Analysis Summary: Age of Voice Deepen

Phenotype Description

Quantitative trait based on the following question:

- Research Snippets
  - “How old were you when your voice began to crack/deepen?” (Under 9, 9-10 years old, 11-12 years old, 13-14 years old, 15-16 years old, 17-18 years old, 19 years old or older, I’m not sure)

Responses were restricted to male customers and were scored from 0 to 6 from youngest to oldest.

Phenotype Statistics

The following table shows demographics of unrelated, European individuals included in the GWAS.

Phenotype	Group	Total	M	F	(0,30]	(30,45]	(45,60]	(60,Inf]
age_voice_deepened	under_9	211	211	0	36	57	56	62
	9-10	1361	1361	0	242	423	321	375
	11-12	13480	13480	0	2281	4281	3345	3573
	13-14	29513	29513	0	4470	9219	7901	7923
	15-16	9119	9119	0	1557	2869	2444	2249
	17-18	1541	1541	0	234	501	419	387
	19+	646	646	0	83	177	167	219

The following table shows the phenotypic distribution across 23andMe genotyping platforms for individuals included in the GWAS.

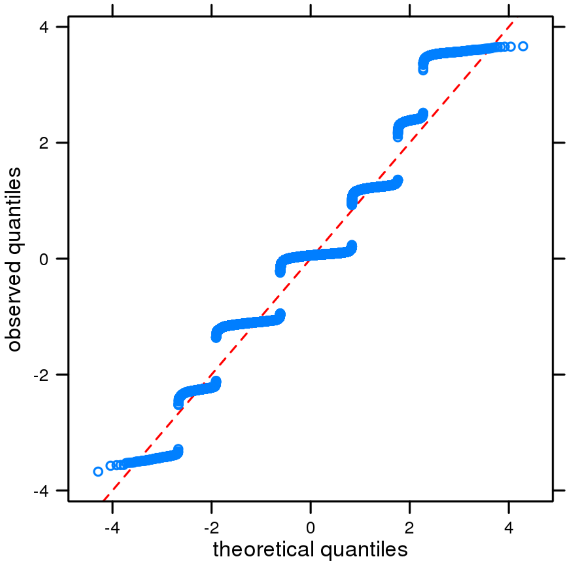
Phenotype	Group	Total	v1/v2	v3	v4
age_voice_deepened	under_9	211	5	171	35
	9-10	1361	23	1068	270
	11-12	13480	354	10829	2297
	13-14	29513	793	23940	4780
	15-16	9119	268	7468	1383
	17-18	1541	51	1230	260
	19+	646	15	530	101

Null Model with Covariates

The following table shows results of fitting a model for the trait based on just the covariates. Principal coordinates have been standardized, so these effect sizes are in units of standard deviations.

	Estimate	Std. Error	t value	Pr(>|t|)
age	0.000470	0.000231	2.0	0.042
pc.0	−0.005311	0.003661	−1.5	0.15
pc.1	0.033576	0.003685	9.1	8.3×10^{-20}
pc.2	−0.000139	0.003672	−0.0	0.97
pc.3	0.020241	0.003674	5.5	3.6×10^{-8}
pc.4	0.000392	0.003663	0.1	0.91

Q-Q plot of scaled residuals



SNP-level QC information

The following table shows results for QC filters on the genotyped data:

	failed	passed
no filters	0	1030430
not V1-only, chrM, chrY	4790	1025640
parent-offspring test	2129	1023511
MAF > 0%	3203	1020494
HWE > 1e-20	48225	972832
gt.rate > 90%	30775	952826
batch effects	28267	945446

The following table shows results for QC filters on the imputed dosage data:

	failed	passed
no filters	0	13733809
MAF > 0%	0	13733809
imputation quality	0	13733809
batch effects	2168	13731641

The following table shows results for QC filters on the merged association test results:

	passed	total
imputed only	12833621	12833621
both passed	898002	13731623
genotyped only	47444	13779067
no test result	−13980	13765087
MAF < 0.1%	−1725596	12039491

Genetic Association Tests

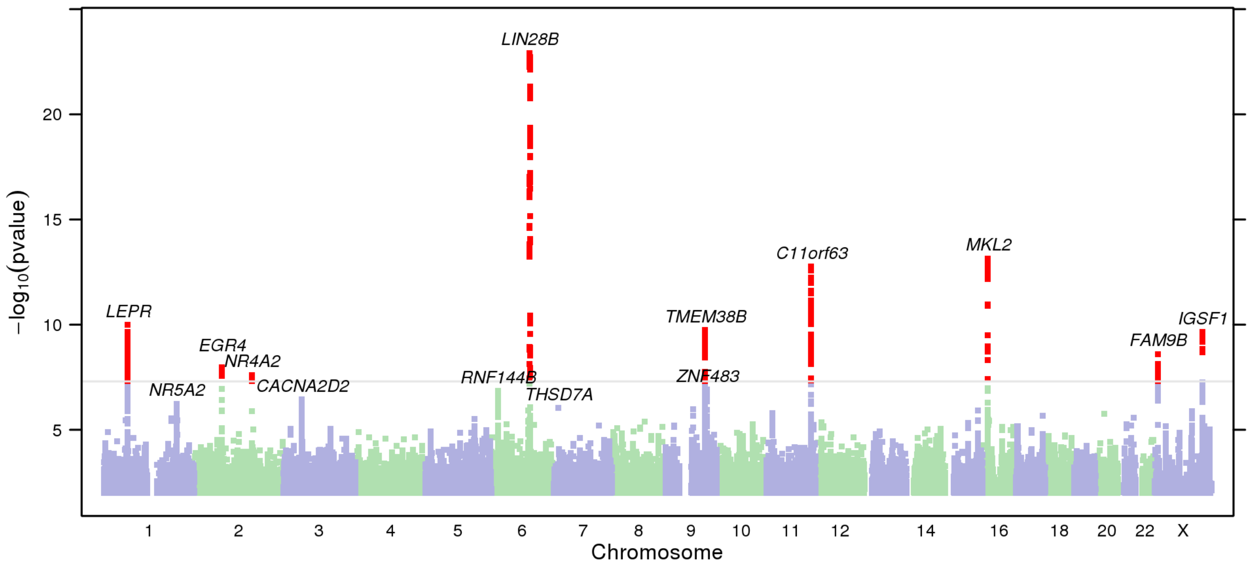
We performed linear regression assuming an additive model for allelic effects, using the model:

age_voice_deepened ~ age + pc.0 + pc.1 + pc.2 + pc.3 + pc.4 + genotype

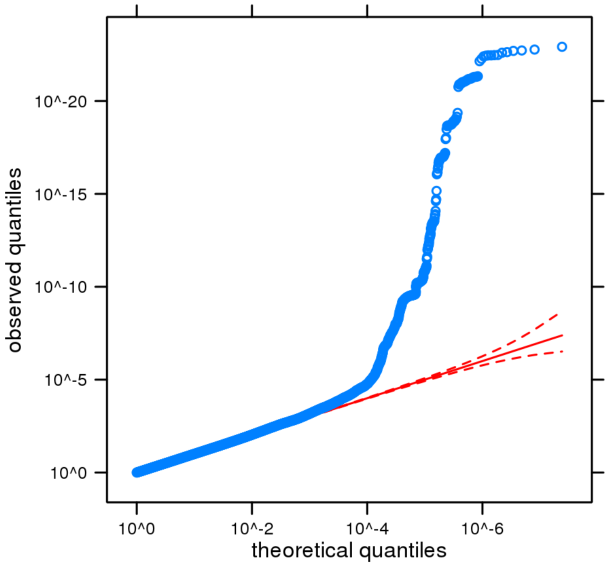
This genome-wide association analysis includes data from 55871 individuals of European ancestry, filtered to remove close relatives.

The results in this report have been adjusted for a genomic control inflation factor λ=1.077. The equivalent inflation factor rescaled for a sample size of 2000 would be λ_{2000}= 1.003 , and for 20000, λ_{20000}= 1.028 .

