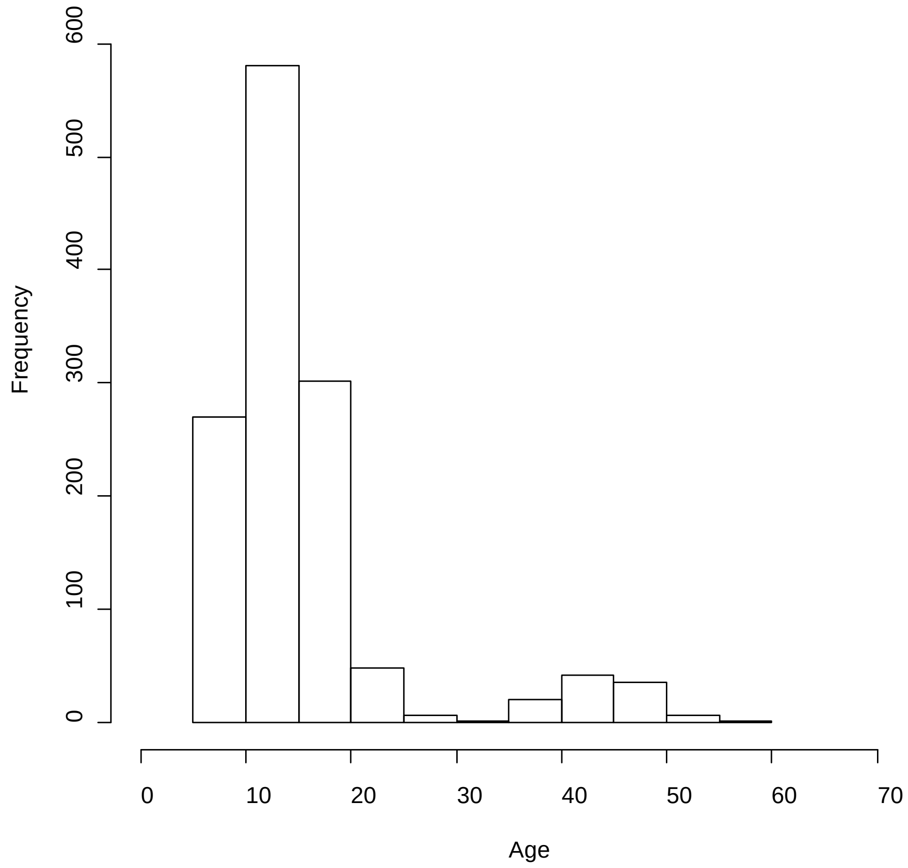
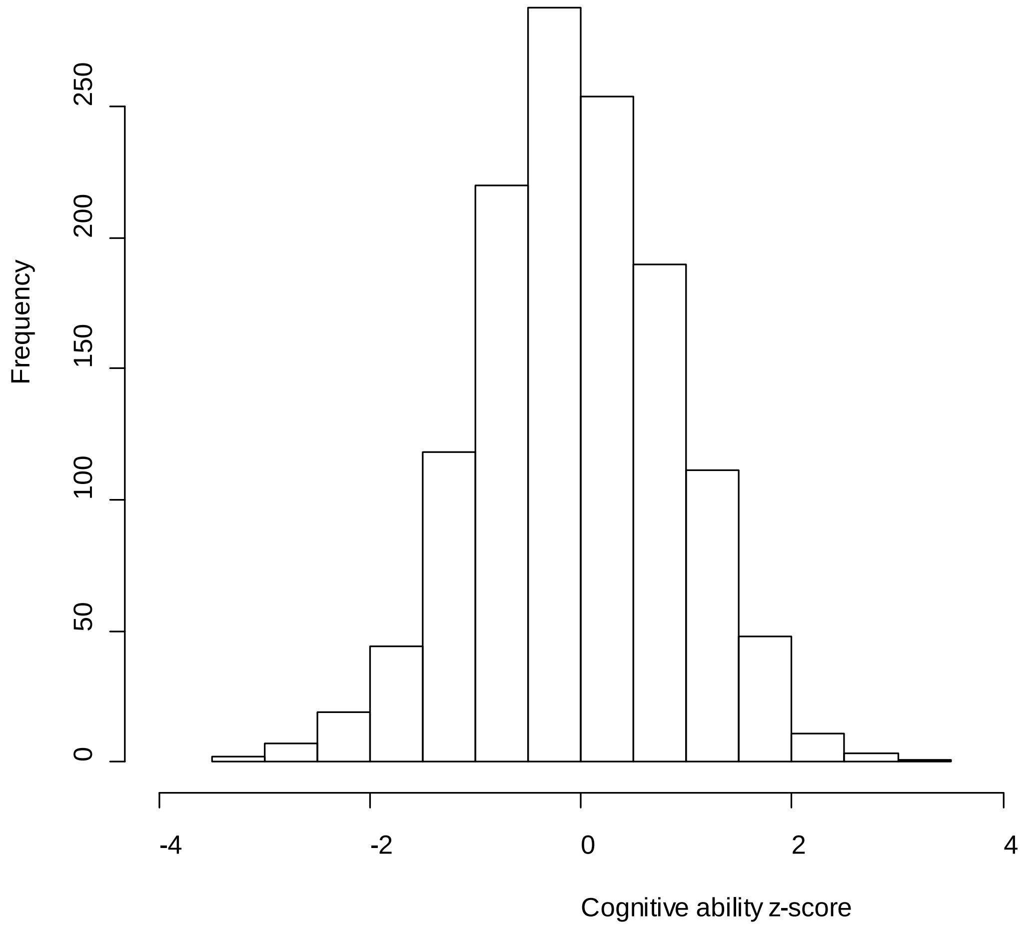
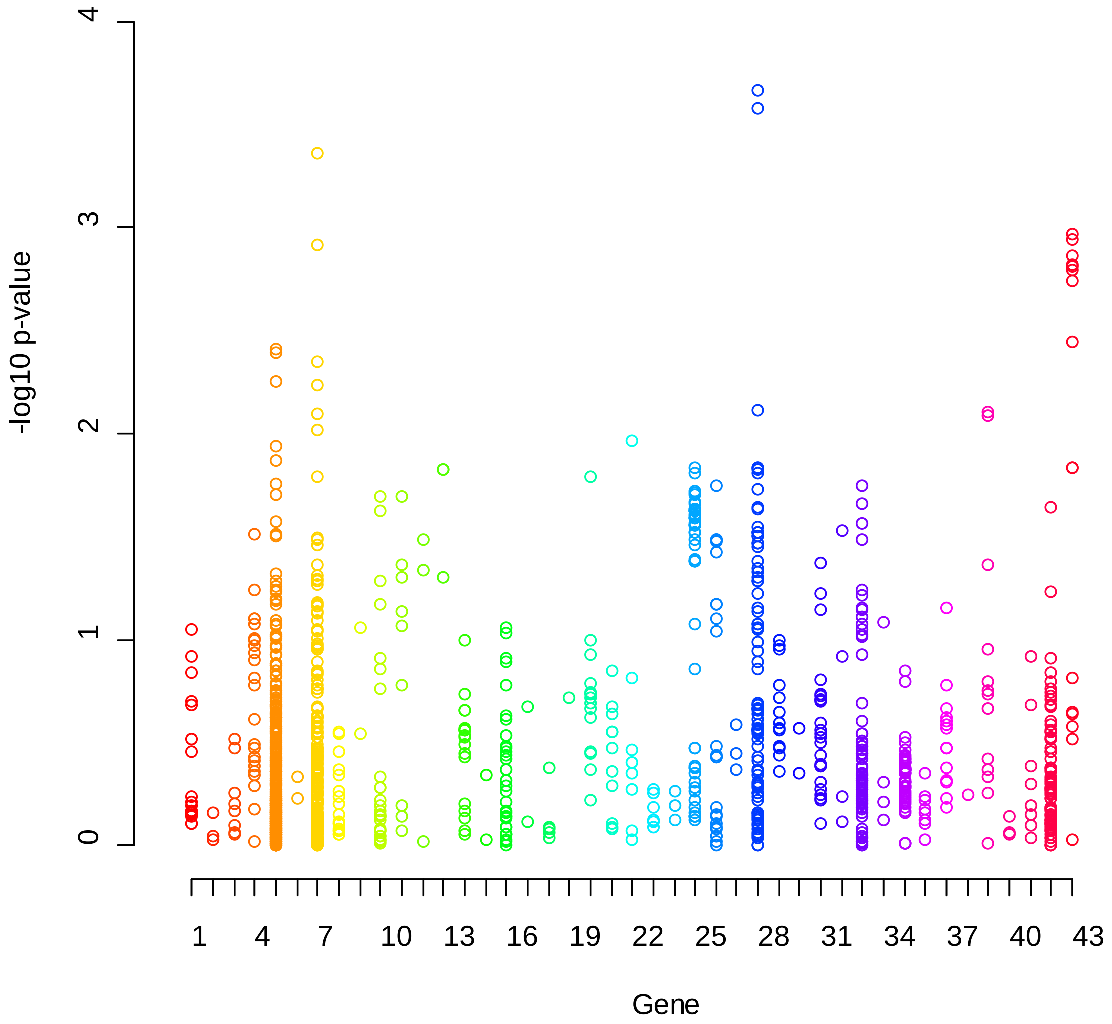
Supplementary Figures



