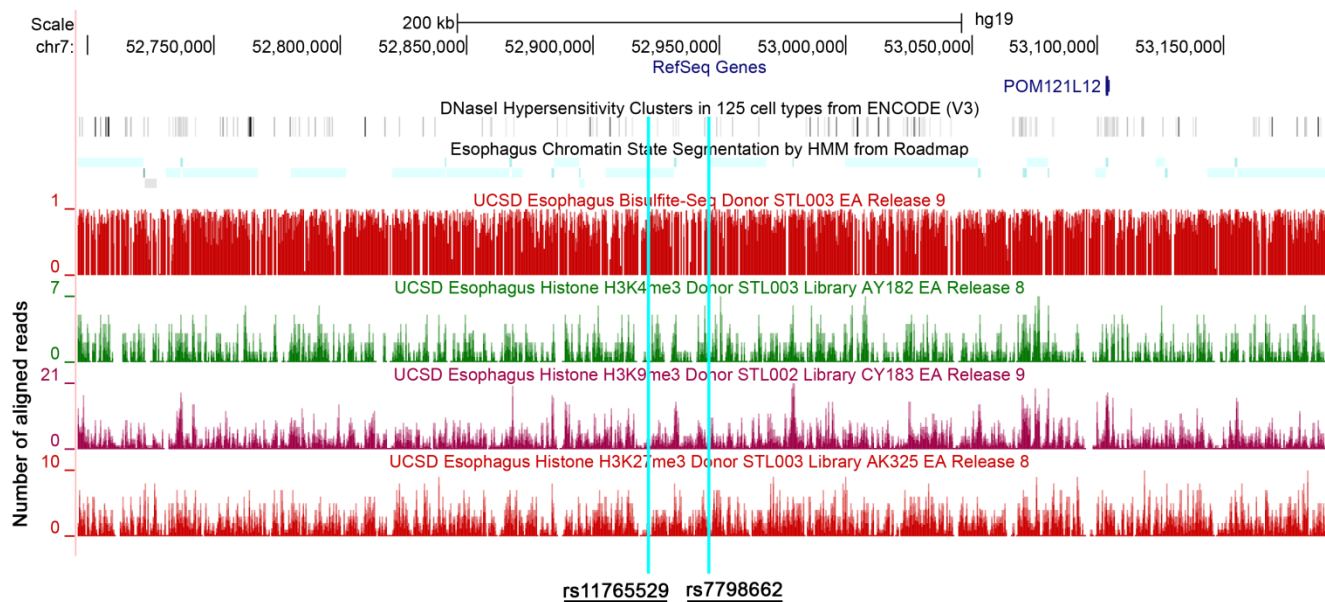


Figure S6A. NIH Roadmap Epigenome Atlas characterization of a ~500-kb region encompassing rs7798662 and rs11765529. Patterns of DNA methylation (Bisulfite-Seq) and key histone modifications (H3K4me3, H3K9me3, H3K27me3) detected in esophageal tissue are displayed. The locus is segmented into regions of “integrative chromatin states” based on a Hidden Markov Model (HMM)-based algorithm (<http://www.roadmapepigenomics.org/>). Genomic positions are indicated for the two SNPs of interest (underlined).

