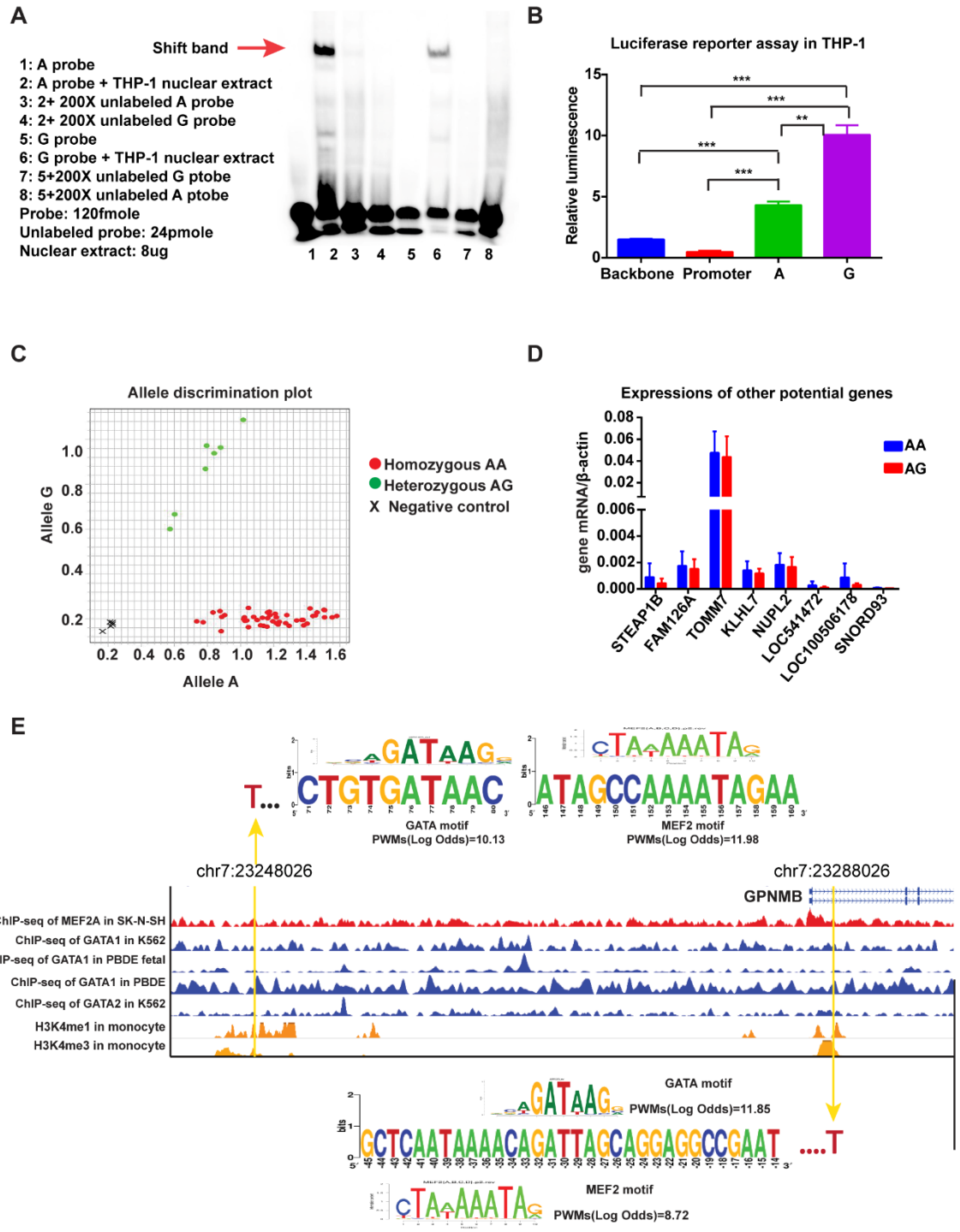
Supplementary Material

Supplementary Figure1

A. EMSA assay in THP-1 cells demonstrating increased protein binding to the probe with A allele compared to G allele. More DNA-protein complexes were shifted with the probe with allele A (lane 2) than allele G (lane 6); both unlabeled probes with A allele or G allele (24 pmol, 200X) can totally compete out the corresponding shifted band separately (lane 3 and lane 7); using 200X unlabeled probe with G allele can also compete out the shifted band formed with the probe with A allele (lane 4); unlabeled probe with A allele was also able to compete out the shifted band formed in the presence of probe with G allele (lane 8). **B.** The enhancer function of rs2069837 locus was also confirmed in THP-1 cells. Significantly increased luciferase expression was detected in both vectors with intronic sequence (A/G), with significantly higher expression in the construct with G allele than that with A allele ($p < 0.05$). **C.** The allele discrimination plot of 48 healthy subjects genotyped for rs2069837. **D.** No differences were observed between macrophages with AA and AG in the expressions of other genes interacting with rs2069837 based on DNase hypersensitivity correlations maps. **E.** Other epigenetic markers (H3K4me1 and H3K4me3) in monocytes also indicated the locus upstream *GPNMB* and the locus in the first intron of *GPNMB* are regulatory regions. GATA binding motif (72bp downstream of chr7:23248026 and 26bp upstream of chr7: 23288026) and MEF2 binding motif (149bp downstream of chr7:23248026 and 32bp upstream of chr7:23288026) close to these two loci are predicted, which were also demonstrated in ChIP-seq data of some cell lines (no ChIP-seq data of GATA and MEF2 in monocytes were available).


A
Shift band
1: A probe
2: A probe + THP-1 nuclear extract
3: 2+ 200X unlabeled A probe
4: 2+ 200X unlabeled G probe
5: G probe