Supplementary Figure 1. Distribution of participants' (N=1316) mean age at the time of intelligence assessment.

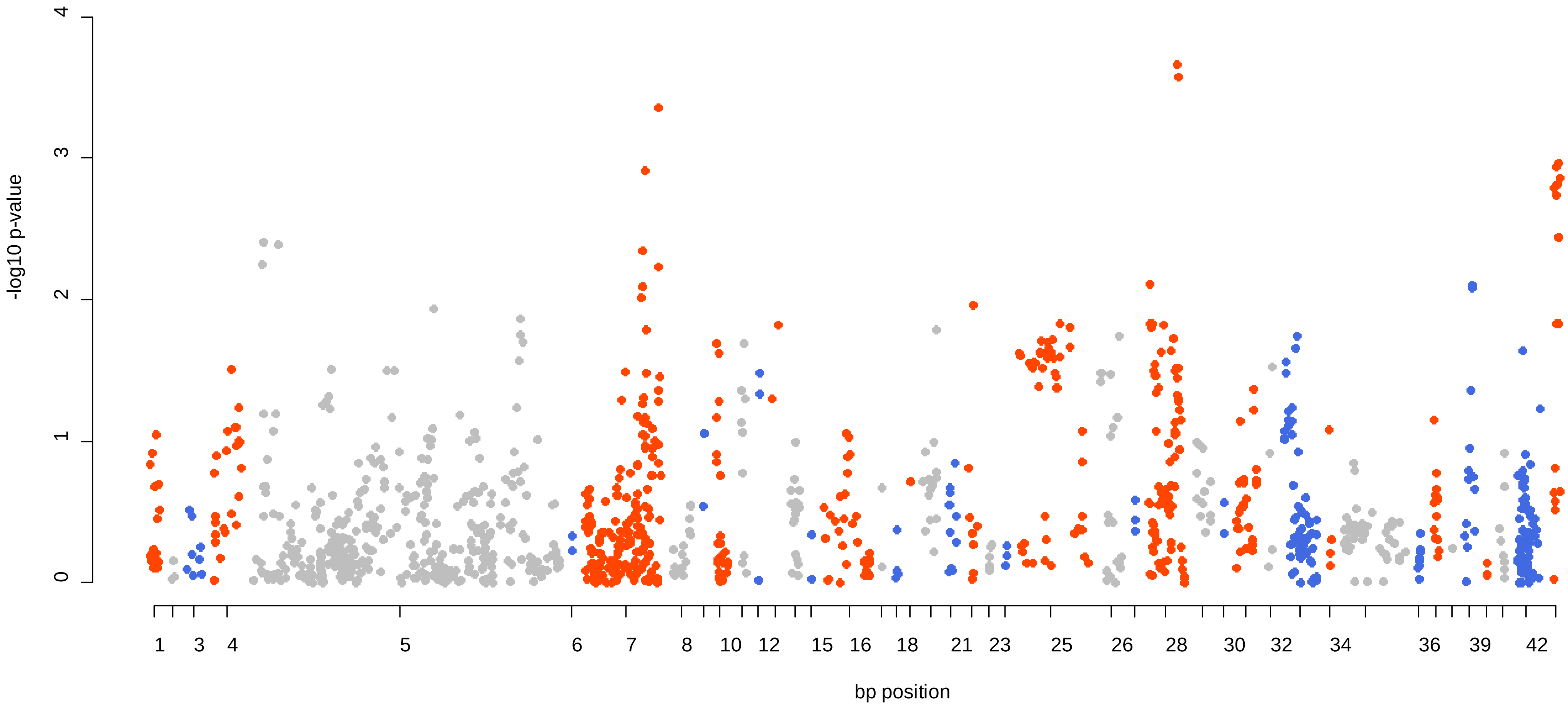


Supplementary Figure 2. Distribution of intelligence scores.

