Supplementary materials

SUPPLEMENTARY FIGURE LEGENDS

Figure S1. Online analysis tools. (A) Input parameters. (B) The scores result table, including the mean and sum, and input genes that are presence or absence in the selected network. (C) Correlation analysis. (D) The results of diseases with the highest absolute correlation coefficient (Top 20).

Figure S2. Enhancer-disease score distribution under the genomic region of 9p21. (A) The overall enhancer-disease score distribution in the region of 9p21. (B) The enhancer-disease score distribution in the genomic region is highly correlated with glaucoma and coronary artery disease. (C), (D), (E), (F) and (G) The enhancer-disease score distribution in these regions showing the highest score, and they are associated with diseases of small carcinoma of lung, blood vessels, obesity, amyotrophic lateral sclerosis and congenital disorder of glycosylation, respectively. GWAS: The GWAS hits from the GWAS catalog and gwasdb database. The LD heat map was based on the genotype data from 1000 genome project (Phase 3, including 2,504 individuals, with minor allele frequency greater than 0.05).

Figure S3. The usage examples results of application of HEDD. (A) The density distribution of diseases associated enhancers for the chromosome 9p21 locus, a 13.3-Mb genomic region known for its association with multiple human complex diseases. Eight clusters of enriched enhancers were highlighted by green color and numbered on the top. The blue dash line: 0.04. (B) The distribution of broad disease groups by considering the top 10% enhancer-disease connections for each cluster of enriched enhancers in the chromosome 9p21 locus. (C) The gene regulatory network for the disease of acute erythroblastic leukemia.

SUPPLEMENTARY FIGURES

Score enhancers given a list of genes in a network

Select network : HINT

Click here to learn more about these networks.

or

Upload network : Browse... No file selected.

Click here to see an example of custom gene network.

Disease gene list :
DISC1
HTR2A
COMT
RGS4
DRD3
MTHFR
SYN2
RTN4R
CHI3L1
CD40LG

A list of disease genes or genes of interest, one per line.

Reset

Clear the form.

Score

Among 242 genes that you provided for this analysis, 145 are in the selected network and 97 are not.

Genes in the network	Genes not in the network
DISC1; COMT; RGS4; DRD3; MTHFR; RTN4R; CD40LG; DTNBP1; NRG1; DAO; DRD2; AKT1; RELN; APOL4; DRD4; CHRNA7; SHANK3; NOTCH4; PRL; CLINT1; GABRB1; BDNF; PDE4B; QKI; ZNF804A; NRXN1; HTR1A; HTR2C; SLC1A1; GAD1; MC4R; SULT4A1; SLC6A3; PPP3CC; GRIN1; DRD1; YWHAH; GRIN2B; NTF3; NOS1; CACNG2; FEZ1; NTS; GRIA4; GRIK4; PDLIM5; GRM2; FOLH1; MED12; GRIN2C; RTN4; PIP4K2A; CHRNA4; FXYD6; NDUFV2; DPYSL2; GABBR1; NTNG1; CNTNAP2; GRIN2A; MAP6; ITIH3; VRK2; PPP1R1B; ERBB4; SP4; ERVW-1; TH; DLG4; NOS1AP; MEGF10; UHMK1; RSRC1; SMARCA2; MAOB; ATP2A2; TSNAX; SELENBP1; PLA2G4A; SNAP25; SLC6A1; GRIK5; CACNA1C; SEMA3A; ADRA2A; NR4A2; CNP; MOBP; CHN2; GRIK1; DLG3; CYP3A4; GRIK2; INS; ANK3; HCRT; APOD; PAFAH1B1; GRIA2; PICK1; IMPA2; HTR1B; CCK; NRGN; PLXNA2; NCS1; GABRA4; CCKAR; GRIA3; SLC1A2; HINT1; MLC1; DGKH; WWC1; CRP; GNB3; GAP43; APOL1; NPY; PCNT; GSK3B; GAD2; NTRK2; VIPR2; ADORA2A; MAP2; PIK3C3; TIMELESS; CALY; SLC1A3; PAX6; CIT; IL2RB; TDO2; DNMT1; APP; MBP ; MARCKS; PSAT1; NMBR; ULK4; SLC27A5; NPAS2; ARNTL; GABRG2	HTR2A; SYN2; CHI3L1; ETM1; TAAR6; DAOA; DISC2; PRODH; SCZD6; SCZD1; SCZD2; SCZD7; SCZD8; SCZD3; SCZD11; SCZD5; SCZD12; APOL2; NPAS3; ECSCR; KCNN3; TPH1; ZDHHC8; SLC6A4; GRIK3; GRM3; NRG3; FZD3; CYP2D6; DBH; CPLX2; DGCR6; LRRTM1; HTR3A; TSNAX-DISC1; GRM1; DRD5; CHRM1 ; GRIA1; ARVCF; GNAL; SYN3; MAOA; PVALB; HTR7; CYP1A2; HTR6; HRH2; GRM5; GRIN3B; CHRFAM7A; SRR; MIAT; CACNG5; SLC6A9; CNR1; ASTN2; CDC42SE2; KYAT1; MIR137; TBX1; GRM4; SLC17A7; GPR78; CALB1; HRH3; CNIH1; GRID1; CALB2; CNIH2; SLC18A1; SLC18A2; TPH2; CHL1; EGR3; CHRNB2; ADRA1A; GABRB3; SST; SCZD10; ACSL6; GABRA5; FAN1; SLC6A2; MICB; GSTT2; SLC6A5; ST8SIA2; TACR3; PLA2G6; SCZD4; SCZD13; HTR1D; MAG; ADGRA3; C9orf72; SLC17A6