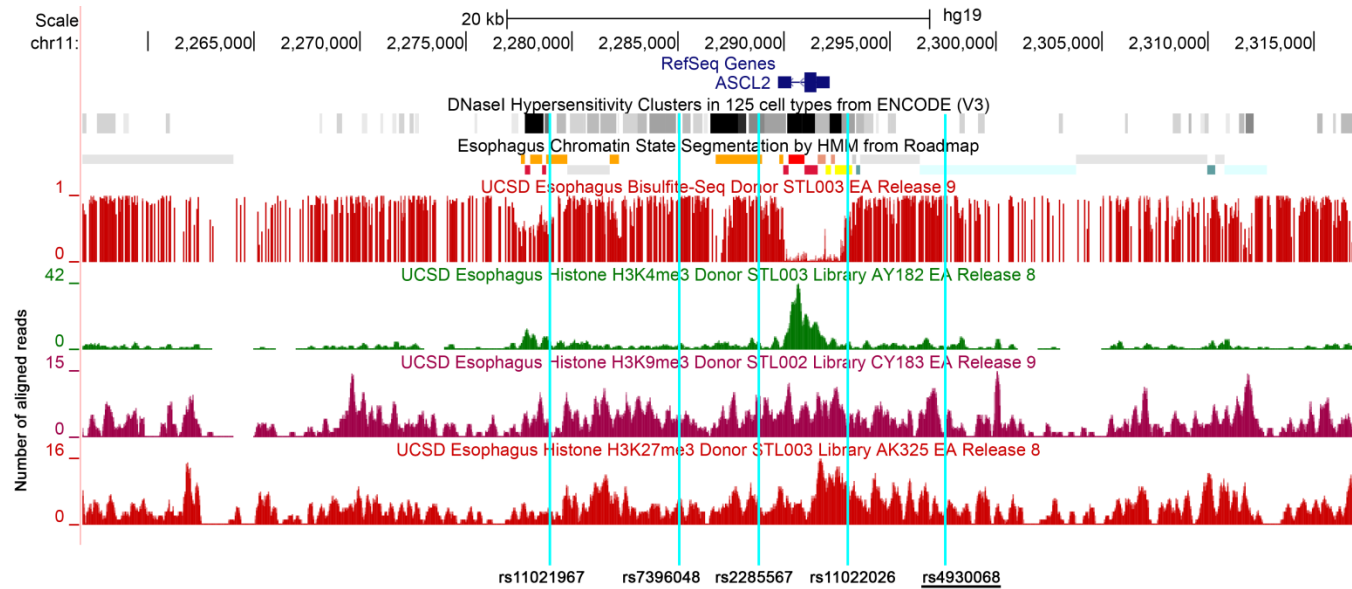


Figure S6B. NIH Roadmap Epigenome Atlas characterization of a ~60-kb region encompassing rs4930068. Patterns of DNA methylation (Bisulfite-Seq) and key histone modifications (H3K4me3, H3K9me3, H3K27me3) detected in esophageal tissue are displayed. The locus is segmented into regions of “integrative chromatin states” based on a Hidden Markov Model (HMM)-based algorithm (<http://www.roadmapepigenomics.org/>). Genomic positions are indicated for the index SNP (underlined) and four additional variants in high LD ($r^2 > 0.8$) with rs4930068.

Table S1. Functional annotations for variants in high LD ($r^2 > 0.8$) with rs7798662.

