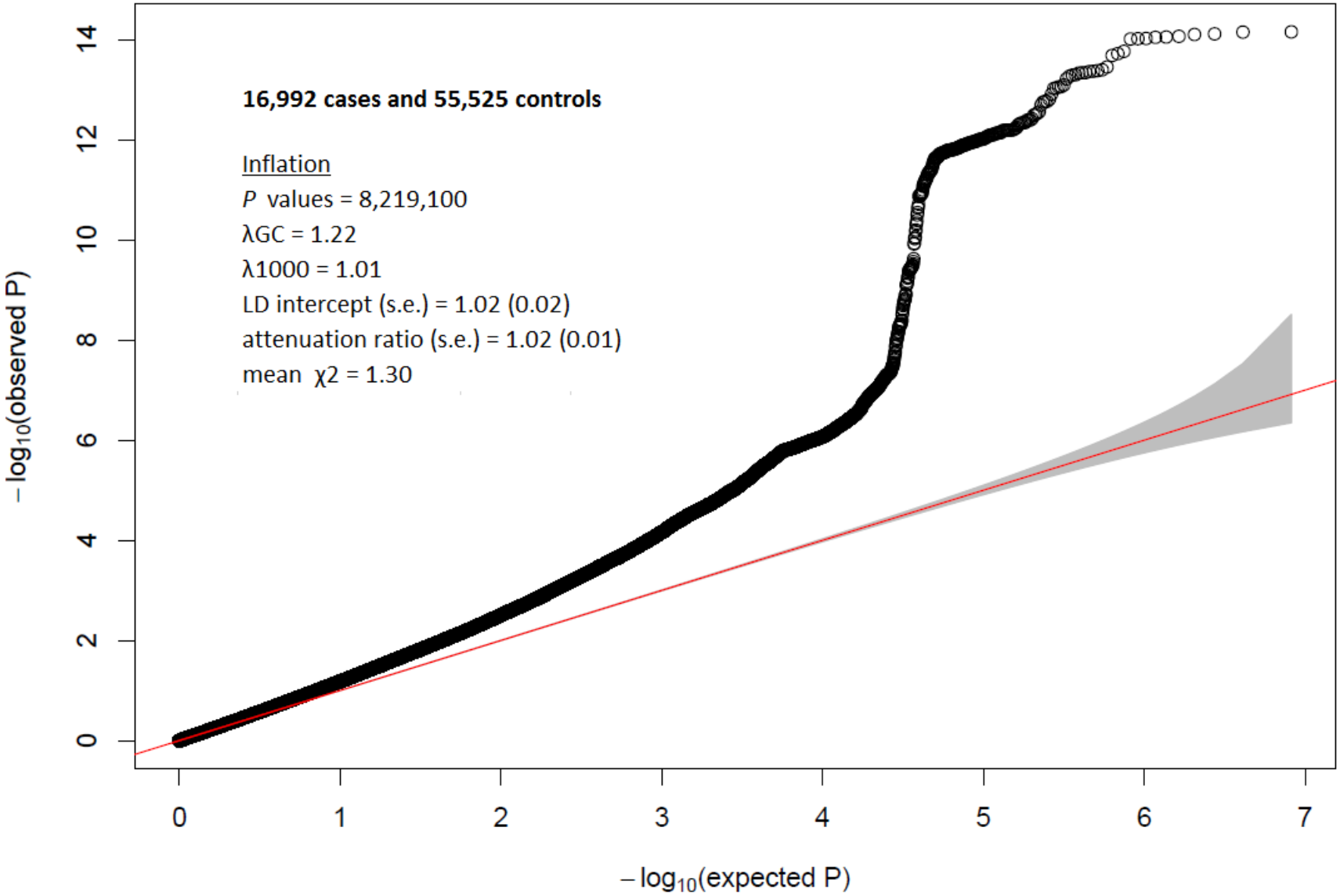
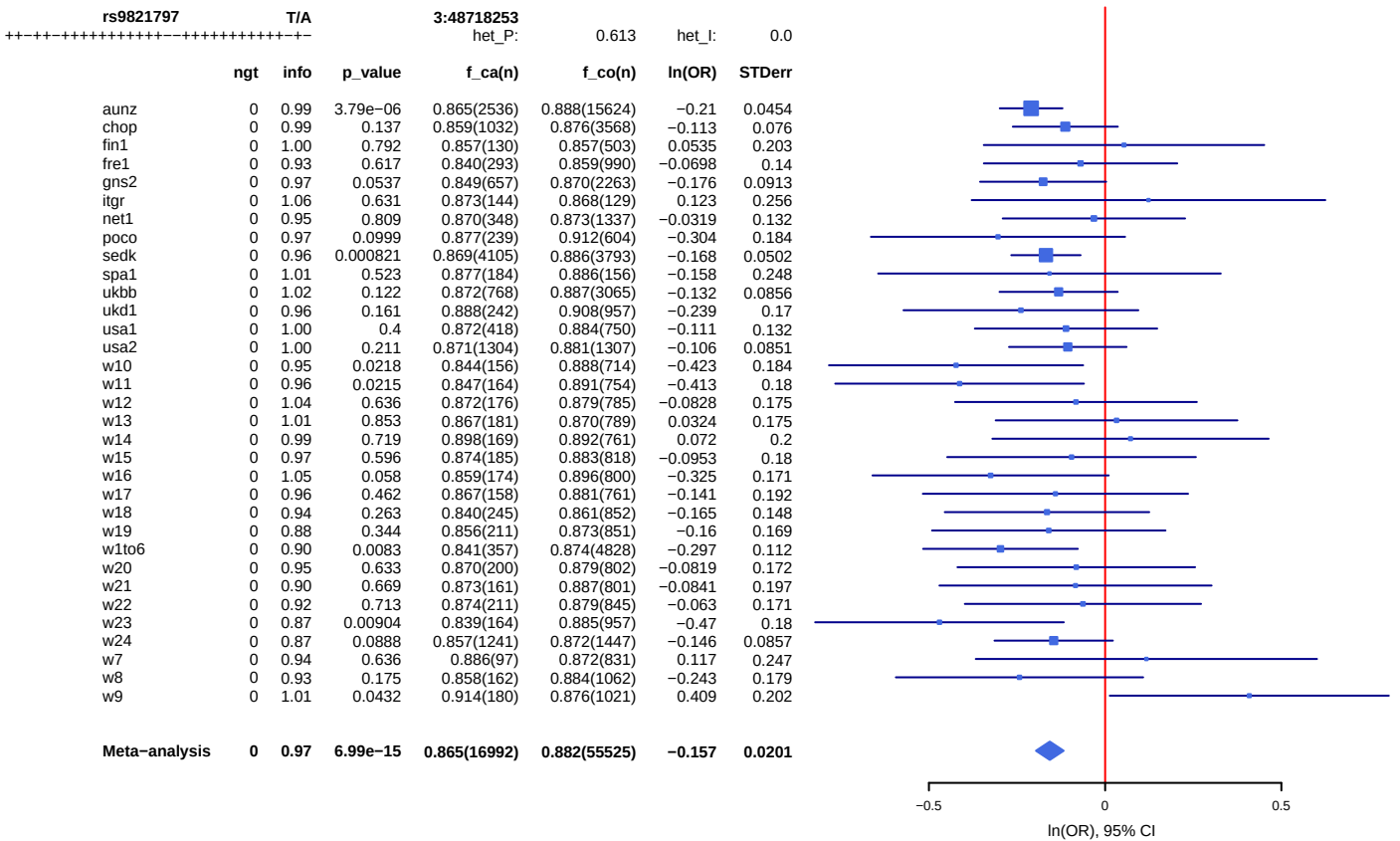
Supplementary Figure 1. Quantile-quantile (QQ) plot of association P values for the meta-analysis of anorexia nervosa (MAF ≥ 0.01 and INFO score ≥ 0.7). The red diagonal line shows the theoretical null distribution. The shading shows the 95% confidence interval bounds. MAF = minor allele frequency and INFO = imputation quality score.



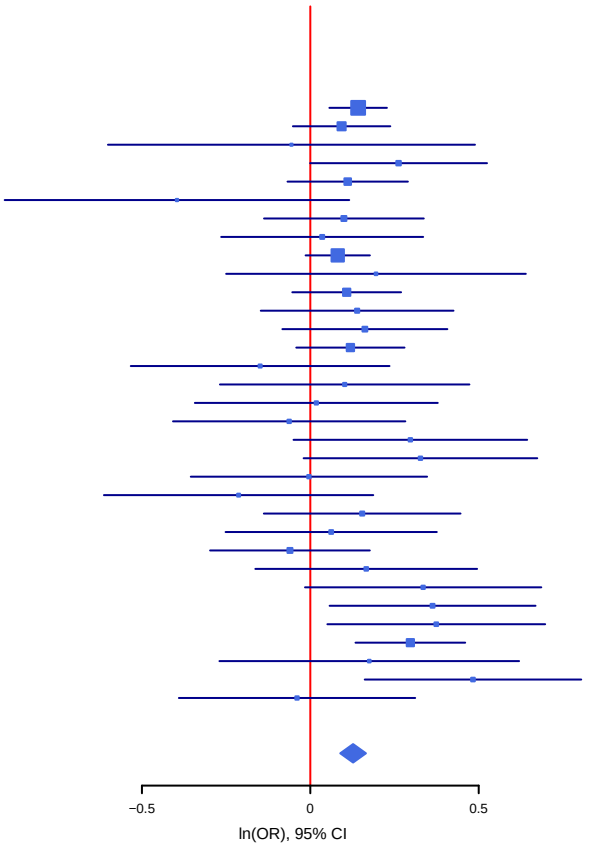
Supplementary Figure 2a-h legend. Forest plots of GWAS meta-analysis results for all genome-wide significant SNPs ($P < 5 \times 10^{-8}$). The overall sample size is 16,992 cases and 55,525 controls. For specific cohort sample sizes, see Supplementary Table 1. Two SNPs were located in regions that overlapped (index SNPs of rs9821797 and rs73088112), therefore we refer to only one of these (rs9821797) in the main manuscript. The red vertical line is the reference line of no effect. The center values are ln(OR) estimates from logistic regression association analyses and the error bars show the 95% confidence interval.

(a) chr3:rs9821797.



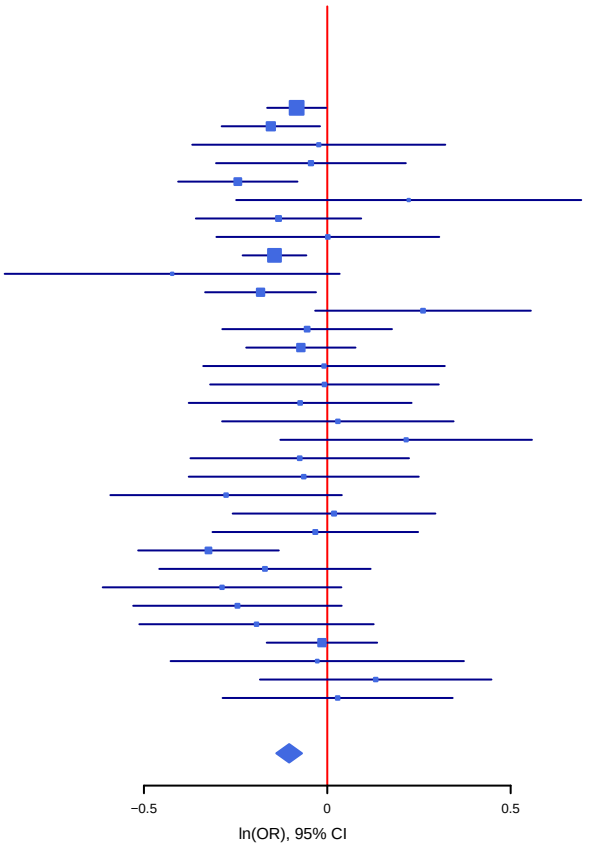
(b) chr11:6589488.

	rs6589488		A/T		11:115096956			
					het_P:	0.339	het_I:	7.9
		ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
	aunz	0	0.96	0.00117	0.152(2536)	0.135(15624)	0.142	0.0436
	chop	0	0.94	0.208	0.158(1032)	0.148(3568)	0.0929	0.0738
	fin1	0	0.92	0.84	0.076(130)	0.078(503)	−0.056	0.278
	fre1	0	0.94	0.0509	0.180(293)	0.145(990)	0.262	0.134
	gns2	0	0.92	0.223	0.157(657)	0.146(2263)	0.111	0.0912
	itgr	0	0.87	0.13	0.140(144)	0.175(129)	−0.396	0.261
	net1	0	0.98	0.41	0.157(348)	0.151(1337)	0.0997	0.121
	poco	0	0.92	0.818	0.179(239)	0.173(604)	0.0352	0.153
	sedk	0	0.98	0.0947	0.136(4105)	0.123(3793)	0.0814	0.0487
	spa1	0	0.93	0.39	0.173(184)	0.148(156)	0.195	0.227
	ukbb	0	0.97	0.19	0.148(768)	0.136(3065)	0.108	0.0824
	ukd1	0	0.96	0.339	0.157(242)	0.139(957)	0.139	0.146
	usa1	0	0.94	0.197	0.157(418)	0.140(750)	0.162	0.125
	usa2	0	0.96	0.146	0.148(1304)	0.135(1307)	0.119	0.082
	w10	0	0.90	0.449	0.132(156)	0.146(714)	−0.149	0.196
	w11	0	0.91	0.589	0.135(164)	0.123(754)	0.102	0.189
	w12	0	0.90	0.923	0.133(176)	0.132(785)	0.0178	0.184
	w13	0	0.91	0.721	0.149(181)	0.148(789)	−0.0628	0.176
	w14	0	0.95	0.0925	0.150(169)	0.118(761)	0.297	0.177
	w15	0	0.93	0.0641	0.147(185)	0.112(818)	0.327	0.177
	w16	0	0.91	0.982	0.144(174)	0.141(800)	−0.00411	0.179
	w17	0	0.90	0.297	0.114(158)	0.140(761)	−0.213	0.204
	w18	0	0.96	0.302	0.150(245)	0.132(852)	0.154	0.149
	w19	0	0.94	0.698	0.150(211)	0.143(851)	0.062	0.16
	w1to6	0	0.93	0.619	0.126(357)	0.133(4828)	−0.0605	0.121
	w20	0	0.89	0.323	0.150(200)	0.133(802)	0.166	0.168
	w21	0	0.92	0.0614	0.158(161)	0.120(801)	0.335	0.179
	w22	0	0.96	0.0198	0.164(211)	0.121(845)	0.363	0.156
	w23	0	0.95	0.0235	0.175(164)	0.131(957)	0.374	0.165
	w24	0	0.92	0.000345	0.154(1241)	0.122(1447)	0.297	0.0831
	w7	0	0.91	0.439	0.148(97)	0.124(831)	0.175	0.227
	w8	0	0.93	0.00317	0.189(162)	0.129(1062)	0.483	0.164
	w9	0	0.95	0.825	0.123(180)	0.127(1021)	−0.0395	0.179
	Meta−analysis	**0**	**0.95**	**6.31e−11**	**0.148(16992)**	**0.134(55525)**	**0.127**	**0.0195**



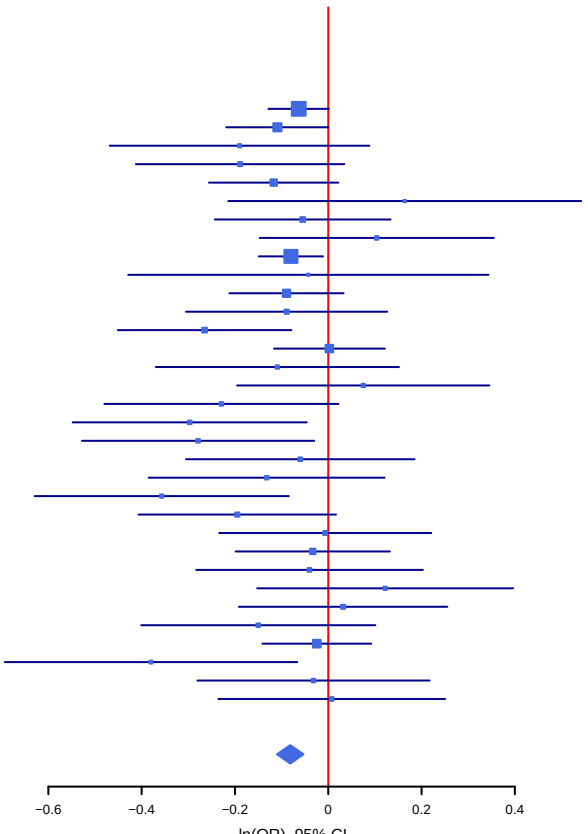
(c) chr2:2287348.

	rs2287348		C/T		2:54039813			
					het_P:	0.309	het_I:	9.7
		ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
	aunz	0	0.99	0.0412	0.830(2536)	0.843(15624)	−0.0836	0.041
	chop	1	1.01	0.0244	0.822(1032)	0.845(3568)	−0.154	0.0684
	fin1	1	1.01	0.894	0.796(130)	0.804(503)	−0.0233	0.176
	fre1	0	0.99	0.735	0.834(293)	0.835(990)	−0.0446	0.132
	gns2	0	0.98	0.00322	0.808(657)	0.845(2263)	−0.244	0.083
	itgr	1	0.96	0.355	0.851(144)	0.818(129)	0.222	0.24
	net1	1	0.97	0.247	0.816(348)	0.835(1337)	−0.133	0.115
	poco	0	1.04	0.993	0.849(239)	0.839(604)	0.0014	0.155
	sedk	0	0.99	0.00112	0.830(4105)	0.848(3793)	−0.144	0.0443
	spa1	0	1.02	0.0693	0.824(184)	0.884(156)	−0.423	0.233
	ukbb	1	1.00	0.0184	0.829(768)	0.853(3065)	−0.182	0.0771
	ukd1	1	1.00	0.0823	0.872(242)	0.840(957)	0.261	0.15
	usa1	1	0.99	0.64	0.830(418)	0.839(750)	−0.055	0.118
	usa2	0	1.00	0.343	0.834(1304)	0.844(1307)	−0.0721	0.076
	w10	0	1.02	0.958	0.833(156)	0.833(714)	−0.00894	0.168
	w11	0	1.01	0.961	0.821(164)	0.823(754)	−0.00773	0.159
	w12	0	1.02	0.634	0.826(176)	0.840(785)	−0.074	0.155
	w13	0	1.02	0.858	0.845(181)	0.836(789)	0.0288	0.161
	w14	0	1.05	0.219	0.873(169)	0.846(761)	0.215	0.175
	w15	0	0.98	0.622	0.819(185)	0.825(818)	−0.0752	0.152
	w16	0	1.00	0.688	0.828(174)	0.837(800)	−0.0642	0.16
	w17	0	0.99	0.0858	0.791(158)	0.838(761)	−0.276	0.161
	w18	0	0.99	0.896	0.841(245)	0.838(852)	0.0184	0.141
	w19	0	1.01	0.819	0.822(211)	0.827(851)	−0.0327	0.143
	w1to6	0	0.98	0.000925	0.792(357)	0.839(4828)	−0.324	0.0978
	w20	0	1.05	0.247	0.828(200)	0.851(802)	−0.17	0.147
	w21	0	0.99	0.0831	0.823(161)	0.856(801)	−0.287	0.166
	w22	0	1.00	0.0899	0.820(211)	0.853(845)	−0.245	0.145
	w23	0	0.95	0.237	0.821(164)	0.845(957)	−0.193	0.163
	w24	0	0.97	0.85	0.843(1241)	0.845(1447)	−0.0146	0.0768
	w7	0	1.00	0.893	0.825(97)	0.833(831)	−0.0274	0.204
	w8	0	1.04	0.413	0.845(162)	0.825(1062)	0.132	0.161
	w9	0	1.00	0.86	0.847(180)	0.844(1021)	0.0282	0.16
	Meta−analysis	**7**	**0.99**	**5.62e−09**	**0.830(16992)**	**0.842(55525)**	**−0.104**	**0.0179**



(d) chr10:rs2008387.

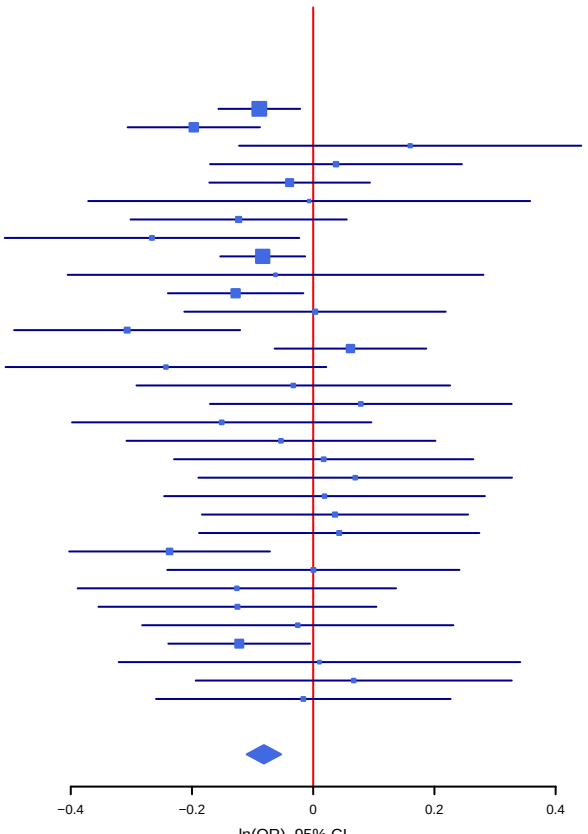
rs2008387		G/A		10:131448764			
				het_P:	0.358	het_I:	6.7
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.93	0.0565	0.650(2536)	0.663(15624)	−0.0633	0.0332
chop	0	0.93	0.0522	0.638(1032)	0.668(3568)	−0.109	0.056
fin1	0	1.01	0.182	0.556(130)	0.600(503)	−0.19	0.142
fre1	0	0.82	0.0967	0.653(293)	0.687(990)	−0.189	0.114
gns2	0	0.89	0.0999	0.653(657)	0.677(2263)	−0.117	0.0708
itgr	0	0.94	0.397	0.677(144)	0.642(129)	0.164	0.193
net1	0	0.93	0.569	0.680(348)	0.698(1337)	−0.0548	0.0961
poco	0	0.91	0.414	0.693(239)	0.661(604)	0.104	0.128
sedk	0	0.93	0.0226	0.645(4105)	0.661(3793)	−0.08	0.0351
spa1	0	0.77	0.829	0.677(184)	0.676(156)	−0.0427	0.197
ukbb	0	0.93	0.153	0.652(768)	0.670(3065)	−0.0895	0.0625
ukd1	0	0.97	0.416	0.653(242)	0.674(957)	−0.0893	0.11
usa1	0	0.93	0.0052	0.622(418)	0.674(750)	−0.265	0.0949
usa2	0	0.94	0.969	0.652(1304)	0.654(1307)	0.0024	0.0606
w10	0	0.99	0.413	0.643(156)	0.664(714)	−0.109	0.133
w11	0	0.92	0.586	0.692(164)	0.677(754)	0.0751	0.138
w12	0	0.95	0.0747	0.645(176)	0.696(785)	−0.229	0.128
w13	0	0.92	0.0199	0.620(181)	0.679(789)	−0.297	0.128
w14	0	0.99	0.0276	0.617(169)	0.681(761)	−0.279	0.127
w15	0	0.96	0.632	0.648(185)	0.665(818)	−0.06	0.125
w16	0	0.97	0.307	0.658(174)	0.681(800)	−0.132	0.129
w17	0	0.93	0.00996	0.635(158)	0.706(761)	−0.357	0.139
w18	0	0.99	0.0714	0.630(245)	0.675(852)	−0.195	0.108
w19	0	1.02	0.956	0.672(211)	0.671(851)	−0.00652	0.116
w1to6	0	0.95	0.693	0.666(357)	0.674(4828)	−0.0332	0.0844
w20	0	0.94	0.745	0.675(200)	0.683(802)	−0.0402	0.124
w21	0	0.93	0.383	0.706(161)	0.676(801)	0.122	0.14
w22	0	1.02	0.779	0.660(211)	0.653(845)	0.0319	0.114
w23	0	1.00	0.241	0.656(164)	0.685(957)	−0.15	0.128
w24	0	0.95	0.681	0.663(1241)	0.668(1447)	−0.0245	0.0595
w7	0	0.99	0.0175	0.598(97)	0.678(831)	−0.38	0.16
w8	0	1.02	0.803	0.682(162)	0.688(1062)	−0.0317	0.127
w9	0	0.98	0.952	0.667(180)	0.661(1021)	0.00747	0.124
Meta−analysis	**0**	**0.94**	**1.72e−08**	**0.651(16992)**	**0.670(55525)**	**−0.0815**	**0.0145**



(e) chr3:rs9874207.

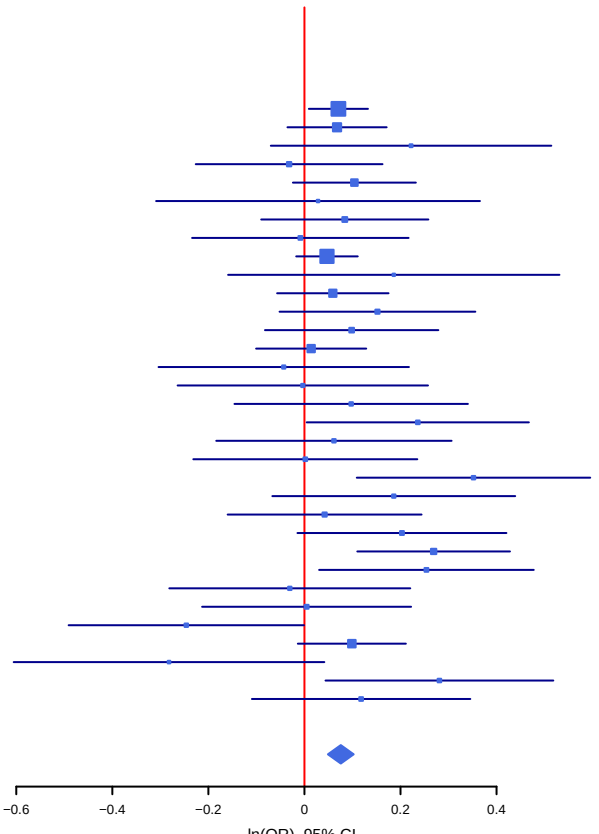
rs9874207 **T/C** **3:71019750**
het_P: 0.212 het_I: 16.0

	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
aunz	0	0.79	0.00971	0.483(2536)	0.500(15624)	−0.0889	0.0344
chop	0	0.87	0.0004	0.472(1032)	0.512(3568)	−0.197	0.0557
fin1	0	0.97	0.265	0.554(130)	0.522(503)	0.16	0.144
fre1	0	0.84	0.723	0.488(293)	0.485(990)	0.0376	0.106
gns2	0	0.88	0.564	0.486(657)	0.492(2263)	−0.0389	0.0676
itgr	0	0.89	0.972	0.469(144)	0.466(129)	−0.00662	0.186
net1	0	0.91	0.178	0.472(348)	0.500(1337)	−0.123	0.091
poco	0	0.86	0.0313	0.452(239)	0.497(604)	−0.266	0.124
sedk	0	0.82	0.0197	0.512(4105)	0.532(3793)	−0.0833	0.0357
spa1	0	0.85	0.723	0.470(184)	0.493(156)	−0.0621	0.175
ukbb	1	1.01	0.0246	0.467(768)	0.499(3065)	−0.128	0.057
ukd1	0	0.87	0.979	0.485(242)	0.486(957)	0.003	0.11
usa1	0	0.86	0.00122	0.450(418)	0.514(750)	−0.307	0.0951
usa2	0	0.77	0.335	0.488(1304)	0.477(1307)	0.0615	0.0638
w10	0	0.87	0.0727	0.460(156)	0.517(714)	−0.243	0.135
w11	0	0.86	0.804	0.485(164)	0.494(754)	−0.0329	0.132
w12	0	0.88	0.535	0.506(176)	0.491(785)	0.0786	0.127
w13	0	0.87	0.233	0.483(181)	0.520(789)	−0.151	0.126
w14	0	0.86	0.683	0.500(169)	0.512(761)	−0.0532	0.13
w15	0	0.87	0.891	0.519(185)	0.518(818)	0.0173	0.126
w16	0	0.83	0.599	0.542(174)	0.527(800)	0.0693	0.132
w17	0	0.88	0.889	0.528(158)	0.524(761)	0.0187	0.135
w18	0	0.86	0.748	0.522(245)	0.517(852)	0.036	0.112
w19	0	0.86	0.716	0.525(211)	0.514(851)	0.0429	0.118
w1to6	0	0.85	0.00504	0.460(357)	0.511(4828)	−0.237	0.0845
w20	0	0.83	0.998	0.538(200)	0.536(802)	0.0003	0.123
w21	0	0.85	0.346	0.500(161)	0.524(801)	−0.126	0.134
w22	0	0.88	0.285	0.489(211)	0.515(845)	−0.125	0.117
w23	0	0.85	0.846	0.513(164)	0.517(957)	−0.0254	0.131
w24	0	0.85	0.0416	0.495(1241)	0.520(1447)	−0.122	0.0597
w7	0	0.84	0.951	0.512(97)	0.507(831)	0.0103	0.169
w8	0	0.81	0.616	0.520(162)	0.510(1062)	0.0669	0.133
w9	0	0.86	0.895	0.512(180)	0.517(1021)	−0.0163	0.124
Meta−analysis	**1**	**0.84**	**2.05e−08**	**0.493(16992)**	**0.507(55525)**	**−0.0813**	**0.0145**



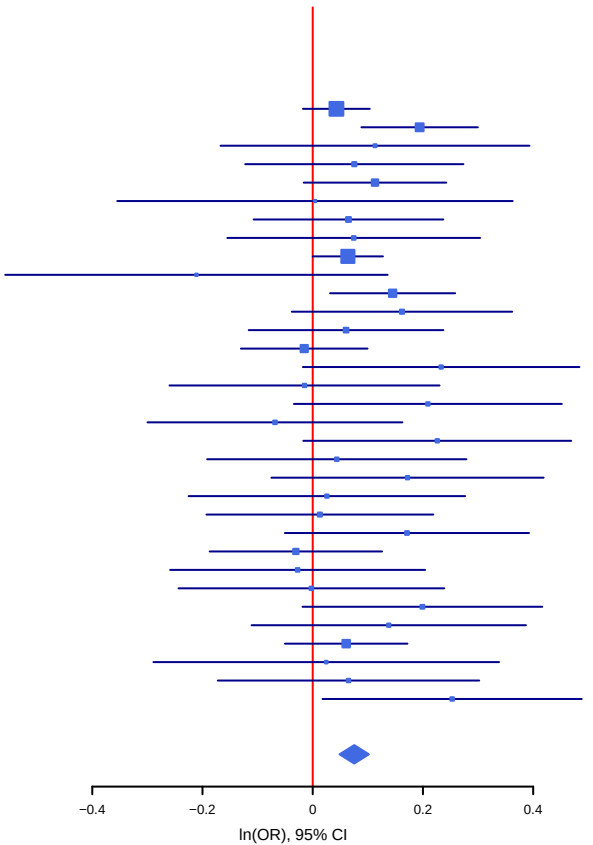
(f) chr1:rs10747478.