Manhattan Plot



Q-Q Plot of GWAS Results



Index SNPs for Strongest Associations

cytoband	assay.name	scaffold	position	alleles	src	pvalue	effect	95% CI	gene.context
6q16.3	rs9391253	chr6	105367616	A/T	I	1.2×10^{-23}	0.058	[0.046,0.069]	HACE1--[]--LIN28B
16p13.12	rs246185	chr16	14395432	C/T	I	7.1×10^{-14}	−0.044	[-0.056,-0.032]	MKL2--[]---PARN
11q24.1	rs7110373	chr11	122813224	C/T	I	1.7×10^{-13}	0.040	[0.029,0.050]	[C11orf63]
1p31.3	rs140410685	chr1	66118329	D/I	I	1.0×10^{-10}	0.045	[0.032,0.059]	LEPR--[]---PDE4B
9q31.2	rs9408817	chr9	108911979	A/G	I	1.8×10^{-10}	0.037	[0.025,0.048]	TMEM38B---[]---ZNF462
Xq26.2	rs5932886	chrX	130434001	C/T	I	2.3×10^{-10}	0.031	[0.022,0.041]	IGSF1--[]---OR13H1
Xp22.31	rs5978985	chrX	8895216	G/T	I	2.5×10^{-9}	−0.024	[-0.032,-0.016]	FAM9A---[]--FAM9B
2p13.1	rs35327298	chr2	73540044	C/T	I	1.1×10^{-8}	−0.159	[-0.214,-0.105]	EGR4--[]--ALMS1
2q24.1	rs142058842	chr2	156621725	C/G	I	2.4×10^{-8}	0.040	[0.026,0.054]	KCNJ3---[]---NR4A2
9q31.3	rs10980922	chr9	114280868	A/T	I	1.3×10^{-7}	0.052	[0.033,0.072]	KIAA0368--[]-ZNF483
6p22.3	rs9350100	chr6	19076417	C/T	I	1.4×10^{-7}	−0.036	[-0.049,-0.023]	RNF144B---[]---ID4
3p21.31	rs2282752	chr3	50433967	C/G	I	3.6×10^{-7}	−0.038	[-0.053,-0.024]	[CACNA2D2]
1q32.1	rs6681737	chr1	199857582	A/G	I	5.8×10^{-7}	0.027	[0.017,0.038]	[]---NR5A2
7p21.3	rs148707903	chr7	11512876	D/I	I	9.2×10^{-7}	0.471	[0.283,0.659]	[THSD7A]

Quality Statistics for Index SNPs

assay.name	is.v2	is.v3	is.v4	gt.rate	hw.p.value	p.date	freq.b	avg.rsqr	min.rsqr	p.batch	dose.b	qc.mask
rs9391253	FALSE	FALSE	FALSE					0.9918	0.9815	0.26	0.3190	v2v3v4
rs246185	FALSE	TRUE	FALSE	0.9365	1.3×10^{-36}	2.3×10^{-5}	0.6700	0.9388	0.6954	0.024	0.6746	v2v3v4
rs7110373	FALSE	FALSE	FALSE					0.9966	0.9917	0.032	0.5089	v2v3v4
rs140410685	FALSE	FALSE	FALSE					0.9820	0.9799	0.00010	0.8189	v2v3v4
rs9408817	FALSE	FALSE	FALSE					0.9927	0.9853	0.50	0.6732	v2v3v4
rs5932886	FALSE	FALSE	FALSE					0.9927	0.9884	0.0095	0.8177	v2v3v4
rs5978985	FALSE	FALSE	FALSE					0.8970	0.8686	0.00024	0.4991	v2v3v4
rs35327298	FALSE	FALSE	FALSE					0.9071	0.8562	0.00053	0.9895	v2v3v4
rs142058842	FALSE	FALSE	FALSE					0.9864	0.9670	0.043	0.1700	v2v3v4
rs10980922	FALSE	FALSE	FALSE					0.9396	0.9229	0.46	0.0868	v2v3v4
rs9350100	FALSE	FALSE	FALSE					0.9960	0.9903	0.72	0.8075	v2v3v4
rs2282752	FALSE	FALSE	FALSE					0.9688	0.9647	0.21	0.8463	v2v3v4
rs6681737	FALSE	FALSE	FALSE					0.9782	0.9740	0.61	0.5562	v2v3v4
rs148707903	FALSE	FALSE	FALSE					0.6969	0.3285	3.5×10^{-10}	0.0012	v2v3v4

SNP Statistics in the GWAS Sample

assay.name	AA.0	AB.0	BB.0	im.num.0	dose.b.0
rs9391253				55871	0.3191
rs246185	4789	18088	18949	55871	0.6750
rs7110373				55871	0.5075
rs140410685				55871	0.8161
rs9408817				55871	0.6745
rs5932886				55871	0.8176
rs5978985				55871	0.4991
rs35327298				55871	0.9897
rs142058842				55871	0.1714
rs10980922				55871	0.0860
rs9350100				55871	0.8089
rs2282752				55871	0.8461
rs6681737				55871	0.5560
rs148707903				55871	0.0011

Annotations from NHGRI GWAS Catalog

The following table shows, for each index SNP, all entries in the NHGRI GWAS Catalog that are within 500kb and in at least moderate linkage disequilibrium ($r^2 > 0.5$).

region	position	our.name	our.pval	dist	rsqr	assay.name	pvalue	pubmed.id	trait	genes
6q16.3	105367616	rs9391253	1.2×10^{-23}	0	1.000	rs9391253	5.0×10^{-12}	23563607	Height	LIN28B
6q16.3	105367616	rs9391253	1.2×10^{-23}	11338	0.988	rs7759938	4.0×10^{-9}	23449627	Pubertal anthropometrics	LIN28B
6q16.3	105367616	rs9391253	1.2×10^{-23}	11338	0.988	rs7759938	5.0×10^{-60}	21102462	Menarche (age at onset)	LIN28B
6q16.3	105367616	rs9391253	1.2×10^{-23}	11338	0.988	rs7759938	8.0×10^{-31}	20881960	Height	LIN28B
6q16.3	105367616	rs9391253	1.2×10^{-23}	11338	0.988	rs7759938	7.0×10^{-9}	19448620	Menarche (age at onset)	LIN28B
6q16.3	105367616	rs9391253	1.2×10^{-23}	33221	0.588	rs314280	2.0×10^{-14}	19448622	Menarche (age at onset)	LIN28B, HACE1, …
6q16.3	105367616	rs9391253	1.2×10^{-23}	40383	0.960	rs314276	4.0×10^{-16}	19448623	Menarche (age at onset)	LIN28B
6q16.3	105367616	rs9391253	1.2×10^{-23}	50362	0.960	rs314268	8.0×10^{-7}	18391951	Height	LIN28B, HACE1, …
6q16.3	105367616	rs9391253	1.2×10^{-23}	75573	0.654	rs364663	5.0×10^{-7}	23667675	Menarche (age at onset)	LIN28B
16p13.12	14395432	rs246185	7.1×10^{-14}	−7127	0.870	rs1659127	4.0×10^{-9}	21102462	Menarche (age at onset)	MKL2
16p13.12	14395432	rs246185	7.1×10^{-14}	−7127	0.870	rs1659127	1.0×10^{-11}	20881960	Height	MKL2
1p31.3	66118329	rs140410685	1.0×10^{-10}	−125704	0.548	rs1751492	6.0×10^{-13}	20167575	Soluble leptin receptor levels	LEPR
9q31.2	108911979	rs9408817	1.8×10^{-10}	24695	0.528	rs7861820	3.0×10^{-9}	19448621	Menarche and menopause (age at onset)	Intergenic
9q31.2	108911979	rs9408817	1.8×10^{-10}	55109	0.929	rs2090409	2.0×10^{-6}	23449627	Pubertal anthropometrics	TMEM38B
9q31.2	108911979	rs9408817	1.8×10^{-10}	55109	0.929	rs2090409	2.0×10^{-33}	21102462	Menarche (age at onset)	TMEM38B
9q31.2	108911979	rs9408817	1.8×10^{-10}	55109	0.929	rs2090409	2.0×10^{-9}	19448620	Menarche (age at onset)	TMEM38B, SLC44A1, …
9q31.3	114280868	rs10980922	1.3×10^{-7}	22811	0.664	rs7873730	2.0×10^{-6}	23599027	Menarche (age at onset)	ZNF483

Replication of GWAS Catalog Results

The following table shows, for each GWAS Catalog result for similar traits, our association test result for our best available proxy (distance < 100kb, $r^2 > 0.8$).

no relevant GWAS catalog terms were available

Nearby Nonsynonymous SNPs

region	position	our.name	our.pval	dist	rsqr	assay.name	gene	aa.chg
1p31.3	66118329	rs140410685	1.0×10^{-10}	−81888	0.598	rs1137100	LEPR	K109R
2p13.1	73540044	rs35327298	1.1×10^{-8}	259588	1.000	rs45501594	ALMS1	T3542S
3p21.31	50433967	rs2282752	3.6×10^{-7}	163125	0.551	rs1034405	C3orf18	A162V