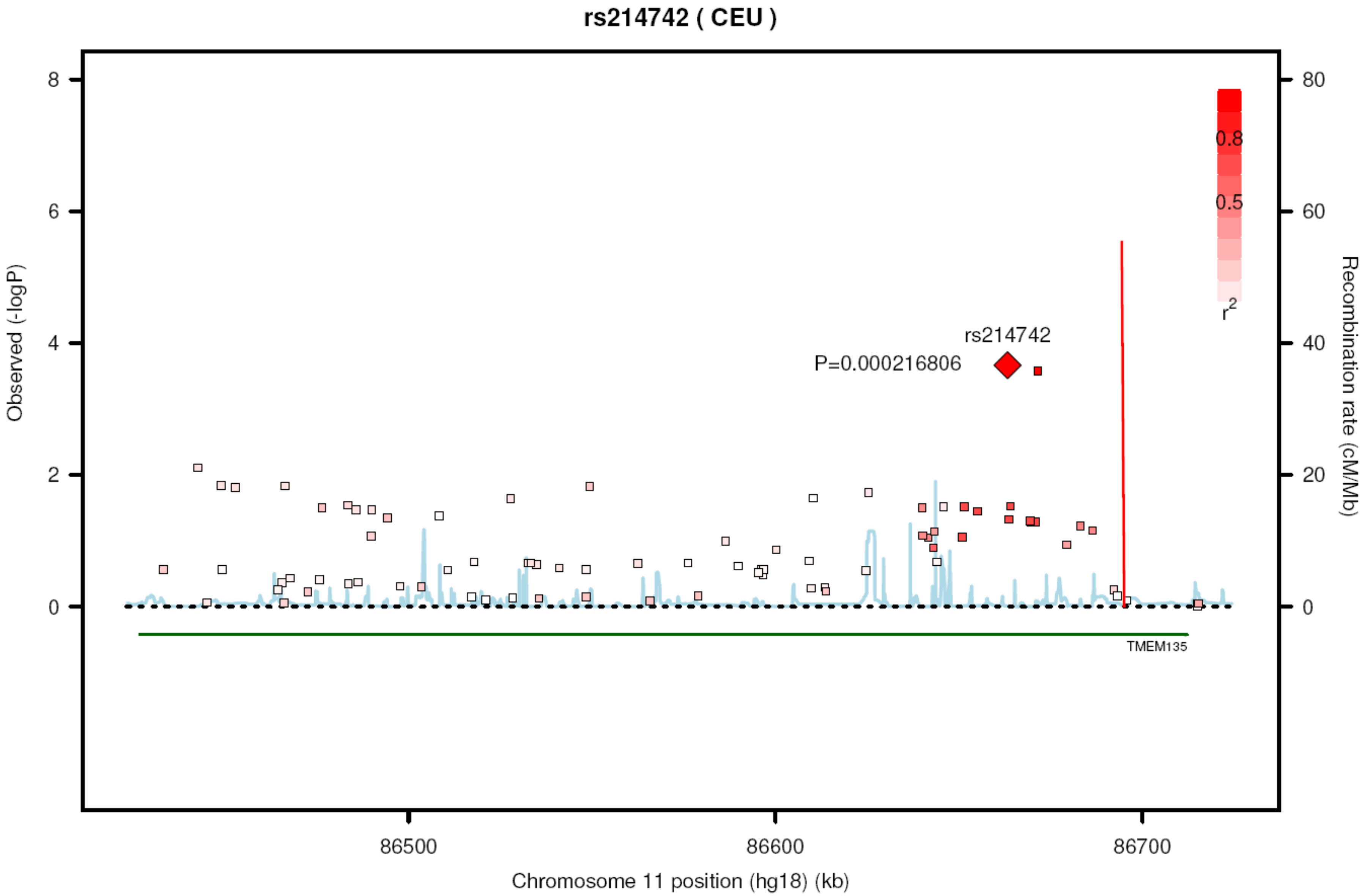


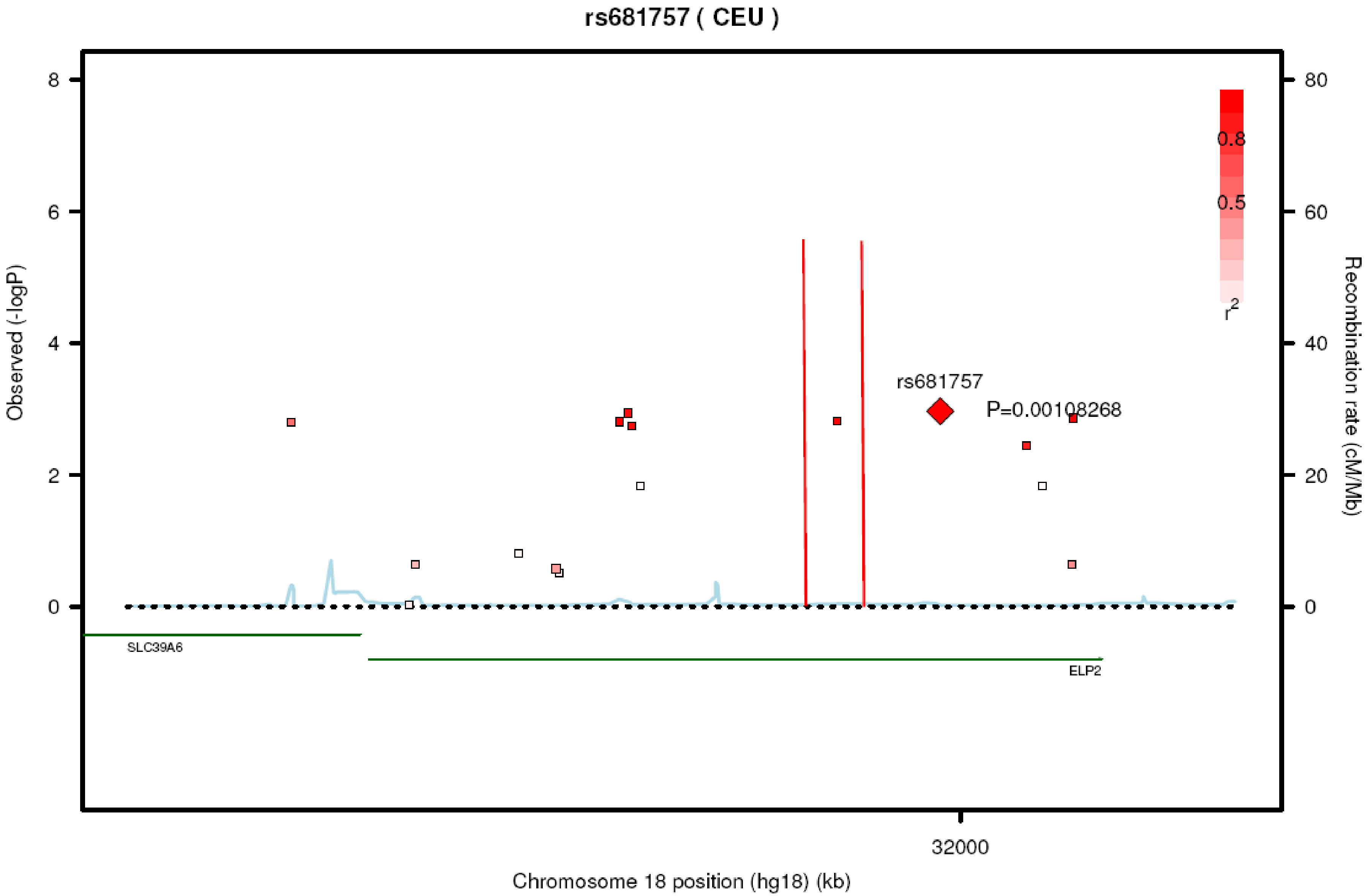
1	ZBTB40	10	PECR	19	ERLIN2	28	TMEM135	37	LINS
2	CNKSR1	11	CAPN10	20	TAF2	29	KDM5A	38	KDM6B
3	GON4L	12	CCNA2	21	SLC31A1	30	ASCL1	39	CACNA1G
4	ACBD6	13	PRMT10	22	RALGDS	31	POLR3B	40	FASN
5	PARP1	14	NDST1	23	C9orf86	32	ZCCHC8	41	WDR45L
6	HIST3H3	15	HIST1H4B	24	MAN1B1	33	FRY	42	LAMA1
7	RGS7	16	ASCC3	25	ADK	34	UBR7	43	ELP2
8	INPP4A	17	CASP2	26	ENTPD1	35	SCAPER		
9	EEF1B2	18	TTI2	27	C11orf46	36	KIF7		