rs10747478		T/G		1:96901455			
				het_P:	0.149	het_I:	20.6
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.97	0.0241	0.421(2536)	0.401(15624)	0.0707	0.0314
chop	0	1.00	0.198	0.438(1032)	0.427(3568)	0.0679	0.0527
fin1	0	0.96	0.136	0.411(130)	0.366(503)	0.222	0.149
fre1	0	0.98	0.748	0.415(293)	0.427(990)	−0.0319	0.0992
gns2	0	0.96	0.111	0.455(657)	0.429(2263)	0.104	0.0653
itgr	0	1.04	0.87	0.513(144)	0.500(129)	0.0283	0.172
net1	0	0.96	0.344	0.437(348)	0.420(1337)	0.084	0.0888
poco	0	0.98	0.941	0.439(239)	0.447(604)	−0.00854	0.115
sedk	0	1.00	0.151	0.430(4105)	0.421(3793)	0.0469	0.0327
spa1	0	0.93	0.291	0.419(184)	0.387(156)	0.186	0.176
ukbb	0	0.96	0.318	0.419(768)	0.405(3065)	0.0591	0.0592
ukd1	0	1.01	0.146	0.417(242)	0.376(957)	0.152	0.104
usa1	0	0.93	0.286	0.434(418)	0.410(750)	0.0983	0.0921
usa2	0	0.94	0.811	0.421(1304)	0.419(1307)	0.014	0.0585
w10	0	0.94	0.746	0.418(156)	0.424(714)	−0.0431	0.133
w11	0	0.87	0.98	0.441(164)	0.440(754)	−0.00341	0.133
w12	0	0.94	0.435	0.438(176)	0.415(785)	0.0973	0.124
w13	0	1.02	0.0445	0.465(181)	0.408(789)	0.236	0.118
w14	0	0.96	0.624	0.440(169)	0.424(761)	0.0614	0.125
w15	0	0.99	0.988	0.439(185)	0.430(818)	0.0018	0.119
w16	0	0.96	0.00441	0.482(174)	0.404(800)	0.352	0.124
w17	0	0.98	0.149	0.443(158)	0.386(761)	0.186	0.129
w18	0	1.04	0.683	0.407(245)	0.397(852)	0.042	0.103
w19	0	0.99	0.0667	0.474(211)	0.424(851)	0.203	0.111
w1to6	0	0.93	0.000906	0.479(357)	0.420(4828)	0.269	0.0811
w20	0	0.99	0.0261	0.475(200)	0.411(802)	0.254	0.114
w21	0	0.95	0.812	0.416(161)	0.420(801)	−0.0305	0.128
w22	0	0.99	0.968	0.415(211)	0.412(845)	0.00449	0.111
w23	0	1.00	0.049	0.372(164)	0.427(957)	−0.246	0.125
w24	0	0.95	0.0856	0.421(1241)	0.399(1447)	0.0987	0.0574
w7	0	0.92	0.087	0.367(97)	0.430(831)	−0.282	0.165
w8	0	0.99	0.0203	0.473(162)	0.406(1062)	0.281	0.121
w9	0	1.00	0.308	0.449(180)	0.421(1021)	0.118	0.116
Meta−analysis	**0**	**0.97**	**3.13e−08**	**0.431(16992)**	**0.412(55525)**	**0.0757**	**0.0137**



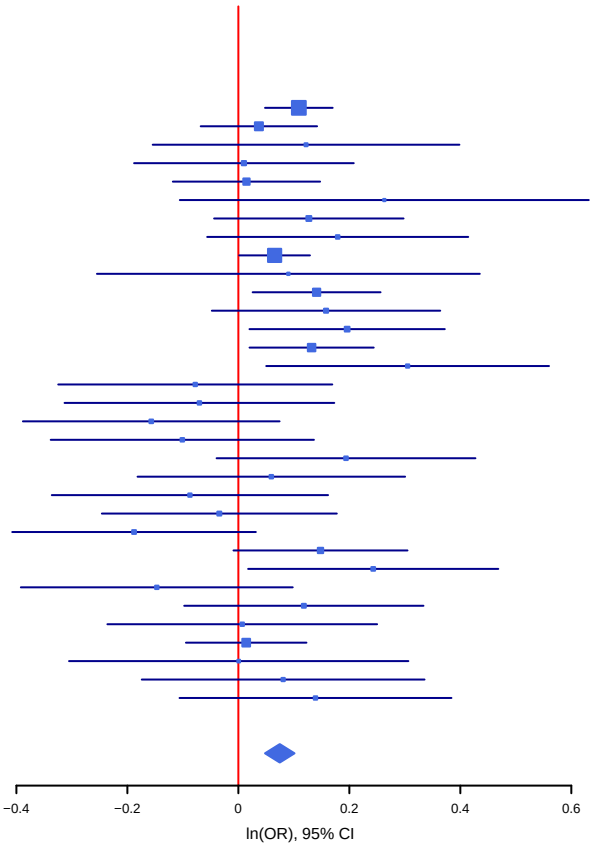
(g) chr5:rs370838138.

rs370838138		G/C		5:25081845			
				het_P:	0.637	het_I:	0.0
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.99	0.164	0.574(2536)	0.560(15624)	0.043	0.0309
chop	0	0.99	0.000315	0.607(1032)	0.563(3568)	0.194	0.0539
fin1	0	0.99	0.429	0.535(130)	0.504(503)	0.113	0.143
fre1	0	0.98	0.455	0.617(293)	0.589(990)	0.0755	0.101
gns2	0	0.95	0.0855	0.590(657)	0.563(2263)	0.113	0.066
itgr	0	0.97	0.982	0.625(144)	0.629(129)	0.00409	0.183
net1	0	1.02	0.46	0.597(348)	0.576(1337)	0.0649	0.0878
poco	0	0.92	0.527	0.546(239)	0.520(604)	0.0744	0.117
sedk	0	1.00	0.0499	0.563(4105)	0.548(3793)	0.0638	0.0325
spa1	0	0.93	0.233	0.609(184)	0.664(156)	−0.211	0.177
ukbb	0	1.01	0.0125	0.592(768)	0.555(3065)	0.145	0.0579
ukd1	0	1.04	0.11	0.578(242)	0.535(957)	0.162	0.102
usa1	0	0.96	0.502	0.588(418)	0.567(750)	0.0605	0.0901
usa2	0	0.95	0.793	0.586(1304)	0.592(1307)	−0.0154	0.0586
w10	0	1.03	0.0683	0.618(156)	0.559(714)	0.233	0.128
w11	0	0.98	0.905	0.568(164)	0.575(754)	−0.0149	0.125
w12	0	0.97	0.0919	0.614(176)	0.565(785)	0.209	0.124
w13	0	1.00	0.563	0.549(181)	0.567(789)	−0.0685	0.118
w14	0	1.02	0.0676	0.622(169)	0.570(761)	0.226	0.124
w15	0	0.95	0.716	0.572(185)	0.562(818)	0.0437	0.12
w16	0	0.96	0.174	0.614(174)	0.573(800)	0.172	0.126
w17	0	0.96	0.841	0.576(158)	0.559(761)	0.0257	0.128
w18	0	0.98	0.902	0.564(245)	0.563(852)	0.013	0.105
w19	0	0.99	0.131	0.614(211)	0.575(851)	0.171	0.113
w1to6	0	0.96	0.702	0.571(357)	0.579(4828)	−0.0306	0.0798
w20	0	0.93	0.816	0.586(200)	0.591(802)	−0.0274	0.118
w21	0	1.04	0.984	0.591(161)	0.590(801)	−0.0024	0.123
w22	0	1.03	0.0724	0.617(211)	0.569(845)	0.199	0.111
w23	0	0.93	0.278	0.595(164)	0.564(957)	0.138	0.127
w24	0	0.96	0.284	0.589(1241)	0.574(1447)	0.0607	0.0567
w7	0	0.93	0.879	0.555(97)	0.558(831)	0.0245	0.16
w8	0	1.00	0.592	0.577(162)	0.562(1062)	0.0649	0.121
w9	0	0.98	0.0358	0.633(180)	0.572(1021)	0.253	0.12
Meta−analysis	**0**	**0.98**	**3.17e−08**	**0.582(16992)**	**0.564(55525)**	**0.0753**	**0.0136**

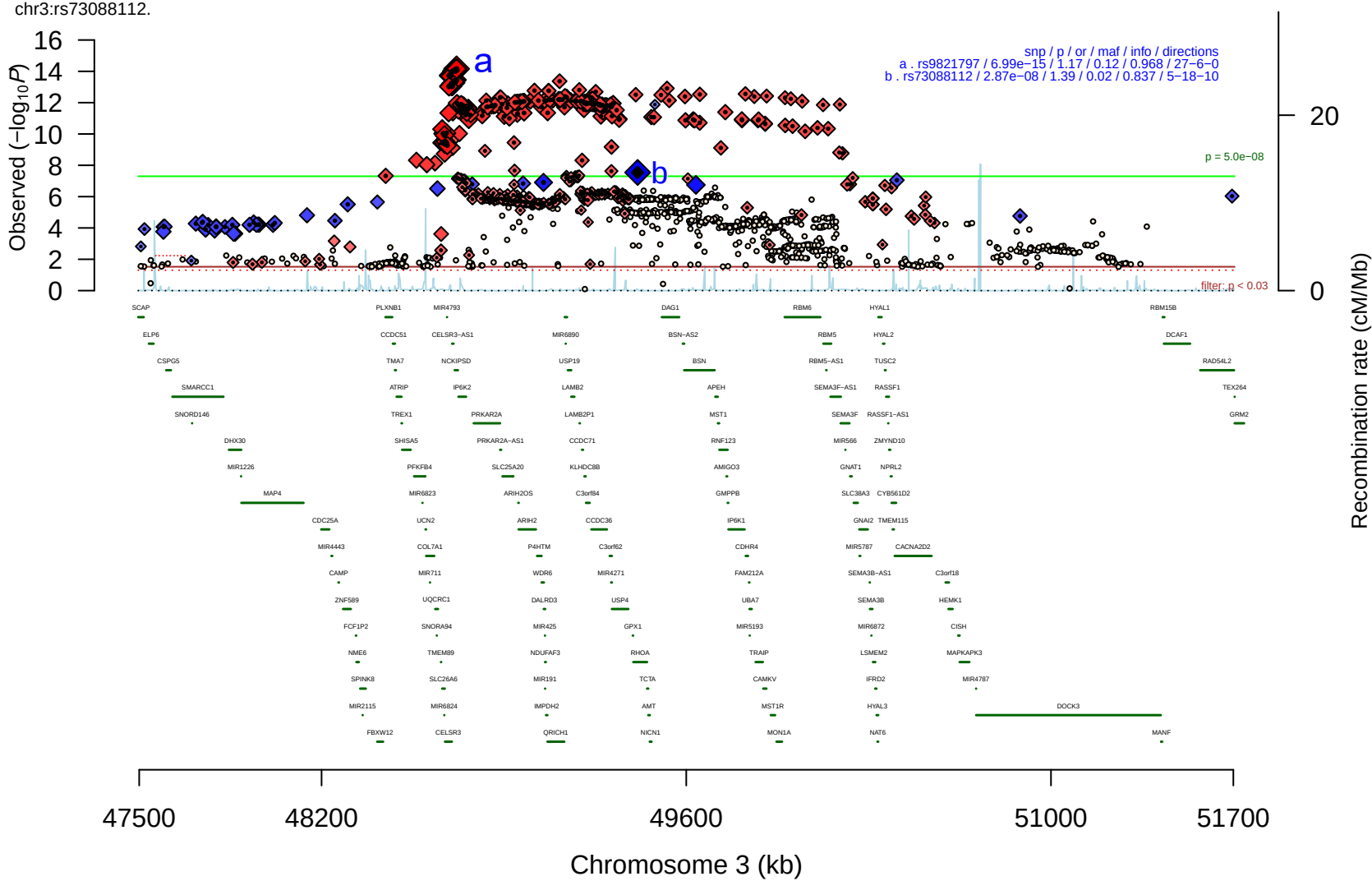


(h) chr3:rs13100344.

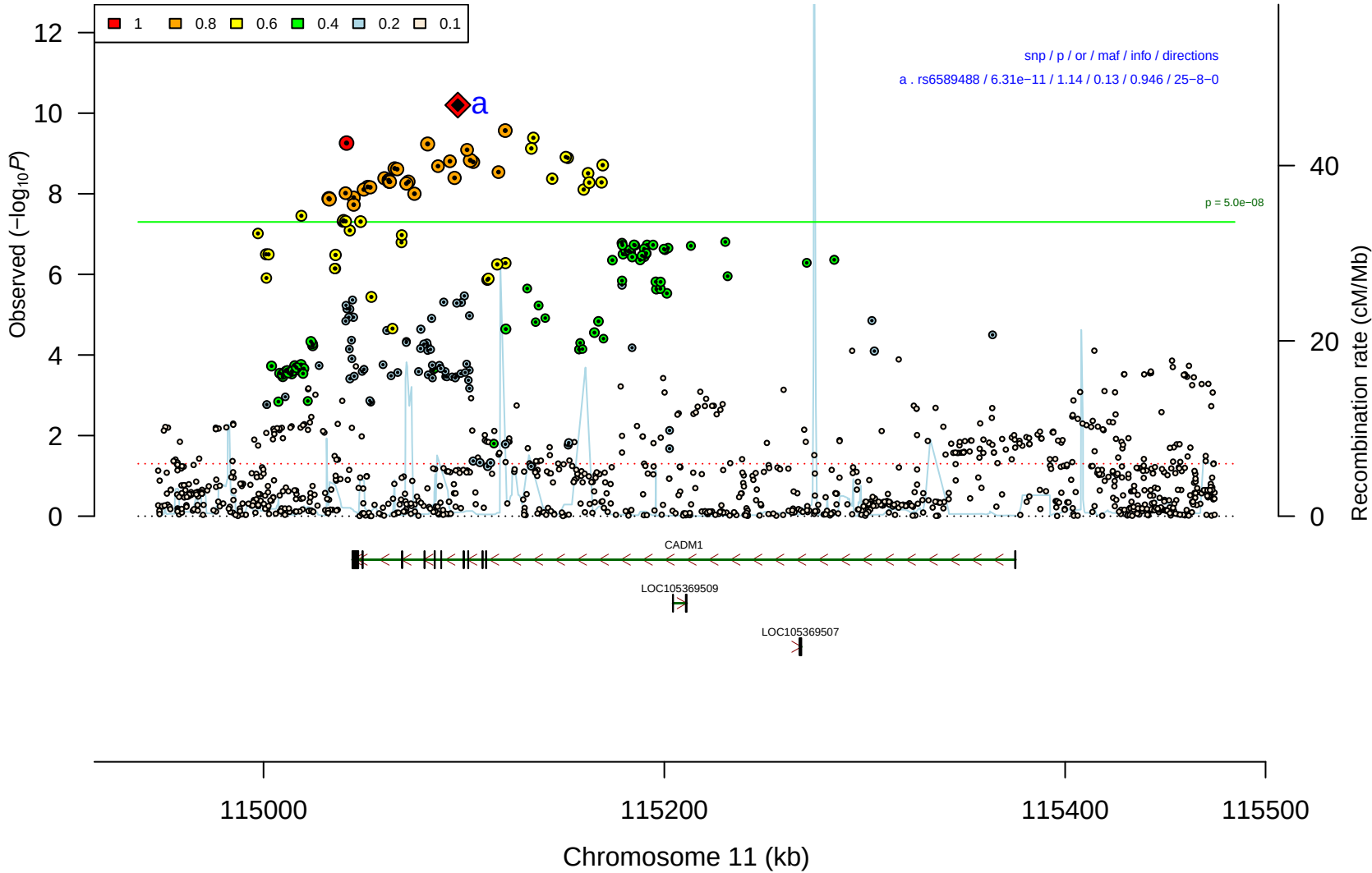
rs13100344		T/A		3:94605107			
				het_P:	0.175	het_I:	18.6
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
aunz	0	0.98	0.000439	0.564(2536)	0.536(15624)	0.109	0.0311
chop	0	0.95	0.489	0.545(1032)	0.541(3568)	0.037	0.0535
fin1	0	1.03	0.388	0.482(130)	0.448(503)	0.122	0.141
fre1	0	0.93	0.921	0.535(293)	0.524(990)	0.01	0.101
gns2	0	0.88	0.829	0.530(657)	0.526(2263)	0.0146	0.0677
itgr	0	0.94	0.162	0.626(144)	0.580(129)	0.263	0.188
net1	0	1.00	0.145	0.534(348)	0.505(1337)	0.127	0.0871
poco	0	0.91	0.135	0.581(239)	0.535(604)	0.179	0.12
sedk	0	0.99	0.0447	0.530(4105)	0.513(3793)	0.0653	0.0325
spa1	0	0.86	0.608	0.550(184)	0.541(156)	0.0901	0.176
ukbb	0	0.97	0.0162	0.581(768)	0.547(3065)	0.141	0.0588
ukd1	0	0.98	0.131	0.585(242)	0.549(957)	0.158	0.105
usa1	0	0.97	0.0291	0.580(418)	0.528(750)	0.196	0.0898
usa2	0	0.97	0.021	0.567(1304)	0.538(1307)	0.132	0.0571
w10	0	0.99	0.0194	0.617(156)	0.547(714)	0.305	0.13
w11	0	0.96	0.539	0.535(164)	0.554(754)	−0.0777	0.126
w12	0	0.92	0.57	0.517(176)	0.534(785)	−0.0702	0.124
w13	0	1.02	0.184	0.513(181)	0.553(789)	−0.157	0.118
w14	0	1.00	0.404	0.528(169)	0.552(761)	−0.101	0.121
w15	0	0.98	0.104	0.582(185)	0.535(818)	0.194	0.119
w16	0	0.97	0.63	0.572(174)	0.553(800)	0.0594	0.123
w17	0	0.98	0.49	0.521(158)	0.543(761)	−0.0873	0.127
w18	0	0.92	0.752	0.526(245)	0.532(852)	−0.0343	0.108
w19	0	0.97	0.0935	0.531(211)	0.571(851)	−0.188	0.112
w1to6	0	0.98	0.0646	0.586(357)	0.551(4828)	0.148	0.08
w20	0	0.98	0.0342	0.574(200)	0.514(802)	0.243	0.115
w21	0	0.98	0.24	0.521(161)	0.553(801)	−0.147	0.125
w22	0	1.00	0.284	0.561(211)	0.535(845)	0.118	0.11
w23	0	0.97	0.955	0.535(164)	0.541(957)	0.00698	0.124
w24	0	0.99	0.8	0.556(1241)	0.553(1447)	0.0141	0.0554
w7	0	0.99	0.997	0.557(97)	0.557(831)	0.0006	0.156
w8	0	0.86	0.534	0.555(162)	0.539(1062)	0.0807	0.13
w9	0	0.86	0.268	0.566(180)	0.536(1021)	0.139	0.125
Meta−analysis	**0**	**0.96**	**4.21e−08**	**0.551(16992)**	**0.537(55525)**	**0.0746**	**0.0136**



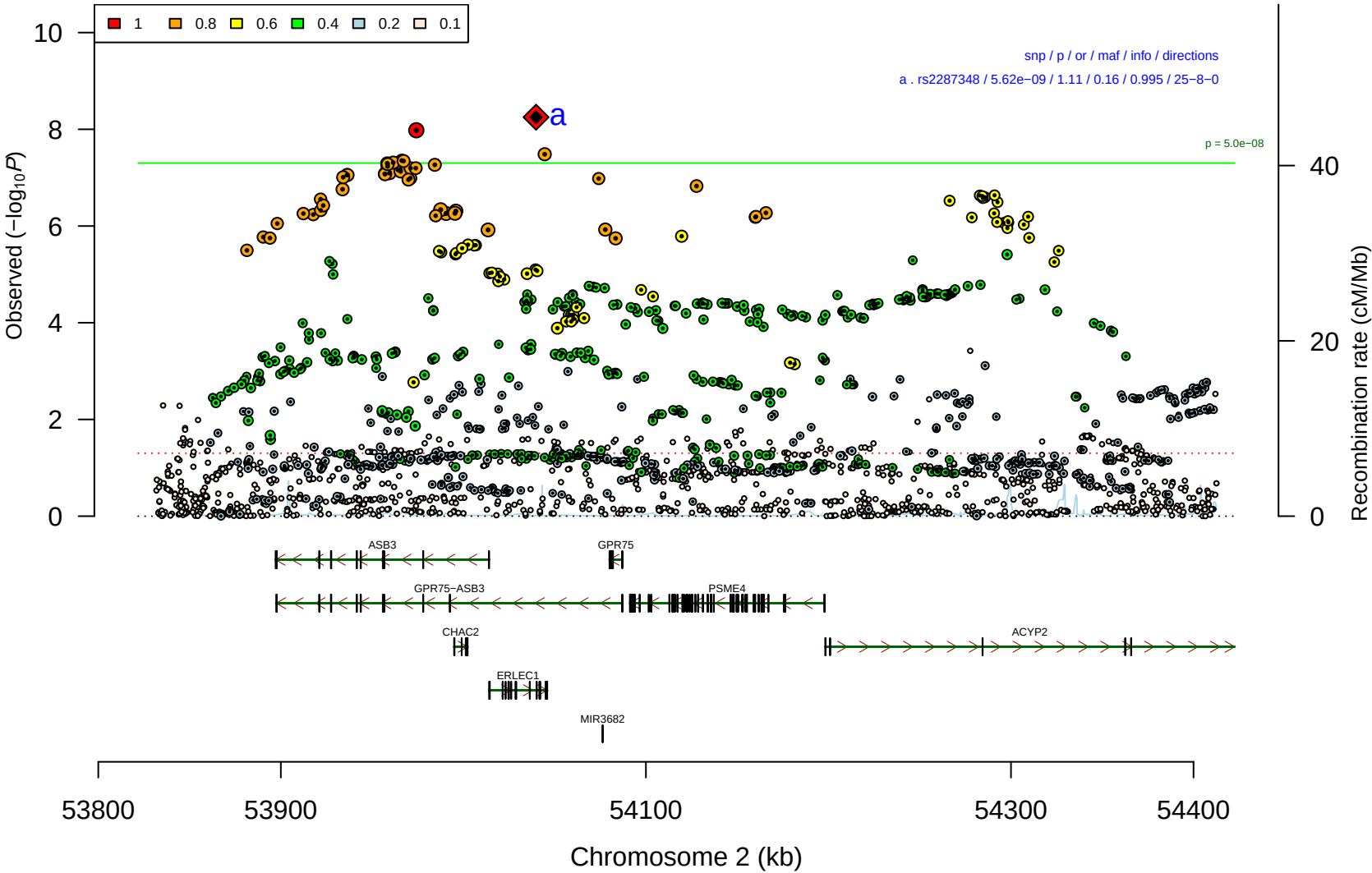
Supplementary Figure 3a-h legend. Regional plot of GWAS meta-analysis results for all genome-wide significant loci. The sample size is 16,992 cases and 55,525 controls. Two loci overlapped (index SNPs of rs9821797 and rs73088112), therefore we refer to only one of these (rs9821797) in the main manuscript. (a) chr3:rs9821797 and chr3:rs73088112.



(b) chr11:6589488.

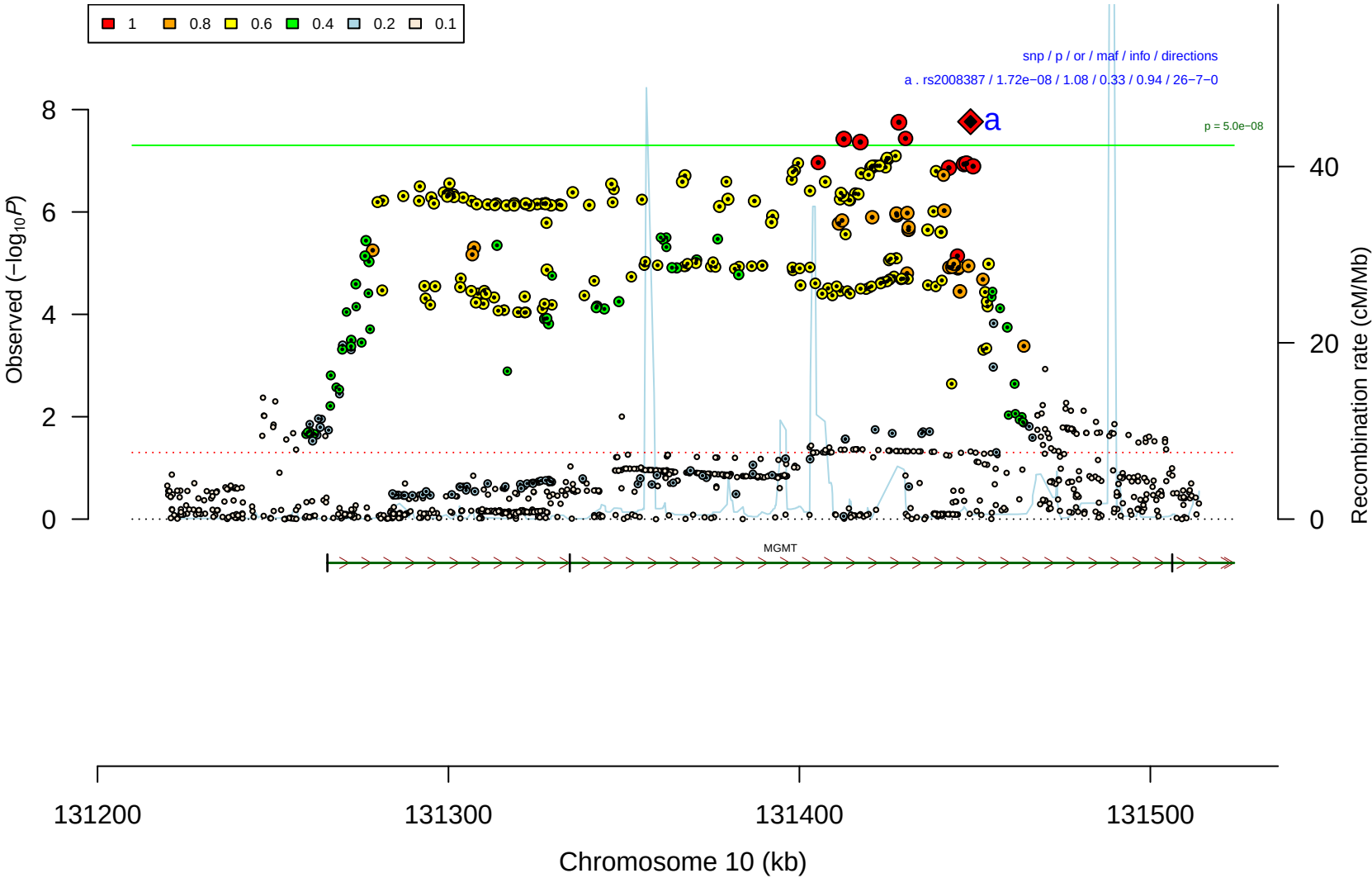


(c) chr2:2287348.

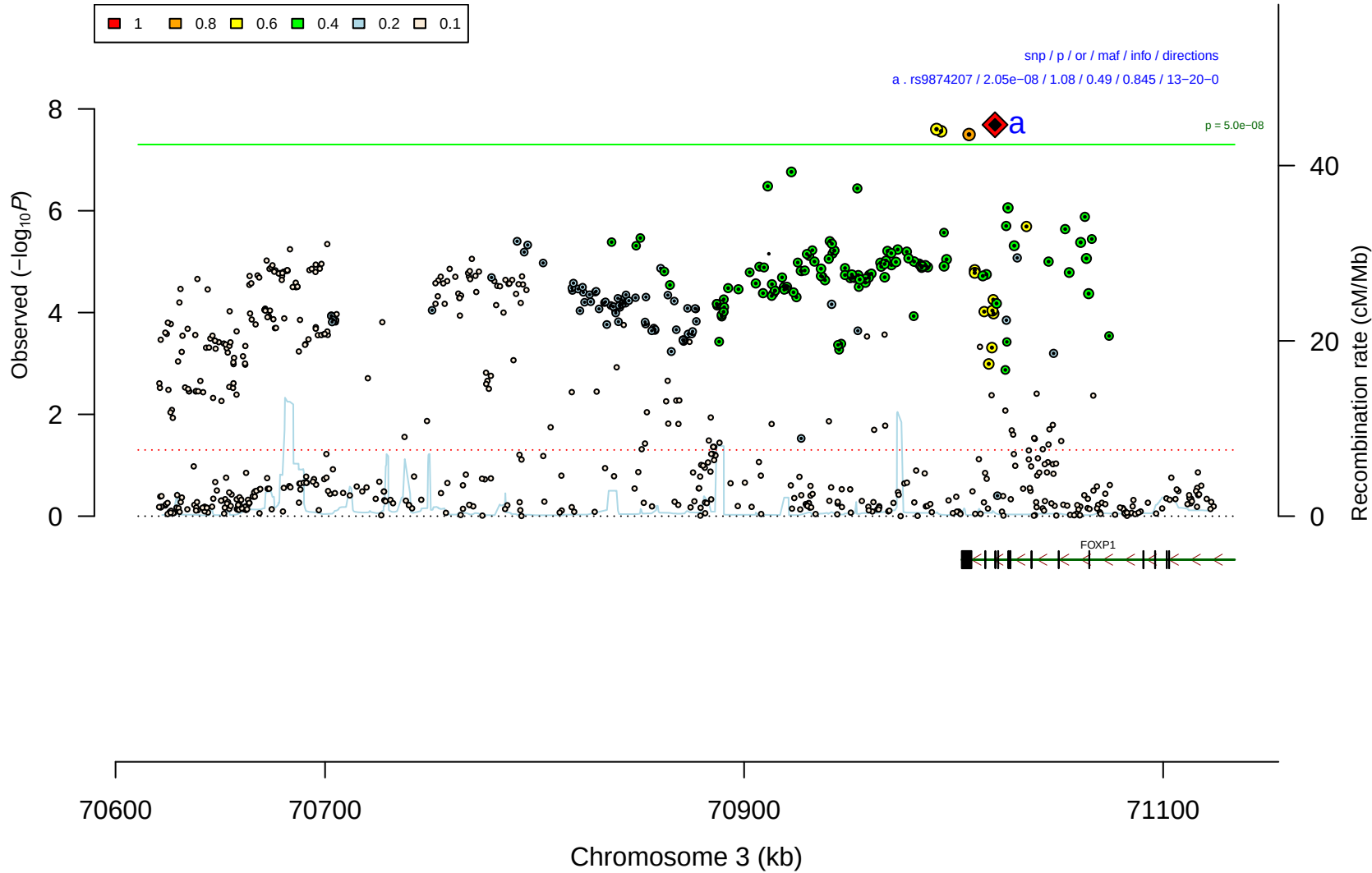


database: gwascatalog.txt.ow.short.new.sorted, refGene.txt.May_2017.out

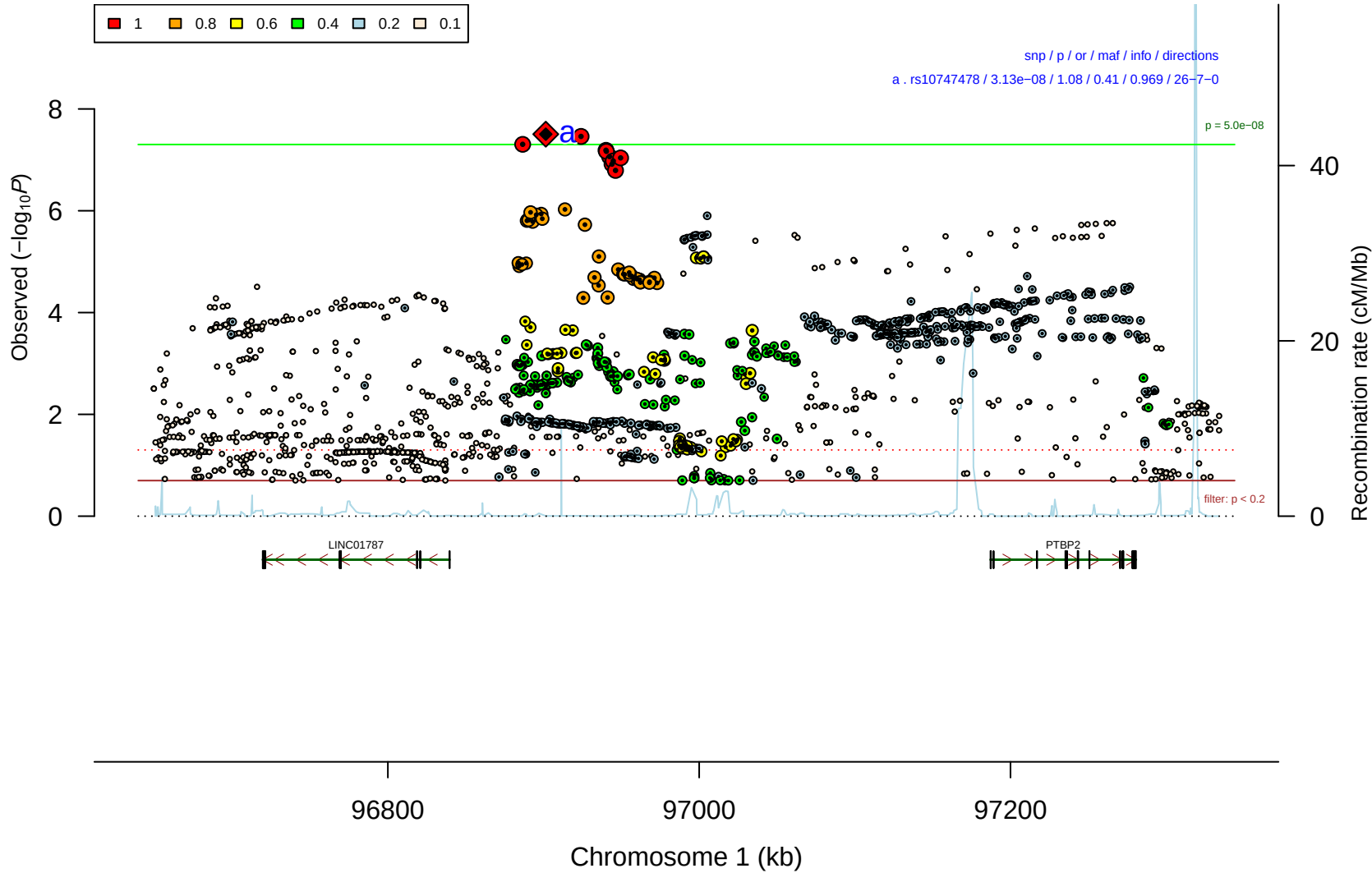
(d) chr10:rs2008387.