Data table (HINT network is selected, top 15 enhancer scores, full results download)

Show 10 entries

EnhID ♦	Chr ♦	Start ♦	End ♦	Target gene ♦	Gene score ♦	Mean ♦	Sum ♦	Source ♦
[illegible]2	14	76638448	76638519	GPATCH2L	9.998722898966968E-5	9.99872[illegible]898967E-5	9.998722[illegible]98967E-5	Roadmap
[illegible]4	14	76640036	76640681	GPATCH2L	9.998722898966968E-5	9.99872[illegible]898967E-5	9.998722[illegible]98967E-5	Roadmap
2113947	14	76653474	76653709	GPATCH2L	9.998722898966968E-5	9.99872[illegible]898967E-5	9.998722[illegible]98967E-5	Roadmap
2113950	14	76656475	76656518	GPATCH2L	9.998722898966968E-5	9.998722898967E-5	9.998722898967E-5	Roadmap
2113951	14	76657197	76657258	GPATCH2L	9.998722898966968E-5	9.998722898967E-5	9.998722898967E-5	Roadmap
2113955	14	76660092	76660295	GPATCH2L	9.998722898966968E-5	9.998722898967E-5	9.998722898967E-5	Roadmap
2113957	14	76660873	76660932	GPATCH2L	9.998722898966968E-5	9.998722898967E-5	9.998722[illegible]98967E-5	Roadmap
2113958	14	76667287	76667937	GPATCH2L	9.998722898966968E-5	9.99872[illegible]898967E-5	9.998722[illegible]98967E-5	Roadmap
2113962	14	76669306	76669364	GPATCH2L	9.998722898966968E-5	9.99872[illegible]898967E-5	9.998722[illegible]98967E-5	Roadmap
2113976	14	76674641	76675180	GPATCH2L	9.998722898966968E-5	9.99872[illegible]898967E-5	9.998722[illegible]98967E-5	Roadmap

Search:

First Previous 1 2 Next Last

Correlation analysis

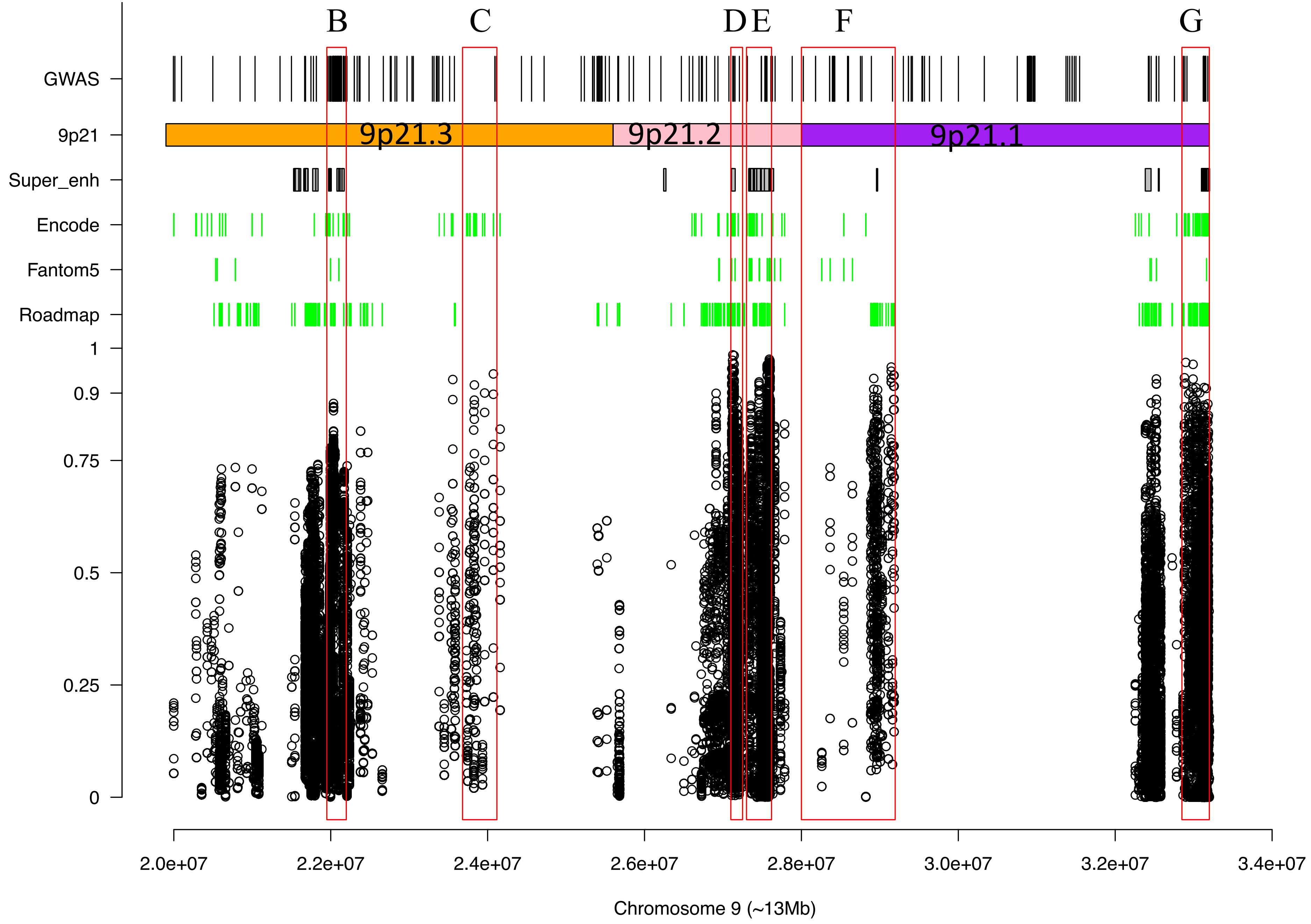
Select Measure : Sum