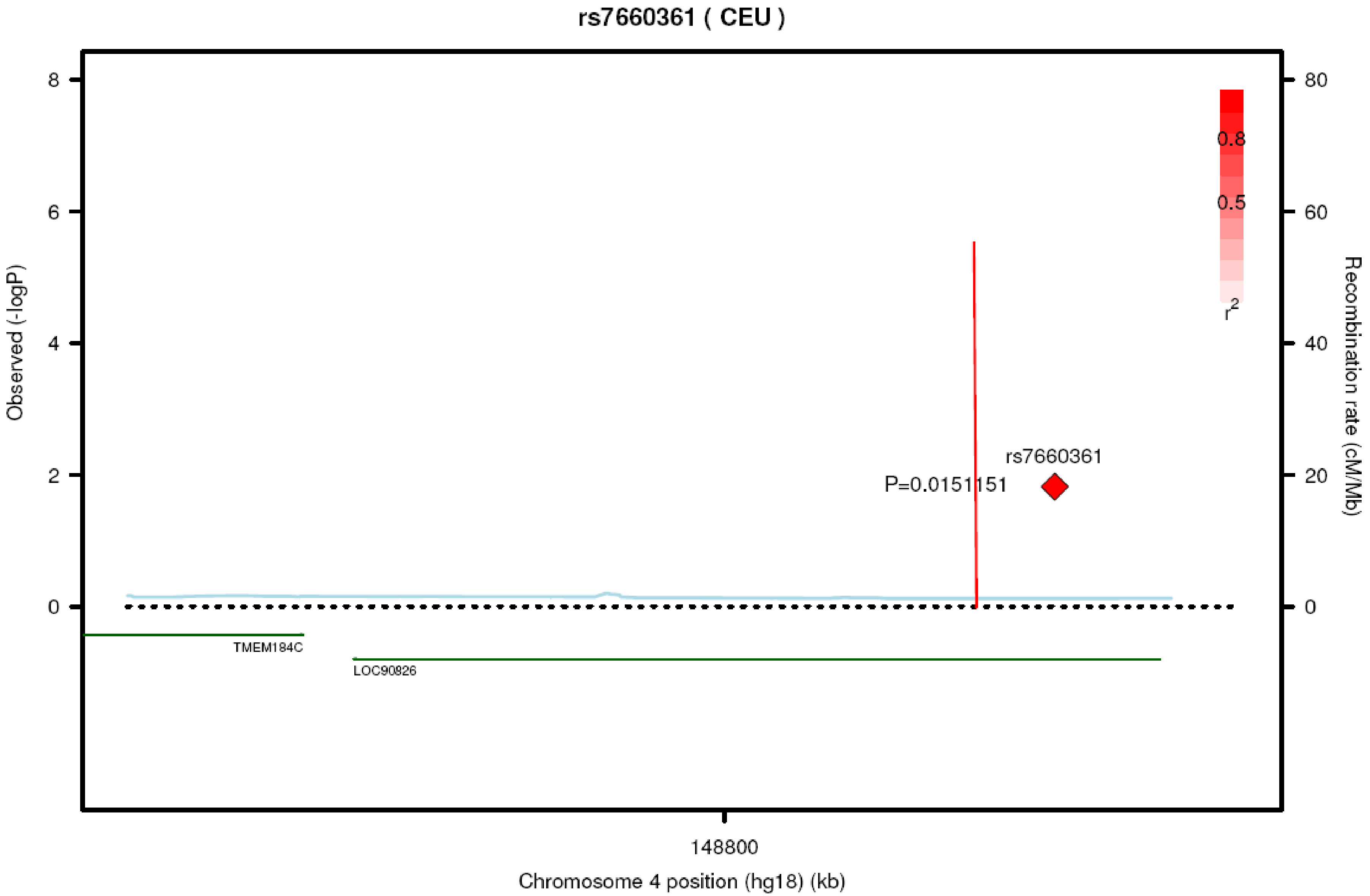
Supplementary Figure 3. Manhattan plot of the 1227 association p-values. x-axis: gene index (1-43; see legend).