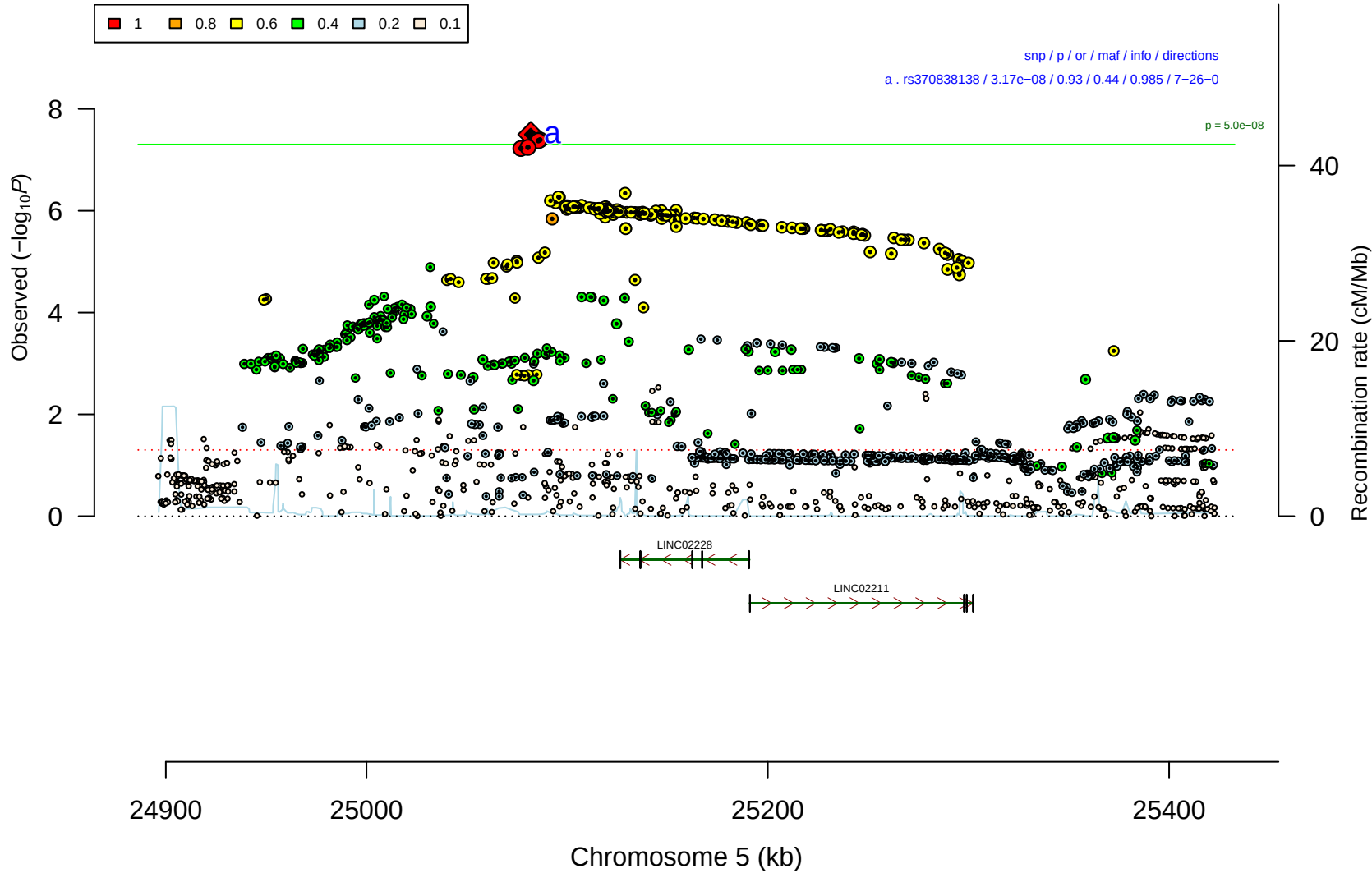
(e) chr3:rs9874207.



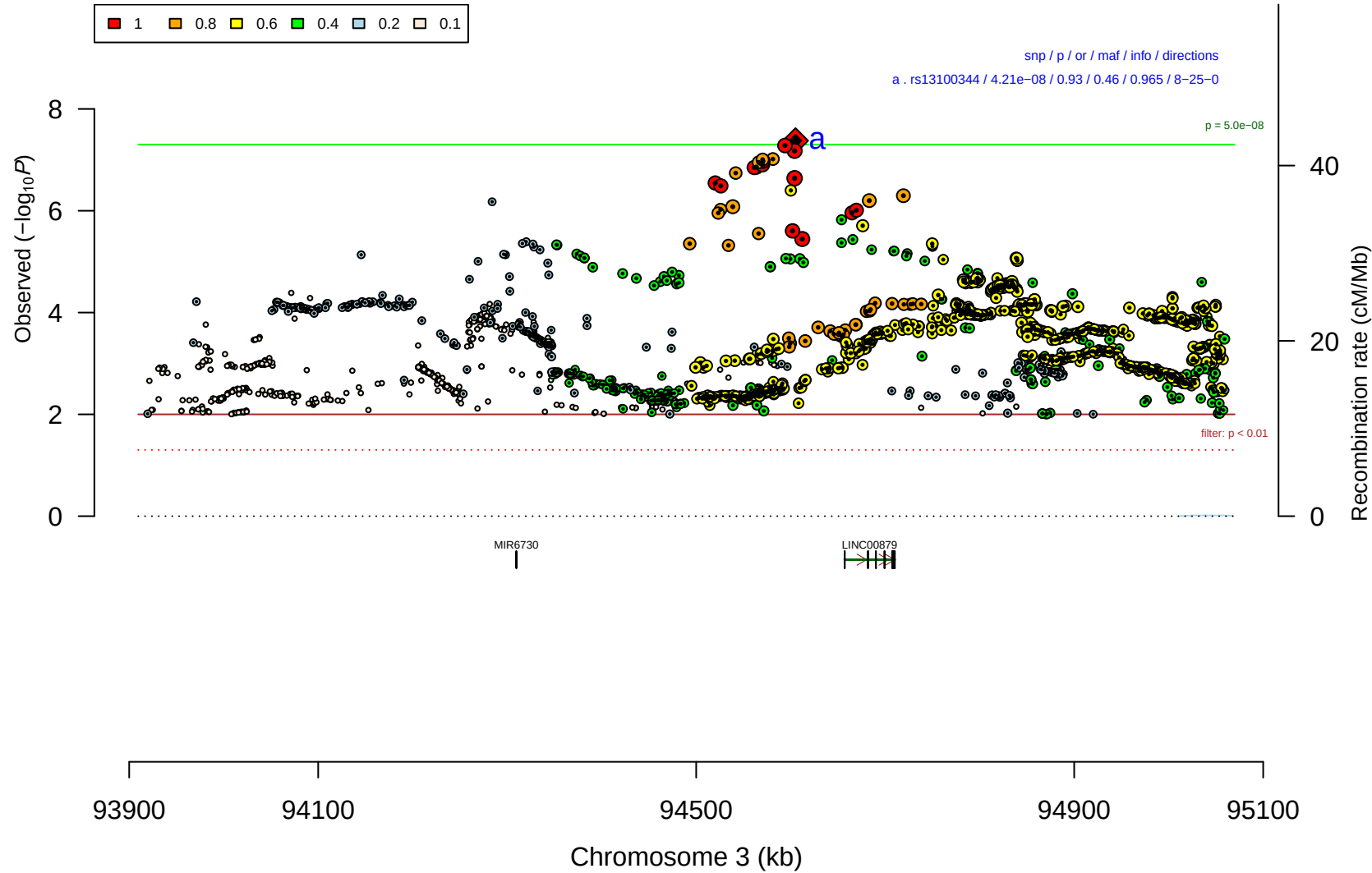
(f) chr1:rs10747478.



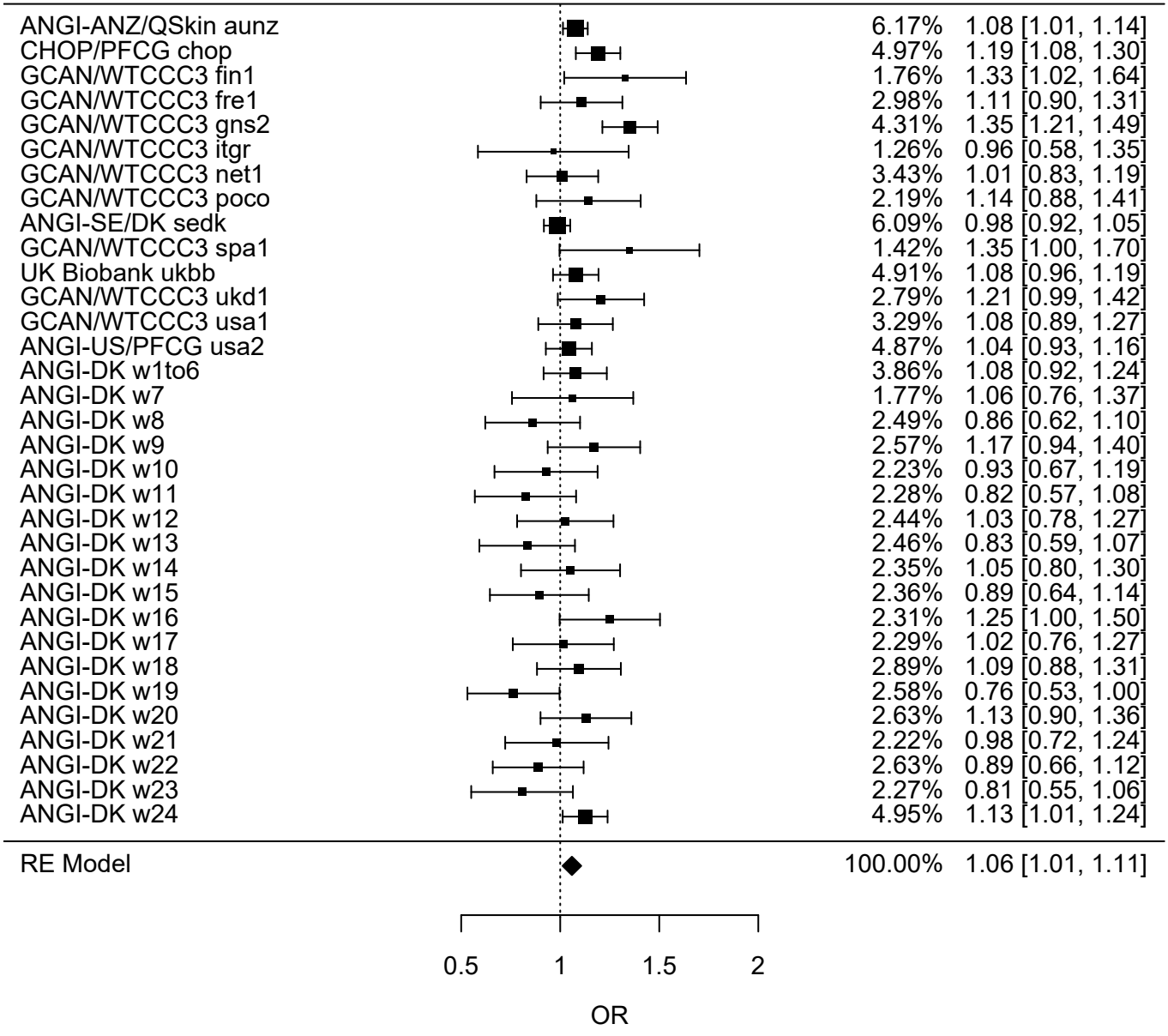
(g) chr5:rs370838138.



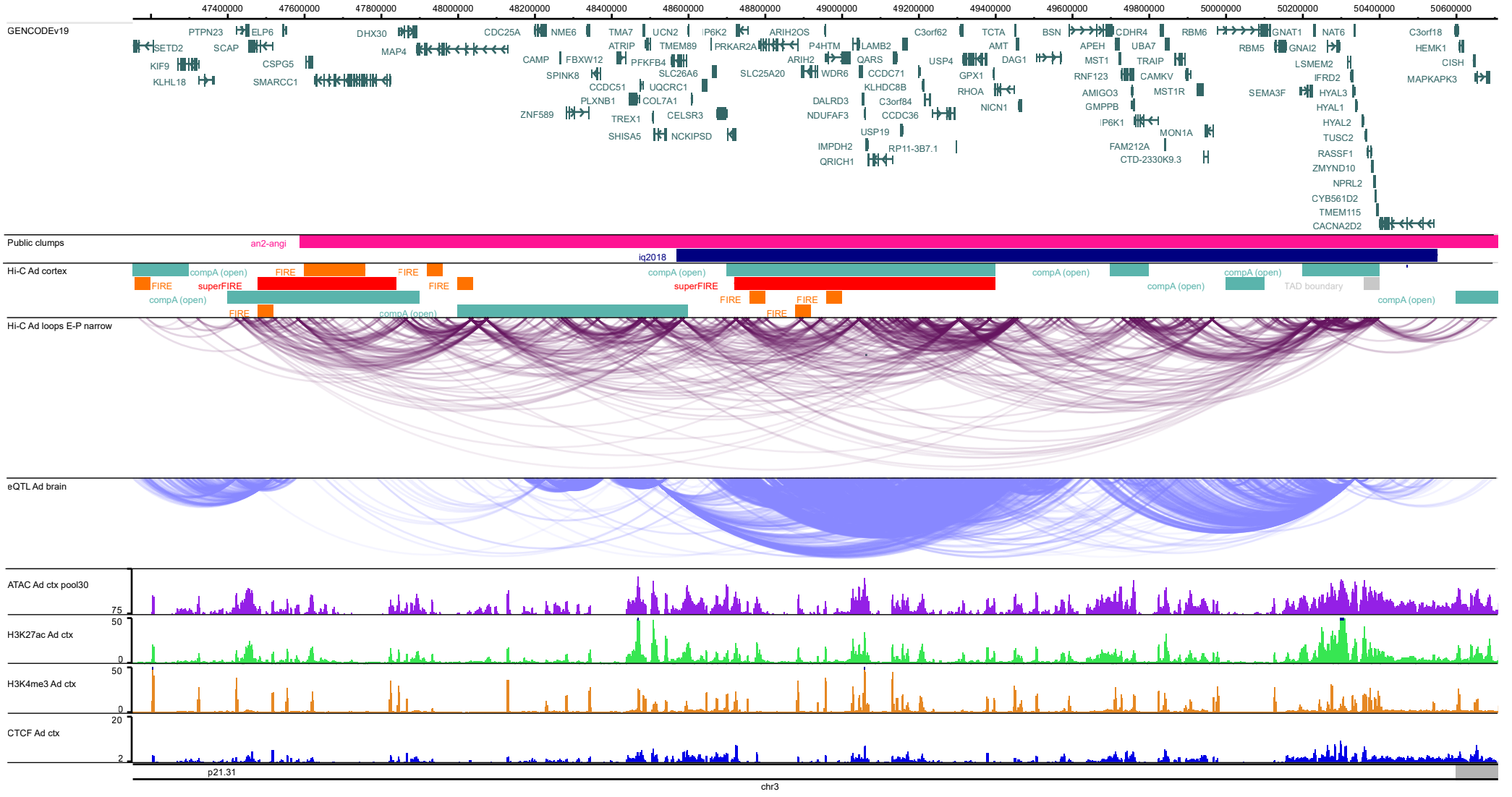
(h) chr3:rs13100344.



Supplementary Figure 4. A random-effects meta-analysis of the association between rs4622308 and anorexia nervosa. Previously, the first freeze of the PGC-ED revealed that this SNP was genome-wide significant (Duncan et al., 2017). In the present study, this SNP was not genome-wide significant in the primary GWAS meta-analysis using a fixed-effects model, and in a subsequent random effects meta-analysis as shown in this figure was also non-significant and showed evidence of heterogeneity (odds ratio [OR] = 1.06, 95% CI = 1.01-1.11, $P_{\text{two-tailed}} = 0.0002$, $I^2 = 53.76$). The percentages refer to the weight assigned to each cohort. The figures on the right are the percentage weight assigned to each cohort, the center values are the OR, and the error bar is the 95% confidence interval. The vertical line is the reference line of no effect. The sample size is 16,992 cases and 55,525 controls.


ANGI-ANZ/QSkin aunz 6.17% 1.08 [1.01, 1.14]
CHOP/PFCG chop 4.97% 1.19 [1.08, 1.30]
GCAN/WTCCC3 fin1 1.76% 1.33 [1.02, 1.64]
GCAN/WTCCC3 fre1 2.98% 1.11 [0.90, 1.31]
GCAN/WTCCC3 gns2 4.31% 1.35 [1.21, 1.49]
GCAN/WTCCC3 itgr 1.26% 0.96 [0.58, 1.35]
GCAN/WTCCC3 net1 3.43% 1.01 [0.83, 1.19]
GCAN/WTCCC3 poco 2.19% 1.14 [0.88, 1.41]
ANGI-SE/DK sedk 6.09% 0.98 [0.92, 1.05]
GCAN/WTCCC3 spa1 1.42% 1.35 [1.00, 1.70]
UK Biobank ukbb 4.91% 1.08 [0.96, 1.19]
GCAN/WTCCC3 ukd1 2.79% 1.21 [0.99, 1.42]
GCAN/WTCCC3 usa1 3.29% 1.08 [0.89, 1.27]
ANGI-US/PFCG usa2 4.87% 1.04 [0.93, 1.16]
ANGI-DK w1to6 3.86% 1.08 [0.92, 1.24]
ANGI-DK w7 1.77% 1.06 [0.76, 1.37]
ANGI-DK w8 2.49% 0.86 [0.62, 1.10]
ANGI-DK w9 2.57% 1.17 [0.94, 1.40]
ANGI-DK w10 2.23% 0.93 [0.67, 1.19]
ANGI-DK w11 2.28% 0.82 [0.57, 1.08]
ANGI-DK w12 2.44% 1.03 [0.78, 1.27]
ANGI-DK w13 2.46% 0.83 [0.59, 1.07]
ANGI-DK w14 2.35% 1.05 [0.80, 1.30]
ANGI-DK w15 2.36% 0.89 [0.64, 1.14]
ANGI-DK w16 2.31% 1.25 [1.00, 1.50]
ANGI-DK w17 2.29% 1.02 [0.76, 1.27]
ANGI-DK w18 2.89% 1.09 [0.88, 1.31]
ANGI-DK w19 2.58% 0.76 [0.53, 1.00]
ANGI-DK w20 2.63% 1.13 [0.90, 1.36]
ANGI-DK w21 2.22% 0.98 [0.72, 1.24]
ANGI-DK w22 2.63% 0.89 [0.66, 1.12]
ANGI-DK w23 2.27% 0.81 [0.55, 1.06]
ANGI-DK w24 4.95% 1.13 [1.01, 1.24]
RE Model 100.00% 1.06 [1.01, 1.11]
0.5
1
1.5
2
OR

Supplementary Figure 5a-h legend. Hi-C and eQTL analyses. These figures were generated using the WashU EpiGenome browser (http://epigenomegateway.wustl.edu/browser). Yellow shaded regions show the “clumps” associated with AN. The top track shows GENCODE v19 gene models. The "public clumps" track shows psychiatric GWA regions including AN GWAS. The "Hi-C Ad cortex" track shows "compartment A/B", "FIRES" (frequently interacting regions), "superFIRES" (local aggregates of FIREs), and topologically associated domain boundaries (TADs). The "Hi-C Ad loops E-P narrow" contains arcs that show the positions of high confidence chromatin interactions in adult brain (10 Kb resolution) between enhancers and/or promoters (according to ChIP-seq and brain-expressed TSS data) with a Bonferroni $P < 0.001$. The "eQTL Ad brain" track shows cis eQTL information from GTEx for all available brain tissues. The "ATAC Ad ctx pool30" track shows open chromatin data for 30 adult controls. The next three tracks show brain epigenomic marks from ChIP-seq in adult brain cortex (H3K27ac, H3K4me3, and CTCF). We selected eQTL SNP-gene pairs from CommonMind frontal cortex, GTEx in any brain region ($q < 0.05$), or in fetal cortex. Significant eQTL connections were identified by nominal $P < 0.05$ as supplied by CMC and GTEx and significant chromatin interactions were identified with a stringent Bonferroni correction for multiple testing, and only considered 10 Kb bin pairs with P value $< 2.31 \times 10^{-11}$ (0.001/43,222,677 tests). The chromatin interaction tests came from Fit-Hi-C with default parameters applied and FastHiC. All tests were two-tailed.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C3orf18
HEMK1
CISH
MAPKAPK3
Public clumps
an2-angi
iq2018
Hi-C Ad cortex
compA (open)
FIRE
superFIRE
TAD boundary
Hi-C Ad loops E-P narrow
eQTL Ad brain
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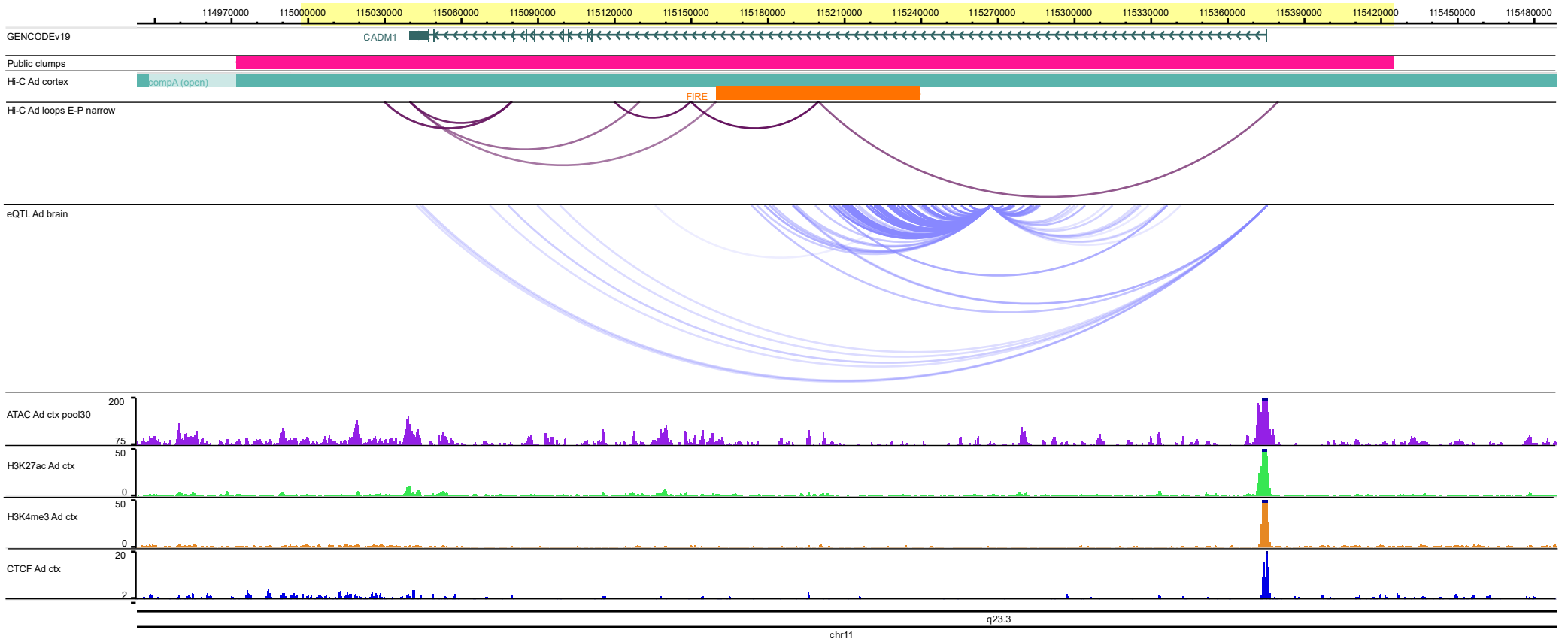
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compA (open)
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CTCF Ad ctx
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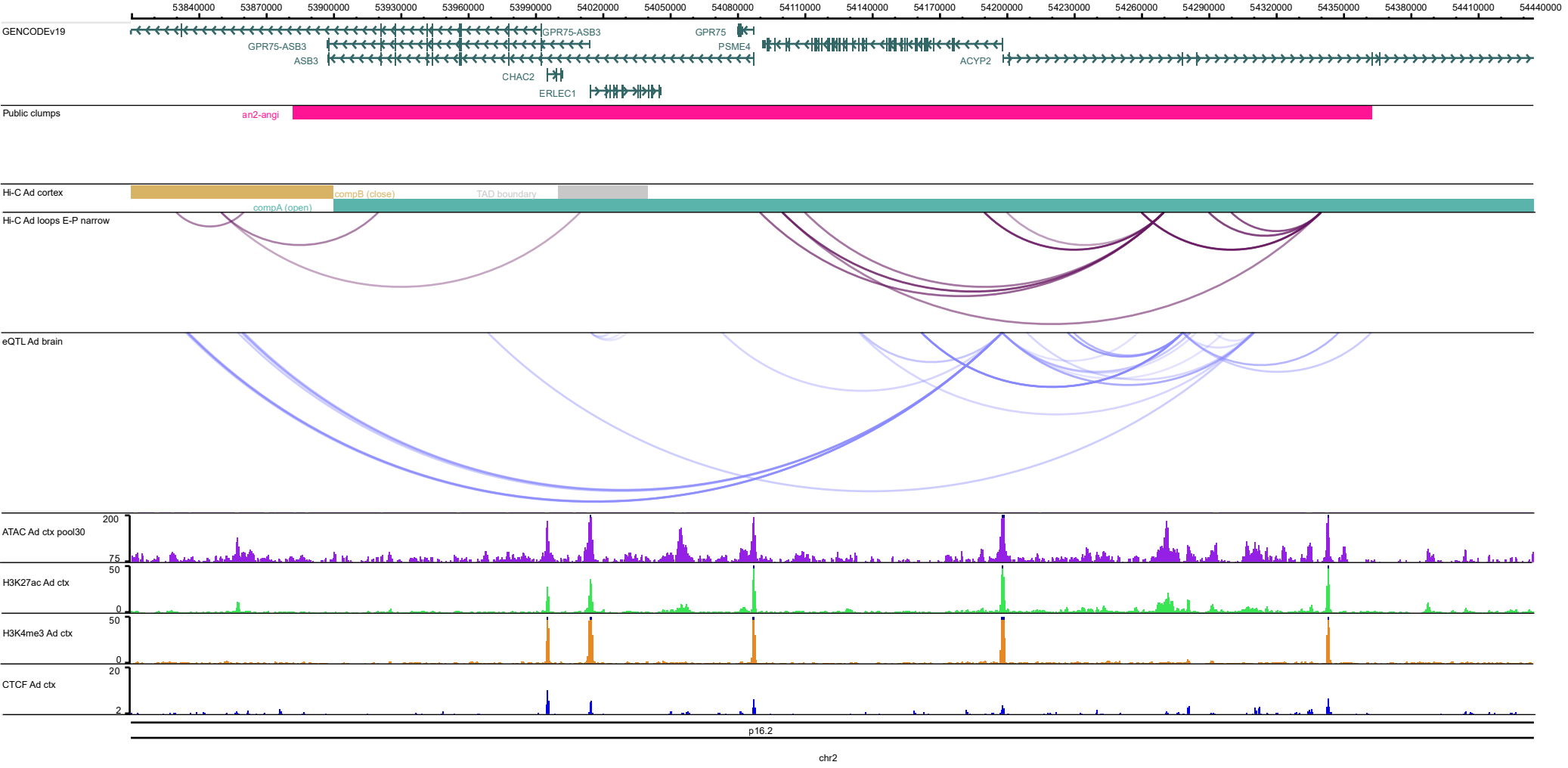
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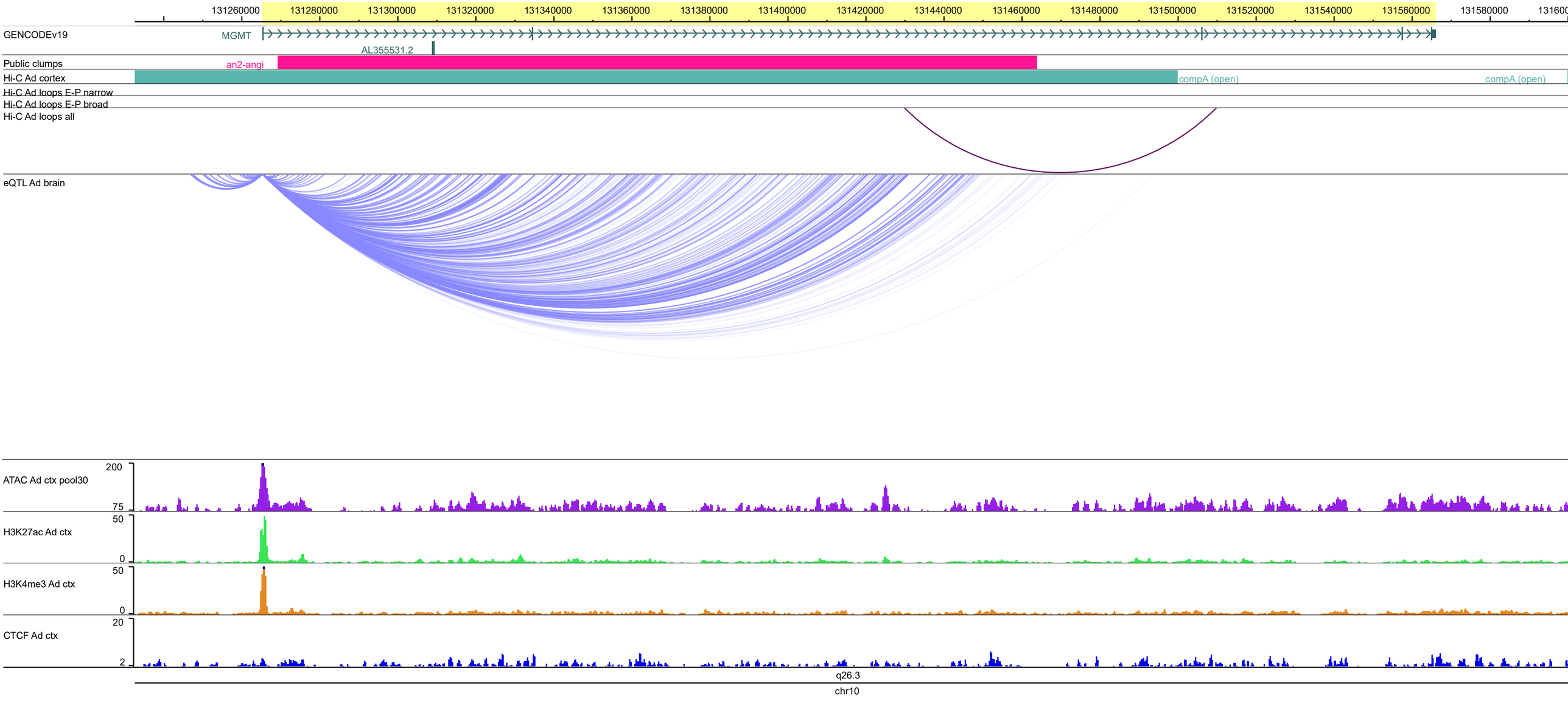
GENCODEv19
GPR75-ASB3
GPR75-ASB3
ASB3
CHAC2
ERLEC1
GPR75
PSME4
ACYP2
Public clumps
an2-angi
Hi-C Ad cortex
compB (close)
TAD boundary
compA (open)
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
200
75
H3K27ac Ad ctx
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
p16.2
chr2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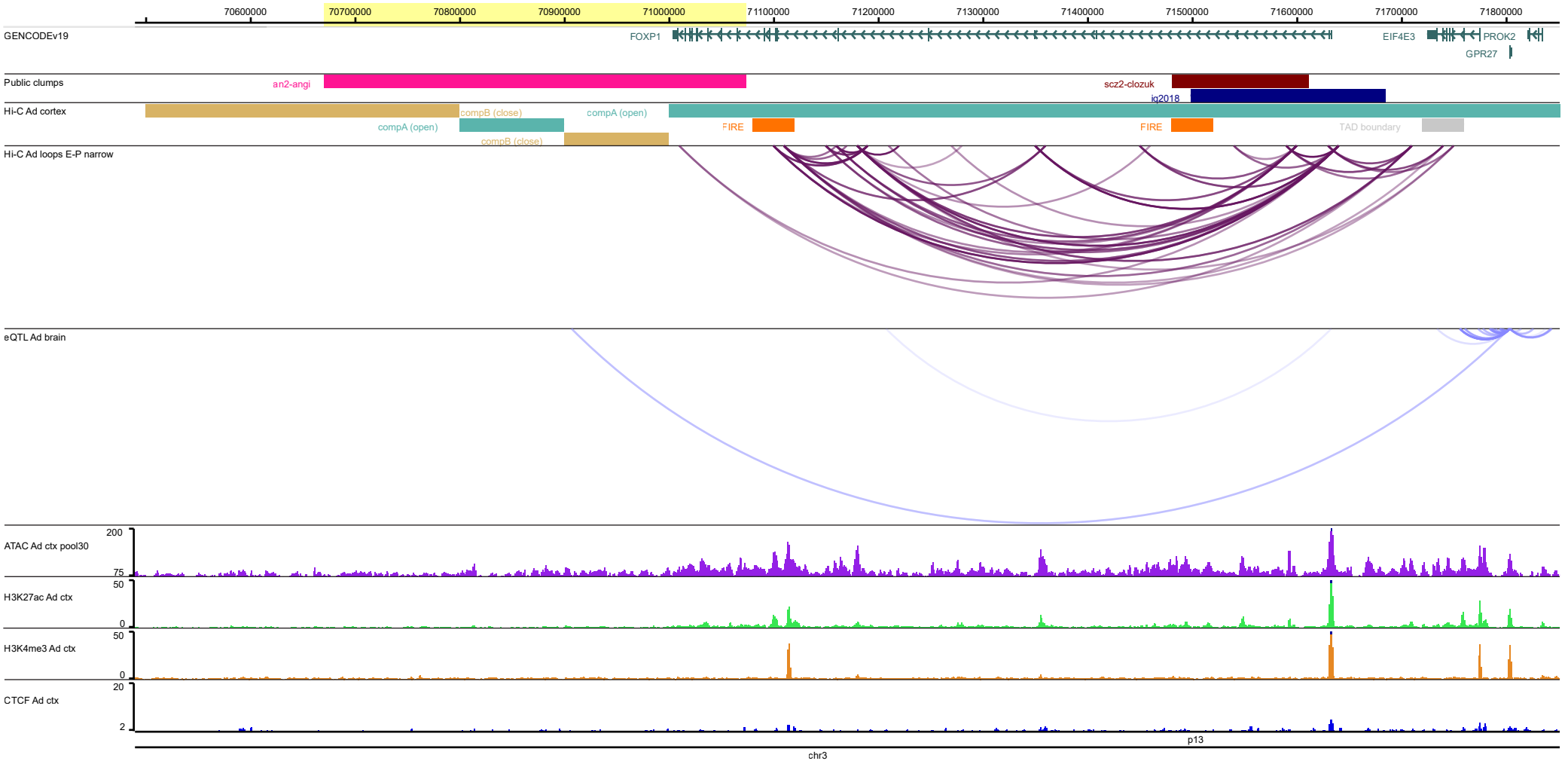
131520000
131540000
131560000
131580000
131600
GENCODEv19
MGMT
AL355531.2
Public clumps
an2-angi
Hi-C Ad cortex
compA (open)
compA (open)
Hi-C Ad loops E-P narrow
Hi-C Ad loops E-P broad
Hi-C Ad loops all
eQTL Ad brain
ATAC Ad ctx pool30
200
75
H3K27ac Ad ctx
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
q26.3
chr10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FOXP1
EIF4E3
PROK2
GPR27
Public clumps
an2-angi
scz2-clozuk
iq2018
Hi-C Ad cortex
compB (close)
compA (open)
compA (open)
compB (close)
FIRE
FIRE
TAD boundary
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
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75
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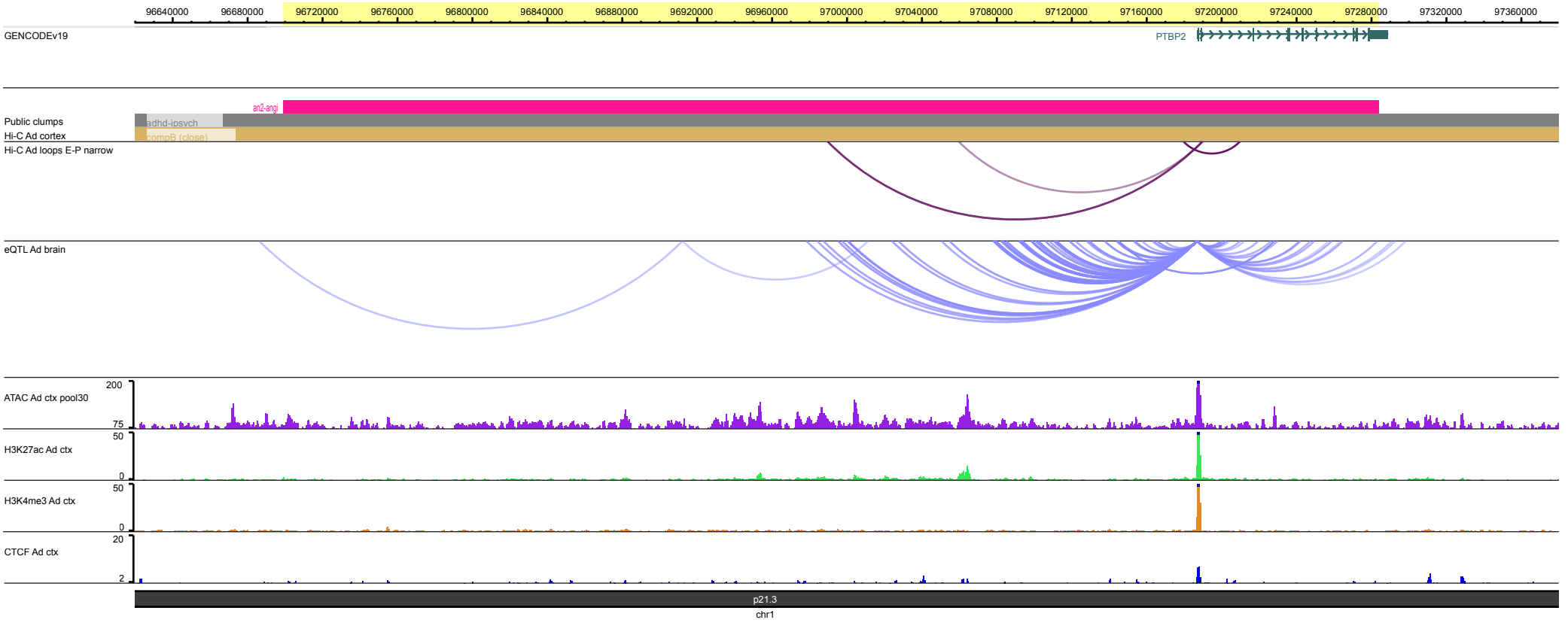
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
p13
chr3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97160000
97200000
97240000
97280000
97320000
97360000
GENCODEv19
PTBP2
an2-angj
Public clumps
adhd-ipsych
Hi-C Ad cortex
compB (close)
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
200
75
H3K27ac Ad ctx
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
p21.3
chr1