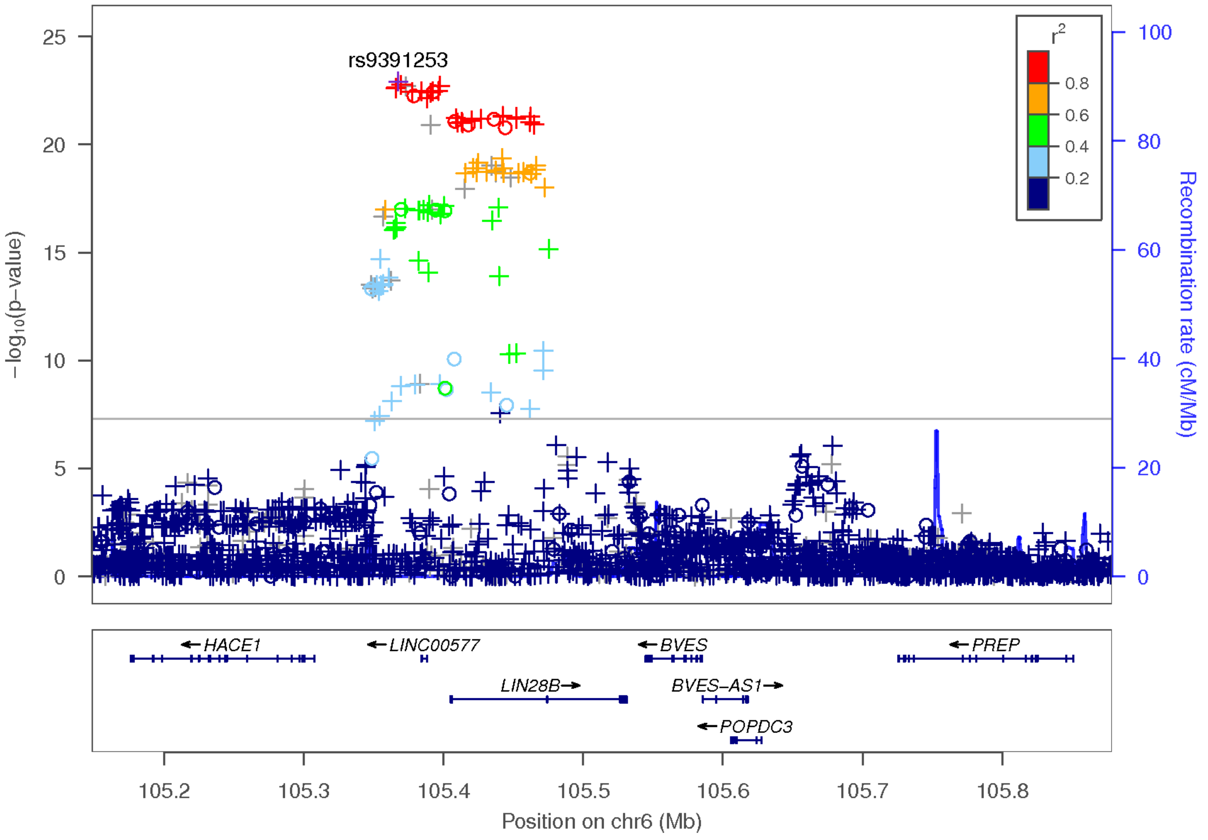
Nearby Expression QTLs

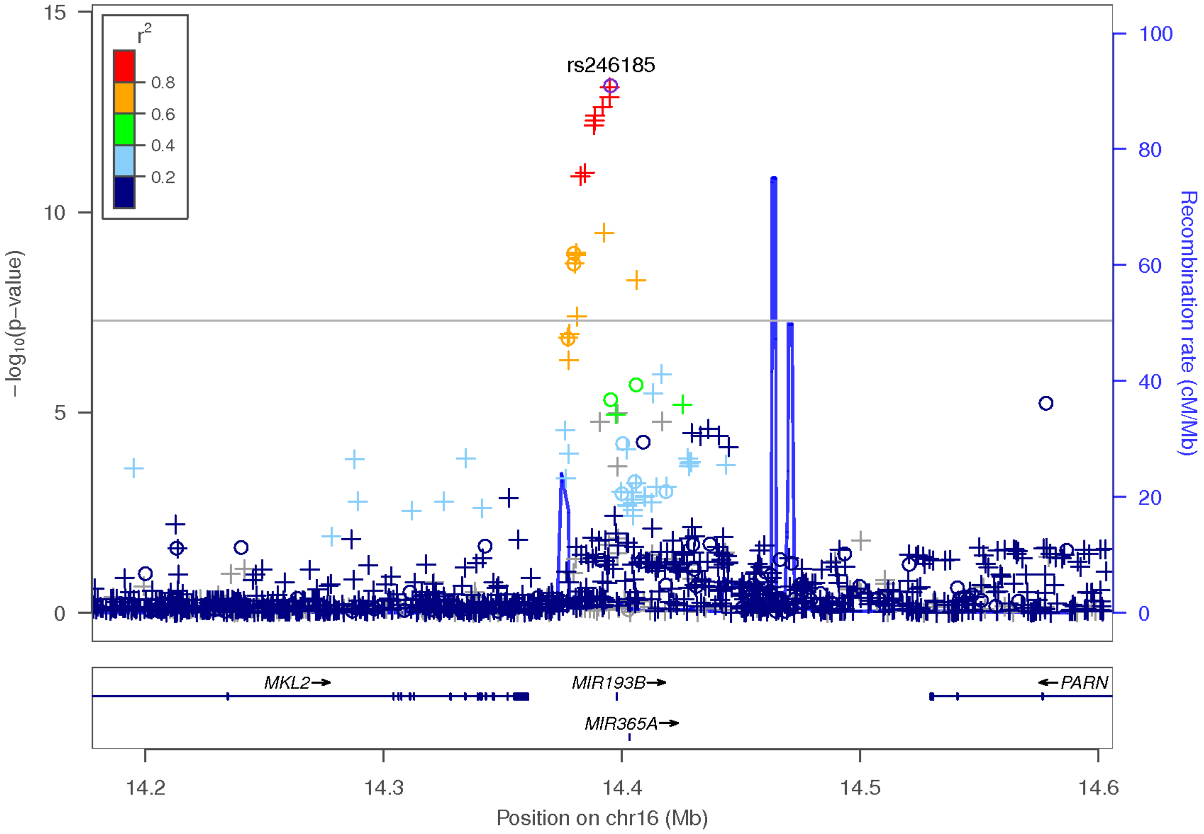
region	position	our.name	our.pval	dist	rsqr	assay.name	eqtl.dist	eqtl.gene	eqtl.pval	eqtl.rsqr	tissue	pubmed.id
11q24.1	122813224	rs7110373	1.7×10^{-13}	34613	0.593	rs6589963	999566	OR10S1	0.00013	0.183	T-cell	19644074
3p21.31	50433967	rs2282752	3.6×10^{-7}	140246	0.662	rs398703	21600	C3ORF18	0.00021	0.048	Monocyte	22446964
3p21.31	50433967	rs2282752	3.6×10^{-7}	150661	0.630	rs2232248	12591	HEMK1	1.5×10^{-7}	0.120	Lymphoblastoid	17873874
3p21.31	50433967	rs2282752	3.6×10^{-7}	223859	0.540	rs375544	28806	MAPKAPK3	2.3×10^{-10}	0.134	Monocyte	22446964
3p21.31	50433967	rs2282752	3.6×10^{-7}	285378	0.533	rs6779819	32626	MAPKAPK3	1.5×10^{-16}	0.045	Monocyte	20502693