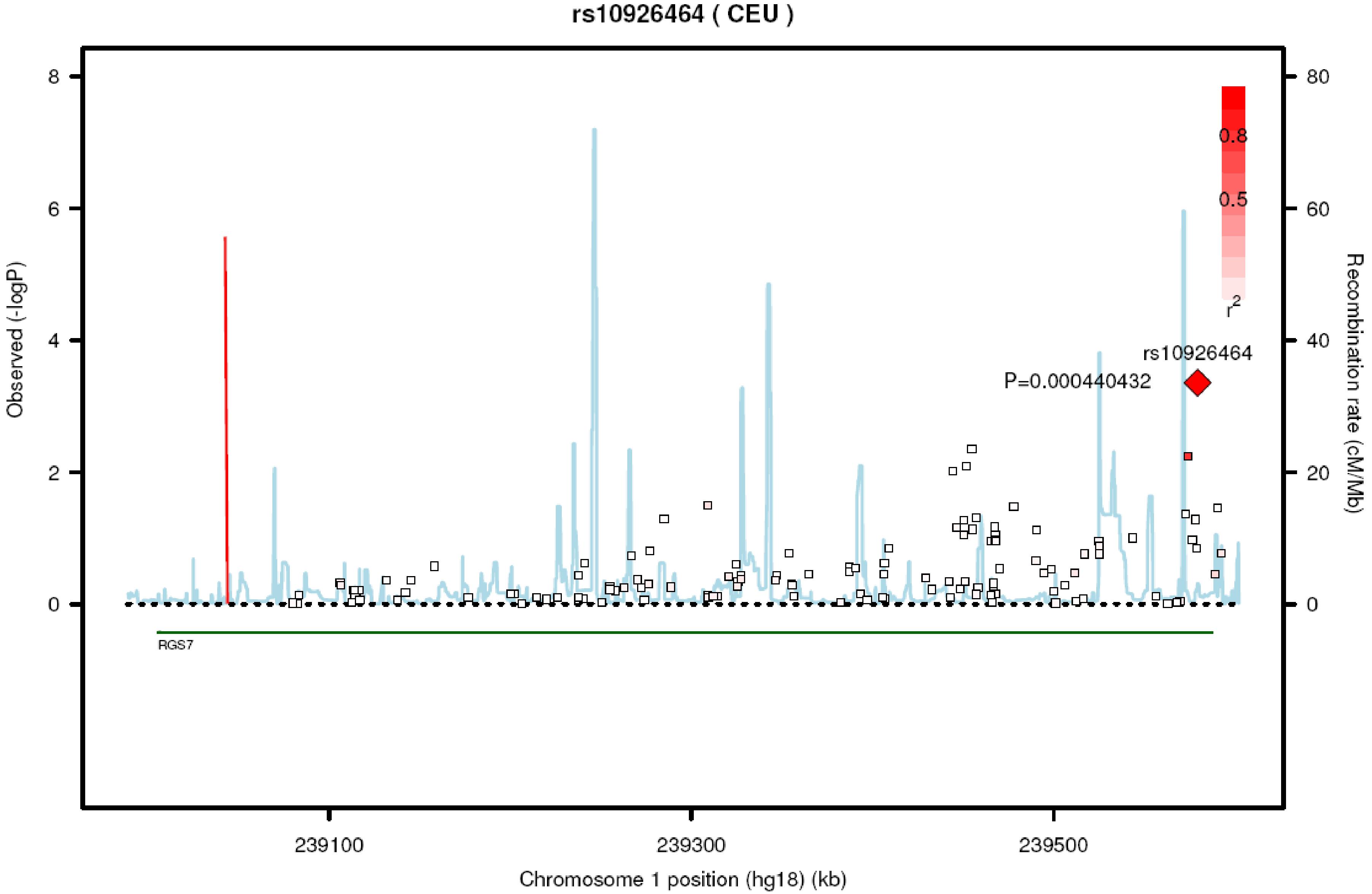


Supplementary Figure 4. Manhattan plot of the 1227 association p-values. x-axis: bp position within gene (numbers 1-43 denote genes; see legend of Figure 4).


rs214742 (CEU)
Observed (-logP)
Recombination rate (cM/Mb)
rs214742
P=0.000216806
0.8
0.5
r^2
TMEM135
86500
86600
86700
Chromosome 11 position (hg18) (kb)
8
6
4
2
0
80
60
40
20
0


rs681757 (CEU)
Observed (-logP)
Recombination rate (cM/Mb)
8
6
4
2
0
80
60
40
20
0
0.8
0.5
r²
rs681757
P=0.00108268
SLC39A6
ELP2
32000
Chromosome 18 position (hg18) (kb)


rs7660361 (CEU)
Observed (-logP)
8
6
4
2
0
Recombination rate (cM/Mb)
80
60
40
20
0
0.8
0.5
r2
rs7660361
P=0.0151151
TMEM184C
LOC90826
148800
Chromosome 4 position (hg18) (kb)



rs10926464 (CEU)
Observed (-logP)
Recombination rate (cM/Mb)
0.8
0.5
r2
rs10926464
P=0.000440432
RGS7
239100
239300
239500
Chromosome 1 position (hg18) (kb)

Supplementary Figure 5. Gene-based plots depicting the -$\log_{10}$ of the association p-values (squares), the LD structure within a gene (expressed as recombination rate; blue line), and the locations of mutations found in the Najmabadi et al[2] study (vertical red lines). The four plots depict the top four genes according to GATES (TMEME135, ELP2, PRMT10 [LOC90826 in the Figure], and RGS7, respectively). The rhombus denotes the top SNP within a gene. The LD structure between the SNPs is represented by the color of the squares (more highly saturated red = higher LD with the top SNP). Note: The apparent discrepancies in kb positions between the present plots and Table 1 are due to the plots and the table using different alignments (hg18 and hg19, respectively).