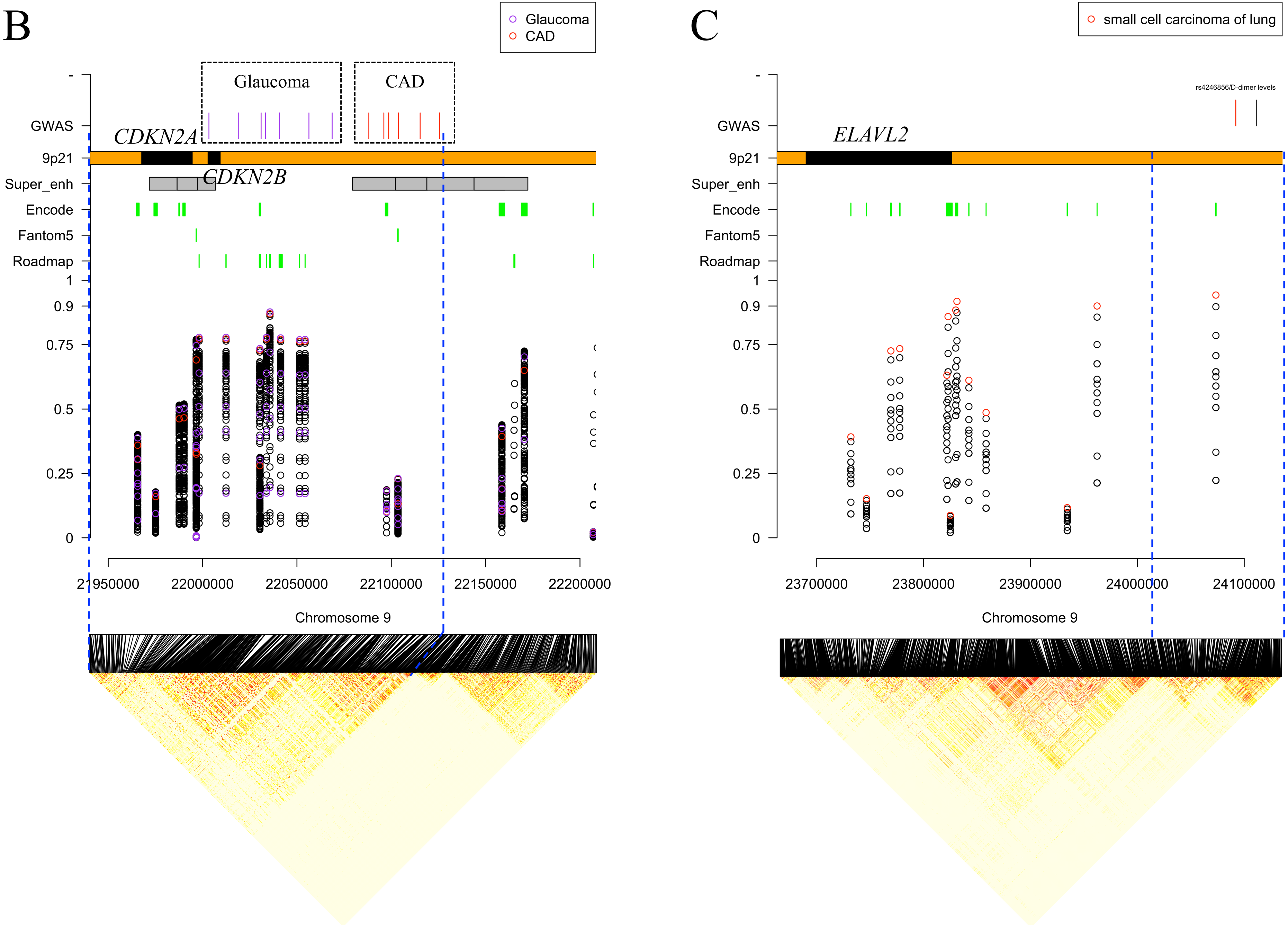
Please choose a measure from the list, and the analysis might require around 30 minutes.