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25050000
25100000
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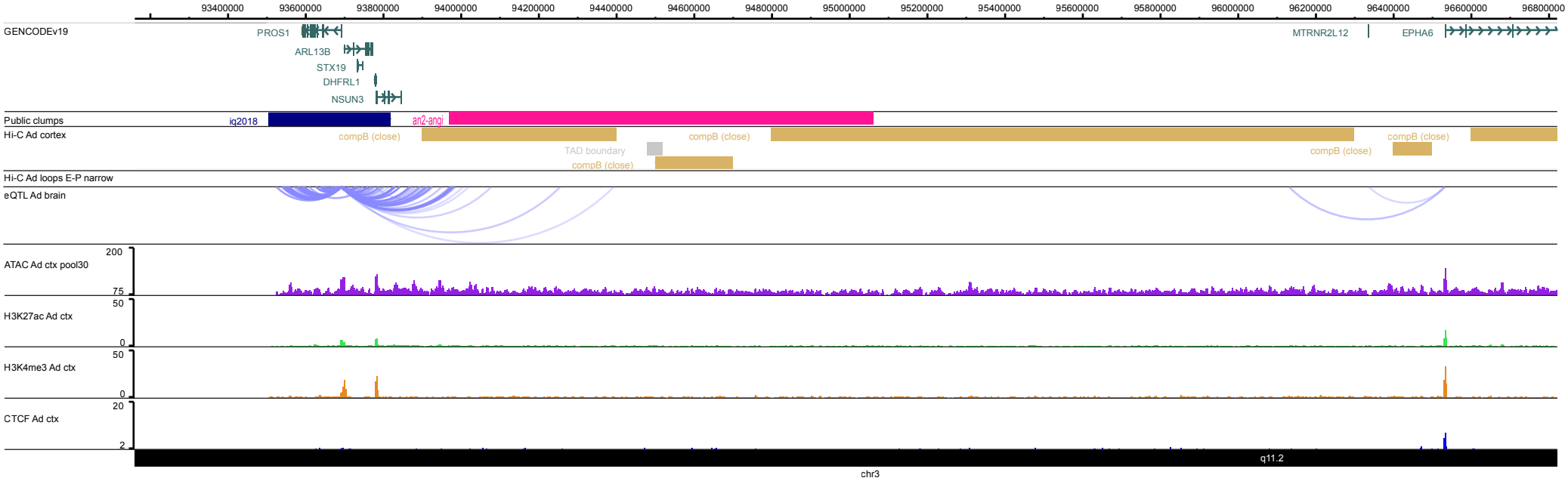
25200000
25250000
25300000
25350000
25400000
GENCODEv19
CDH10
Public clumps
an2-angi
Hi-C Ad cortex
compB (close)
Hi-C Ad loops E-P narrow
Hi-C Ad loops all
eQTL Ad brain
ATAC Ad ctx pool30
200
75
H3K27ac Ad ctx
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
chr5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96200000
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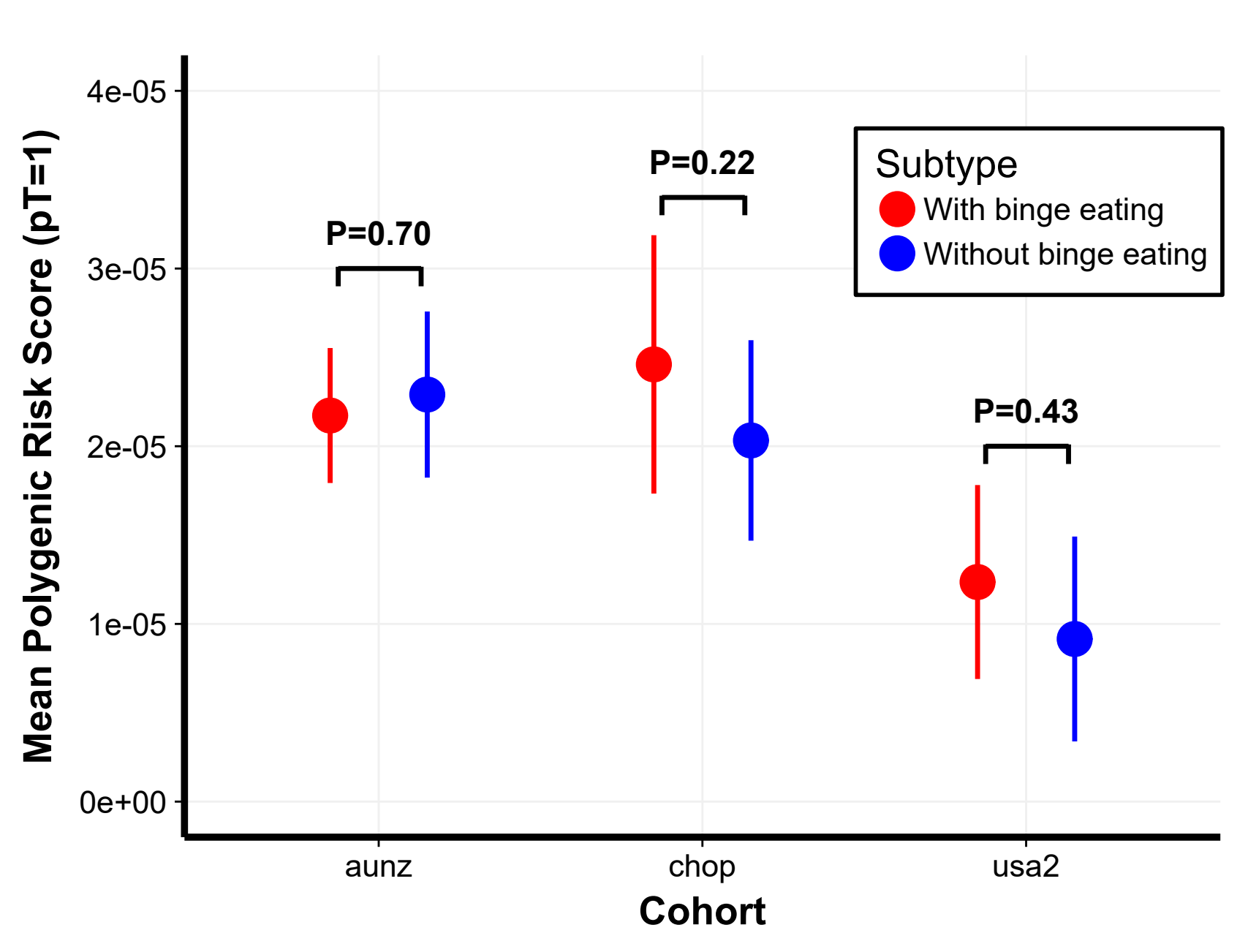
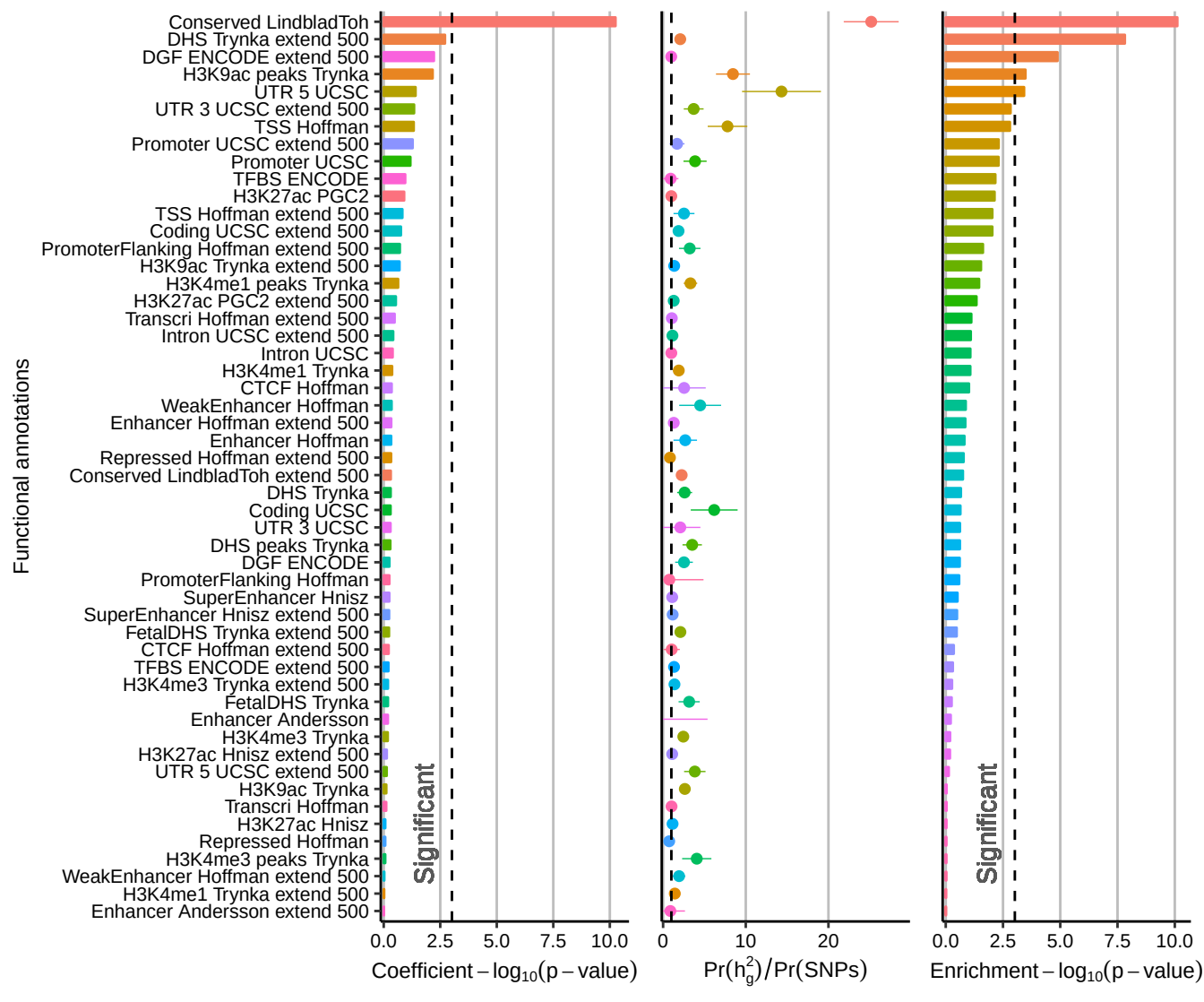
GENCODEv19
PROS1
ARL13B
STX19
DHFRL1
NSUN3
MTRNR2L12
EPHA6
Public clumps
ig2018
an2-angi
Hi-C Ad cortex
compB (close)
compB (close)
compB (close)
TAD boundary
compB (close)
compB (close)
Hi-C Ad loops E-P narrow
eQTL Ad brain
ATAC Ad ctx pool30
200
75
H3K27ac Ad ctx
50
0
H3K4me3 Ad ctx
50
0
CTCF Ad ctx
20
2
q11.2
chr3

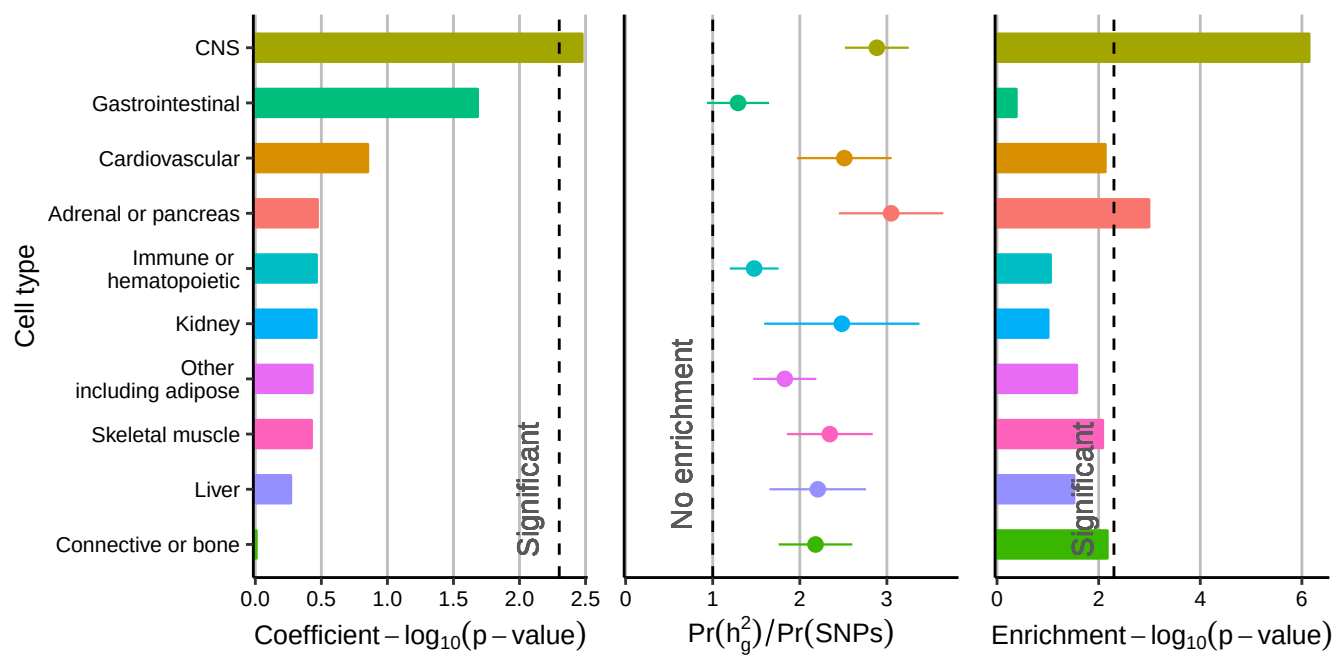
Supplementary Figure 6. Mean polygenic risk scores (PRS) according to anorexia nervosa subtype (+/- binge eating). In the datasets with available subtype data—aunz (1,417 cases with binge eating, 997 cases without binge eating), chop (358 cases with binge eating, 634 cases without binge eating), and usa2 (606 cases with binge eating, 631 cases without binge eating)— AN PRS was computed for each individual. AN PRS was derived from the primary GWAS meta-analysis summary statistics and adjusted for the principal components used in the main GWAS. Individual PRS were then aggregated into subtype group means. The center values show mean PRS and the error bars show the 95% confidence interval. Two-tailed *T* tests testing for significant differences in PRS scores by subtype were conducted for each cohort using a Bonferroni-corrected *P* threshold of < 0.017.


Mean Polygenic Risk Score (pT=1)
4e-05
3e-05
2e-05
1e-05
0e+00
P=0.70
P=0.22
P=0.43
Subtype
With binge eating
Without binge eating
aunz
chop
usa2
Cohort

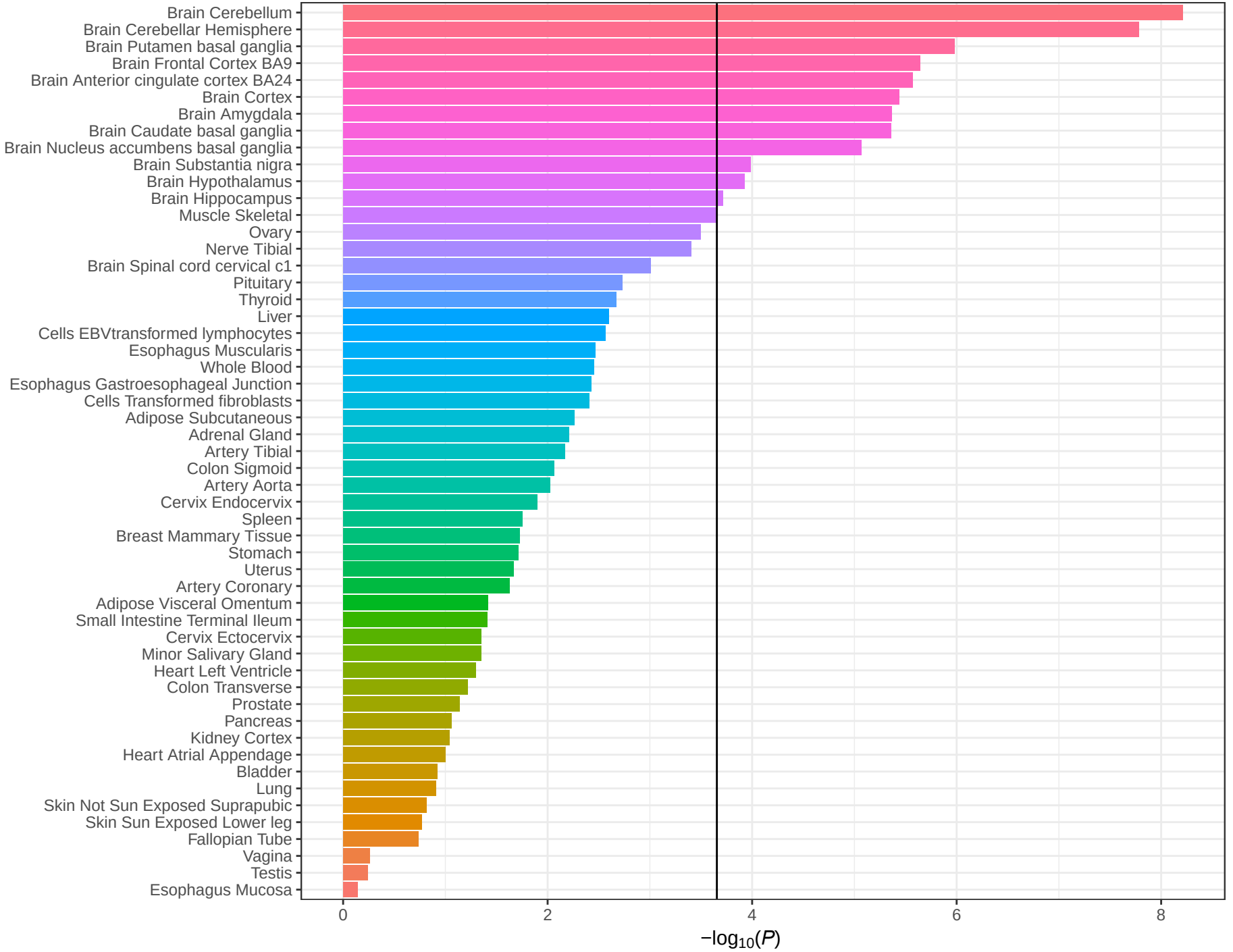
Supplementary Figure 7. Partitioned heritability analysis. The sample size is 16,992 cases and 55,525 controls. The coefficient *P* value (lefthand) tests for enrichment of heritability within each functional element, controlling for all other functional elements to address overlap. The enrichment *P* value (righthand) indicates whether this absolute enrichment is statistically significant. In each analysis, the Bonferroni-corrected threshold (vertical line) is $-\log_{10}(P) > 3.0$. The enrichment (middle) scales the heritability captured by each functional element according to the number of variants in the element (vertical line = 1, that is no enrichment). The error bar is the standard error.


Functional annotations
Conserved LindbladToh
DHS Trynka extend 500
DGF ENCODE extend 500
H3K9ac peaks Trynka
UTR 5 UCSC
UTR 3 UCSC extend 500
TSS Hoffman
Promoter UCSC extend 500
Promoter UCSC
TFBS ENCODE
H3K27ac PGC2
TSS Hoffman extend 500
Coding UCSC extend 500
PromoterFlanking Hoffman extend 500
H3K9ac Trynka extend 500
H3K4me1 peaks Trynka
H3K27ac PGC2 extend 500
Transcri Hoffman extend 500
Intron UCSC extend 500
Intron UCSC
H3K4me1 Trynka
CTCF Hoffman
WeakEnhancer Hoffman
Enhancer Hoffman extend 500
Enhancer Hoffman
Repressed Hoffman extend 500
Conserved LindbladToh extend 500
DHS Trynka
Coding UCSC
UTR 3 UCSC
DHS peaks Trynka
DGF ENCODE
PromoterFlanking Hoffman
SuperEnhancer Hnisz
SuperEnhancer Hnisz extend 500
FetalDHS Trynka extend 500
CTCF Hoffman extend 500
TFBS ENCODE extend 500
H3K4me3 Trynka extend 500
FetalDHS Trynka
Enhancer Andersson
H3K4me3 Trynka
H3K27ac Hnisz extend 500
UTR 5 UCSC extend 500
H3K9ac Trynka
Transcri Hoffman
H3K27ac Hnisz
Repressed Hoffman
H3K4me3 peaks Trynka
WeakEnhancer Hoffman extend 500
H3K4me1 Trynka extend 500
Enhancer Andersson extend 500
Significant
0.0
2.5
5.0
7.5
10.0
Coefficient − log10(p − value)
0
10
20
Pr(h2g)/Pr(SNPs)
Significant
0.0
2.5
5.0
7.5
10.0
Enrichment − log10(p − value)

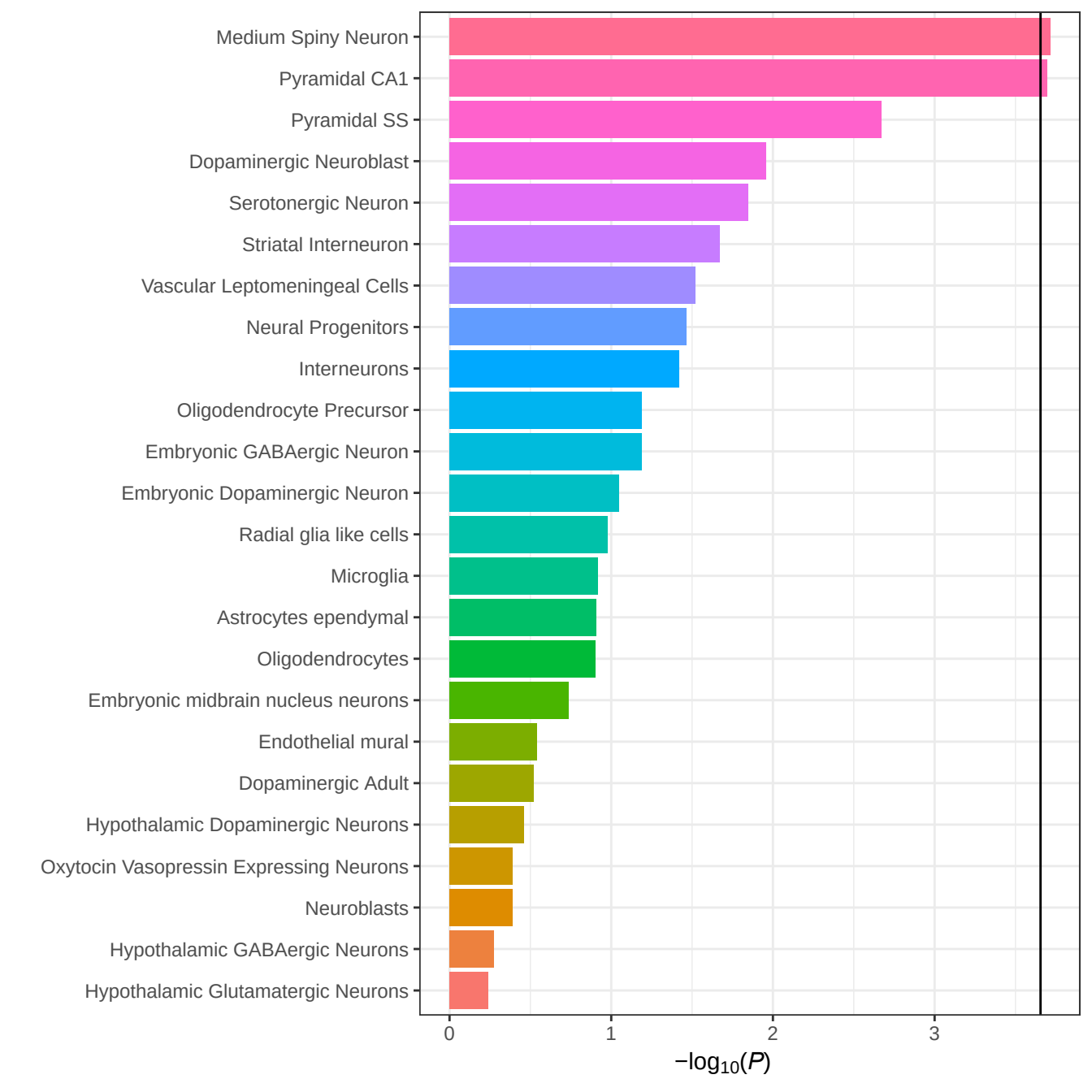
Supplementary Figure 8. Cell type group specific partitioned heritability analysis. The sample size is 16,992 cases and 55,525 controls. The coefficient *P* value (lefthand) tests for enrichment of heritability within each cell group, controlling for all other cell groups to address overlap. The enrichment *P* value (righthand) indicates whether this absolute enrichment is statistically significant. In each analysis, the Bonferroni-corrected threshold (vertical line) is $-\log_{10}(P) > 2.3$ (i.e., 0.05/10 tests). The enrichment (middle) scales the heritability captured by each cell group according to the number of variants in the group (vertical line = 1, that is no enrichment). The error bar is the standard error.