Supplementary Table 1

rs numbers and bp positions (hg19) of the 1227 SNPs

c	rs number	bp position	c	rs number	bp position	c	rs number	bp position
1	rs12133700	22780927	1	rs10915955	226363155	10	rs10740441	76410225
1	rs10917234	22782602	1	rs9660924	226371939	10	rs7901055	76415029
1	rs4233289	22790455	1	rs10495244	226387618	10	rs1538311	76415509
1	rs1267001	22802072	1	rs10915958	226389655	10	rs946186	76420880
1	rs4655067	22814289	1	rs41357249	226397002	10	rs10824218	76421216
1	rs4655068	22814354	1	rs11811952	226401914	10	rs10762636	76438084
1	rs209753	22821968	1	rs2377027	226420536	10	rs7097320	76465803
1	rs10799757	22822670	1	rs6605031	226423150	10	rs10748641	97466391
1	rs4655071	22827931	1	rs7367845	226445528	10	rs11598540	97466427
1	rs1267006	22829423	1	rs12133895	226458035	10	rs7073723	97468768
1	rs10917243	22831961	1	rs9286999	226494515	10	rs17553401	97507473
1	rs209729	22835677	1	rs2666429	226500327	10	rs11188469	97511901
1	rs209722	22843428	1	rs11800726	226523560	10	rs3176893	97514617
1	rs104861	22844951	1	rs10915985	226539750	10	rs10748643	97516764
1	rs7551801	22846452	1	rs1991865	226541051	10	rs4551688	97523780
1	rs12754103	22847797	1	rs3219123	226555348	10	rs2105359	97536795
1	rs962889	22857252	1	rs3219095	226563882	10	rs7096248	97539087
1	rs2783626	26501044	1	rs3219090	226564691	10	rs10882664	97539140
1	rs3819033	26508293	1	rs1805410	226568665	10	rs10786235	97542452
1	rs11247868	26519964	1	rs2117114	226571619	10	rs2185818	97550740
1	rs682020	155715529	1	rs3219058	226572794	10	rs6584028	97558779
1	rs2297775	155735012	1	rs4653445	226576906	10	rs4396219	97561941
1	rs822020	155754117	1	rs932002	226577306	10	rs17111156	97584544
1	rs822022	155755239	1	rs1073991	226581074	10	rs2901873	97590826
1	rs4612618	155762509	1	rs10799349	226585516	10	rs1891536	97591297
1	rs822497	155810293	1	rs1805407	226589833	10	rs1342791	97599997
1	rs822490	155822971	1	rs3219027	226590413	10	rs3176883	97604941
1	rs1749415	155825855	1	rs2230656	228612838	10	rs7089668	97608422
1	rs119465	180239670	1	rs11581974	228617063	10	rs4244321	97622689
1	rs7543669	180242659	1	rs1418479	240932039	10	rs2153914	97631051
1	rs2764453	180249307	1	rs6701248	240933458	11	rs3858431	30353024
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1	rs2794965	180249772	1	rs12410144	240940049	11	rs1222211	30362239
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1	rs2254465	180257692	1	rs7522181	240945441	11	rs11234930	86764925
1	rs2764435	180285573	1	rs6429223	240960073	11	rs2445536	86767388
1	rs17300340	180321718	1	rs12733627	240960268	11	rs10898589	86771207
1	rs4651063	180326512	1	rs6663051	240960611	11	rs12289267	86771488
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1	rs3768543	226253926	10	rs10824174	76186852	18	rs17672308	33712708
1	rs10915928	226266440	10	rs2169682	76191617	18	rs3737473	33719044
1	rs12096737	226276554	10	rs1904058	76197369	18	rs3819174	33721325
1	rs10915933	226279050	10	rs10762615	76203850	18	rs17648916	33721484
1	rs1355391	226285151	10	rs10762618	76208811	18	rs1785929	33725165
1	rs11577282	226287622	10	rs1871087	76210873	18	rs1789547	33725705
1	rs10915935	226292385	10	rs10762622	76222754	18	rs1785928	33725931
1	rs7515023	226300488	10	rs11001043	76225597	18	rs3737468	33726485
1	rs10915942	226305741	10	rs7100550	76237498	18	rs12185396	33738496
1	rs6426106	226315232	10	rs4281434	76242772	18	rs681757	33744766
1	rs12136759	226321051	10	rs7078351	76315562	18	rs8299	33750046
1	rs2666859	226327068	10	rs7918318	76320458	18	rs1539835	33750976

1	rs2306121	226353521	10	rs7088329	76359075	18	rs2032206	33752823
1	rs9729045	226362983	10	rs10509350	76383071	18	rs559289	33752890

Note: c = chromosome.

Supplementary Table 2

Overview of the results obtained for the top 50 SNPs using the multilevel regression model. β = standardized regression coefficient, SE_{β} = standard error of β, p=p-value, MAF = minor allele frequency, N = sample size

rs-number	β	SE_{β}	p	Effect allele	MAF	N	Gene
rs214742	0.1070	0.0288	0.000217	A	0.4993	1316	TMEM135
rs301583	0.1054	0.0287	0.000265	G	0.4993	1316	TMEM135
rs10926464	0.1001	0.0283	0.000440	T	0.0979	1313	RGS7
rs681757	0.0942	0.0287	0.001083	T	0.3578	1314	ELP2
rs1789547	0.0937	0.0287	0.001151	C	0.3558	1316	ELP2
rs1317602	0.0918	0.0283	0.001227	A	0.2945	1312	RGS7
rs559289	0.0922	0.0287	0.001369	A	0.3572	1316	ELP2
rs12185396	0.0915	0.0287	0.001505	C	0.3512	1314	ELP2
rs1785929	0.0913	0.0287	0.001558	G	0.3587	1316	ELP2
rs2236718	0.0910	0.0287	0.001600	G	0.3325	1316	ELP2
rs1785928	0.0902	0.0288	0.001806	G	0.3546	1313	ELP2
rs8299	0.0837	0.0287	0.003615	C	0.3724	1313	ELP2
rs7528514	0.0817	0.0282	0.003932	G	0.3441	1316	PARP1
rs6686449	0.0817	0.0283	0.004063	T	0.0466	1316	PARP1
rs6662036	0.0820	0.0288	0.004510	T	0.1988	1316	RGS7
rs1492689	0.0782	0.0282	0.005630	G	0.0885	1316	PARP1
rs10802951	0.0779	0.0282	0.005807	G	0.0827	1316	RGS7
rs11234930	0.0742	0.0278	0.007765	T	0.0761	1316	TMEM135
rs9898699	0.0756	0.0284	0.007873	C	0.4133	1316	CACNA1G
rs6682206	0.0759	0.0286	0.008056	G	0.2193	1313	RGS7
rs9898731	0.0751	0.0284	0.008264	C	0.4122	1316	CACNA1G
rs12141515	0.0747	0.0287	0.009551	T	0.2021	1316	RGS7
rs598123	0.0711	0.0279	0.010962	C	0.0573	1314	RALGDS
rs12083979	0.0707	0.0279	0.011530	G	0.0452	1316	PARP1
rs11577282	0.0706	0.0285	0.013581	T	0.2674	1311	PARP1
rs10898589	0.0679	0.0277	0.014558	G	0.0758	1316	TMEM135
rs3737468	0.0686	0.0281	0.014662	A	0.0637	1316	ELP2
rs1539835	0.0686	0.0281	0.014662	C	0.0637	1316	ELP2
rs11234958	0.0679	0.0277	0.014705	T	0.0758	1316	TMEM135
rs4281434	0.0699	0.0286	0.014797	G	0.2730	1315	ADK
rs7660361	0.0729	0.0299	0.015115	T	0.0131	1316	PRMT10
rs7687368	0.0729	0.0299	0.015115	A	0.0131	1316	PRMT10
rs473206	0.0687	0.0282	0.015122	A	0.4723	1316	TMEM135
rs10898590	0.0674	0.0278	0.015636	G	0.0758	1315	TMEM135
rs7078351	0.0686	0.0283	0.015680	A	0.1724	1315	ADK

rs1915871	0.0682	0.0283	0.016105	T	0.2781	1315	RGS7
rs10108322	0.0706	0.0293	0.016328	C	0.0933	1312	TAF2
rs1355391	0.0683	0.0287	0.017493	G	0.2861	1314	PARP1
rs3176883	0.0672	0.0283	0.017783	T	0.0891	1312	ENTPD1
rs17077100	0.0674	0.0284	0.018012	C	0.0952	1315	FRY
rs12224600	0.0657	0.0278	0.018547	T	0.0725	1316	TMEM135
rs10824174	0.0673	0.0286	0.019129	A	0.2855	1316	ADK
rs7098200	0.0676	0.0289	0.019568	A	0.4026	1315	ADK
rs12784355	0.0673	0.0289	0.019937	C	0.4035	1316	ADK
rs7515023	0.0663	0.0284	0.019996	T	0.2775	1316	PARP1
rs3770554	0.0672	0.0289	0.020306	G	0.3636	1314	PECR
rs4676348	0.0667	0.0287	0.020392	C	0.4027	1315	CAPN10
rs7918318	0.0655	0.0284	0.021413	T	0.1723	1316	ADK
rs41526255	0.0658	0.0286	0.021818	C	0.0968	1314	FRY