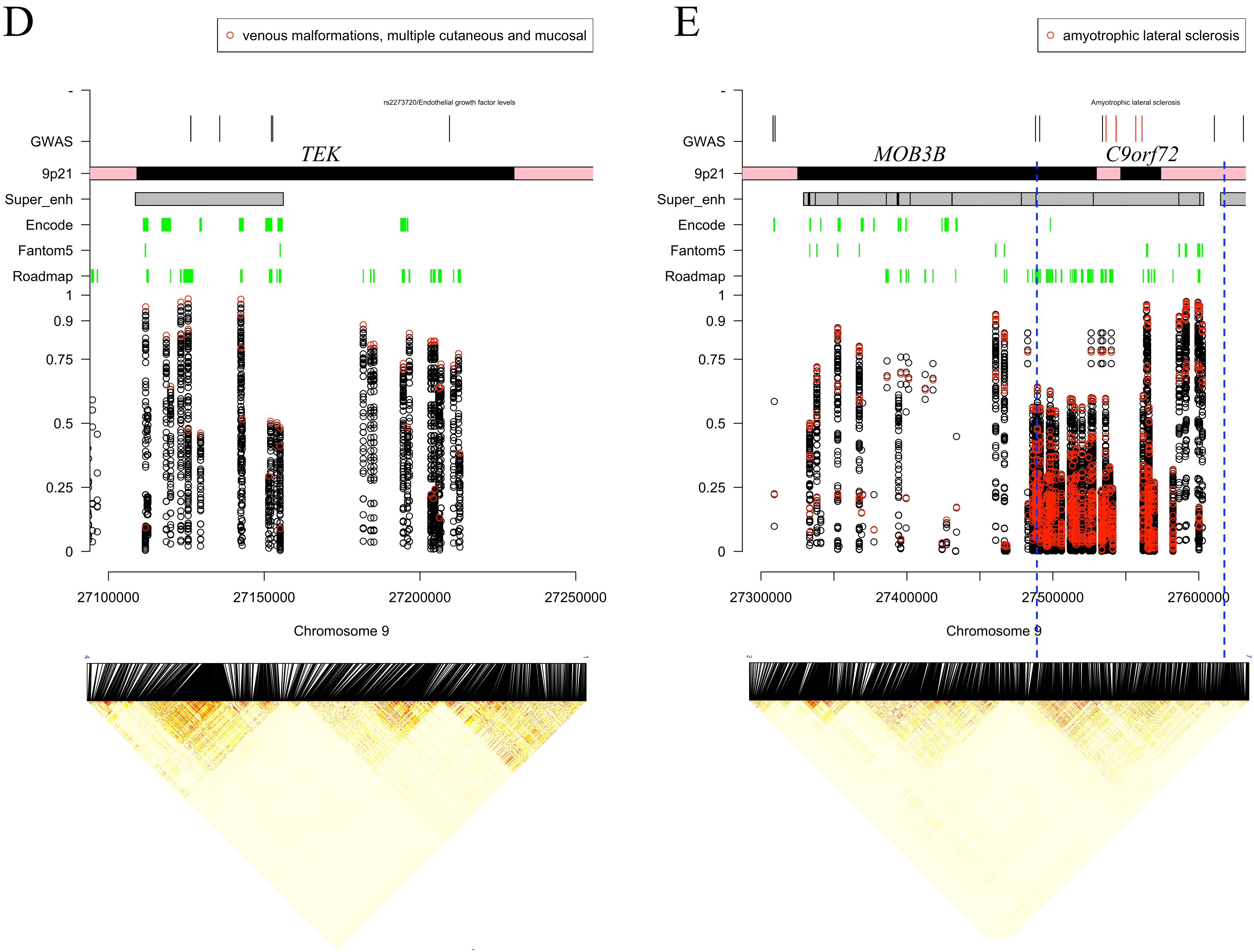
Submit

Figure S1

A


B
C
D
E
F
G
GWAS
9p21
Super_enh
Encode
Fantom5
Roadmap
9p21.3
9p21.2
9p21.1
1
0.9
0.75
0.5
0.25
0
2.0e+07
2.2e+07
2.4e+07
2.6e+07
2.8e+07
3.0e+07
3.2e+07
3.4e+07
Chromosome 9 (~13Mb)