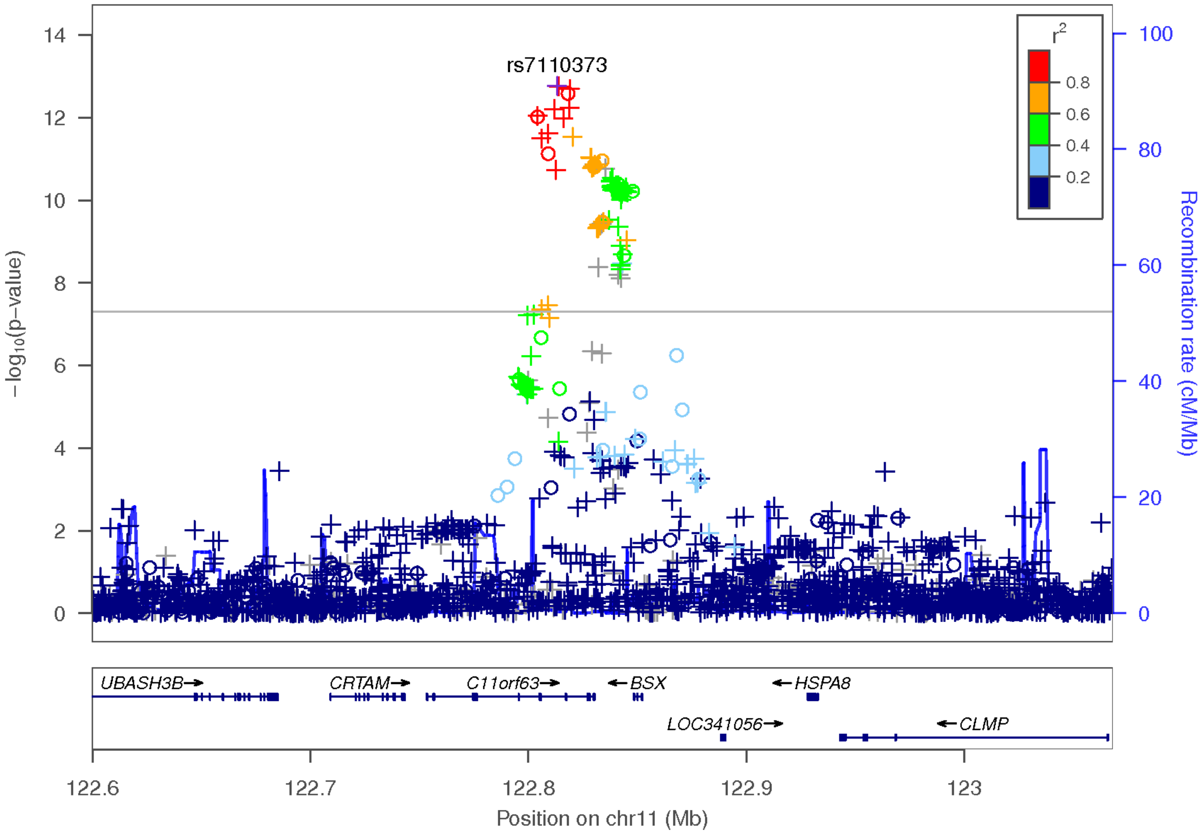
Nearby Clinical Variants

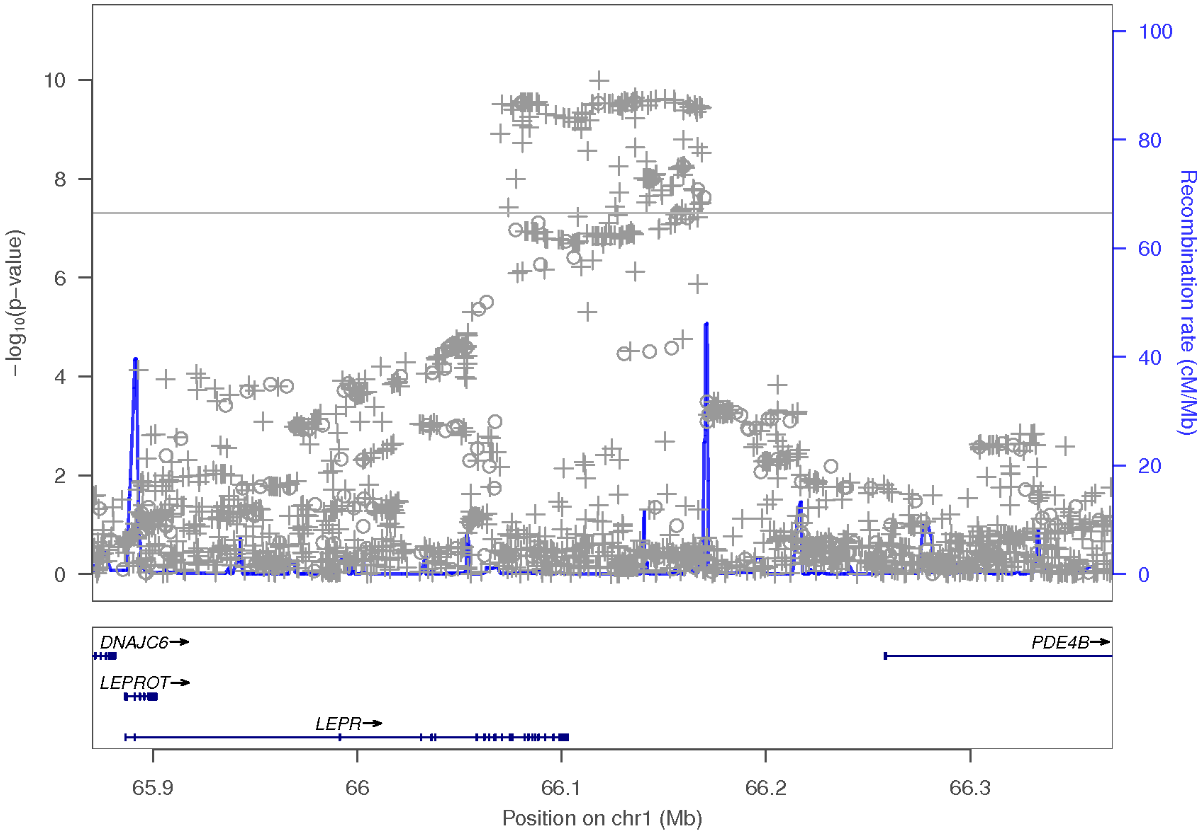
source	region	our.name	our.pval	dist	rsqr	assay.name	gene	phenotype	accession
clinvar	1p31.3	rs140410685	1.0×10^{-10}	−81888	0.598	rs1137100	LEPR	Leptin receptor deficiency	NCBI curation
clinvar	3p21.31	rs2282752	3.6×10^{-7}	215532	0.532	rs414171	CISH	Mycobacterium tuberculosis, susceptibility to	NCBI curation
clinvar	3p21.31	rs2282752	3.6×10^{-7}	215532	0.532	rs414171	CISH	Susceptibility to malaria	NCBI curation
clinvar	3p21.31	rs2282752	3.6×10^{-7}	215532	0.532	rs414171	CISH	Bacteremia, susceptibility to, 2	NCBI curation