Cell type
CNS
Gastrointestinal
Cardiovascular
Adrenal or pancreas
Immune or hematopoietic
Kidney
Other including adipose
Skeletal muscle
Liver
Connective or bone
Significant
No enrichment
Significant
0.0
0.5
1.0
1.5
2.0
2.5
Coefficient – log10(p – value)
0
1
2
3
Pr(h2g)/Pr(SNPs)
0
2
4
6
Enrichment – log10(p – value)

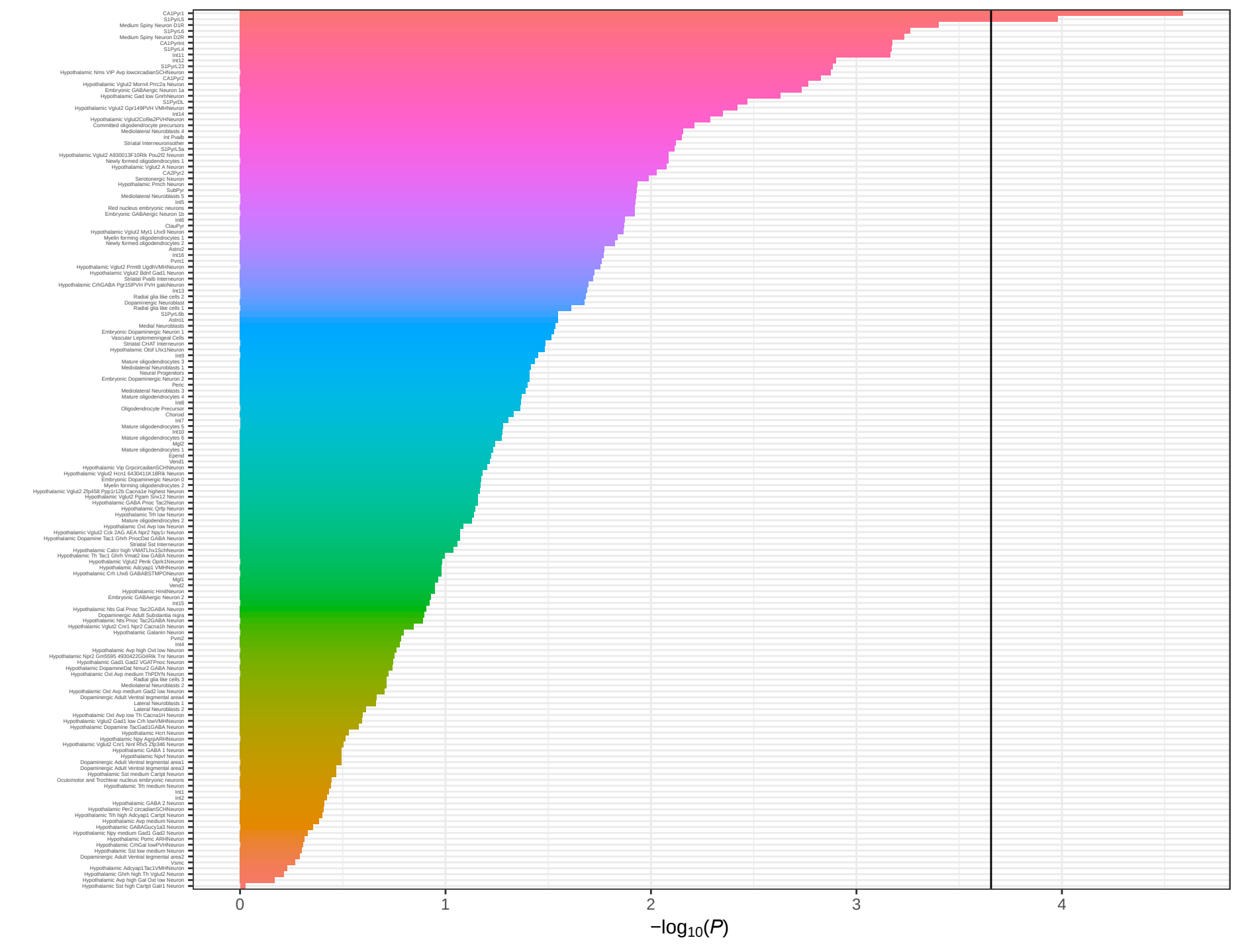
Supplementary Figure 9. *P* value of association between tissue specificity in GTEx and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Brain Cerebellum
Brain Cerebellar Hemisphere
Brain Putamen basal ganglia
Brain Frontal Cortex BA9
Brain Anterior cingulate cortex BA24
Brain Cortex
Brain Amygdala
Brain Caudate basal ganglia
Brain Nucleus accumbens basal ganglia
Brain Substantia nigra
Brain Hypothalamus
Brain Hippocampus
Muscle Skeletal
Ovary
Nerve Tibial
Brain Spinal cord cervical c1
Pituitary
Thyroid
Liver
Cells EBVtransformed lymphocytes
Esophagus Muscularis
Whole Blood
Esophagus Gastroesophageal Junction
Cells Transformed fibroblasts
Adipose Subcutaneous
Adrenal Gland
Artery Tibial
Colon Sigmoid
Artery Aorta
Cervix Endocervix
Spleen
Breast Mammary Tissue
Stomach
Uterus
Artery Coronary
Adipose Visceral Omentum
Small Intestine Terminal Ileum
Cervix Ectocervix
Minor Salivary Gland
Heart Left Ventricle
Colon Transverse
Prostate
Pancreas
Kidney Cortex
Heart Atrial Appendage
Bladder
Lung
Skin Not Sun Exposed Suprapubic
Skin Sun Exposed Lower leg
Fallopian Tube
Vagina
Testis
Esophagus Mucosa
0
2
4
6
8
−log10(P)

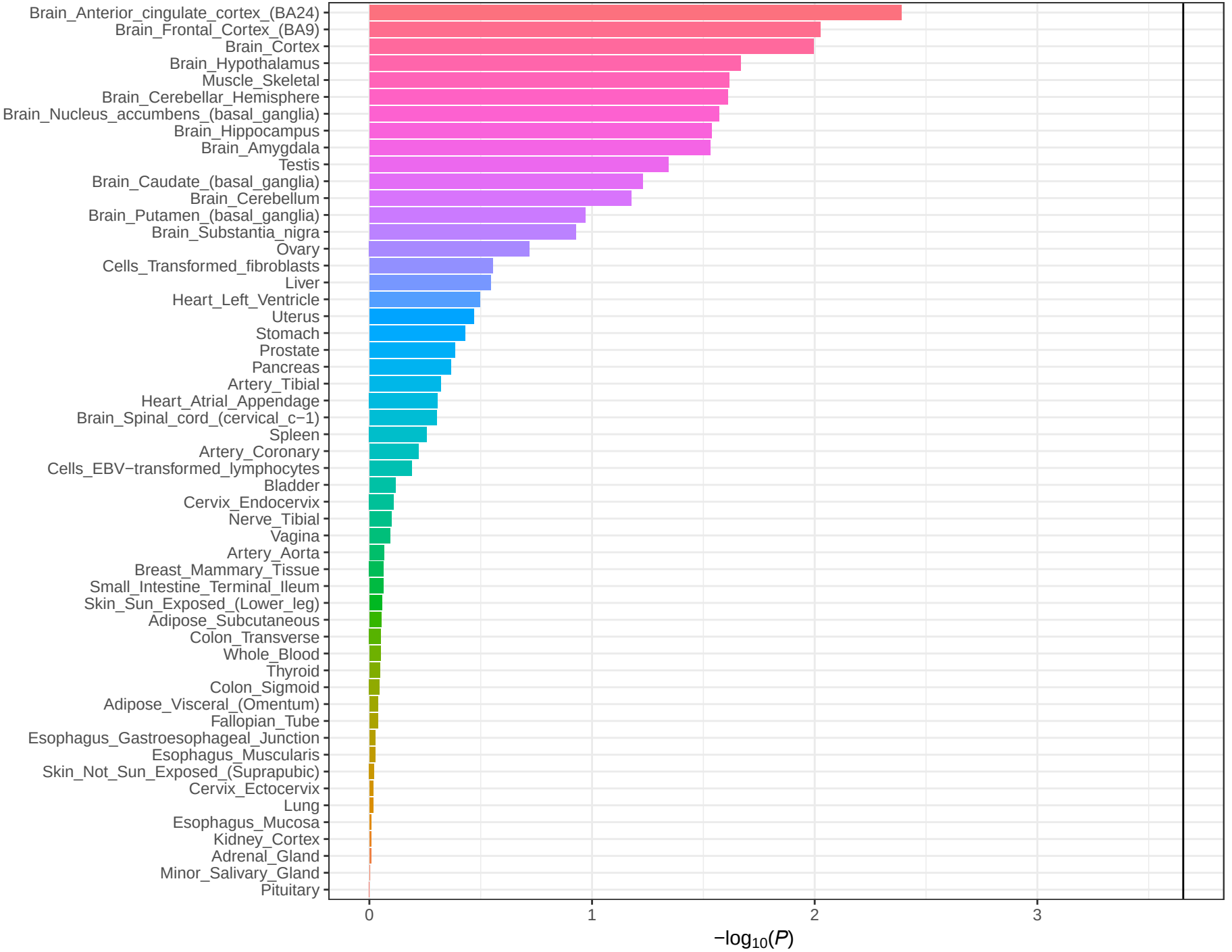
Supplementary Figure 10. *P* value of association between tissue specificity in 24 brain cell types (level 1) and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Medium Spiny Neuron
Pyramidal CA1
Pyramidal SS
Dopaminergic Neuroblast
Serotonergic Neuron
Striatal Interneuron
Vascular Leptomeningeal Cells
Neural Progenitors
Interneurons
Oligodendrocyte Precursor
Embryonic GABAergic Neuron
Embryonic Dopaminergic Neuron
Radial glia like cells
Microglia
Astrocytes ependymal
Oligodendrocytes
Embryonic midbrain nucleus neurons
Endothelial mural
Dopaminergic Adult
Hypothalamic Dopaminergic Neurons
Oxytocin Vasopressin Expressing Neurons
Neuroblasts
Hypothalamic GABAergic Neurons
Hypothalamic Glutamatergic Neurons
0
1
2
3
−log10(P)

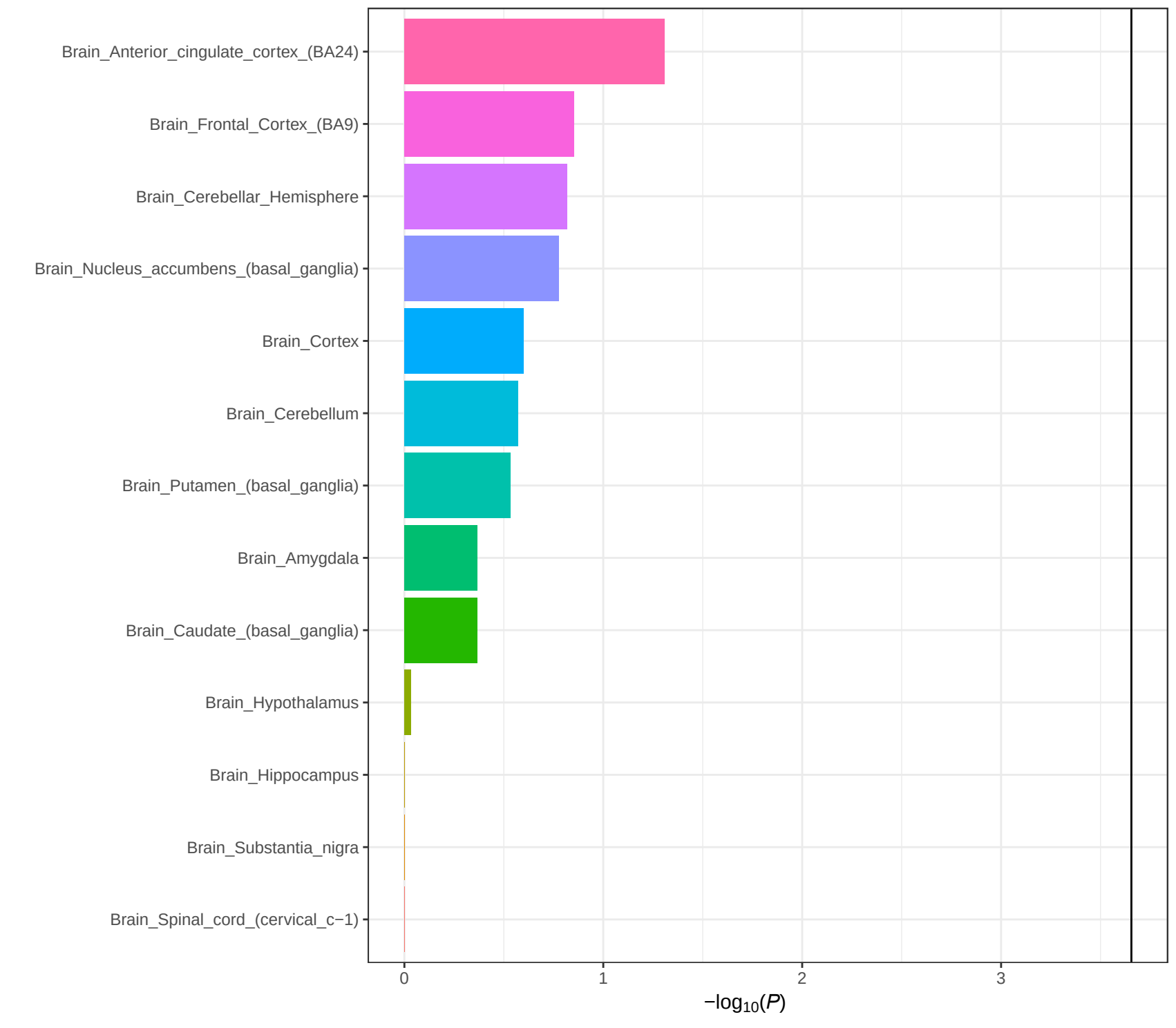
Supplementary Figure 11. *P* value of association between tissue specificity in 149 brain cell types (level 2) and gene-level genetic association with anorexia nervosa using MAGMA. The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


CA1Pyr1
S1PyrL5
Medium Spiny Neuron D1R
S1PyrL6
Medium Spiny Neuron D2R
CA1PyrInt
S1PyrL4
Int11
Int12
S1PyrL23
Hypothalamic Nms VIP Avp lowcircadianSCHNeuron
CA1Pyr2
Hypothalamic Vglut2 Morn4 Prrc2a Neuron
Embryonic GABAergic Neuron 1a
Hypothalamic Gad low GnrhNeuron
S1PyrDL
Hypothalamic Vglut2 Gpr149PVH VMHNeuron
Int14
Hypothalamic Vglut2Col9a2PVHNeuron
Committed oligodendrocyte precursors
Mediolateral Neuroblasts 4
Int Pvalb
Striatal Interneuronsother
S1PyrL5a
Hypothalamic Vglut2 A930013F10Rik Pou2f2 Neuron
Newly formed oligodendrocytes 1
Hypothalamic Vglut2 A Neuron
CA2Pyr2
Serotonergic Neuron
Hypothalamic Pmch Neuron
SubPyr
Mediolateral Neuroblasts 5
Int5
Red nucleus embryonic neurons
Embryonic GABAergic Neuron 1b
Int6
ClauPyr
Hypothalamic Vglut2 Myt1 Lhx9 Neuron
Myelin forming oligodendrocytes 1
Newly formed oligodendrocytes 2
Astro2
Int16
Pvm1
Hypothalamic Vglut2 Prmt8 UgdhVMHNeuron
Hypothalamic Vglut2 Bdnf Gad1 Neuron
Striatal Pvalb Interneuron
Hypothalamic CrhGABA Ppr15PVH PVH galoNeuron
Int13
Radial glia like cells 2
Dopaminergic Neuroblast
Radial glia like cells 1
S1PyrL6b
Astro1
Medial Neuroblasts
Embryonic Dopaminergic Neuron 1
Vascular Leptomeningeal Cells
Striatal CHAT Interneuron
Hypothalamic Otof Lhx1Neuron
Int9
Mature oligodendrocytes 3
Mediolateral Neuroblasts 1
Neural Progenitors
Embryonic Dopaminergic Neuron 2
Peric
Mediolateral Neuroblasts 3
Mature oligodendrocytes 4
Int8
Oligodendrocyte Precursor
Choroid
Int7
Mature oligodendrocytes 5
Int10
Mature oligodendrocytes 6
Mgl2
Mature oligodendrocytes 1
Epend
Vend1
Hypothalamic Vip GrpcircadianSCHNeuron
Hypothalamic Vglut2 Hcn1 6430411K18Rik Neuron
Embryonic Dopaminergic Neuron 0
Myelin forming oligodendrocytes 2
Hypothalamic Vglut2 Zfp458 Ppp1r12b Cacna1e highest Neuron
Hypothalamic Vglut2 Pgam Strx12 Neuron
Hypothalamic GABA Pnoc Tac2Neuron
Hypothalamic Qrfp Neuron
Hypothalamic Trh low Neuron
Mature oligodendrocytes 2
Hypothalamic Oxt Avp low Neuron
Hypothalamic Vglut2 Cck 2AG AEA Npr2 Npy1r Neuron
Hypothalamic Dopamine Tac1 Ghrh PnocDat GABA Neuron
Striatal Sst Interneuron
Hypothalamic Calcr high VMATLhx1SchNeuron
Hypothalamic Th Tac1 Ghrh Vmat2 low GABA Neuron
Hypothalamic Vglut2 Penk Oprk1Neuron
Hypothalamic Adcyap1 VMHNeuron
Hypothalamic Crh Lhx6 GABABSTMPONeuron
Mgl1
Vend2
Hypothalamic HmhNeuron
Embryonic GABAergic Neuron 2
Int15
Hypothalamic Nts Gal Pnoc Tac2GABA Neuron
Dopaminergic Adult Substantia nigra
Hypothalamic Nts Pnoc Tac2GABA Neuron
Hypothalamic Vglut2 Cnr1 Npr2 Cacna1h Neuron
Hypothalamic Galanin Neuron
Pvm2
Int4
Hypothalamic Avp high Oxt low Neuron
Hypothalamic Npr2 Gm5595 4930422G04Rik Tnr Neuron
Hypothalamic Gad1 Gad2 VGATPnoc Neuron
Hypothalamic DopamineDat Nmur2 GABA Neuron
Hypothalamic Oxt Avp medium ThPDYN Neuron
Radial glia like cells 3
Mediolateral Neuroblasts 2
Hypothalamic Oxt Avp medium Gad2 low Neuron
Dopaminergic Adult Ventral tegmental area4
Lateral Neuroblasts 1
Lateral Neuroblasts 2
Hypothalamic Oxt Avp low Th Cacna1H Neuron
Hypothalamic Vglut2 Gad1 low Crh lowVMHNeuron
Hypothalamic Dopamine TacGad1GABA Neuron
Hypothalamic Hcrt Neuron
Hypothalamic Npy AgrpARHNeuron
Hypothalamic Vglut2 Cnr1 Nin1 Rfx5 Zfp346 Neuron
Hypothalamic GABA 1 Neuron
Hypothalamic Npvf Neuron
Dopaminergic Adult Ventral tegmental area1
Dopaminergic Adult Ventral tegmental area3
Hypothalamic Sst medium Cartpt Neuron
Oculomotor and Trochlear nucleus embryonic neurons
Hypothalamic Trh medium Neuron
Int1
Int2
Hypothalamic GABA 2 Neuron
Hypothalamic Per2 circadianSCHNeuron
Hypothalamic Trh high Adcyap1 Cartpt Neuron
Hypothalamic Avp medium Neuron
Hypothalamic GABAGucy1a3 Neuron
Hypothalamic Npy medium Gad1 Gad2 Neuron
Hypothalamic Pomc ARHNeuron
Hypothalamic CrhGal lowPVHNeuron
Hypothalamic Sst low medium Neuron
Dopaminergic Adult Ventral tegmental area2
Vsmc
Hypothalamic Adcyap1Tac1VMHNeuron
Hypothalamic Ghrh high Th Vglut2 Neuron
Hypothalamic Avp high Gal Oxt low Neuron
Hypothalamic Sst high Cartpt Galr1 Neuron
0
1
2
3
4
−log10(P)

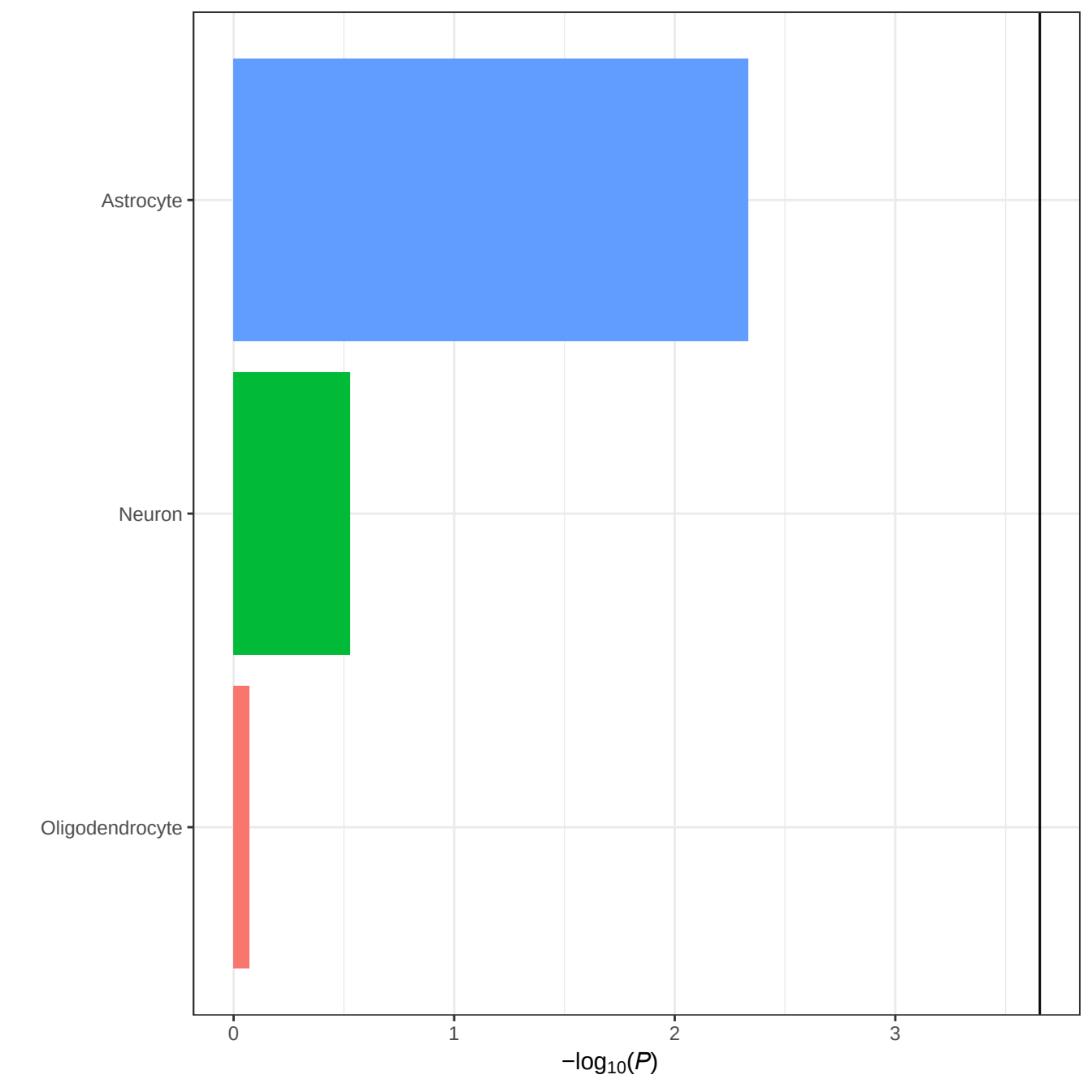
Supplementary Figure 12. *P* value of enrichment of heritability of anorexia nervosa in each tissue in GTEx using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Brain_Anterior_cingulate_cortex_(BA24)
Brain_Frontal_Cortex_(BA9)
Brain_Cortex
Brain_Hypothalamus
Muscle_Skeletal
Brain_Cerebellar_Hemisphere
Brain_Nucleus_accumbens_(basal_ganglia)
Brain_Hippocampus
Brain_Amygdala
Testis
Brain_Caudate_(basal_ganglia)
Brain_Cerebellum
Brain_Putamen_(basal_ganglia)
Brain_Substantia_nigra
Ovary
Cells_Transformed_fibroblasts
Liver
Heart_Left_Ventricle
Uterus
Stomach
Prostate
Pancreas
Artery_Tibial
Heart_Atrial_Appendage
Brain_Spinal_cord_(cervical_c−1)
Spleen
Artery_Coronary
Cells_EBV−transformed_lymphocytes
Bladder
Cervix_Endocervix
Nerve_Tibial
Vagina
Artery_Aorta
Breast_Mammary_Tissue
Small_Intestine_Terminal_Ileum
Skin_Sun_Exposed_(Lower_leg)
Adipose_Subcutaneous
Colon_Transverse
Whole_Blood
Thyroid
Colon_Sigmoid
Adipose_Visceral_(Omentum)
Fallopian_Tube
Esophagus_Gastroesophageal_Junction
Esophagus_Muscularis
Skin_Not_Sun_Exposed_(Suprapubic)
Cervix_Ectocervix
Lung
Esophagus_Mucosa
Kidney_Cortex
Adrenal_Gland
Minor_Salivary_Gland
Pituitary
0
1
2
3
−log10(P)

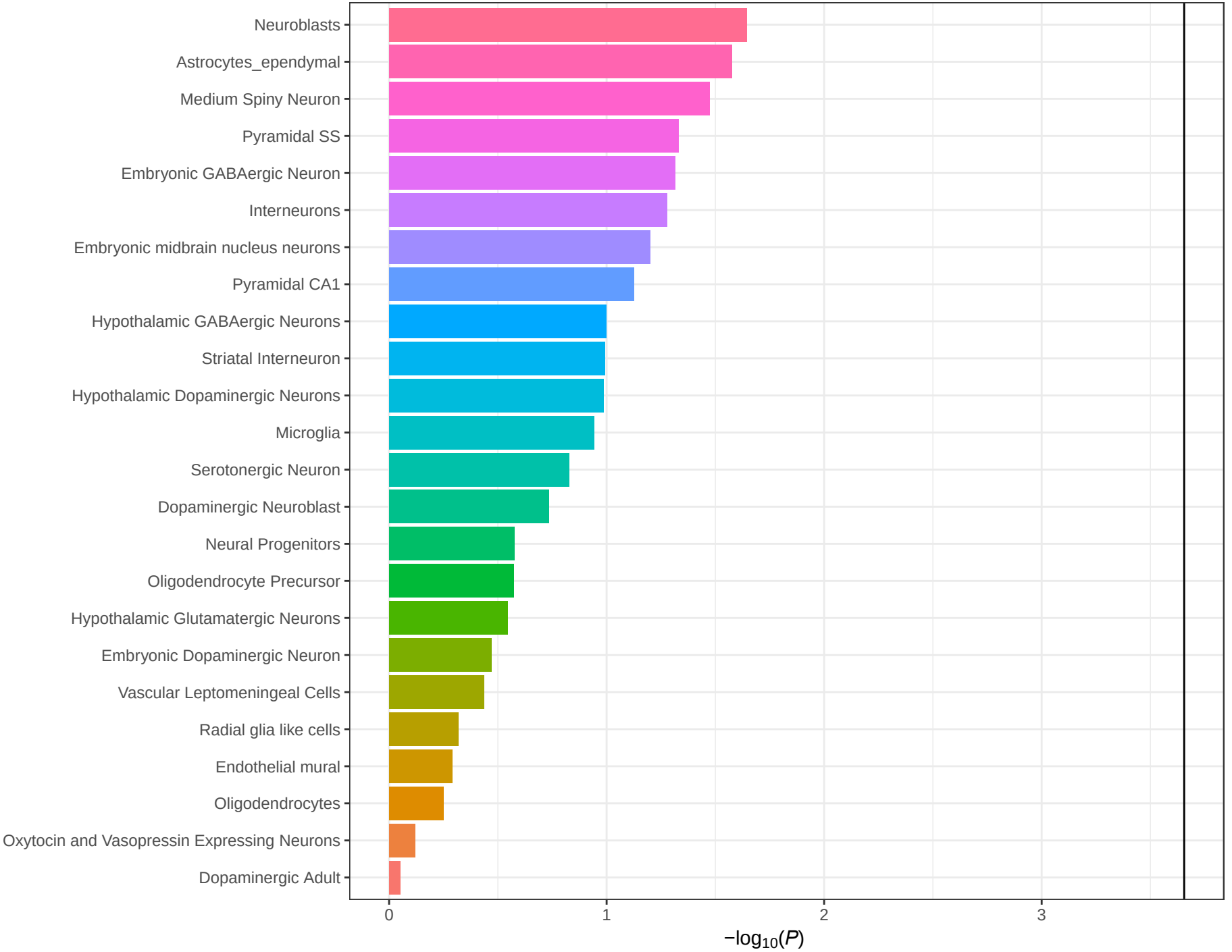
Supplementary Figure 13. *P* value of enrichment of heritability of anorexia nervosa in brain tissues in GTEx using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Brain_Anterior_cingulate_cortex_(BA24)
Brain_Frontal_Cortex_(BA9)
Brain_Cerebellar_Hemisphere
Brain_Nucleus_accumbens_(basal_ganglia)
Brain_Cortex
Brain_Cerebellum
Brain_Putamen_(basal_ganglia)
Brain_Amygdala
Brain_Caudate_(basal_ganglia)
Brain_Hypothalamus
Brain_Hippocampus
Brain_Substantia_nigra
Brain_Spinal_cord_(cervical_c−1)
0
1
2
3
−log10(P)

Supplementary Figure 14. *P* value of enrichment of heritability of anorexia nervosa in cell types in Cahoy database using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Astrocyte
Neuron
Oligodendrocyte
0
1
2
3
−log10(P)

Supplementary Figure 15. *P* value of enrichment of heritability of anorexia nervosa in 24 brain cell types from the single-cell RNA-sequencing database (broad categories) using LD score regression applied to specifically expressed genes (LDSC-SEG). The sample size is 16,992 cases and 55,525 controls. The Bonferroni-corrected threshold (black vertical line) is $-\log_{10}(P) > 3.6$ and is based on tests across 53 tissues, 24 broad categories of cell types, and 149 KI level 2 cell types, a total of 226 tests.