B
Glaucoma
CAD
Glaucoma
CAD
GWAS
9p21
Super_enh
Encode
Fantom5
Roadmap
CDKN2A
CDKN2B
1
0.9
0.75
0.5
0.25
0
21950000
22000000
22050000
22100000
22150000
22200000
Chromosome 9
C
small cell carcinoma of lung
rs4246856/D-dimer levels
GWAS
9p21
Super_enh
Encode
Fantom5
Roadmap
ELAVL2
1
0.9
0.75
0.5
0.25
0
23700000
23800000
23900000
24000000
24100000
Chromosome 9


D
venous malformations, multiple cutaneous and mucosal
rs2273720/Endothelial growth factor levels
GWAS
TEK
9p21
Super_enh
Encode
Fantom5
Roadmap
1
0.9
0.75
0.5
0.25
0
27100000
27150000
27200000
27250000
Chromosome 9
E
amyotrophic lateral sclerosis
Amyotrophic lateral sclerosis
GWAS
MOB3B
C9orf72
9p21
Super_enh
Encode
Fantom5
Roadmap
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0.9
0.75
0.5
0.25
0
27300000
27400000
27500000
27600000
Chromosome 9

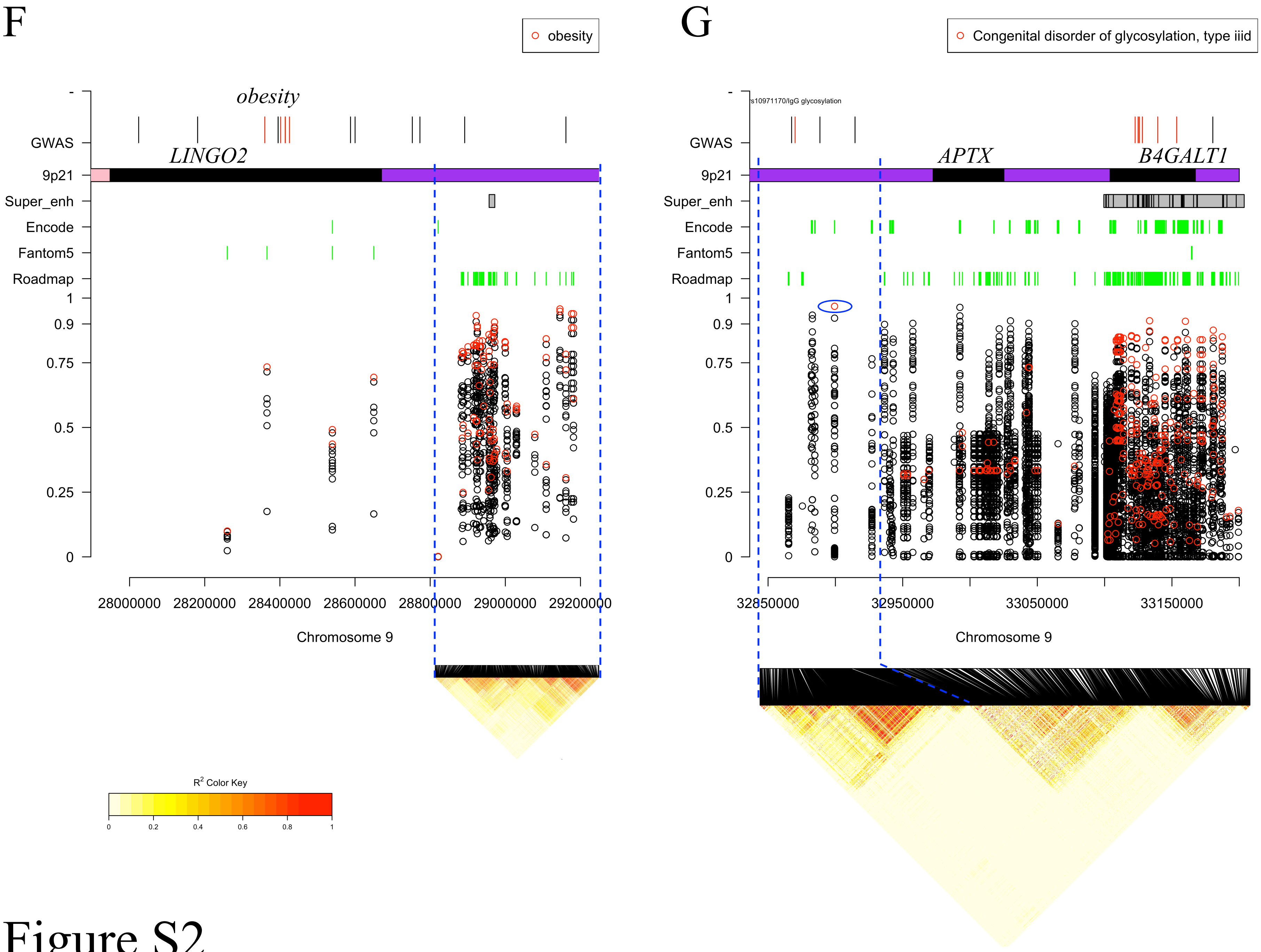
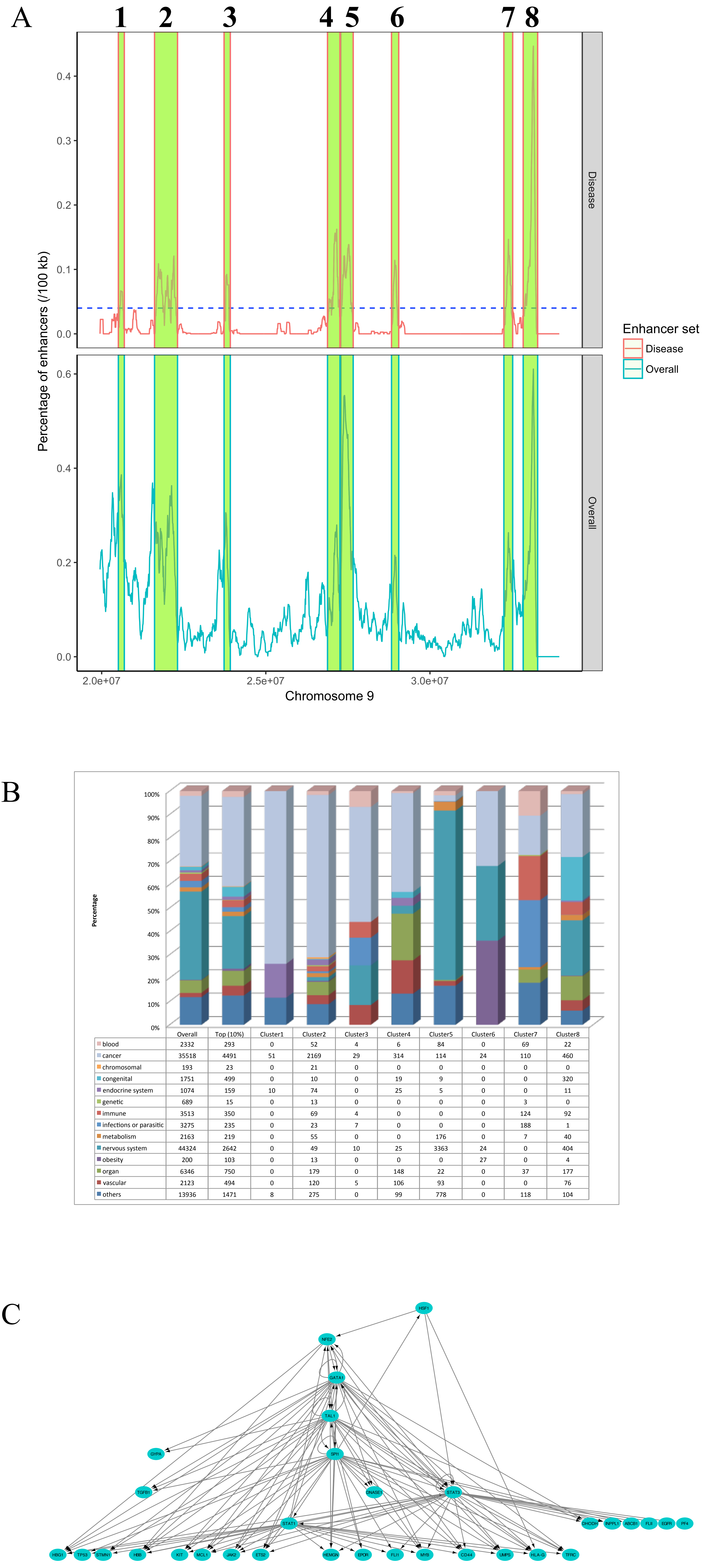