	SNP	$r^{2(a)}$	Distance ^b	Location	Promoter ^c	Enhancer ^d	DNase ^e	Proteins ^f	eQTL ^g	Motifs ^h
1	rs17691637	1	38367	196kb 5' of POM121L12		ESDR, GI , OVRY, PLCNT, VAS				ZBTB33
2	rs10488504	1	38256	196kb 5' of POM121L12						DMRT2,DMRT3,DMRT7,Sox,Zfp187
3	rs112884530	1	36857	194kb 5' of POM121L12						EWSR1-FLI1, Hbp1, MAZ, Mef2, Znf143
4	rs17613916	1	36086	193kb 5' of POM121L12		BRN				
5	rs11766226	1	32207	190kb 5' of POM121L12						E2F,Maf,NF-kappaB,Sox,Zfp410
6	rs112045720	1	31243	189kb 5' of POM121L12						Arid3a,CTCF,Foxq1,Pou3f2
7	rs75557256	1	30940	188kb 5' of POM121L12						CDP,RREB-1
8	rs79160007	1	30930	188kb 5' of POM121L12						GR,Sox
9	rs78469163	1	30884	188kb 5' of POM121L12						CDP
10	rs80103923	1	30882	188kb 5' of POM121L12						CDP,Pou1f1
11	rs111641968	1	30462	188kb 5' of POM121L12						CACD,NRSF,Zfx
12	rs113515559	0.93	30381	188kb 5' of POM121L12						GR,YY1
13	rs74620601	1	30124	188kb 5' of POM121L12			BRN	JUND		AP-1,Gfi1
14	rs112264971	1	29939	187kb 5' of POM121L12						Crx,XBP-1
15	rs79429223	1	29407	187kb 5' of POM121L12						AP-1
16	rs75314167	1	28589	186kb 5' of POM121L12						Gfi1,Pax-5,SP2
17	rs74676024	1	28144	186kb 5' of POM121L12			BLD			Irf,Pax-5,RXRA,p300
18	rs75276194	1	28114	186kb 5' of POM121L12						CDP
19	rs111642729	1	27892	185kb 5' of POM121L12						Irf,Pou2f2,Pou3f3,Pou5f1,Sox
20	rs113494626	1	27414	185kb 5' of POM121L12						Foxj1,Foxk1,RXRA
21	rs75710970	1	27357	185kb 5' of POM121L12						Cdc5,Pax-4,p53
22	rs76973260	1	26484	184kb 5' of POM121L12						ATF3,Arnt,BHLHE40,Ets,Gfi1,Myc,NF-E2,SIRT6,SREBP,Sin3Ak-20,TFE
23	rs80121386	1	26403	184kb 5' of POM121L12						E2F,Hoxa10,Nanog,Pou2f2,Pou3f2,Sox
24	rs17614229	1	26381	184kb 5' of POM121L12						HMG-IY,Irf,Nanog,Pbx-1, Pou1f1, Pou2f2, Pou3f2, Pou3f3, Pou5f1, TATA
25	rs76100117	1	24792	182kb 5' of POM121L12		ESC, OVRY				Foxp1,IRC900814,Mef2,NRSF,RFX5
26	rs75931245	1	24784	182kb 5' of POM121L12		ESC, OVRY				Foxf2,Mef2,Myf,NRSF,Sin3Ak-20,ZEB1

27	rs111256487	1	24624	182kb 5' of POM121L12		ESC, OVRY				Bcl6b,CEBPB,Hsf,STAT
28	rs74629733	1	24560	182kb 5' of POM121L12		ESC, OVRY				
	SNP	r^{2(a)}	Distance^b	Location	Promoter^c	Enhancer^d	DNase^e	Proteins^f	eQTL^g	Motifs^h
29	rs77873291	1	24520	182kb 5' of POM121L12		OVRY				AIRE,Gfi1,Ik-2,NF-AT,Pou2f2
30	rs77842860	1	24385	182kb 5' of POM121L12		OVRY				HNF1,Mef2,Pbx-1
31	rs75082417	1	24370	182kb 5' of POM121L12		OVRY				Pou2f2
32	rs11765529	1	23722	181kb 5' of POM121L12						HDAC2,Zbtb3
33	rs11769735	1	23708	181kb 5' of POM121L12						
34	rs11772201	1	23704	181kb 5' of POM121L12						Arid5b
35	rs11769032	1	23691	181kb 5' of POM121L12						Arid5b,Fox,p300
36	rs78683211	1	23505	181kb 5' of POM121L12						Arid5a,Foxa,Pou5f1,Sox
37	rs75960827	1	23121	181kb 5' of POM121L12						Arid5b,Cdx2,Hoxa10,Hoxb13,Hoxb9,Hoxd10,Pou2f2,Sox
38	rs77416190	1	22654	180kb 5' of POM121L12						Foxa,Foxf1,TCF12,p300
39	rs111384348	1	22307	180kb 5' of POM121L12						
40	rs11767295	1	22045	179kb 5' of POM121L12						CEBPB,GATA,XBP-1,p300
41	rs11767394	1	21753	179kb 5' of POM121L12						Foxa
42	rs11767396	1	21736	179kb 5' of POM121L12						
43	rs11760456	1	21678	179kb 5' of POM121L12						Cdx,Evi-1,Foxj1,TATA
44	rs112287825	1	21195	179kb 5' of POM121L12						HNF4,Pou2f2,RAR,RXR::LXR,RXRA,TATA
45	rs112743003	1	21086	178kb 5' of POM121L12						AhR,Egr-1,Pax-6,RFX5
46	rs77462617	1	20423	178kb 5' of POM121L12						
47	rs77737967	1	20296	178kb 5' of POM121L12						RXRA
48	rs111231293	1	19389	177kb 5' of POM121L12						Evi-1,FAC1
49	rs11773824	1	18959	176kb 5' of POM121L12						Foxk1,Foxp1,Irf,Mef2
50	rs11763206	1	18930	176kb 5' of POM121L12						Arnt,E2A,Mtf1,Myc,Rad21
51	rs11770293	1	18761	176kb 5' of POM121L12						GATA
52	rs75553733	1	17969	175kb 5' of POM121L12						Foxj2,PLZF,Pou3f2,Sox,TATA
53	rs113629168	1	17823	175kb 5' of POM121L12						
54	rs17692657	1	17523	175kb 5' of POM121L12						AP-1,E2F,Foxp1,Irf,NF-Y,Pbx3,RFX5,SP1,SP2,Znf143
55	rs79478382	1	17334	175kb 5' of POM121L12						LUN-1,Roaz
56	rs74496138	1	17287	175kb 5' of POM121L12						Hdx,NF-Y,STAT
57	rs77799175	1	17267	175kb 5' of POM121L12						TATA