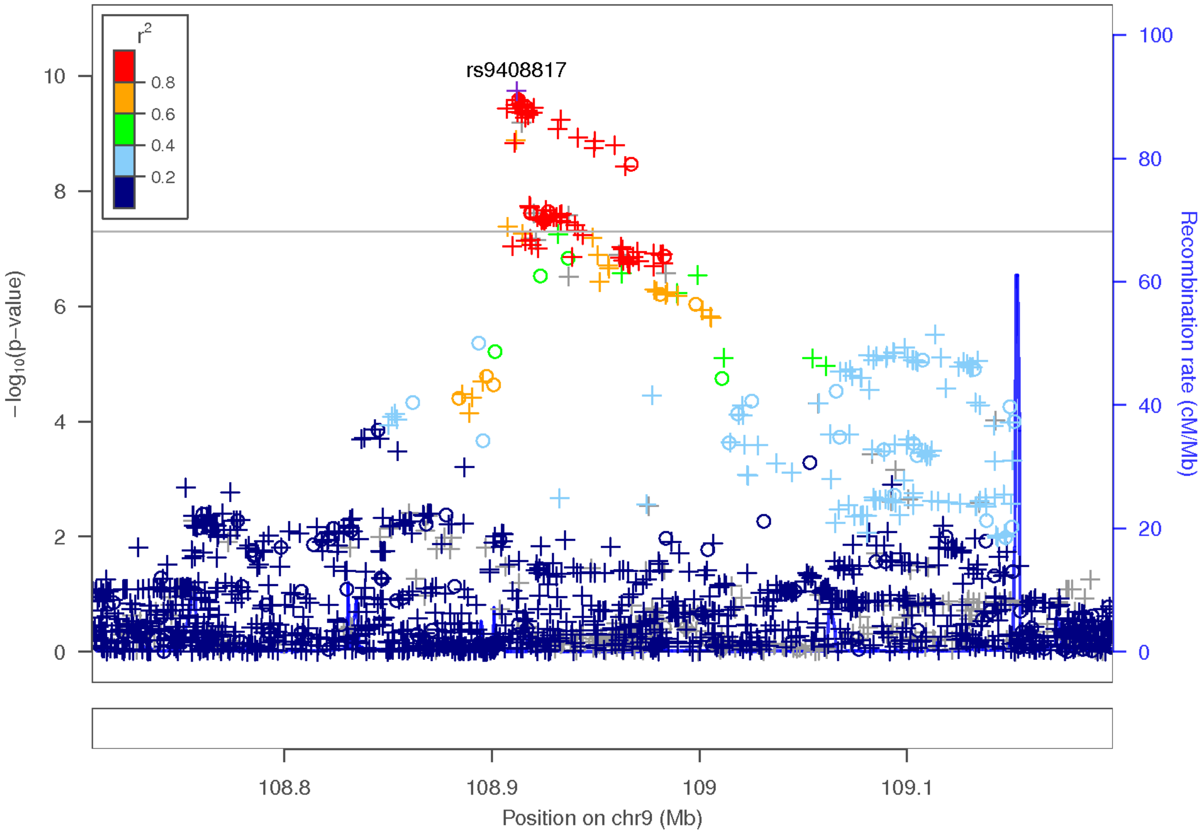
Regional Association Plots

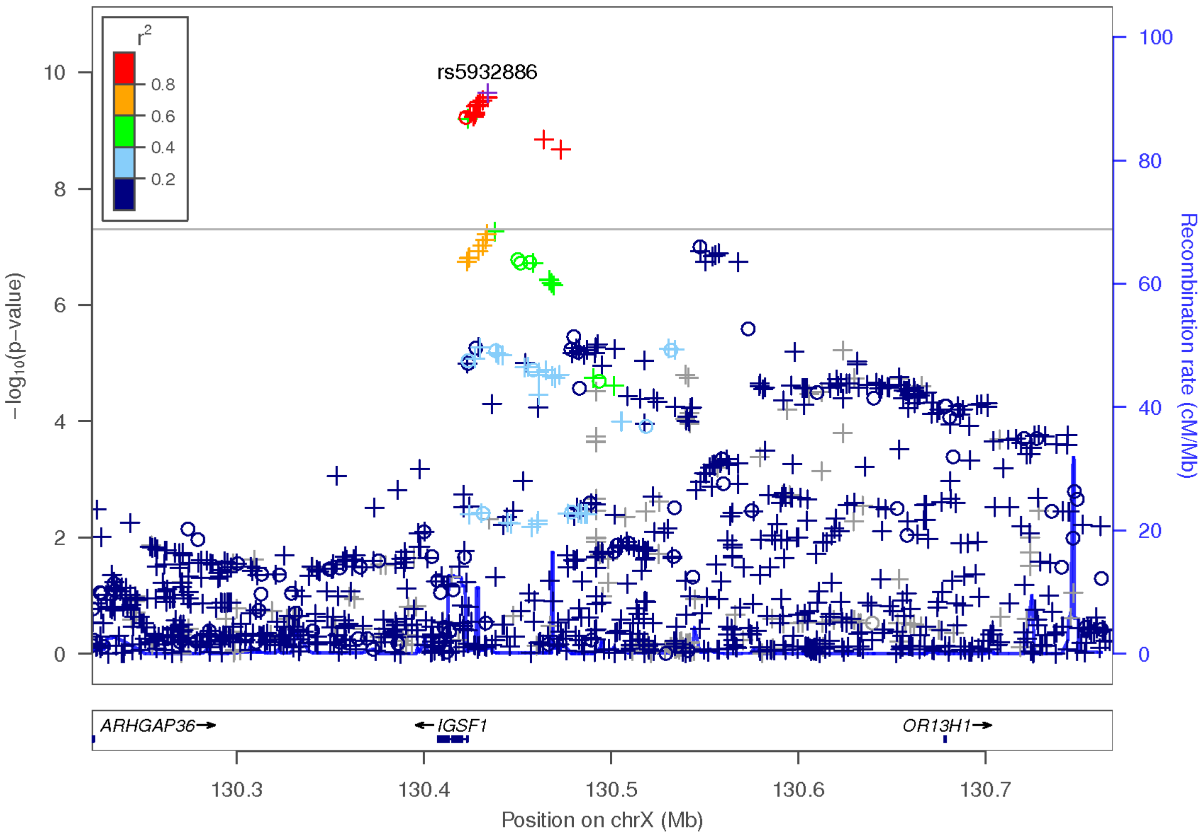


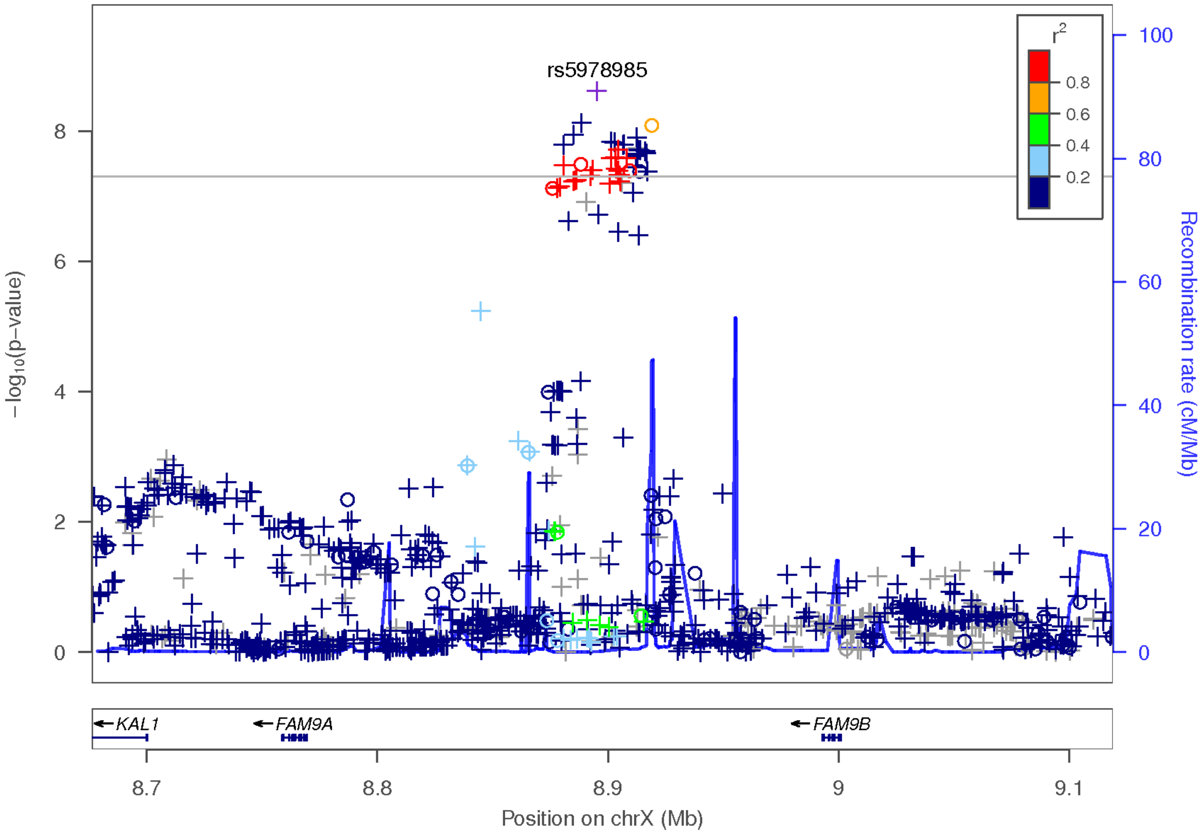

r2
0.8
0.6
0.4
0.2
rs246185
−log10(p−value)
15
10
5
0
100
80
60
40
20
0
Recombination rate (cM/Mb)
MKL2
MIR193B
PARN
MIR365A
14.2
14.3
14.4
14.5
14.6
Position on chr16 (Mb)