F
obesity
obesity
GWAS
LINGO2
9p21
Super_enh
Encode
Fantom5
Roadmap
1
0.9
0.75
0.5
0.25
0
28000000
28200000
28400000
28600000
28800000
29000000
29200000
Chromosome 9
R2 Color Key
0
0.2
0.4
0.6
0.8
1
G
Congenital disorder of glycosylation, type iiid
s10971170/IgG glycosylation
GWAS
APTX
B4GALT1
9p21
Super_enh
Encode
Fantom5
Roadmap
1
0.9
0.75
0.5
0.25
0
32850000
32950000
33050000
33150000
Chromosome 9

Figure S2



	Overall	Top (10%)	Cluster1	Cluster2	Cluster3	Cluster4	Cluster5	Cluster6	Cluster7	Cluster8
■ blood	2332	293	0	52	4	6	84	0	69	22
■ cancer	35518	4491	51	2169	29	314	114	24	110	460
■ chromosomal	193	23	0	21	0	0	0	0	0	0
■ congenital	1751	499	0	10	0	19	9	0	0	320
■ endocrine system	1074	159	10	74	0	25	5	0	0	11
■ genetic	689	15	0	13	0	0	0	0	3	0
■ immune	3513	350	0	69	4	0	0	0	124	92
■ infections or parasitic	3275	235	0	23	7	0	0	0	188	1
■ metabolism	2163	219	0	55	0	0	176	0	7	40
■ nervous system	44324	2642	0	49	10	25	3363	24	0	404
■ obesity	200	103	0	13	0	0	0	27	0	4
■ organ	6346	750	0	179	0	148	22	0	37	177
■ vascular	2123	494	0	120	5	106	93	0	0	76
■ others	13936	1471	8	275	0	99	778	0	118	104

Figure S3

SUPPLEMENTARY TABLE

Table S1. Summary of the enhancer clusters associated with diseases in 9p21 region.

Cluster	Start	End	Length	Count[1]	Percentage	Disease[2]
1	20,510,000	20,690,000	180 kb	22	4.2%	Cancer
2	21,610,000	22,310,000	700 kb	68	6.1%	Cancer
3	23,730,000	23,920,000	190 kb	11	5.1%	Cancer
4	26,880,000	27,290,000	410 kb	77	7.3%	Cancer
5	27,260,000	27,660,000	400 kb	82	8.2%	Nervous system
6	28,830,000	29,050,000	220 kb	42	5.6%	Obesity
7	32,250,000	32,520,000	270 kb	51	6.8%	Infections / parasitic
8	32,840,000	33,280,000	440 kb	166	14.4%	Cancer, nervous system

Notes:

1. The count of enhancers within each cluster.
2. Enrichment of disease among the top 10% of the highest enhancer disease score in each cluster.