Supplementary Table 3

Gene-based p-values obtained using the GATES and the VEGAS tests

Gene	GATES p-value	VEGAS p-value
ELP2	0.007	0.002
TMEM135	0.007	0.023
PRMT10	0.019	-
RGS7	0.044	0.241
CCNA2	0.070	0.061
CACNA1G	0.076	0.040
RALGDS	0.076	0.204
ADK	0.084	0.028
ZCCHC8	0.114	0.119
EEF1B2	0.132	0.122
TAF2	0.141	0.102
CAPN10	0.150	0.045
PECR	0.189	0.382
ERLIN2	0.191	0.200
ENTPD1	0.194	0.124
KDM5A	0.222	-
UBR7	0.245	0.427
ACBD6	0.250	0.138
POLR3B	0.292	0.249
FRY	0.345	0.309
PARP1	0.370	0.889
CASP2	0.421	0.438
C11orf46	0.425	0.405
ASCL1	0.444	0.426
NDST1	0.497	0.392
ZBTB40	0.504	0.429
HIST3H3	0.521	0.543
LINS	0.521	0.318
KDM6B	0.567	-
GON4L	0.578	0.673
WDR45L	0.621	0.575
SLC31A1	0.654	0.438
TTI2	0.655	0.698
SCAPER	0.719	0.730
MAN1B1	0.725	0.660
INPP4A	0.761	0.678
C9orf86	0.772	0.688
KIF7	0.828	0.855
LAMA1	0.886	0.765
FASN	0.887	0.885
HIST1H4B	0.912	0.757

CNKSR1	0.935	0.940
ASCC3	0.965	0.552

Note: VEGAS and GATES used the hg18 and the hg19 assembly, respectively, in assigning SNPs to genes; therefore the sets of SNPs assigned to each gene differ marginally between the two methods. Genes PRMT10, KDM5A, and KDM6B were not assigned any of the 1227 SNPs in VEGAS; therefore the p-values for those genes are missing from the table.

Supplementary Methods

Supplementary Script 1. R script used to implement the multilevel regression model.

```
# This is the R script used to perform a series of multilevel regression analyses for the 1227
# SNPs. The core of the script is given in bold font below; the reader may skip to this part for
# comprehension of the analysis. The remainder of the script serves only to manipulate data,
# and is included to facilitate replication.

# The input file, 'data.sav', is structured as follows: 1) npv (npv=6 in this case) columns
containing family ID, individual ID, maternal ID, paternal ID, sex, phenotype; 2) npc (npc=8
in this case) columns containing principal component (PC) scores, 3) nsnp*2 (nsnp=1227 in
this case) columns containing genotype data (2 columns per SNP; allele 1 and allele 2)
# Thus, the columns are: family ID, individual ID, maternal ID, paternal ID, sex, phenotype,
PC1, PC2, PC3, PC4, PC5, PC6, PC7, PC8, snp1allele1, snp1allele2, snp2allele1,
snp2allele2, …, snp1227allele1, snp1227allele2
# One can use a Plink .ped file and insert PCs after the first 6 columns (if desired;
alternatively one can set 'npc' below to 0)

library(foreign)
library(nlme)
library(GenABEL)
source("http://www.StephenTurner.us/qqman.r")
nsnp=1227 # number of SNPs
```

```
npv=6 # number of columns preceding the PC columns

npc=8 # number of PC columns

np=npv+npc


d=as.data.frame(read.spss('data.sav',to.data.frame=T,use.value.labels=F))

d[,-((npv):(npv+npc))][d[,-((npv):(npv+npc))]==0]=NA # recode as missing all zeros in the
first 5 columns and the SNP columns (not in the phenotype and the PC columns!)

for (i in (np+1):(nsnp*2+np)){d[,i]=as.character(d[,i])} # convert all SNP

# columns into character vectors

all.equal((dim(d)[2]-np)/2,nsnp) # check, should be TRUE


# All SNPs are diallelic. In the gen.rec matrix the genetic data will be recoded from 'G', 'C',

# 'T', and 'A' into 0 and 1. The coding scheme is as follows:

# 'G' is always coded as 1.

# 'C' is coded 0 if the possible alleles at a SNP are C and G; it is coded 1 in all other

# cases.

# 'T' is coded 0 if the possible alleles at a SNP are T and G, or T and C; it is coded 1 in

# all other cases.

# 'A' is always coded as 0.


gen.rec=as.matrix(d)

gen.rec[gen.rec=='G']=1

gen.rec[gen.rec=='A']=0

for (i in np+seq(1,nsnp*2,by=2)){

z=unique(d[,i])
```

```
if(length(z)>2) {z=z[-which(is.na(z)==T)]}

a=z[1]

b=z[2]

if(a=='G' & b=='C'){

gen.rec[,i][gen.rec[,i]=='C']=0

gen.rec[,i+1][gen.rec[,i+1]=='C']=0}

if(a=='C' & b=='G'){

gen.rec[,i][gen.rec[,i]=='C']=0

gen.rec[,i+1][gen.rec[,i+1]=='C']=0}

if(a=='G' & b=='T'){

gen.rec[,i][gen.rec[,i]=='T']=0

gen.rec[,i+1][gen.rec[,i+1]=='T']=0}

if(a=='T' & b=='G'){

gen.rec[,i][gen.rec[,i]=='T']=0

gen.rec[,i+1][gen.rec[,i+1]=='T']=0}


if(a=='C' & b=='T'){

gen.rec[,i][gen.rec[,i]=='C']=1

gen.rec[,i+1][gen.rec[,i+1]=='C']=1

gen.rec[,i][gen.rec[,i]=='T']=0

gen.rec[,i+1][gen.rec[,i+1]=='T']=0}

if(a=='T' & b=='C'){

gen.rec[,i][gen.rec[,i]=='C']=1

gen.rec[,i+1][gen.rec[,i+1]=='C']=1

gen.rec[,i][gen.rec[,i]=='T']=0
```

```
gen.rec[,i+1][gen.rec[,i+1]=='T']=0}
if(a=='A' & b=='C'){
gen.rec[,i][gen.rec[,i]=='C']=1
gen.rec[,i+1][gen.rec[,i+1]=='C']=1}
if(a=='C' & b=='A'){
gen.rec[,i][gen.rec[,i]=='C']=1
gen.rec[,i+1][gen.rec[,i+1]=='C']=1}

if(a=='T' & b=='A'){
gen.rec[,i][gen.rec[,i]=='T']=1
gen.rec[,i+1][gen.rec[,i+1]=='T']=1}
if(a=='A' & b=='T'){
gen.rec[,i][gen.rec[,i]=='T']=1
gen.rec[,i+1][gen.rec[,i+1]=='T']=1}
}

gr=matrix(0,dim(gen.rec)[1],dim(gen.rec)[2]) # gr is same as gen.rec but with columns as
numeric vectors
for (j in 1:dim(gen.rec)[2]){gr[,j]=as.numeric(gen.rec[,j])}

rec=gr[,1:np] # rec will contain a single column per SNP, with the 0s and 1s added over the 2
alleles
for (i in np+seq(1,nsnp*2,by=2)){
a=gr[,i]+gr[,i+1]
rec=cbind(rec,a)}
```