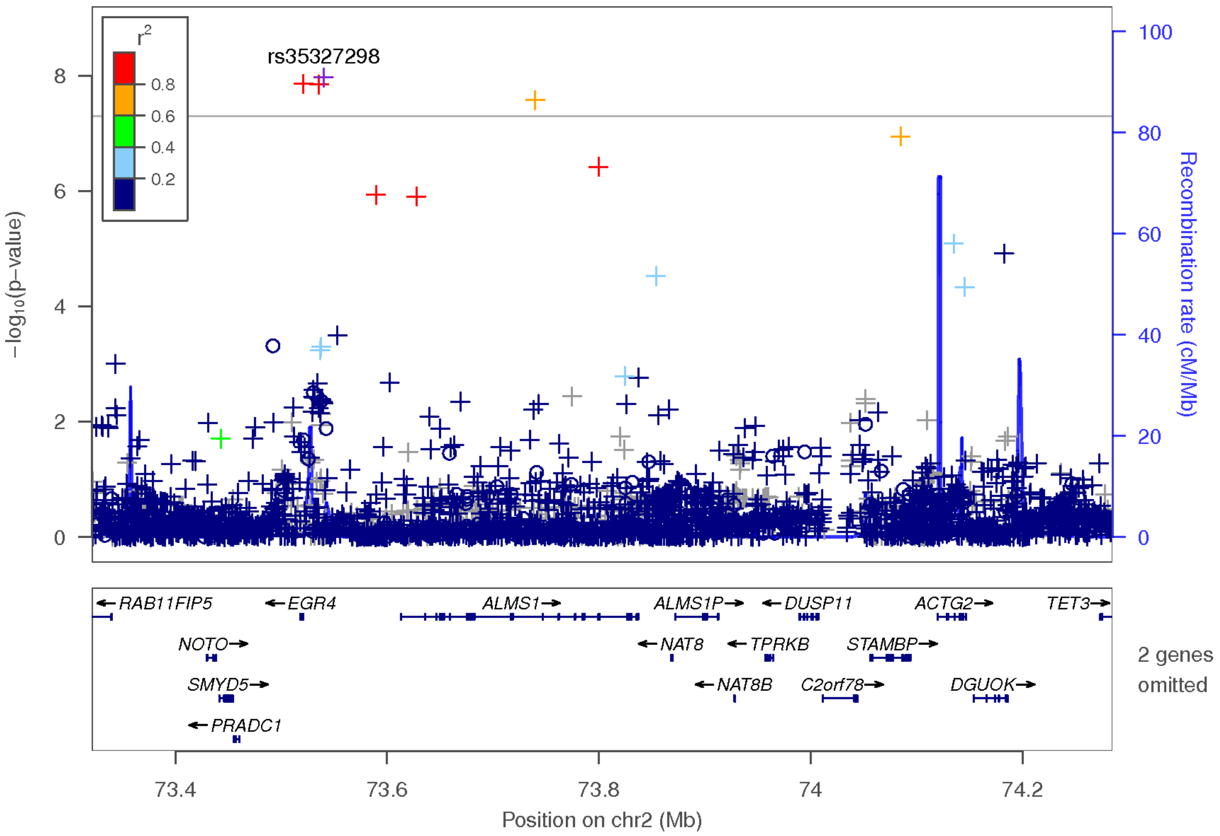

r2
0.8
0.6
0.4
0.2
rs7110373
−log10(p−value)
14
12
10
8
6
4
2
0
100
80
60
40
20
0
Recombination rate (cM/Mb)
UBASH3B
CRTAM
C11orf63
BSX
HSPA8
LOC341056
CLMP
122.6
122.7
122.8
122.9
123
Position on chr11 (Mb)

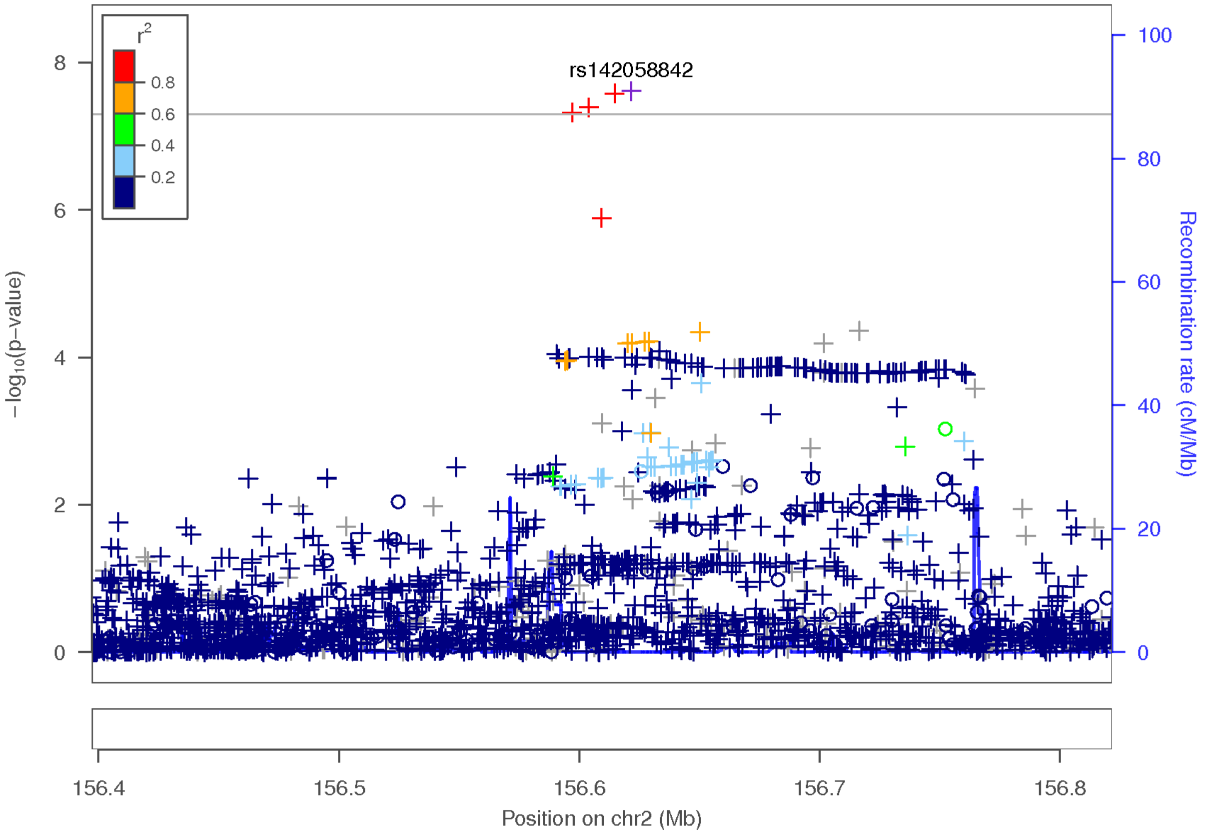

−log₁₀(p−value)
0
2
4
6
8
10
Recombination rate (cM/Mb)
0
20
40
60
80
100
DNAJC6
PDE4B
LEPROT
LEPR
65.9
66
66.1
66.2
66.3
Position on chr1 (Mb)

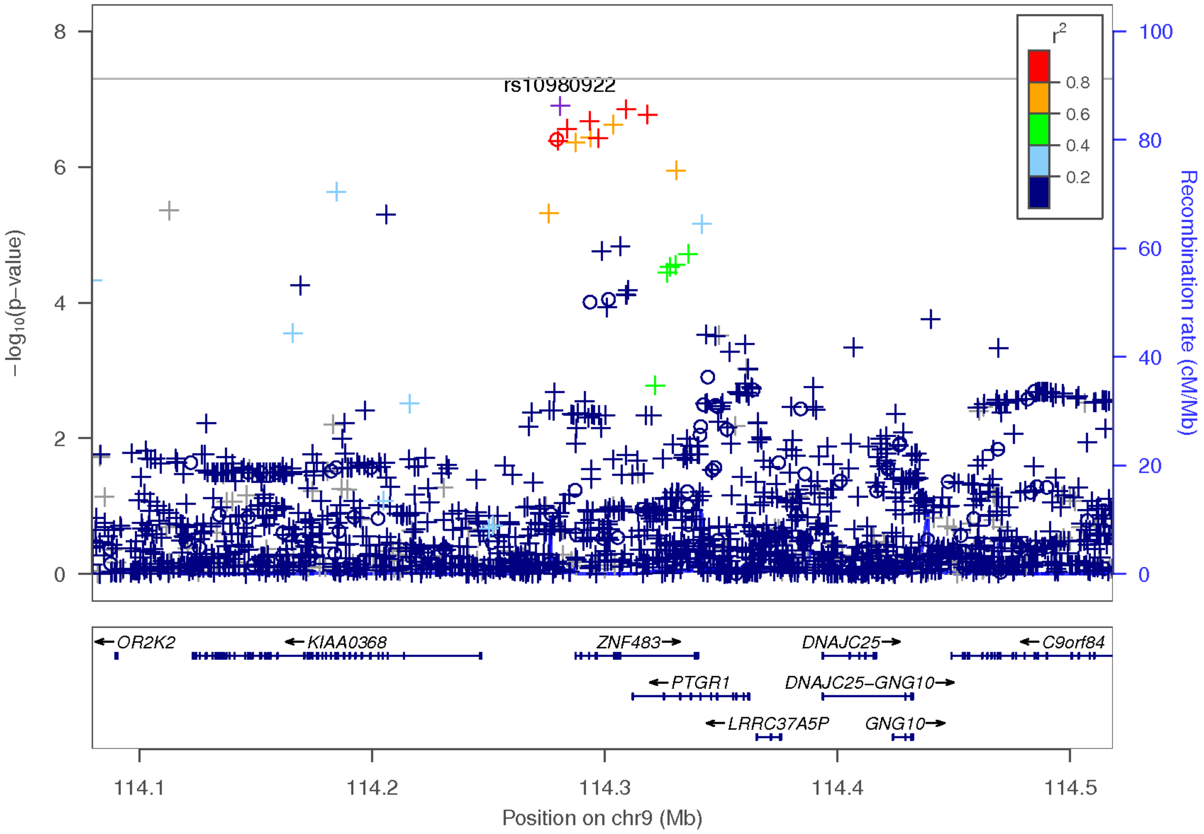

r²
0.8
0.6
0.4
0.2
rs9408817
−log₁₀(p−value)
0
2
4
6
8
10
Recombination rate (cM/Mb)
0
20
40
60
80
100
108.8
108.9
109
109.1
Position on chr9 (Mb)