Neuroblasts
Astrocytes_ependymal
Medium Spiny Neuron
Pyramidal SS
Embryonic GABAergic Neuron
Interneurons
Embryonic midbrain nucleus neurons
Pyramidal CA1
Hypothalamic GABAergic Neurons
Striatal Interneuron
Hypothalamic Dopaminergic Neurons
Microglia
Serotonergic Neuron
Dopaminergic Neuroblast
Neural Progenitors
Oligodendrocyte Precursor
Hypothalamic Glutamatergic Neurons
Embryonic Dopaminergic Neuron
Vascular Leptomeningeal Cells
Radial glia like cells
Endothelial mural
Oligodendrocytes
Oxytocin and Vasopressin Expressing Neurons
Dopaminergic Adult
0
1
2
3
−log10(P)

Supplementary Figure 16. Polygenic risk score (PRS) leave-one-out analysis: results for each cohort. PRS was constructed with the leave-one-out method from a GWAS with all datasets excluding the target dataset. Then, PRS was used to predict change in residualized phenotype score for anorexia nervosa (AN) risk in the target dataset (shown as the center value and an error bar which represents the 95% confidence interval of this estimate). The decile with the lowest PRS (i.e., subjects whose AN PRS is in the bottom 10%) serves as the referent. A higher residualized phenotype score indicates a higher risk of AN.

-

Dataset no	PGC abbreviation	*Total N*
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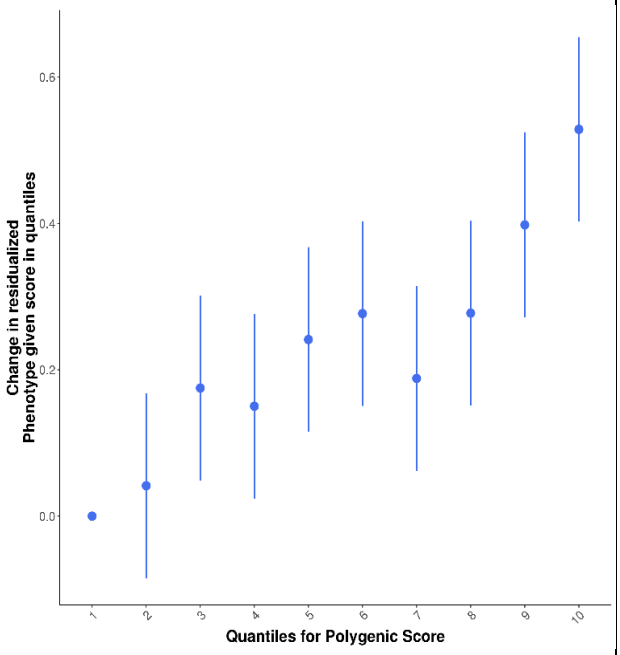

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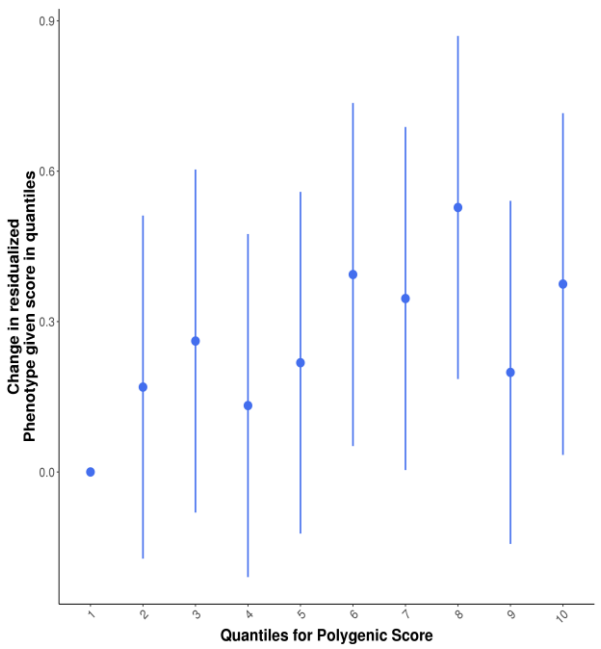

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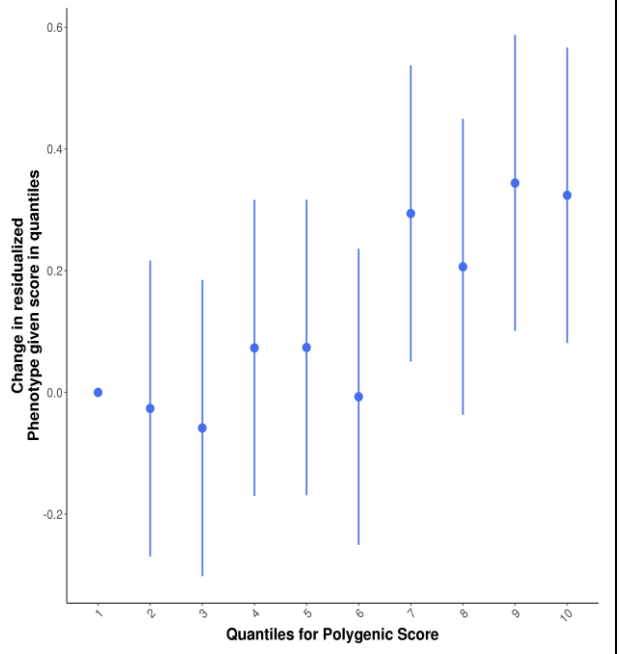

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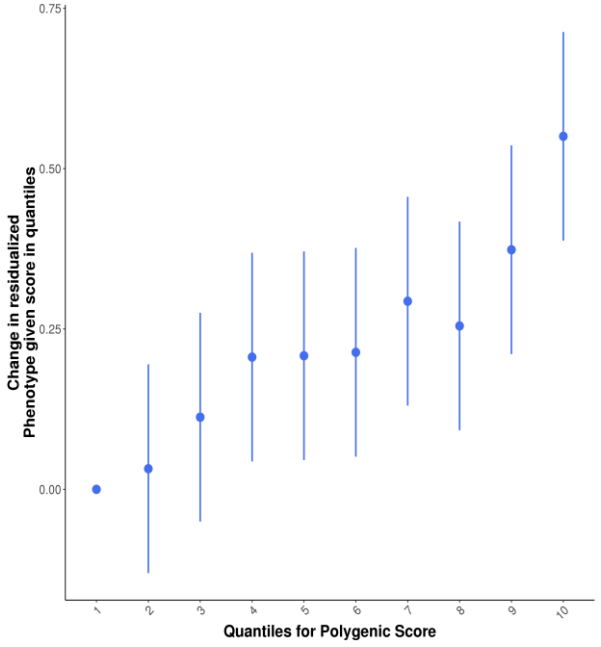

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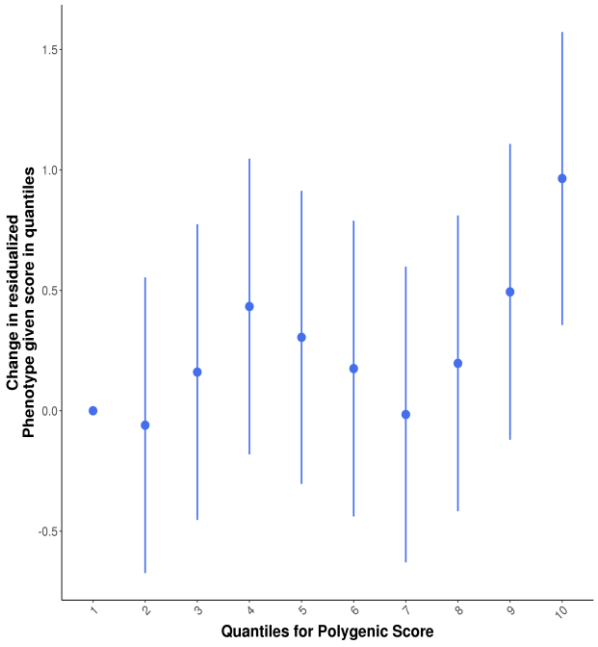

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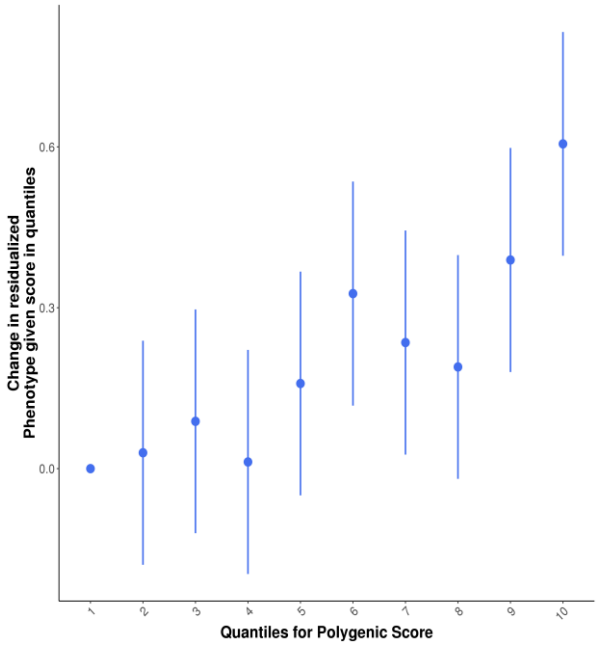

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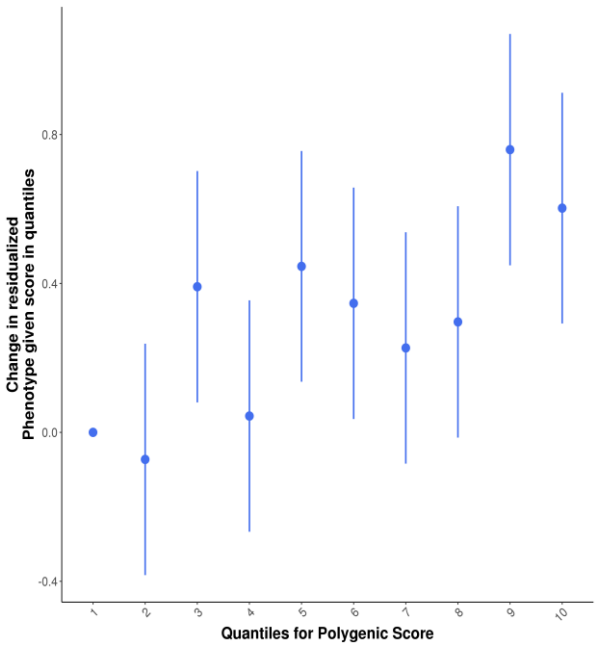

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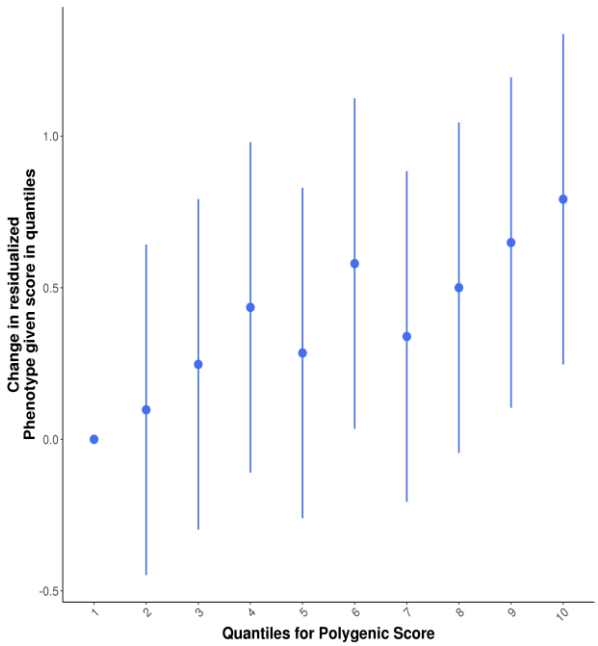

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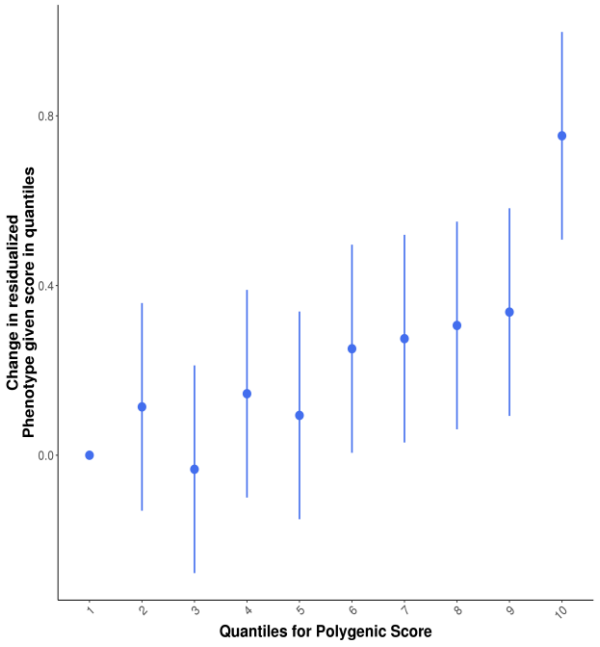

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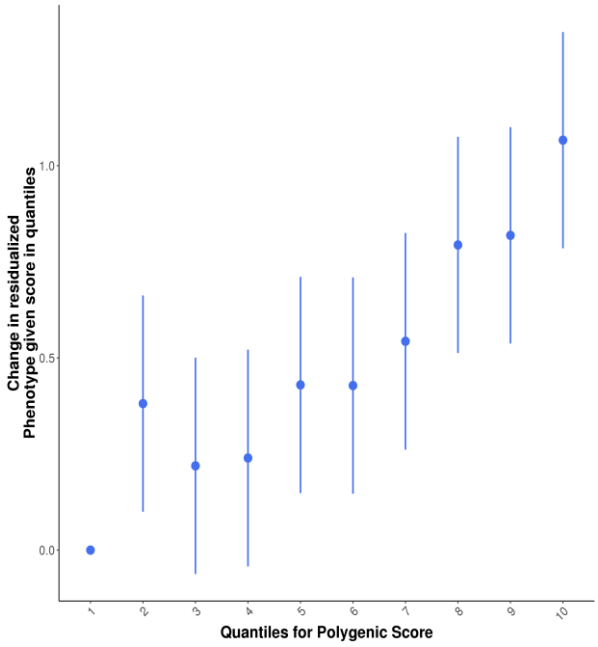

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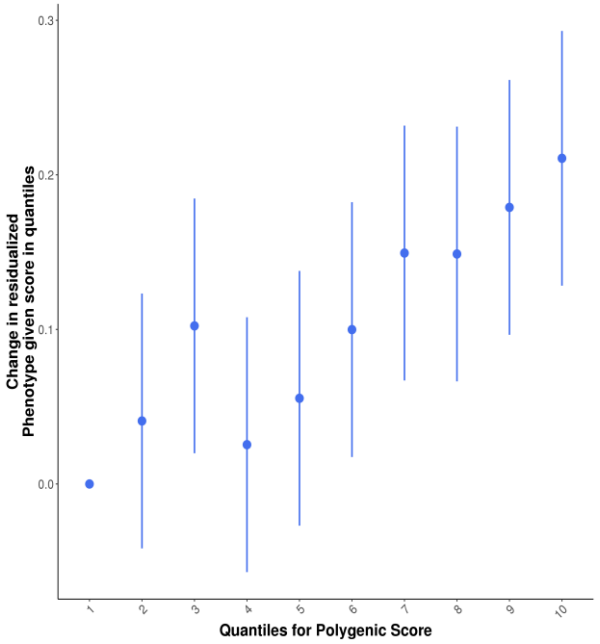

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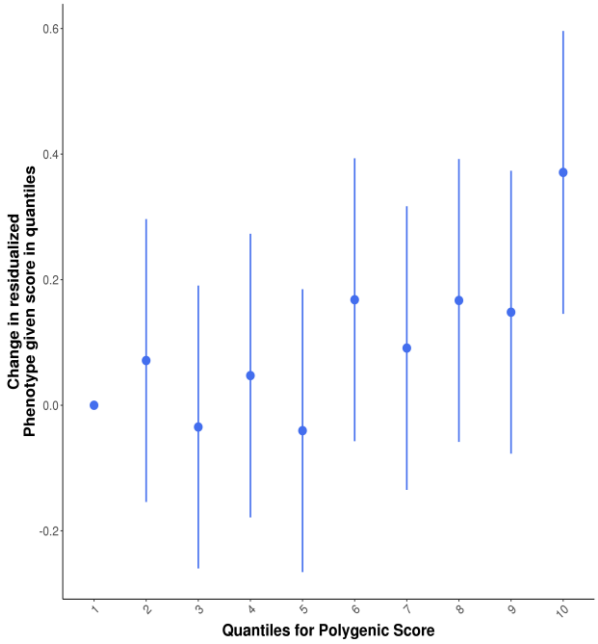

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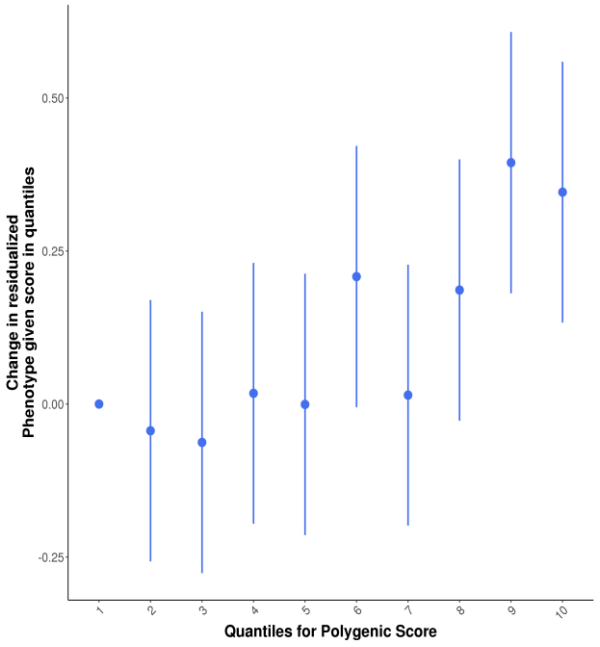

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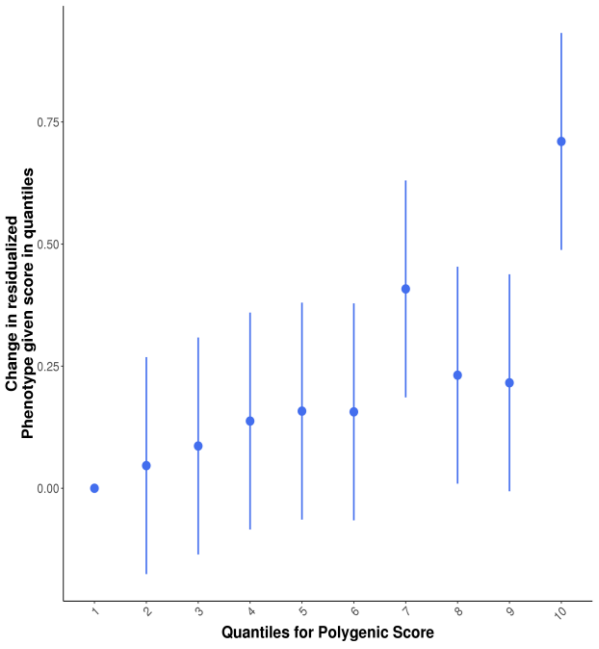

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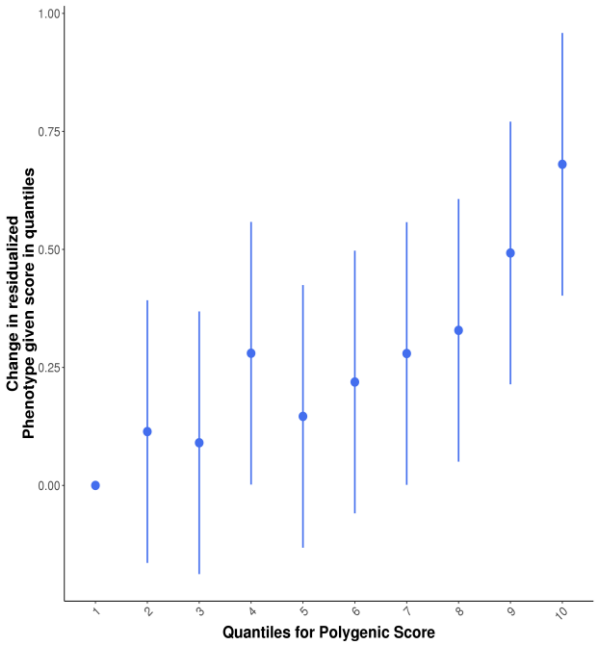

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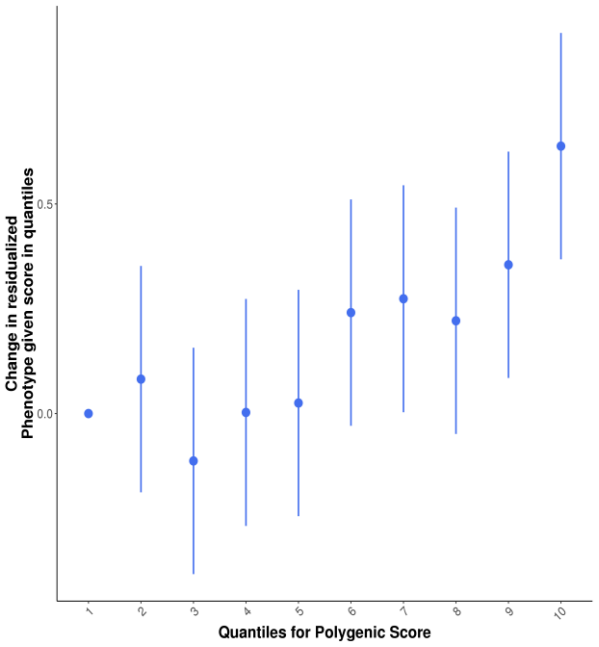

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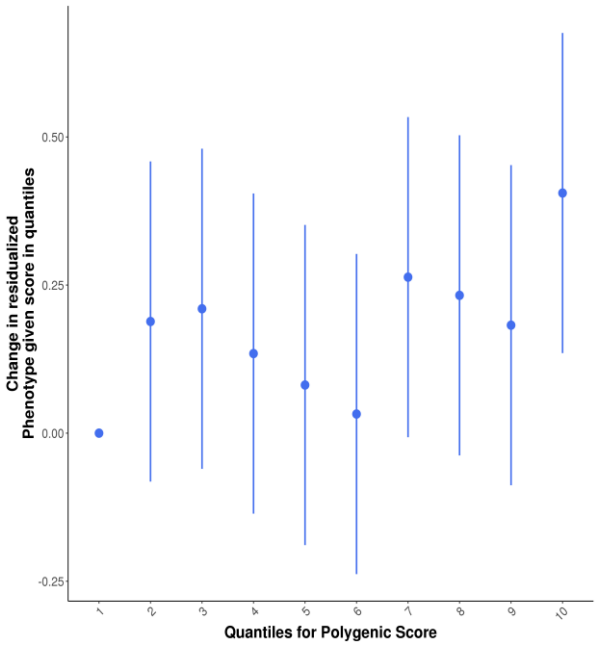

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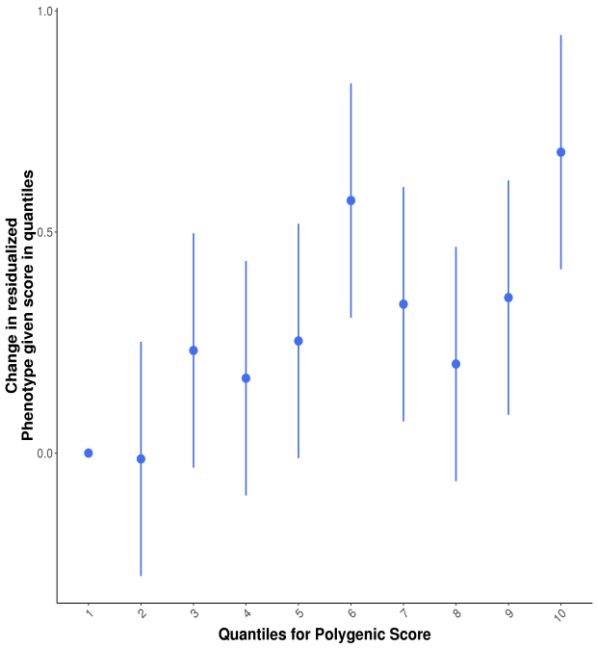

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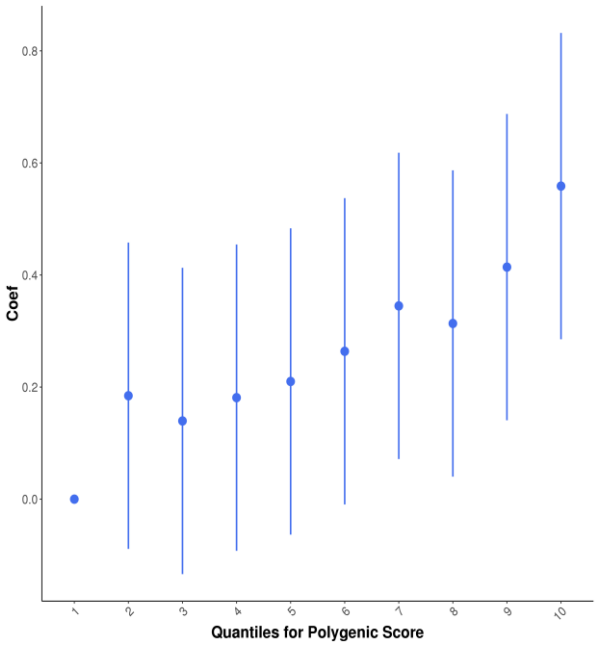

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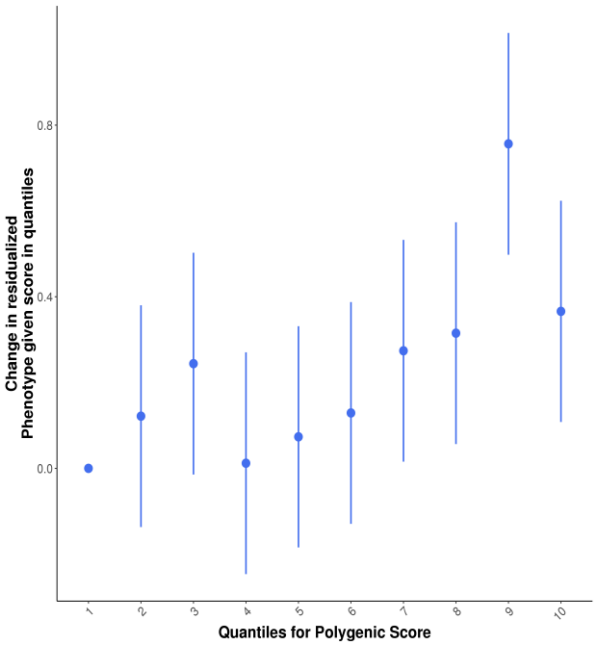

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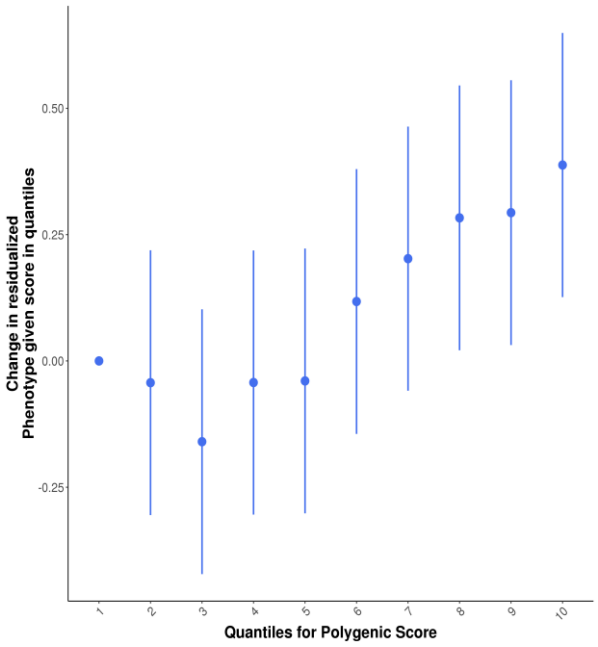

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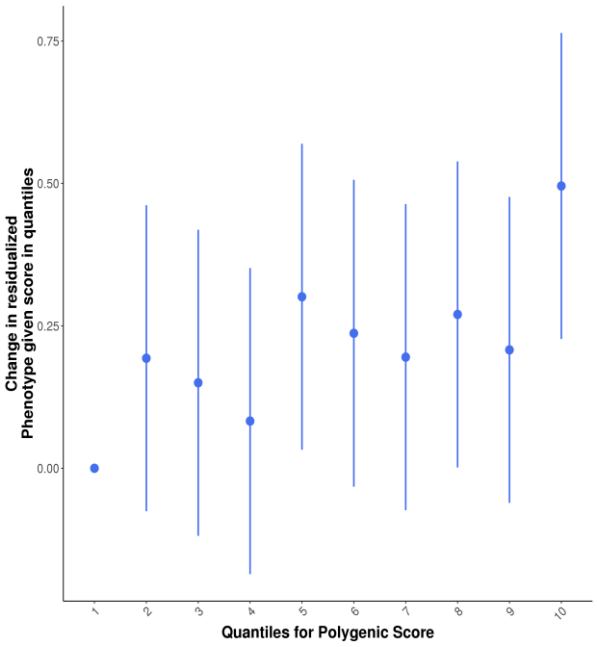

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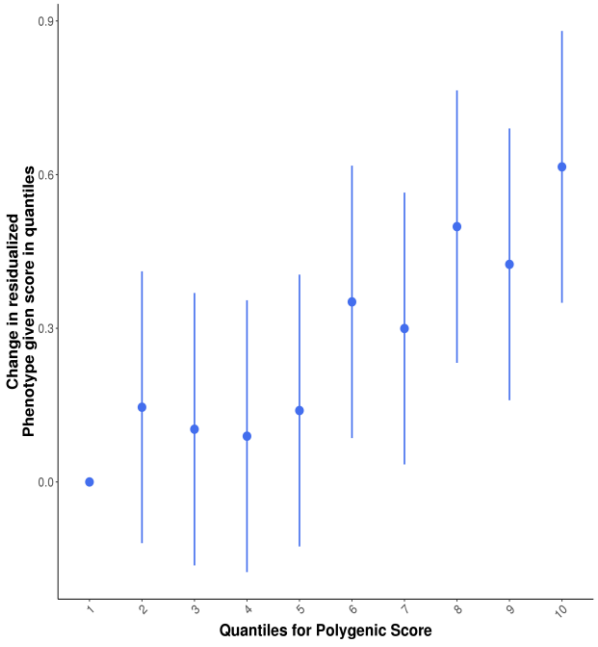