58	rs111781807	1	16981	174kb 5' of POM121L12						ERalpha-a,ZID
59	rs112685756	1	16615	174kb 5' of POM121L12						AP-1,ELF1
	SNP	r^{2(a)}	Distance^b	Location	Promoter^c	Enhancer^d	DNase^e	Proteins^f	eQTL^g	Motifs^h
60	rs10488501	1	16218	174kb 5' of POM121L12						Evi-1,GATA,Hltf
61	rs113188931	1	15714	173kb 5' of POM121L12						CTCF,E2A,ERalpha-a,Esr2,Mrg,SREBP,Tgif1
62	rs80001306	1	15387	173kb 5' of POM121L12		VAS				HNF4,Pax-4
63	rs77106104	1	15257	173kb 5' of POM121L12						Bbx,Bsx,Cart1,Dbx2,Esx1,Foxj2,Gbx1,HMG-IY, Hoxa5, Hoxa7, Hoxb7, Hoxd8, Lhx3, Ncx, Nkx6-1, Pax-4, Pou2f2, Pou3f2, Pou3f4, Pou6f1
64	rs113303892	1	15075	172kb 5' of POM121L12						Crx,Gsc,Obox3,Otx2,Pitx3,RORalpha1,RREB-1,SIX5
65	rs111886202	1	14855	172kb 5' of POM121L12						Mef2
66	rs75350842	1	14712	172kb 5' of POM121L12						CDP,Pax-4,Pou2f2,Pou3f2
67	rs112225991	1	14669	172kb 5' of POM121L12						Pax-4,Spz1
68	rs4358759	1	14140	172kb 5' of POM121L12						
69	rs11762984	1	13796	171kb 5' of POM121L12			PANC			ATF3
70	rs77503606	1	13578	171kb 5' of POM121L12						
71	rs77874117	1	13456	171kb 5' of POM121L12						Mrg1::Hoxa9
72	rs112393748	1	13093	171kb 5' of POM121L12			IPSC			Foxp3,Nkx3,SIX5
73	rs11771017	1	12782	170kb 5' of POM121L12						Arid5b,LBP-1,TATA
74	rs11760967	1	12545	170kb 5' of POM121L12						AIRE
75	rs11761682	1	12258	170kb 5' of POM121L12						
76	rs112670870	1	11785	169kb 5' of POM121L12						Dobox4,Nkx3
77	rs77846464	1	11602	169kb 5' of POM121L12						AIRE,CIZ,DMRT1
78	rs77201830	1	11275	169kb 5' of POM121L12	VAS					
79	rs76176075	1	11228	169kb 5' of POM121L12	VAS					CTCF,Mef2,Rad21
80	rs76947106	1	11085	168kb 5' of POM121L12	VAS					STAT,Sox,ZEB1
81	rs113653466	1	10431	168kb 5' of POM121L12						Foxm1,Nkx2,Nkx3,YY1
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83	rs112321404	1	9929	167kb 5' of POM121L12						Tgif1
84	rs113117967	1	9599	167kb 5' of POM121L12						FAC1,Foxo,Foxp1,Pax-4,RREB-1, SIX5, STAT, Zfp105
85	rs11765486	1	8758	166kb 5' of POM121L12						Irx,TR4
86	rs111437435	1	8067	165kb 5' of POM121L12						
87	rs76909095	1	7891	165kb 5' of POM121L12						GATA,Lhx8