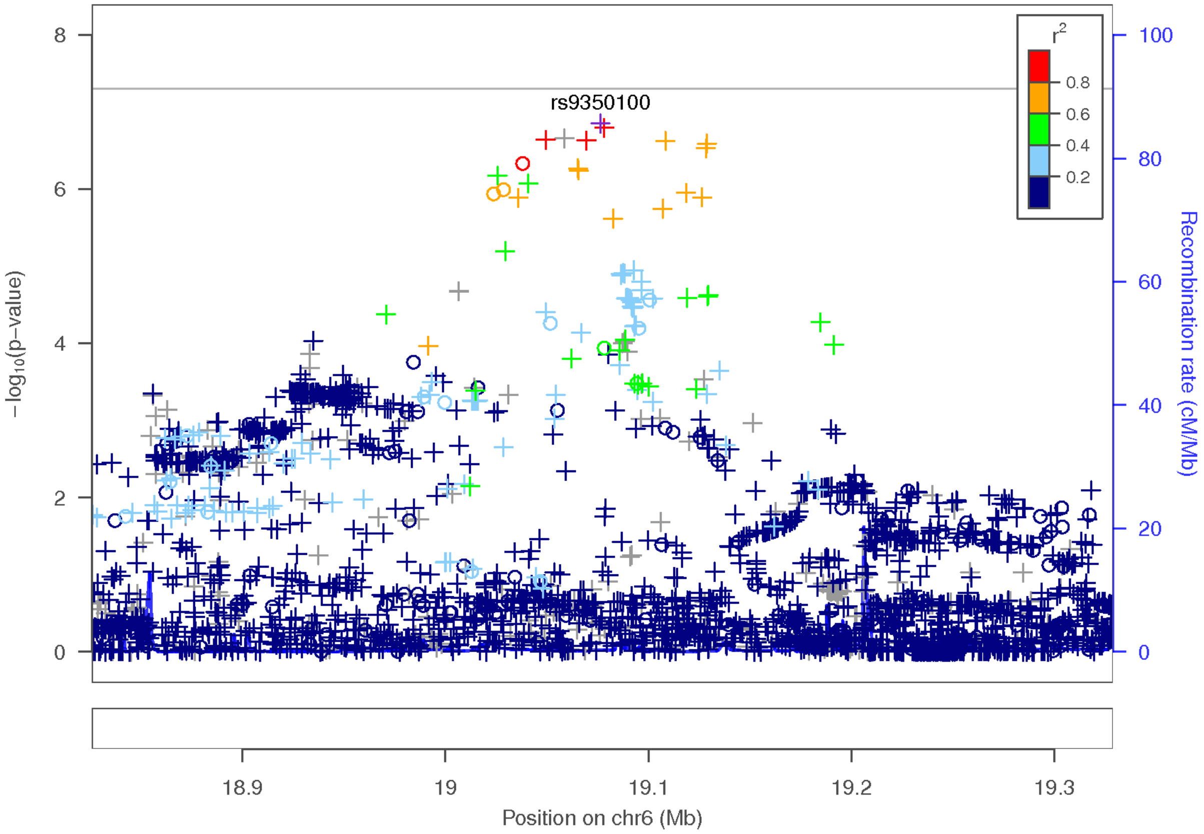

r²
0.8
0.6
0.4
0.2
rs5932886
−log₁₀(p−value)
0
2
4
6
8
10
Recombination rate (cM/Mb)
0
20
40
60
80
100
ARHGAP36→
←IGSF1
OR13H1→
130.3
130.4
130.5
130.6
130.7
Position on chrX (Mb)

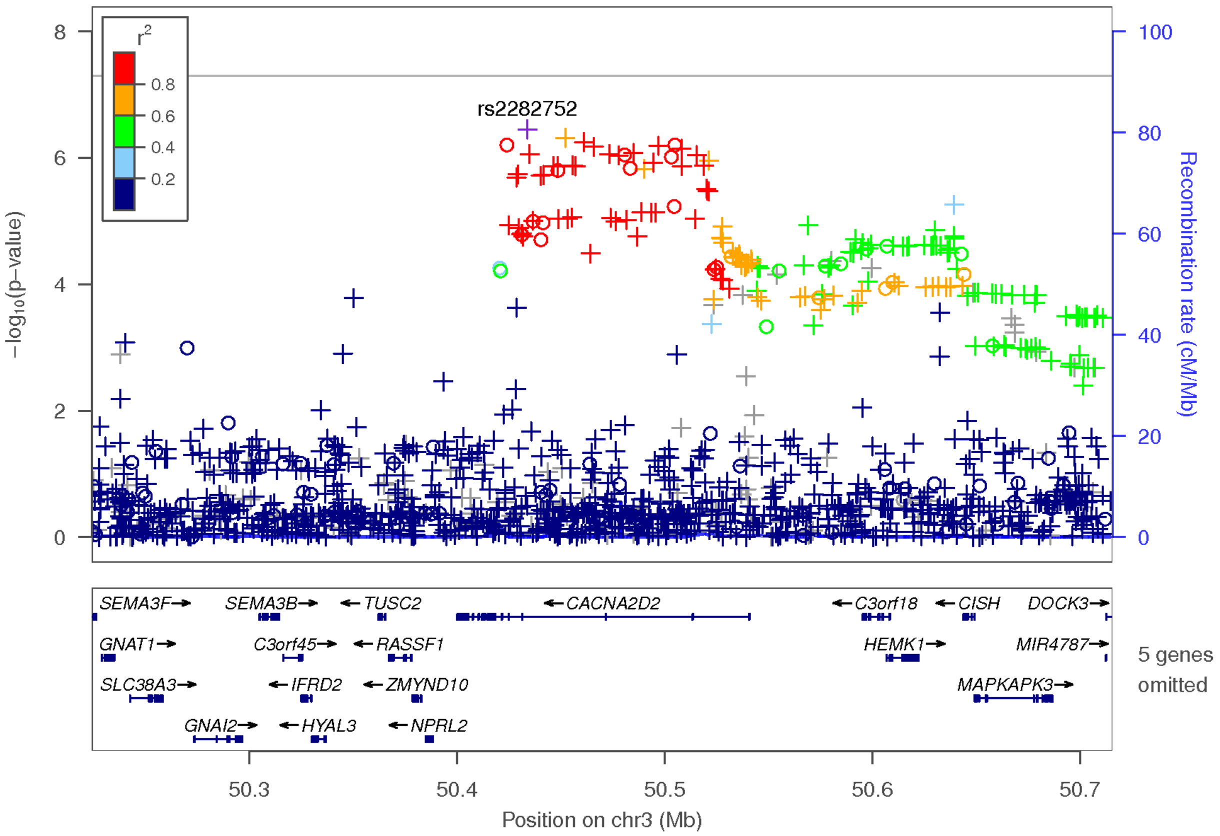

r²
0.8
0.6
0.4
0.2
rs5978985
−log₁₀(p−value)
0
2
4
6
8
Recombination rate (cM/Mb)
0
20
40
60
80
100
←KAL1
←FAM9A
←FAM9B
8.7
8.8
8.9
9
9.1
Position on chrX (Mb)


r²
0.8
0.6
0.4
0.2
rs35327298
−log₁₀(p−value)
8
6
4
2
0
Recombination rate (cM/Mb)
100
80
60
40
20
0
RAB11FIP5
EGR4
ALMS1
ALMS1P
DUSP11
ACTG2
TET3
NOTO
NAT8
TPRKB
STAMBP
SMYD5
NAT8B
C2orf78
DGUOK
PRADC1
2 genes omitted
73.4
73.6
73.8
74
74.2
Position on chr2 (Mb)