rec=as.data.frame(rec)

colnames(rec)=c(colnames(d)[1:np],1:nsnp)

 # The data are now contained in the data frame 'rec', which is structured as follows:

 # npv columns containing: family ID, individual ID, maternal ID, paternal ID,sex,

 # phenotype;

 # npc columns containing principal component (PC) scores;

 # nsnp columns containing genotype data (single column per SNP; data coded as 0, 1, # or 2).

 # Perform regression with random intercepts over families, using PCs as covariates:

res=list(0)

for(i in np+(1:nsnp)){

data=as.data.frame(cbind(rec[,1:np],rec[,i]))

colnames(data)=c(colnames(d)[1:np],'snp')

reg=lme(phenotype~snp+pc1+pc2+pc3+pc4+pc5+pc6+pc7+pc8,random=~1|familyID,method='ML',data=data,na.action=na.omit)

res[[i-np]]=reg}

p=c()

for(i in 1:nsnp){p=c(p,summary(res[[i]])$tTable[2,5])}

hist(p) # histogram of p-values

qq(p) # QQ-plot

estlambda(p) # inflation factor

map=as.data.frame(t(matrix(scan('data.map',what='c'),4,))) # one can read in a Plink .map file corresponding to the .ped file used to create the original input

summ=cbind(map,p)[,c(2,5)] # rs names and the corresponding p-values

Supplementary Script 2. Implementation of the GATES test.

```
#  R script for the GATES test in which tests for individual SNPs are combined and
# corrected for the LD structure that causes dependency between the p-values. The script is
# an implementation of the method described in Li, Gui, Kwan & Sham (2011), AJHG, 88,
# 283-293. It uses p-values from an association test (in the present case, the multilevel
# regression model given in Supplementary Methods 1) as input.

library(psych)
library(foreign)
m1=1227 # number of p-values

###############################################################################
# ------------------------------------------------ Read in data: ----------------------------------------------- #
###############################################################################

d=as.data.frame(t(matrix(scan('data.dat',what='c'),3,))) # read in the data. 1st column = SNP,
2nd column = gene, 3rd column = the p-value associated with the SNP. The SNPs must be in
the order corresponding to that in the correlation matrix ('cors.ld') below.

colnames(d)=c('rs','gene','p')
for(i in 1:2) {d[,i]=as.character(d[,i])}
d$p=as.numeric(as.character(d$p))
g=unique(d$gene) # list of genes included in the analysis
ng=length(g) # number of genes included in the analysis
```

cors=matrix(scan('cors.ld'),m1,m1) # read in a correlation matrix of all SNPs used in the analysis (obtainable, e.g., in Plink, using the --r option)

genps=as.data.frame(matrix(0,ng,2)) # this will hold the gene-based p-values

##
--------------- Perform the GATES procedure iteratively for each of the genes: --------------
##

for(k in g){
data=d[d$gene==k,] # select only the data for a particular gene
ps=data$p # p-values of SNPs on this gene
index=which(d$gene==k)
m=length(index) # the number of SNPs on this gene
r=matrix(cors[index,index],m,m) # correlation matrix of SNPs on this gene (a subset of the complete allelic correlation matrix 'cors')

tmp=sort(ps,index.return=T) # sort the p-values
pj=tmp$x # sorted p-values
iorder=tmp$ix # rank order index: rank of each p-value (unsorted)

r2=matrix(0,m,m)
r2=r[iorder,iorder] # gives a sorted version of the correlation matrix r between SNPs, where the sorting takes place on the rank order of the p-values of the SNPs. Note that sorting is

convenient because GATES consists of a part that concerns the entire correlation matrix and a part that concerns subparts of the correlation matrix between the top X SNPs. this part (the top X SNP part) can now easily be accessed.

```
# ----------  weigh SNP correlations by regression weights determined by Li et al. 2011 --------

# correlation matrix of SNP p-values (a 6th order polynomial function of SNP correlations):
ro=diag(m)
for (i1 in 1:m)  {  for (i2 in 1:i1)  {
if (i1>i2) {
er=r2[i1,i2]
ro[i1,i2]=ro[i2,i1]=.2982*er^6-.0127*er^5+.0588*er^4+.0099*er^3+.6281*er^2-.0009*er
}}}

# ----------------- determine eigenvalues based on entire p-value correlation matrix --------------

alllam=eigen(ro[1:m,1:m])$values # eigenvalues of the ro matrix
mepj=m

# estimate effective number of independent p-values (Li et al., page 284)
for (i1 in 1:m) {mepj=mepj-(alllam[i1]>1)*(alllam[i1]-1)}

# ---------- determine eigenvalues based on p-value correlation matrix for the top x SNPs -----

# object 'sellam' will contain eigenvalues based on varying number of top SNPs
```

```
mej=matrix(c(seq(1,m,1)),m,1,byrow=T)

for (j in 1:m) {
sellam=eigen(ro[1:j,1:j])$values # eigenvalues of the ro matrix
id=j
# obtain effective number of independent p-values among the top x SNPs
for (i1 in 1:id) {mej[j,1]=mej[j,1]-(sellam[i1]>1)*(sellam[i1]-1)}
}

# ---------------------------- weigh sorted p-values by eigenvalues ratio ----------------------------

pg=matrix(0,m,1)
for (i in 1:m) {pg[i,1]=(mepj/mej[i,1])*pj[i]}

# ------------------------------------- determine gene-wide p-value -----------------------------------

genp=min(pg)

genps[which(g==k),1]=genp
genps[which(g==k),2]=k
}

genps # genes with their corresponding p-values
genps[which(genps[,1]<.05),] # genes with p<.05
```