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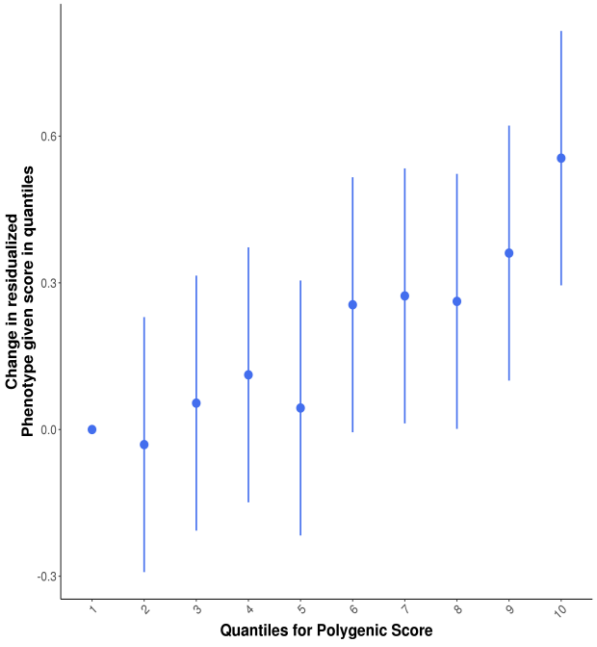

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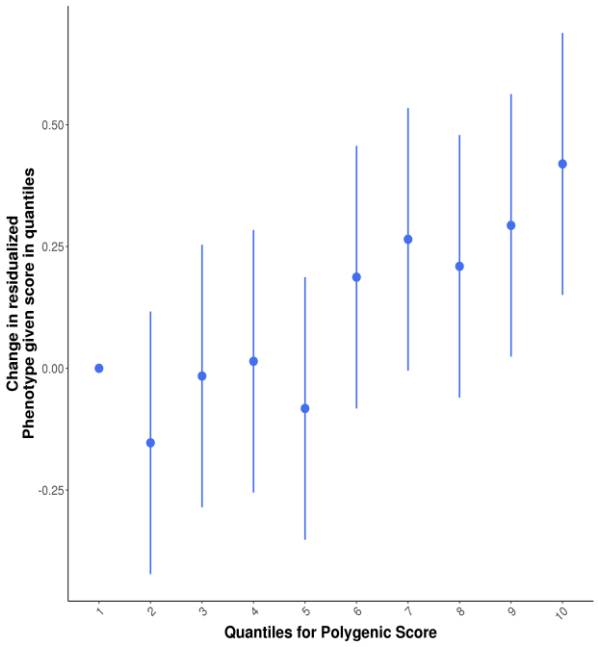

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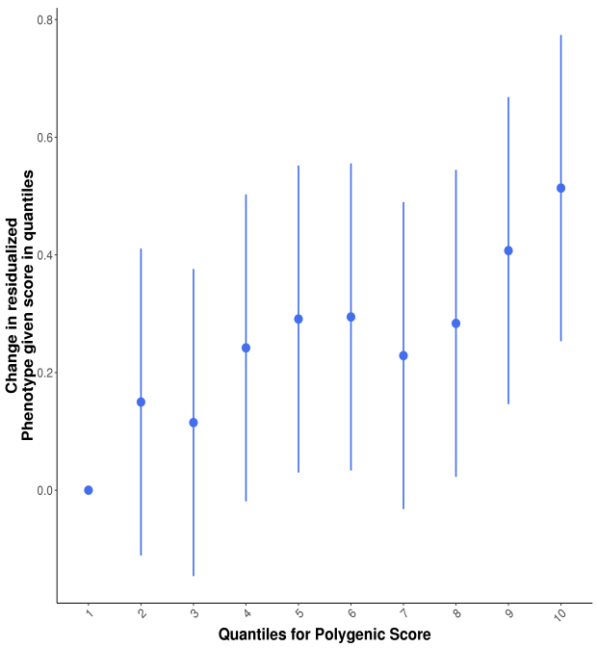

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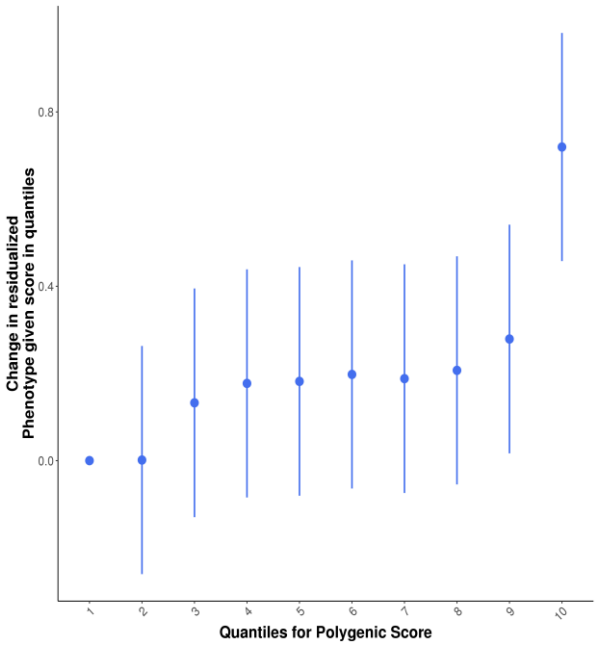

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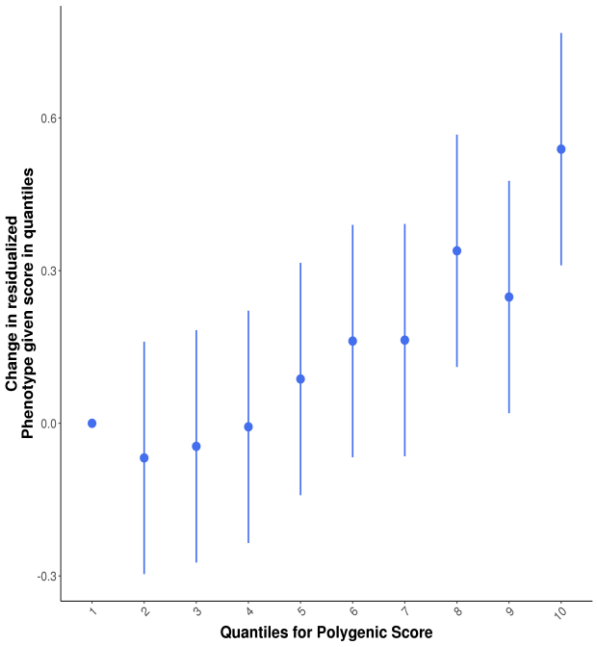

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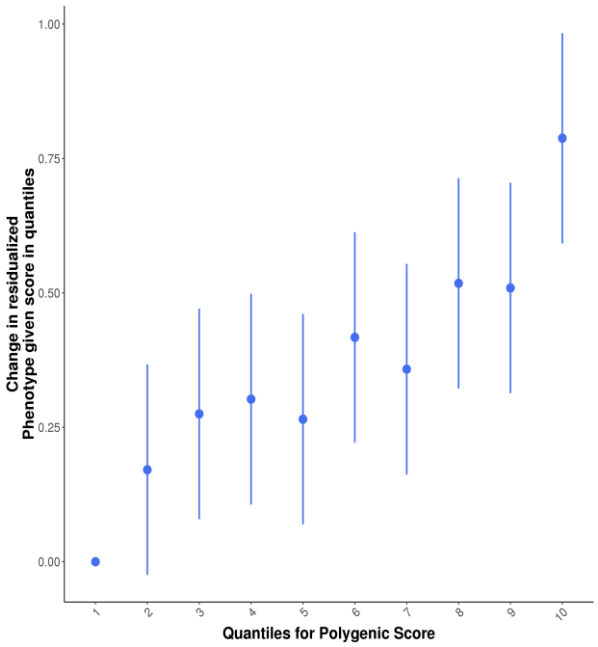

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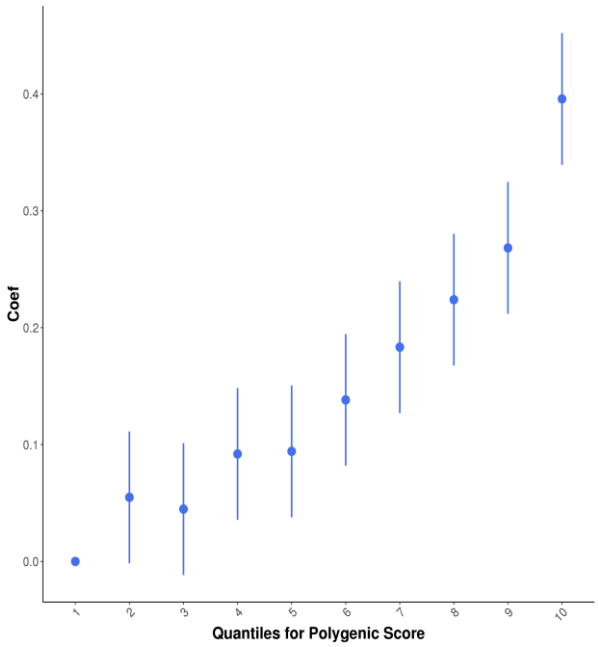

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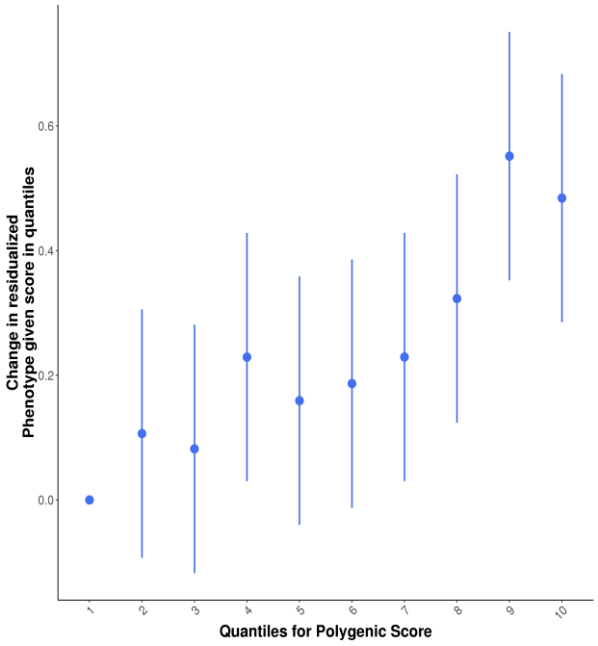

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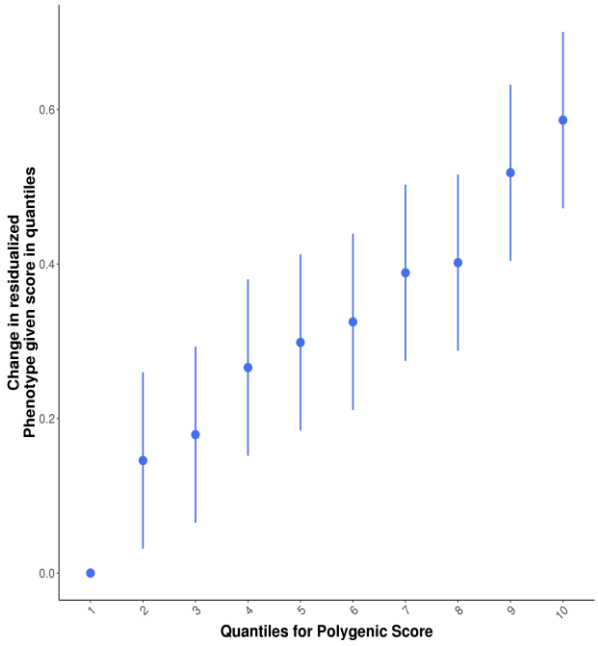

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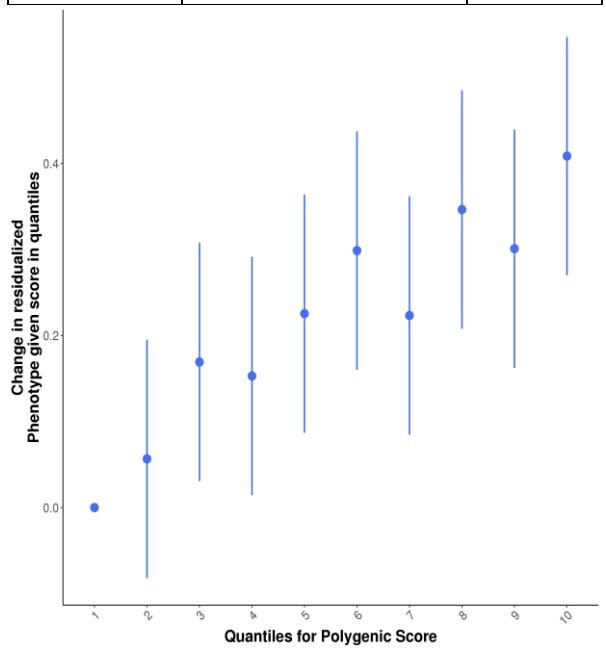

Watson, H. J., Yilmaz, Z., Thornton, L. M., Hübel, C., Coleman, J. R. I., Gaspar, H. A., . . . Bulik, C. M. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nature Genetics.

Supplementary Information

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Supplementary Note

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Additional Methods

Samples and study design

Psychiatric Genomics Consortium (PGC) abbreviations for the 33 datasets meta-analyzed in this study are shown in **Supplementary Table 1**. **Supplementary Table 1** shows cohort case and control numbers, SNP numbers, and lambda at ascertainment [pre-quality control (QC)] and post-QC, **Supplementary Table 2** describes ascertainment including how cases were evaluated in the primary studies, and case and control sources and inclusion and exclusion criteria. **Supplementary Table 3** gives the genotyping platforms used. Details of the contributing studies and cohorts are provided below. The study is a secondary analysis of data collected from the studies described and did not involve direct recruitment and contact with participants or collection of identifiers linked to participants. The IRB of the University of North Carolina at Chapel Hill gave approval for this project (reference number 15-3307).

Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) Freeze 1

Full details of these data are given in the Freeze 1 paper of the PGC-ED (http://www.med.unc.edu/pgc) authored by Duncan et al.[1]

To summarize, Duncan et al. datasets included the Children's Hospital of Philadelphia/Price Foundation Collaborative Group (CHOP/PFCG) case-control data from the anorexia nervosa GWAS of Wang et al.[6], case-only data from the Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC-3; https://www.wtccc.org.uk) included in Boraska et al.[2], and since many of the controls used in Boraska et al. were not permitted to be re-used, control cohorts were sourced as described in Duncan et al.[1]. Control cohorts from a similar geographic location and genotyped on an Illumina platform were preferentially sought. Briefly, eethical approval for each site in GCAN/WTCCC3 was obtained from the local ethics committee. All participants provided written informed consent in accordance with the Declaration of Helsinki[1,2]. Ethical approval for each site in the PFCG was obtained separately from their own institution's human subjects committee. Informed consent was obtained from all study participants[3-5]. Controls for the PFCG cases were obtained from CHOP. The Research Ethics Board of CHOP approved the study, and written informed consent was obtained from all subjects or their parents[6]. All cases and controls in PGC-ED Freeze 1 were also included in the current analysis[1]. As per Freeze 1, the Italy-North cases from Boraska et al. were not included due to a lack of ancestrally-matched controls accessible for our study. Pre-QC datasets with < 100 cases were identified (Germany, Greece, Italy-South, Norway) and merged with other data to form larger datasets. The combinations were an excellent ancestral match according to principal components analysis (PCA). Italy-South and Greece were merged to form the cohort *itgr*. Czech and Poland data were merged and formed the cohort *poco*, and Norway, Germany, and Sweden data were merged and formed the cohort *gns2* (see the section below called "Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3" for information about Poland and Sweden data). These samples are included in *chop*, *fin1*, *fre1*, *itgr, gns2, net1, poco, spa1, ukd1, and usa1* (see the section below for other data in *poco* and *gns2*).

Genetic Consortium for Anorexia Nervosa/Wellcome Trust Case Control Consortium-3 (GCAN/WTCCC-3)

Additional GCAN/WTCCC-3 cohorts that were not part of Duncan et al. due to a lack of controls (Poland) or small $N < 100$ of cases (Sweden) were included in our analysis as we were able to identify ancestrally matched cases and/or controls. We sourced Poland controls from the BoMa/MooDS-PGC study (Bonn/Mannheim Bipolar study; Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia study)[7,8]. These controls were also used in the PGC bipolar disorder GWAS[9]. These controls were produced by the International Agency for Research on Cancer (IARC; https://www.iarc.fr) and the Centre National de Génotypage (CNG; https://www.cng.fr) GWAS Initiative for a study of upper aerodigestive tract cancers[10] and genotyped on the Illumina HH317k. They were drawn from a hospital-based case-control sample recruited by the Nofer Institute of Occupational Medicine in Lodz and a population-based case-control sample recruited by the Cancer-Center and Institute of Oncology in Warsaw. Controls were not screened for neuropsychiatric phenotypes. These combinations above proved an excellent ancestral match according to PCA. These samples are included in *poco* and *gns2*.

Anorexia Nervosa Genetics Initiative (ANGI)

ANGI (https://www.med.unc.edu/psych/eatingdisorders/our-research/angi) is a multi-country effort to identify the genetic causes of anorexia nervosa and involves international research teams in the US, Sweden, Denmark, and Australia with assistance from New Zealand. Details on recruitment strategies, case definitions, and methods for ANGI have been reported previously and are outlined briefly below[11,12]. All ANGI controls were screened for eating disorder phenotypes and some for additional psychiatric phenotypes.

Australia and New Zealand (ANGI-ANZ).

Cases from ANGI-ANZ were recruited the following way. Individuals who resided in Australia (age ≥ 13 years) or New Zealand (age ≥ 14 years) self-identified or were referred to the study. Those interested in study participation completed the consent process and online diagnostic questionnaire (ED100K-V1). Cases met anorexia nervosa criteria based on DSM-IV-TR. Once the questionnaire was completed, the participant provided a blood sample. In New Zealand, witnessed informed consent was obtained prior to sample collection. Genotyping was conducted at the Broad Institute on the Illumina Global Screening Array. Controls were obtained from the QSkin Sun and Health Study (https://qskin.qimrberghofer.edu.au)[13]. Briefly, ~40,000 men and women aged 40-69 years were randomly sampled from Queensland, Australia. Those who indicated no eating disorders history from a checklist were included as controls. QSkin was established to study the etiology of cutaneous melanoma and other cancers of the skin; the cohort is followed up passively through linkage with health registers. QSkin participants provided Oragene saliva samples, and DNA was genotyped at Erasmus University Rotterdam in the Netherlands on the Illumina Global Screening Array. Ethical approval for the Australian component of the study was provided by the QIMR Berghofer Human Research Ethics Committee (QIMR-HREC approval P1339). Those interested in study participation completed the informed consent process via online submission prior to taking an online diagnostic questionnaire (ED100K-V1). Participants younger than 18 years then completed a paper questionnaire which required parent/guardian co-signature. Ethical approval for the New Zealand component was provided by the Health and Disability Ethics Committee of the New Zealand

Ministry of Health. In New Zealand, witnessed informed consent was obtained prior to sample collection. Participants under 18 years required parent/guardian co-signature. Ethical approval for the QSkin study was provided by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute (QIMR-HREC approval P1309). QSkin participants were given the option to provide written informed consent or to consent online in order to take part in the QSkin study. The samples described formed cohort *aunz*.

Denmark (ANGI-DK). National register and biobank. Cases and controls were identified primarily using the national register and biobank system. Genotypes came from Guthrie cards held by the Danish Neonatal Screening Biobank at Statens Serum Institute. Samples from this biobank are linked to the Danish register system via the unique Danish personal identification number. The individuals were born between 1981 and 2005 and had to be alive and a resident of Denmark on their first birthday and have a known mother. Cases had International Classification of Diseases (ICD-10) anorexia nervosa (F50.0)[14] diagnoses assigned by psychiatrists at inpatient and outpatient psychiatric services, and were identified using the Danish Psychiatric Central Research Register[15]. Controls were randomly selected from the same nationwide birth cohort. Cases and controls were specifically ascertained and genotyped as a part of ANGI, and additional control genotypes came from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; http://ipsych.au.dk)[16]. DNA from the dried blood spots was extracted, whole-genome amplified in triplicates, and genotyped in 23 batches based on birth year. The first wave (batch) contains the youngest participants (born in 2004) and wave 23 consists of the oldest participants (born in 1981). Wave 24, a supplementary batch, comprised all participants with an ICD-10 atypical anorexia nervosa lifetime diagnosis (F50.1, most commonly diagnosed when all anorexia nervosa criteria except amenorrhea were met) up to and including 2013 and F50.0 cases diagnosed during 2013. Comparisons showed that F50.0 and F50.1 samples matched on register information tested, i.e., age of diagnosis, frequency of lifetime psychiatric diagnoses and intellectual disability, urbanicity, and maternal and paternal age at childbirth. Genotyping was performed on the Illumina PsychChip array at the Broad Institute of Harvard and MIT. GenCall[17] and Birdseed[18] were used to call variants with MAF > 0.01. Call sets were merged after pre-QC on individual call sets. Data processing and GWAS analyses were performed on secure servers at the GenomeDK high-performance computing cluster (http://genome.au.dk).

DNA preparation, genotyping, genotype calling, QC methods, and imputation were performed on the broader iPSYCH cohort waves, which also included psychiatric cases with non-anorexia nervosa diagnoses (schizophrenia, depression, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder). The full iPSYCH cohort described contains ~86,000 individuals, including about 57,000 cases with at least one of the noted psychiatric disorders and around 30,000 controls. Each wave that was processed had ~3,500 participants.

Case-control data were filtered for the primary GWAS analysis such that cases required an anorexia nervosa or atypical anorexia nervosa lifetime diagnosis and controls required no lifetime anorexia nervosa or iPSYCH psychiatric diagnoses listed above. To address batch effects, a GWAS was conducted on waves separately, except waves 1 to 6 which were combined in a block due to smaller case sample sizes. Ancestry principal components (PCs) and PCs that

captured batch effects and other possible sources of variation were included as covariates (**Supplementary Table 18**). ANGI-DK samples formed cohorts *w1* to *w24*.

Individuals in ANGI-DK did not provide written informed consent. The register data collection is pseudo-anonymized (http://ipsych.au.dk/about-ipsych/data-processing-and-data-security-atipsych) and the re-identification key for linking the Danish civil registration number is stored separately from phenotype and genotype data. An exemption from consent is legally possible in Denmark if approved by The Danish Scientific Ethics Committee (Videnskabsetisk Komité). This exemption was given for all samples and was provided in 2012 to the iPSYCH study, with the most recent approval granted in 2018.

Denmark clinic samples**.** A Danish clinical cohort was obtained. Cases were defined as patients with at least one recorded hospital admission during which an ICD-10[14] diagnosis of F50.0 or F50.1 was given. Clinical cases consisted of women born 1947-1980 (age range: 35 to 68 years). Samples were genotyped at the Broad Institute on the Illumina Global Screening Array. Ethical approval with the protocol no. H-KF-01-024/01 was obtained from the competent Danish authority, De Videnskabsetiske Komiteer for Region Hovedstaden (The Capital Region of Denmark's Committees on Health Research Ethics). All participants provided written informed consent prior to being included into the study. The samples described are included in cohort *sedk*.

Sweden (ANGI-SE). The primary recruitment strategy involved Riksät-National Quality Register for Eating Disorders Treatment[19], which includes eating disorder-specific information from individuals seeking eating disorder treatment in Sweden since 1999. Potential cases identified through Riksät were sent a letter asking them to complete a follow-up questionnaire, which included the ED100K-V1 questionnaire. In the second recruitment strategy, study nurses at the Stockholm Centre for Eating Disorders (http://stockholmatstorningar.se) (SCÄ) recruited cases for ANGI. When patients with anorexia nervosa came into this center, a research nurse discussed the study with them and reviewed the consent. When participants consented, a blood sample was taken, and the participant was directed to complete the online diagnostic questionnaire. The third strategy was community outreach, specifically using traditional media (i.e., TV, radio, and newspapers) and social media including the Swedish ANGI website (http://www.angi.se), directly linking to the questionnaire. The final recruitment strategy for cases and controls involved LifeGene (https://www.lifegene.se)[20], an ongoing study initiated in 2010 to evaluate how genes, environment, and lifestyle affect health. Individuals enrolled in LifeGene completed an eating disorder assessment similar to the online diagnostic questionnaire and provided a blood sample. An anorexia nervosa algorithm for LifeGene was harmonized with the ED100K-V1 questionnaire for case and control identification. All cases met anorexia nervosa criteria based on DSM-IV-TR[21], and controls screened negative for a history of eating disorders. Genotyping was performed at the Broad Institute on the Illumina Global Screening Array. The Swedish component of ANGI (Riksät, SCÄ, and Community) was approved by the Regional Ethical Review Board in Stockholm (dnr: 2013/112-31/2). Individuals who wished to participate were mailed consent forms along with the vials for blood samples. Signed consent forms were returned with the samples. The Regional Ethical Review Board of Stockholm provided initial ethical approval of LifeGene. All participants provided consent online[20]. The Swedish component of ANGI obtained approval, as stated above, for use of LifeGene samples and data as

part of ANGI-SE. These samples described are included in cohort *sedk* (see the section above called "Denmark Clinic Samples" for other samples included in *sedk*.

United States (ANGI-US). Individuals who resided in the US (ages ≥ 12 years) self-identified or were referred to the study. Individuals completed a brief online screener to determine eligibility as a case or control for ANGI. Those deemed eligible completed the consent process and online diagnostic questionnaire (ED100K-V1). All cases met anorexia nervosa criteria based on DSM-IV-TR, and controls screened negative for a history of eating disorders. Once the questionnaire was completed, the participant provided a blood sample. Approximately 1,000 controls were recruited from the community. Additional control samples were obtained from The Price Foundation Anorexia Nervosa Trios Study[5,22]. These additional controls reported no history of eating disorders, had no first degree relative with an eating disorder, and screened negative for other Axis I psychopathology. Genotyping was performed at the Broad Institute on the Illumina Global Screening Array. Ethical approval for the US component of ANGI was granted by the University of North Carolina at Chapel Hill's Institutional Review Board (IRB# 13-0081). Individuals who were interested in study participation (and deemed eligible by the brief screen in the US) contacted the study team and completed the consent process. Although some provided written consent, most participants provided consent over the phone after a complete review of the consent forms. These samples formed cohort *usa2*.

UK Biobank

The UK Biobank (http://www.ukbiobank.ac.uk/) is a large prospective study of ~500,000 residents of the United Kingdom aged from 40 to 69 years old[23]. UK Biobank aims to provide insights into the causes, prevention, and treatment of various illnesses. Recruitment occurred between 2006-2010. The present study uses data from the July 2017 release including the second wave of genetic data. Cases were identified by primary and secondary ICD-10[14] diagnosis from linked health care records and self-report diagnosis of anorexia nervosa by a clinical professional in the UK Biobank mental health questionnaire. Controls were screened for any psychiatric disorder (Chapter V: Mental and behavioral disorders). UK Biobank participants provided electronic signed consent at their baseline assessment visit. UK Biobank was approved by the NHS Health Research Authority North West-Haydock Research Ethics Committee (reference 16/NW/0274). The current study was completed as part of approved UK Biobank application 27456. The samples described formed cohort *ukbb*.

Merging of case and control data

When sourcing control data, we prioritized controls that were ancestrally matched and genotyped on a similar platform to cases. There are two instances whereby cases were matched with controls from another country [i.e., *aunz* New Zealand cases (n = 430) were merged with Australian cases (n = 2,261) and controls (n = 17,158), and *sedk* Denmark cases (n = 129) were merged with Sweden cases (n = 4,118) and controls (n = 4,035)]. Country is unlikely to be confounded with case-control status in these cohorts. Ancestral matching was undertaken by visual inspection of a principal components analysis PC1 v PC2 plot for the merged data, and the matches were excellent with cases and controls randomly interspersed. Further, the first five ancestry PCs and any PCs that significantly differed ($P < 0.05$) between case and control cohort were included as covariates in GWAS to capture nuanced ancestry or batch effect differences.

Statistical power

Identified susceptibility variants in psychiatric genetics typically have an OR of ~1.1[24]. Our study was acceptably powered to detect susceptibility variants in this range (80% power to detect an OR of 1.09-1.19 with an additive model, 0.9% lifetime risk[25], $\alpha = 5 \times 10^{-8}$, MAF 0.05–0.5). Prior experience in other PGC disorders gives us reason to believe that when sample sizes reach an inflection point for power to detect multiple GWAS hits, the number of significant loci begins to increase linearly as samples were added after this inflection point. It is not surprising to see several borderline significant hits when first exceeding the inflection point, as has been observed in schizophrenia[26-28]. As more cases are added, it is probable that we will get more lead hits above this borderline range.

Quality control and covariates

For the GWAS analysis, the default QC parameters in Ricopili were used and are described as follows. Ricopili QC begins with a pre-filter SNP call rate of > 0.95, which is useful for cases and controls genotyped on different platforms. Next, QC involves sample filters, then SNP filters. Default sample filters are a call rate (cases/controls) ≥ 0.98, heterozygosity inbreeding coefficient ≤ 0.2 (cases/controls), and sex violations. Default SNP filters are a call rate ≥ 0.98, case-control missingness difference ≤ 0.02, no valid association *P* value (invariant), and violations of Hardy-Weinberg equilibrium (in controls $P > 10^{-6}$, in cases $P > 10^{-10}$). Some cohorts required the application of more stringent thresholds to reduce bias (**Supplementary Table 18**). Ancestry outliers were removed based on plotting the first two principal components (PCs) in a principal components analysis (PCA) containing each cohort and five reference cohorts (1000 Genomes Phase 3 EUR, AFR, EAS, SAS, AMR)[29] to retain European samples. Samples showing familial structure and/or cryptic relatedness, or duplicates were removed ($\hat{\pi} > 0.2$) during PCA. For the Danish waves, we conducted additional relatedness testing across all the waves combined, and then removed one individual from each related pair ($\hat{\pi} > 0.2$). PCs significantly associated with the phenotype were identified for inclusion as covariates. For the *aunz* cohort, QC and PCA was done externally. For QC, see **Supplementary Table 18**. PCA (20 principal components) were computed using smartpca (EigenSoft 6.0.1) on the cleaned data from all individuals used in the current paper in conjunction with the genotypes of ~50,000 additional individuals available at QIMR Berghofer, and the population reference data from the Genome-EUTWIN populations (https://ega-archive.org/datasets/EGAD00000000043) and HapMap Phase 3 populations[30]. Analyses were run using a filtered set of genotypes available across all genotyping projects (*N* SNPs ~40,000). Individuals beyond six standard deviations (*SD*s) of the European PC1 and PC2 centroid were excluded from analysis. The data were then put through Ricopili PCA module; the first five ancestry components and PCs significantly associated with the phenotype were always included as covariates (**Supplementary Table 18**). To the extent that national laws and regulations permitted, we examined sample overlap across cohorts by performing LD score bivariate regressions and estimating genetic covariance intercepts to assess sample overlap[31,32] (**Supplementary Table 19**).

Some of the cohorts required additional QC beyond the default process and parameters used in PGCs GWAS pipeline, Ricopili. **Supplementary Table 18** shows the additional QC steps applied, if any, and the PCs used as covariates, by cohort. The first five PCs were automatically

included to adjust for ancestry effects. Tests were done on post-QC data to investigate whether any of the PCs differ significantly between cases and controls, and if so, PCs nominally associated with the phenotype ($P < 0.05$) were also included in the GWAS as covariates.

Anorexia nervosa subtype phenotypes

We defined subtypes based on the presence or absence of binge eating. The rationale for this choice was that the current DSM-5[33] subtyping (i.e., restricting versus binge/purge) is a clinical, rather than a biological distinction. "Purging" behavior is a heterogeneous category and includes several behaviors either alone or in combination (e.g., self-induced vomiting, laxative abuse, diuretic abuse, other inappropriate compensatory behaviors), and our sample size is insufficiently powered—and phenotyping in several samples inadequately detailed—to identify individuals with various purging behavior constellations. In contrast, binge eating is more uniformly defined, represents a clear departure from restrictive eating behavior, and lies on the appetite continuum. Although the twin-based genetic correlation between binge eating and self-induced vomiting is high ($r_g = 0.74$)[34], less is known about other purging methods. Larger samples sizes will enable additional group distinctions and allow us to comment on the biological appropriateness of the current DSM-5 subtypes.