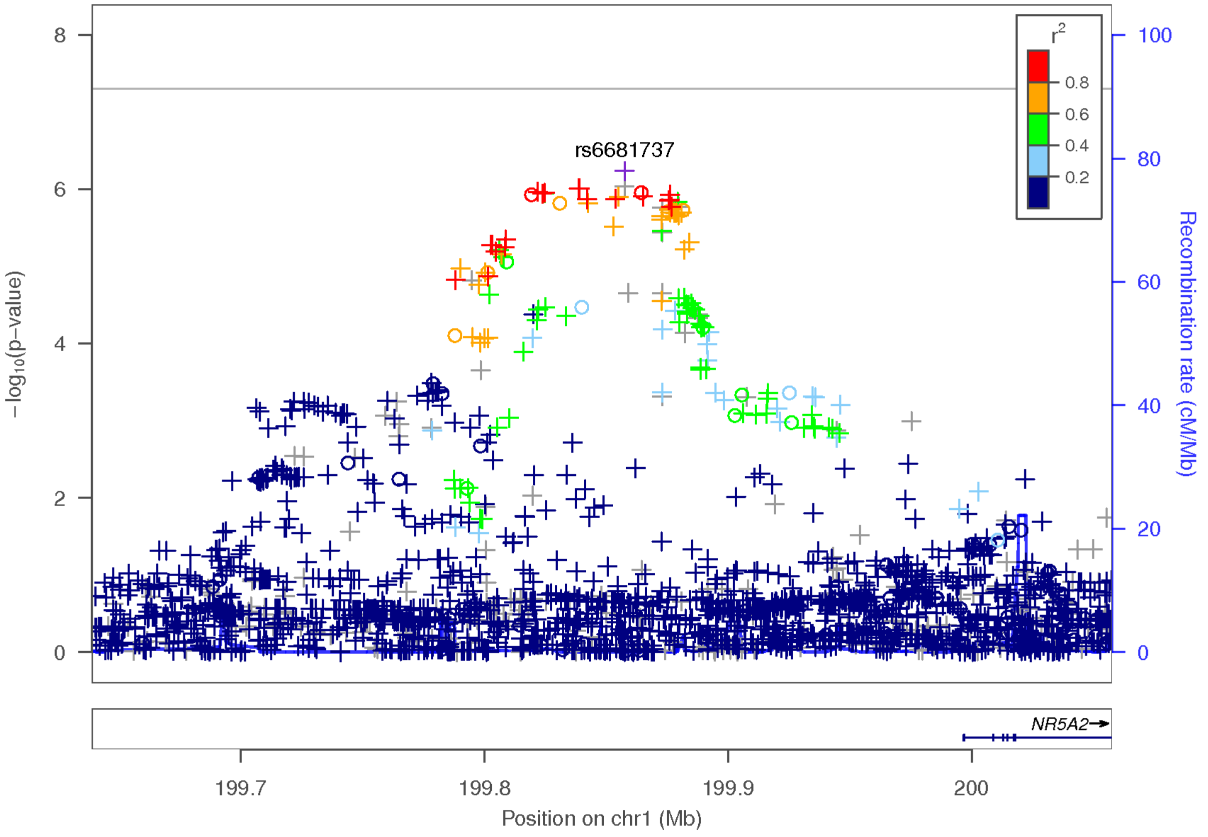

r²
0.8
0.6
0.4
0.2
rs142058842
−log₁₀(p−value)
8
6
4
2
0
Recombination rate (cM/Mb)
100
80
60
40
20
0
156.4
156.5
156.6
156.7
156.8
Position on chr2 (Mb)


rs10980922
r²
0.8
0.6
0.4
0.2
8
6
4
2
0
−log₁₀(p−value)
100
80
60
40
20
0
Recombination rate (cM/Mb)
OR2K2
KIAA0368
ZNF483
DNAJC25
C9orf84
PTGR1
DNAJC25−GNG10
LRRC37A5P
GNG10
114.1
114.2
114.3
114.4
114.5
Position on chr9 (Mb)

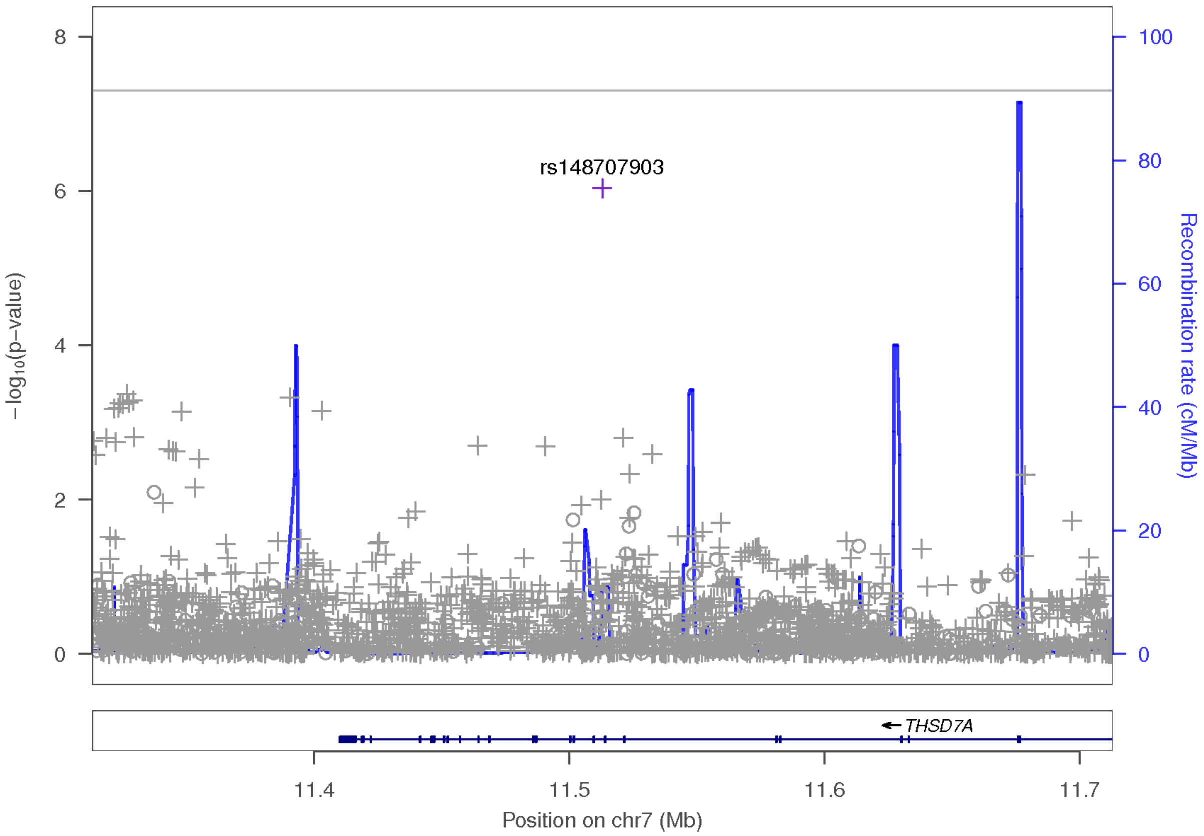

rs9350100
r²
0.8
0.6
0.4
0.2
8
6
4
2
0
−log₁₀(p−value)
100
80
60
40
20
0
Recombination rate (cM/Mb)
18.9
19
19.1
19.2
19.3
Position on chr6 (Mb)



r²
0.8
0.6
0.4
0.2
rs2282752
−log₁₀(p−value)
0
2
4
6
8
Recombination rate (cM/Mb)
0
20
40
60
80
100
SEMA3F→
SEMA3B→
←TUSC2
←CACNA2D2
←C3orf18
←CISH
DOCK3→
GNAT1→
C3orf45→
←RASSF1
HEMK1→
MIR4787→
SLC38A3→
←IFRD2
←ZMYND10
MAPKAPK3→
GNAI2→
←HYAL3
←NPRL2
5 genes omitted
50.3
50.4
50.5
50.6
50.7
Position on chr3 (Mb)



r²
0.8
0.6
0.4
0.2
rs6681737
−log₁₀(p−value)
0
2
4
6
8
Recombination rate (cM/Mb)
0
20
40
60
80
100
NR5A2→
199.7
199.8
199.9
200
Position on chr1 (Mb)


rs148707903
−log₁₀(p−value)
0
2
4
6
8
Recombination rate (cM/Mb)
0
20
40
60
80
100
THSD7A
11.4
11.5
11.6
11.7
Position on chr7 (Mb)