88	rs113691255	1	7799	165kb 5' of POM121L12						CDP,CTCF,SEF-1,Sox
89	rs77466972	1	7733	165kb 5' of POM121L12			GI			PLZF,Pou6f1,Zfp187
	SNP	$r^{2(a)}$	Distance^b	Location	Promoter^c	Enhancer^d	DNase^e	Proteins^f	eQTL^g	Motifs^h
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91	rs74687520	1	7303	165kb 5' of POM121L12						EWSR1-FLI1,Ik-1,TFII-I
92	rs117249146	1	6987	164kb 5' of POM121L12						Foxp1,HDAC2,HMG-IY,HNF1,Mef2,TATA
93	rs75267662	1	6106	164kb 5' of POM121L12			IPSC			Maf,Sox
94	rs77267459	1	6084	163kb 5' of POM121L12			IPSC			
95	rs78645775	1	5085	162kb 5' of POM121L12						RFX5,ZEB1,Zfp105
96	rs76627272	1	5025	162kb 5' of POM121L12						DBP,Fox,Foxa,Foxd1,Foxd3,Foxi1,Foxj1,Foxj2,Foxq1,HDA C2,Hmx,NF-Y,p300
97	rs6977746	1	4547	162kb 5' of POM121L12						CEBPB,Evi-1,HNF1,Mef2,Osf2,PEBP,Pax-4
98	rs6958403	1	4474	162kb 5' of POM121L12						ERalpha-a,PLZF,Pax-5,RXRA
99	rs6943949	1	4455	162kb 5' of POM121L12						GATA,ZEB1
100	rs112665251	1	4001	161kb 5' of POM121L12			BLD			Nanog
101	rs111700951	1	3684	161kb 5' of POM121L12						BAF155,Mef2,Myc
102	rs111787575	1	3404	161kb 5' of POM121L12						HNF4,Maf,NR4A,SREBP
103	rs111972542	1	3322	161kb 5' of POM121L12						Ets,Myf,ZEB1,Znf143
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106	rs112779901	1	3212	161kb 5' of POM121L12						Ik-1,NRSF,Zfx
107	rs77470508	1	2627	160kb 5' of POM121L12						PLAG1,RREB-1,TBX5
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111	rs77618686	1	1532	159kb 5' of POM121L12						Homez
112	rs76355749	1	1219	159kb 5' of POM121L12						Evi-1,Pou1f1
113	rs75588263	1	1082	158kb 5' of POM121L12						VDR
114	rs6978398	1	630	158kb 5' of POM121L12						CDP
115	rs7779800	1	169	158kb 5' of POM121L12						Foxq1,HNF4
116	rs7798662	1	0	157kb 5' of POM121L12						Smad3
117	rs74777222	1	339	157kb 5' of POM121L12						Evi-1

118	rs117339222	0.87	900	157kb 5' of POM121L12						Foxc1,Pax-4
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³Pair-wise correlation (r^2) with rs7798662, ⁴Distance from rs7798662 (bp), ^{5,6}Tissue/cell types in which indicated chromatin marks were detected (NIH Roadmap Epigenomics Consortium), ⁷DNase hypersensitivity (Roadmap), ⁸Protein recruitment determined by chromatin-immunoprecipitation (ENCODE), ⁹Evidence for expression quantitative trait locus (eQTL) (Y: Yes), ¹⁰Predicted binding motifs altered. Annotations extracted from HaploReg-v4 and Regulome-DB. Abbreviations for tissue/cell types accessible online.