We defined anorexia nervosa with and without binge eating using available phenotypic data. We were able to use *chop*, *aunz*, and *usa2* datasets for this analysis. For *aunz* (ANGI-ANZ) and *usa2* (ANGI-US), anorexia nervosa with binge eating was defined as reporting ever 1) "having eating binges when you ate what most people would regard as an unusually large amount of food in a short period of time" and 2) "having a sense of loss of control during those eating binges". The absence of binge eating was determined by a "no" answer to either item. For *chop* (CHOP/PFCG), the presence of binge eating was defined as reporting a history of binge eating by structured or semi-structured interview. The no binge eating group had to report no lifetime history of bulimia nervosa and no history of binge eating. Purging was not used in these definitions and binge eating did not need to occur within episodes of anorexia nervosa. The percentage of available subtype data within these cohorts was 95% overall. Future analyses with larger samples sizes will increase confidence in results from this analysis.

GWAS of related traits in UK Biobank

Seven UK Biobank GWAS were performed to facilitate genetic correlation investigations. The phenotypes were BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), body fat percentage[35], fat mass (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report), fat-free mass[35], physical activity[35], anxiety[36], and neuroticism[35].

Genotyping, imputation and QC

Briefly, blood samples were genotyped on two arrays, which share nearly all of their content: the UK BiLEVE array ($N = 49{,}949$) or the UK Biobank Axiom array ($N = 438{,}414$). Genotyping was conducted by Affymetrix across 33 different batches of approximately 4,700 samples each. UK Biobank provides extensive information on sample processing on its website (biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583). UK Biobank performed stringent QC on the genotyping data at the Wellcome Trust Centre for Human Genetics (WTCHG). For further

details, see: biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580. Prior to imputation, all variant sites with a call rate below 90% were filtered out. Imputation was carried out by UK Biobank using a merged UK10K-1000 Genomes Phase 3 reference panel and the Haplotype Reference Consortium (HRC) panel[37] (for further information, please see [38]). UK Biobank preferentially retained SNPs imputed to HRC for SNPs present in both imputation panels. Imputation was conducted using the IMPUTE4 program[38].

We excluded non-European participants identified by *k*-means clustering ($k = 4$) on the first two PCs derived from the genotype data, and related individuals (KING relatedness metric > 0.088, equivalent to an identical-by-descent coefficient of 0.25). SNPs were excluded if they had a MAF < 1%, if no call was made in > 2% of samples following imputation, if they were imputed with low confidence (INFO < 0.8), deviated substantially from Hardy-Weinberg equilibrium (HWE test, $P < 10^{-7}$), if they were not genotyped and were not part of the HRC panel. Additional QC and other information about these GWAS is given in **Supplementary Table 20**.

GWAS of BMI, body fat percentage, fat mass, and fat free mass

The GWASs on BMI, body fat percentage, fat mass, and fat free mass were a cross-sectional analysis of 155,961 healthy European participants from the UK Biobank. To identify genetic variation uniquely associated with body composition not confounded by illnesses and their downstream effects or metabolism-altering medication, we applied stringent exclusion criteria (e.g., psychiatric, gastrointestinal and endocrine illnesses, hormonal and antidiabetic medication). Body composition was assessed using Tanita BC-418 MA scale (Tanita Corporation, Arlington Height, IL). We included 7,794,483 genotyped and imputed SNPs and insertion-deletion variants with a MAF ≥ 1%. We covaried for assessment center, genotyping batch, smoking status, alcohol consumption, menopause, age, and socioeconomic status (measured by the Townsend Deprivation Index)[39]. We accounted for underlying population stratification by including the first six ancestry PCs, calculated on the European subsample GWAS cohorts. We used BGENIE v1.2 (https://jmarchini.org/bgenie) for sex-specific analyses and meta-analyzed these sex-specific GWAS using METAL[40] (http://csg.sph.umich.edu/abecasis/metal).

GWAS of physical activity

We calculated sex-specific GWAS of physical activity with imputed genotype data in 29,496 male and 36,758 female ($N = 66,254$) individuals in the UK Biobank, including age (at recruitment), genotyping array, and genetic PCs 1–20 as covariates. Physical activity in the UK Biobank was measured continuously over a period of seven days with a wrist-worn accelerometer. General physical activity quality control of raw data is described in detail elsewhere[41]. They used a wear-time adjusted 7-day average measure of activity, including only individuals meeting UK Biobank QC criterion: good wear-time, good calibration, calibration on own data, and no problem indicators. Analyses were performed on the intersection of this UK Biobank subset with those passing general genotyping QC: in European ancestry subset; used in the calculation of ancestry PCs; without excess relatives in the UK Biobank sample; no putative sex chromosome aneuploidy; and were not outliers for heterozygosity and genotype missingness. General genotyping considerations, raw data QC, and imputation procedure in the UK Biobank are described in detail elsewhere[38]. 20 PCs provided by the UK Biobank were used.

GWAS of anxiety

We conducted sex-specific GWAS of anxiety disorders with imputed genotype data on 25,443 cases and 58,113 controls[36]. Cases met criteria for probable lifetime anxiety disorder diagnosis if they either self-reported a professional diagnosis of any of the five core anxiety disorders (generalized anxiety disorder, panic disorder, specific phobia, agoraphobia, or social anxiety disorder) or met criteria for probable lifetime generalized anxiety disorder according to the Composite International Diagnostic Interview question set[42,43]. Cases did not report a diagnosis of schizophrenia, psychosis, attention-deficit/hyperactivity disorder (ADHD), autism, any eating disorder, or bipolar disorder. Controls were screened for any evidence of psychiatric or substance use disorders. Participants were limited to individuals of European ancestry, who were not excessively related, had no putative sex chromosome aneuploidy, and were not outliers for heterozygosity and genotype missingness. Stratified linear regressions were performed on ~7 million SNPs of high imputation quality (INFO > 0.9) with a minimum MAF ≥ 0.01 in BGENIE v1.2 controlling for six ancestry PCs calculated on the European subsample of UK Biobank, assessment center, genotyping batch, and age.

GWAS of neuroticism

We performed sex-specific GWAS on neuroticism using the genotype data supplied by UK Biobank in males (N = 142,875) and in females (N =144,660; total N = 287,535), following QC as described above and using PCs calculated on the European subsample of UK Biobank. The neuroticism phenotype was calculated as the sum score of neuroticism questions at the baseline assessment[44], corrected for age and sex-specific means and *SD*s from the UK population[45]. In a second analysis, individuals were excluded if they reported any psychiatric illness resulting in 83,413 males and 73,946 females (total N = 157,355). Sex-stratified linear regressions were performed in PLINK using eight ancestry PCs and genotyping batch (as a factor) as covariates and later meta-analyzed using METAL[40].

Gene expression

We first investigated whether anorexia nervosa heritability was enriched in tissue/cell type specifically expressed genes using publicly available gene expression data: GTEx[46] (RNA-seq of macroscopic samples from multiple human tissues) and Cahoy[47] (mouse neural cell-types transcriptome database). Stratified LDSC estimated common variant heritability enrichment in the top 10% of specifically expressed genes in each tissue or cell type, taking into account confounders such as gene size, LD, and functionally enriched genomic regions (e.g., conserved regions across mammals[48]. We followed a published method LDSC-SEG (LDSC applied to specifically expressed genes)[49]. From the datasets, the method has derived a genome annotation corresponding to each tissue or cell type of interest, which contains the top 10% specifically expressed genes of the tissue or cell type together with 100 Kb windows on each side of the transcribed region of each genes. We obtained the derived genome annotations from the LDSC-SEG GitHub repository (https://github.com/bulik/ldsc).

Second, we created a new annotation by performing differential expression analyses among 9,970 single cells, previously clustered into 24 different cell types[50], from five different mouse brain regions. Briefly, we used the scran R package[51] using the 50% of the genes with mean expression higher than the median to compute normalization factor for each single cell. The

normalization factors were computed after clustering cells using the scran package quickCluster function to account for cell type heterogeneity. We then performed 24 differential expression analysis using R package BPSC[52] testing each cell type against the 23 other cell types using the computed normalization factors as a covariate. We then selected the top 10% most upregulated genes for each cell type and used the coordinates of these genes extended by 100 Kb on each side as an extra annotation in LDSC.

We used the "munge_sumstats.py" script built in the LDSC software[31,32] to reformat the ANGI GWAS results. We then applied stratified LDSC regression to estimate heritability enrichment of the annotations[49] (tissue or cell type) conditional on 53 other annotations from the "baseline model" (e.g., conserved regions[48]). We used regression weights computed from phase 3 of the 1000 Genome Project[29] with HLA regions removed (https://data.broadinstitute.org/alkesgroup/LDSCORE/1000G_Phase3_weights_hm3_no_MHC.tgz).

We primarily report the regression coefficient of each annotation (corresponding to gene expression of each tissue or cell type) and an associated *P* value. A positive regression coefficient suggests that the annotation contributes to the heritability of anorexia nervosa while accounting for the contributions of other annotations[49,53]. The *P* value tests whether the regression coefficient was significantly positive (one-tailed), i.e., whether the contribution of the annotation is statistically significant. LDSC analyses are reported in **Supplementary Figs. 12-15**.

We also used MAGMA[54] (v1.06) (https://ctg.cncr.nl/software/magma), as done previously[50], to identify tissues/cell types underlying anorexia nervosa. GTEx data (V6p, median expression across individual per tissue) was downloaded from the GTEx website (https://gtexportal.org/home). Genes not expressed in any tissues (median = 0 for all tissues) were excluded. Gene expression from the different brain cell types was obtained as previously described. Briefly, we performed single cell RNA-seq from 9,970 single cells from five brain regions (neocortex, hippocampus, hypothalamus, striatum, midbrain, plus samples enriched for oligodendrocytes, dopaminergic neurons, and cortical parvalbuminergic interneurons), which allowed us to identify 24 cell types at level 1 (broad clustering) (pyramidal neurons, oligodendrocytes, etc…) and 149 cell types at level 2 (fine grained clustering) (pyramidal neurons from layer 6, layer 4, etc…).

For each gene expression dataset, we computed an index of specificity for each gene in each tissue/cell type by dividing the expression of a gene in a given tissue/cell type by the total expression of the gene in all tissues/cell types (range of specificity: 0-1). For each tissue/cell type, we then binned the specificity measure into 41 bins (0 representing a gene not expressed in the tissue/cell type, 1 gene in the bottom 2.5% quantile of specificity, …, 40 genes that are in the 97.5% to 100% most specific genes in the tissue/cell type). We then used MAGMA to test for a positive correlation between binned tissue specificity and gene-level genetic association with anorexia nervosa for each tissue/cell type. The gene-level genetic association was computed with MAGMA (v1.06) using a window surrounding the gene by 35 kb upstream to 10 kb downstream of the gene. The gene-level association is computed by summing the association *P* value of SNPs located in the gene windows taking into account the LD structure of the region. MAGMA takes

into account confounders such as gene length, LD, and gene-gene correlation. MAGMA analyses are reported in **Supplementary Figs 9-11.**

Predicted tissue-specific gene expression

We predicted differential gene expression using S-PrediXcan v1.0[55] and genomic and transcriptomic reference data from the brain regions assayed in the GTEx project v7[46] and Depression Genes and Networks (DGN) whole-blood cohort[56]. A total 258,158 gene-tissue pairs were tested (**Supplementary Table 13**). Significant genes were compared to genes in the gene-wise analysis performed with MAGMA.

A general note on multiple testing correction

Carrying out multiple testing runs the risk of inflating Type I error and increases the probability of false positive results. To manage this risk, we took the general approach of setting a conservative *a priori P* Bonferroni correction threshold. We did this generally on a within-analysis basis, since different analyses tested different underlying hypotheses, rather than paper-wide. Readers can identify the Bonferroni threshold used for a given analysis in Table and Figure notes.

Additional Results

Primary GWAS meta-analysis

Pre- and post-QC lambda, number of single-nucleotide polymorphisms (SNPs), and *N*s in each of the final 33 datasets analyzed within the primary GWAS can be found in **Supplementary Table 1**. The meta-analysis LD intercept was 1.02 (s.e. = 0.01). The meta-analysis quantile-quantile (Q-Q) plot is shown in **Supplementary Fig. 1**. The LD score regression intercepts for each cohort after QC ranged from 0.98 (s.e. = 0.01) to 1.03 (s.e. = 0.01) (**Supplementary Table 1**). The genetic covariance intercepts in LD score bivariate regression analyses were close to 0 and indicated no evidence of sample overlap among the cohorts (**Supplementary Table 19**). Eight genome-wide significant loci were identified. Follow-up analyses included using genome-wide complex trait analysis (GCTA-COJO)[57] to conduct stepwise regression on markers with *P* values < 10^{-8}. GCTA-COJO identified eight independent signals taking into account the LD correlations between SNPs and running a conditional and joint analysis[58]. All eight identified markers were equivalent to the SNPs resulting from distance- and LD-based clumping shown in **Table 1** (for conditional analyses please see **Supplementary Table 5**).

Genomic inflation and residual confounding

Here we provide detailed information to illustrate that confounding due to population stratification or other reasons was minimal in our primary GWAS. Two relevant parameters were estimated using linkage-disequilibrium (LD) score regression[29]. Firstly, we estimated an LD intercept of 1.02 (s.e. = 0.01) for the meta-analysis and between 0.98-1.03 for individual datasets (**Supplementary Table 1**). The LD score intercept is significantly greater than one, but is in line with the expected small levels of inflation caused by sample size and heritability described in Loh et al.[59]. A second measure, the attenuation ratio [(LDSC intercept – 1) / (mean χ^2 – 1)] for the meta-analysis was 0.07 (s.e. = 0.04) (**Supplementary Fig. 1**), also suggesting a lack of confounding. Together these suggest that deviation from the null was due to polygenic signal and not population structure or bias.

The overall inflation of summary statistics genomewide or λ_{GC} for individual datasets post-QC ranged between 1.00-1.06 (**Supplementary Table 1**) and for the meta-analysis was 1.22 **(Supplementary Fig. 1**). Inflation of tests statistics is known to be due to a combination of polygenicity, uncorrected population stratification, and confounding. The larger λ_{GC} value observed for our GWAS meta-analysis is indeed expected at this sample size, trait polygenicity, and heritability[59]. The LD score regression method for GWAS of highly polygenic phenotypes such as anorexia nervosa and large sample sizes separates the polygenetic component (the slope) from population stratification and other systematic biases (estimated by the intercept and attenuation ratio) [29].

Correcting for λ_{GC} in large GWAS samples of polygenic phenotypes can cause loss of signal and power, as evidenced by the LD intercept of the GWAS summary statistics from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium 2015 body mass index (BMI) paper (0.65)[60,61]. Correction for λ_{GC} at the individual study level has also been shown to bias heritability estimates downward[29].

Previous hit

The chr12 locus identified in Duncan et al.[1] did not reach genome-wide significance. The OR for the index variant at this locus (rs4622308) was in the same direction in the present meta-analysis compared with Duncan et al. (present: A1 = C, A2 = T, OR = 1.06, s.e. = 0.01, $P = 7.02 \times 10^{-5}$; Duncan et al.: A1 = C, A2 = T, OR = 1.20, s.e. = 0.03, $P = 4.25 \times 10^{-9}$) and in 22 of the 33 cohorts ($z = 2.00$, $P = 0.05$, 2-tailed). To further assess this locus, a random-effects meta-analysis was conducted. Similar to the fixed-effect meta-analysis, the random-effects meta-analysis indicated that the effect of this locus was not genome-wide significant (OR = 1.06, s.e. = 0.05, $P = 0.02$) and showed evidence of heterogeneity, $I^2 = 53.7$ (**Supplementary Fig. 4**). There are many possible reasons why the result was not replicated, including winner's curse[62], moderator variables given the heterogeneity observed (such as environmental risks), between-study heterogeneity in ascertainment, and differences in LD structure across cohorts in addition to true non-replication.

Chromosome X

The separate analysis of chrX included $n = 14{,}915$ cases and $n = 27{,}854$ controls. There were no genome-wide ($P < 5 \times 10^{-8}$) or suggestive ($P < 1 \times 10^{-5}$) significant loci.

Female-only secondary GWAS

A supplementary analysis conducted on female cases and controls only—to determine the similarity of results to the main GWAS analysis which included females and males—had 14,896 cases and 27,865 controls. The female-only GWAS revealed one genome-wide significant locus ($P < 5 \times 10^{-8}$) on chr3 (rs9812977; 48.2-49 Mb; $P = 1.31 \times 10^{-9}$; OR = 1.08; 95% CI: 1.03-1.14), which was the top locus in the main GWAS analysis.

eQTL and Hi-C interactions

For locus 1 (multigenic, chr3:47.5-51.3 Mb, **Supplementary Fig. 5a**), our data implicate 100 brain-expressed genes. Locus 1 is gene-dense with a large number of brain eQTLs and regulatory chromatin interactions. Notably, 16 genes with regulatory chromatin interactions mapping to the locus lie outside the LD-defined locus. Locus 3 (multigenic, chr2:53.8-54.3 Mb, **Supplementary Fig. 5c**) is less complex that locus 1. Nonetheless, we implicate 12 genes, six within and 6 outside the LD-defined locus.

For all four single-gene loci, eQTL and/or chromatin interaction connections implicated the gene intersecting the locus. For locus 2 (chr11:114.9-115.4 Mb, **Supplementary Fig. 5b**), both eQTL and regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *CADM1*. Genetic variants near to *CADM1* (cell adhesion molecule 1) have been implicated by GWAS for body mass and age at menarche. CADM1 protein levels appear to be elevated in the hypothalamus of BMI risk variant carriers. Obese mice have been reported to show elevated *CADM1* expression and *CADM1* knockout mice show reduced body weight[63]. For locus 4 (chr10:131.2-131.4 Mb, **Supplementary Fig. 5d**), eQTL data connected to the locus-intersecting gene *MGMT*. *MGMT* (O-6-methylguanine-DNA methyltransferase) encodes an epigenetic regulator important in multiple cancers, including glioblastoma. For locus 5 (chr3:70.6-71.0 Mb, **Supplementary Fig. 5e**), regulatory chromatin interaction data confirmed the connection to the

locus-intersecting gene *FOXP1* (forkhead box P1), which encodes a transcription factor in the forkhead box family. Brain-specific deletion of *FOXP1* results in defects in striatal development and changes in the hippocampus[64]. Interestingly, *FOXP1* knockout mice exhibit a significant reduction in body weight as compared to littermate controls. For locus 5, eQTL data also suggested a functional connection to the more distal *GPR27*, which encodes an orphan G-protein coupled receptor, and is highly expressed in the brain[65]. It has recently been associated with insulin secretion[66]. Finally, for locus 6 (chr1:96.6-97.2 Mb, **Supplementary Fig. 5f**), both eQTL and regulatory chromatin interaction data confirmed the connection to the locus-intersecting gene *PTBP2*. The protein encoded by this gene binds to intronic polypyrimidine clusters in pre-mRNA molecules and is implicated in controlling the assembly of other splicing-regulatory proteins.

One intergenic locus (locus 8, chr5:93.9-95.0 Mb, **Supplementary Fig. 5h**) had eQTL connections to *PROS1* and *ARL13B*. *PROS1* encodes an anticoagulation factor that plays a role in blood-brain-barrier integrity[67]. *ARL13B* encodes a member of the ADP-ribosylation factor-like (ARL) small Ras GTPase family. ARL13B protein is expressed in the cilia of all organs; mutations are associated with Joubert syndrome 8, which like other ciliopathies has been associated with obesity[68,69]. Mutations are also associated with intellectual disability (University of Chicago's Intellectual Disability Exome Panel). Thomas et al.[69] found *ARL13B* expression throughout the developing human brain. Additionally, they identified *ARL13B* expression in primary cilia of hypothalamic neurons of newborn mice. Furthermore, Higginbotham et al.[70] found that mutant ARL13B disrupts the development and migration of interneurons.

For locus 7 (intergenic, chr5:24.9-25.3 Mb, **Supplementary Fig. 5g**), there were no supporting eQTL or regulatory chromatin interactions.

Multi-trait conditional and joint analysis (mt-COJO)

Seven of the eight genome-wide significant loci showed only slight changes in their effect sizes (i.e., betas) after conditioning on education years[71], type 2 diabetes[72], high-density lipoprotein (HDL) cholesterol[73], BMI (Hübel, Gaspar, Coleman, Hanscombe, Purves…Breen, unpublished report; see **Additional Methods**), schizophrenia[28], or neuroticism[35]. The results suggest that the loci are independent of the traits on which they were conditioned and that the traits may not share genetic association at these loci. The association of locus 2 on chr11 tagged by rs6589488 with anorexia nervosa may not be independent of genetic associations with type 2 diabetes as the beta was diminished after conditioning. This suggests, at locus 2, that the association with anorexia nervosa may not be independent of genetic underpinnings of glycemic alterations seen in type 2 diabetes.

Clinical investigations

Anorexia nervosa subtype

One potential source of genetic heterogeneity lies in differing clinical presentations of anorexia nervosa (i.e., with or without the presence of binge eating). This was not supported in preliminary analyses. The SNP-based genetic correlation (SNP-r_g) between the anorexia nervosa subtypes was 0.74 (s.e. = 0.16; $P = 1.74 \times 10^{-6}$). To test for heterogeneity in the genetic variation

associated with these two subtypes, we tested whether their SNP-r_g was significantly different from unity. We used a block jackknife approach using the LD score regression software (LDSC) v1.0[29]. The genetic correlation between anorexia nervosa with and without binge eating was not significantly different from 1 ($P = 0.08$). There were no significant differences in the mean polygenic risk score (PRS) between subtypes in the three cohorts for which anorexia nervosa subtype data were available (**Supplementary Fig. 6**). We also calculated SNP-r_g by anorexia nervosa subtype (**Supplementary Table 9)** and found no significant differences in SNP-r_g with external traits, although small sample sizes limit interpretation. In summary, our preliminary subtype analyses do not indicate significant differences in the genetic architectures of anorexia nervosa with and without binge eating; however, larger sample sizes are necessary for confirmation.

Males with anorexia nervosa

The number of males identified on the basis of genotype sex in the meta-analysis was 447 cases and 20,347 controls. Anorexia nervosa PRS scores derived using the female-only GWAS were associated with a higher risk of anorexia nervosa in males. Those at the highest decile had 4.13 (95% CI: 2.58, 6.62) times the odds of lifetime anorexia nervosa compared with those at the lowest decile. Anorexia nervosa PRS accounted for ~1.8% of the total variance in anorexia nervosa in males for the discovery cohort *P* threshold (pT) = 0.5, comparable to ~1.7% at *P* threshold (pT) = 0.5 in the cohort as whole. Taken together, these preliminary results do not provide evidence for a major sex-specific difference in the common genetic architecture of anorexia nervosa, although our conclusions are limited due to the small sample size.

Within-trait prediction: polygenic risk scoring

We observed that across cohorts, anorexia nervosa cases were more likely to be in the PRS higher deciles than controls based on their anorexia nervosa genetic load **(Supplementary Fig. 16)**. Visual inspection of the decile plots showed that the score distributions across deciles were relatively uniform across target datasets; thus, there was no indication of any extreme outlying datasets. PRS applied to the largest target dataset, *sedk*, showed that those at the highest decile had 2.59 times higher odds (95% CI: 2.12-3.18) of lifetime anorexia nervosa compared with those at the lowest decile. The results also provide evidence of the replicability of the main GWAS results (**Supplementary Fig. 16**).

Gene-wise analysis

Results of MAGMA gene-wise associations are reported in **Supplementary Table 11**. Seventy-nine genes were Bonferroni-significant (threshold = 2.62×10^{-6}), and 506 had a Benjamini and Hochberg[74] FDR *q* value < 0.05. None of the 79 Bonferroni-significant genes are part of the MHC, but 57 genes are located in a gene-rich locus on chr3. The top genes on chr3 were *NCKIPSD*, *CELSR3,* and *IP6K2*. Through the MAGMA analysis we identified 16 additional genes which were not annotated via clumping. These 16 genes are located in loci on chr 1, 2, 3, 7, 10, 11, 12, 17, and 22. Some of these Bonferroni-significant genes have been indicated to be involved in glycemic and metabolic disease phenotypes (*CTNNB1*[75]; *EXOC4*[76]; *FAM19A2*[77]; *VAMP2*[78]).

Pathway analysis

The Bonferroni-significant pathway (**Supplementary Table 12**) GO:positive_regulation_of_embryonic_development (Gene Ontology, 32 genes, 6.31×10^{-6}) has two Bonferroni-significant genes: *DAG1* and *CTNNB1*. *CTNNB1* encodes beta-catenin, an essential component of the canonical Wnt signaling pathway. Beta-catenin can regulate neuronal progenitor proliferation and affect cortical size[79]. *CTNNB1* expression has been associated with adipogenesis, glucose metabolism, and obesity[75]. Metabolic diseases including obesity and type 2 diabetes are influenced by genetic and functional variations in the Wnt signalling pathway[75]. *DAG1* encodes dystroglycan, an essential member of the dystrophin-glycoprotein complex that has been mainly studied in the context of muscular dystrophies. Dystroglycan and other members of the dystrophin-glycoprotein complex are also found in neurons and glia and their disruption has been linked to intellectual disability and altered brain development[80]. Specific ablation of dystroglycan in neurons or glia results in distinct phenotypes[81]. Dystroglycan is expressed in pyramidal cells of the cortex and hippocampus, where it appears to be essential for the establishment and maintenance of CCK-positive basket cell terminals[82].

Tissue and cell type analyses

We first used partitioned heritability analyses in LDSC using annotation of elements in the genome with specific functions. Considering general annotations, enrichment in conserved regions was the main finding (enrichment (s.e.) = 24.97 (3.29), $P = 3.32 \times 10^{-11}$, **Supplementary Fig. 7**). Partitioned heritability analysis was then used to test for cell type-specific enrichment in the GWAS of anorexia nervosa among 10 cell type groups: adrenal and pancreas; cardiovascular; CNS; connective and bone; gastrointestinal; immune and hematopoietic; kidney; liver; skeletal muscle; and other tissue (which includes adipose tissue). The CNS cell type group showed a 2.8-fold significant enrichment (**Supplementary Fig. 8**).

We next investigated whether there were tissue or cell type associations with anorexia nervosa using gene expression data to annotate gene sets characteristic of specific cells or tissues (for details see[50]). Gene expression datasets used were: GTEx (RNA-seq of samples from multiple human tissues); gene expression from neurons; astrocytes and oligodendrocytes from developing and mature mouse forebrain[47]; and gene expression from 149 mouse brain cell types (KI level 1: 24 broad categories, KI level 2: 149 cell types underlying the 24 broad categories)[50].

Using MAGMA[54], the majority of brain tissues in GTEx were significantly associated with anorexia nervosa (**Supplementary Fig. 9**), the strongest hits being brain cerebellum and brain cerebellar hemispheres. Enrichment in muscle-skeletal tissues also appeared likely (**Supplementary Fig. 9**). Medium spiny neurons and pyramidal neurons from the CA1 region of the hippocampus were significantly associated with anorexia nervosa at a Bonferroni threshold in the 24 level 1 cell types (**Supplementary Fig. 10**). Among the 149 level 2 cell types, pyramidal neurons from the CA1 region of the hippocampus and pyramidal neurons from the somatosensory cortex layer 5 were Bonferroni-significant (**Supplementary Fig. 11**).

Medium spiny neurons (MSNs) are dopaminergic and inhibitory. They are the primary cell type of the striatum. The dorsal striatum has been linked to feeding behaviors including food

motivation and reward[83]. D1R-medium-spiny-neurons (medium spiny neurons that express the D1-type dopamine receptor) afferents have been reported to be the primary source of nucleus accumbent inhibition to the lateral hypothalamus[84]. Furthermore, in that study, inhibition of D1R-MSNs increased feeding, while activation decreased feeding[84]. Pyramidal neurons are excitatory and are the primary excitatory cell type found in cortical structures[85]. Kim et al.[86] recently found that *PPP1R1B*-expressing pyramidal neurons from the basolateral amygdala project to DR1-expressing central amygdala neurons, which are known to modulate appetitive behaviors.

Using the LDSC partitioned heritability approach[53], no significant signal was found in the GTEx database for tissues (**Supplementary Figs. 12-13**), in the Cahoy database for cells (**Supplementary Fig. 14**), or in the single-cell RNA-sequencing database (**Supplementary Fig. 15**). Nevertheless, in GTEx, the enrichment of heritability was more common in cell types in the brain, although enrichment in muscle-skeletal tissues was also evident, though no cell type reached significance (**Supplementary Fig. 13**). In the Cahoy database, the enrichment appeared more common in astrocytes compared with neurons and oligodendrocytes, although none of these reached statistical significance after Bonferroni correction (**Supplementary Fig. 14**). In the single-cell RNA-sequencing database, signal was strongest in neuroblasts (**Supplementary Fig. 15**).

Predicted tissue-specific gene expression

The PrediXcan analysis suggested significant effects on the expression of 36 genes across 44 GTEx tissues ($P \leq 1.94 \times 10^{-7}$; **Supplementary Table 13**). *MGMT* is located on chr10 (131.2-131.4 Mb). The majority of others are located within the multi-genic region on chr3. Downregulation and upregulation are presented in **Supplementary Table 13**.

Cross-trait analysis

Genetic correlations

Full results are shown in **Supplementary Table 10** and Bonferroni-significant results are shown graphically in **Fig. 2**. In instances where the same phenotype appears in multiple study sources, the main manuscript and **Fig. 2** report the result from the study source with the largest sample and/or of European ancestry.

Generalized summary data-based Mendelian randomization (GSMR)

BMI. We used GSMR[87] to investigate causal associations between BMI and anorexia nervosa using an extension of GCTA[57] (**Supplementary Table 16**). A one standard deviation (*SD*) decrease in genetically-estimated BMI increased the risk for anorexia nervosa by 4% (OR = 1.04; s.e. = 0.01; $P_{GSMR} = 0.008$) while an increase in genetically-estimated anorexia nervosa had a BMI-lowering effect ($b_{xy} = -0.28$, s.e. = 0.07, $P_{GSMR} = 5.15 \times 10^{-5}$). We only used eight SNPs to build the multiple SNP instrument for anorexia nervosa as an exposure and, hence, these results should be interpreted with caution.

To further separate effects of BMI from the anorexia nervosa phenotype, we used GCTA-mtCOJO[57,87] (multi-trait-based conditional & joint analysis using GWAS summary data) to adjust the anorexia nervosa GWAS summary statistics for BMI, using BMI summary statistics

from our UK Biobank analysis, which excluded individuals with a mental health diagnosis or taking a psychiatric or weight changing medication (see **Additional Methods**) and re-ran the GSMR analysis. The anorexia nervosa and BMI GWAS were performed on independent samples. As expected, after conditioning on BMI, the bidirectional pattern was no longer observable with $OR_{BMI \rightarrow AnorexiaNervosaAdjBMI} = 1.00$ (s.e. = 0.01; $P_{GSMR} = 0.78$). However, the putative causal association from AnorexiaNervosaAdjBMI to BMI was still statistically significant ($b_{xy} = -0.22$, s.e. = 0.08, $P_{GSMR} = 0.004$). The results are consistent with a causal relationship not due to pleiotropy (in the case of the anorexia nervosa→BMI effect) between these two traits.

Type 2 diabetes. We also investigated the causal relationship between Type 2 diabetes and anorexia nervosa using GSMR. The association with Type 2 diabetes as an exposure and anorexia nervosa as an outcome was not statistically significant (bxy = -0.02, s.e. = 0.03, P_{GSMR} = 0.035), nor was the association with anorexia nervosa as an exposure and Type 2 diabetes as an outcome (bxy = -0.09, s.e. = 0.09, $P_{GSMR} = 0.30$). These results do not support either phenotype as having a putative causal effect on the other. The analysis with anorexia nervosa as an exposure had only 7 instrumental variables rather than the recommended minimum of 10, therefore results are to be interpreted cautiously and may change once the anorexia nervosa GWAS sample size increases.

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