6: G probe + THP-1 nuclear extract
7: 5+200X unlabeled G ptobe
8: 5+200X unlabeled A ptobe
Probe: 120fmole
Unlabeled probe: 24pmole
Nuclear extract: 8ug
1 2 3 4 5 6 7 8
B
Luciferase reporter assay in THP-1
Relative luminescence
Backbone Promoter A G
C
Allele discrimination plot
Allele G
Allele A
Homozygous AA
Heterozygous AG
X Negative control
D
Expressions of other potential genes
gene mRNA/β-actin
AA
AG
STEAP1B FAM126A TOMM7 KLHL7 NUPL2 LOC541472 LOC100506178 SNORD93
E
GATA motif
PWMs(Log Odds)=10.13
MEF2 motif
PWMs(Log Odds)=11.98
chr7:23248026
chr7:23288026
GPNMB
ChIP-seq of MEF2A in SK-N-SH
ChIP-seq of GATA1 in K562
ChIP-seq of GATA1 in PBDE fetal
ChIP-seq of GATA1 in PBDE
ChIP-seq of GATA2 in K562
H3K4me1 in monocyte
H3K4me3 in monocyte
GATA motif
PWMs(Log Odds)=11.85
MEF2 motif
PWMs(Log Odds)=8.72

Supplementary Table 1. Primers used in RT-PCR

Gene	Forward primer	Reverse primer
Actin	GTCAGGCAGCTCGTAGCTCT	GCCATGTACGTTG- CTATCCA
GPNMB	CCTCGTGGGCTCAAATATAACAT	ACTGTCCTCTGACCATGCTGT
IL6	ACTCACCTCTTCAGAACGAATTG	CCATCTTTGGAAGGTTCAGG-TTG
STEAP1B	CCCTTCTACTGGGCACAATACA	GCATGGCAGGAATAGTATGCTTT
FAM126A	GTTGTGGAGGAATGGTTGTCA	GACAGGTTCTAGCAACTCACTTT
NUPL2	GCTTTGGATTGTCTGAGAACCC	CAAGCCTCAATTCCTCTGGTG
KLHL7	GTCAAGCGAGTAACACATCTTCT	AACCTGATCCTCTGCTCTCAC
TOMM7	CATTCGCTGGGGCTTTATCC	TCTGCACCCCTCTTAAATCCC
LOC541472	AAATTACTGAAGCCCACTTGGTT	ACTCTGCAAGATGCCACAAGG
LOC100506178	TGCAGAGCTGGTGGTCATAG	TTAGCGTGCACCAGAATGAG
SNORD93	ATCCTGGCCAAGGATGAGAACT	ATCCTGGCCTCAGGTAAATCCT

Supplementary Table 2. Primers used in 3C assay

Primer	BsrDI restriction site
P_C : TTCTCTGATTGTCCCCCTTGA P_R : CAGCATGTTTTGGGACATTG	chr7:22768898
P1: TTCTGTGGCTGGTTTTGGT P2: TTCCAGAGGTGGAGGCTTTA	chr7:23240228
P3: GGAAAAGGTTGCTTGATTGG P4: CAGGCTGTAGCCCCTAGTGA	chr7:23247996
P5: CTGGCGGTTGGTAAACTGA P6: GCTACTTGGGAGGCTGAGG	chr7:23255204
P7: GTCAGGCTGGTCTCGAACTG P8: AGAGCCTTTTACACCATTCCA	chr7:23254931
P9: TGGTGGTGTGTGCCTGTAGT P10: TTCATGTAATGTAAAGCGAATAATG	ch7:23282317
P11: CAGGAGAATGGCTTGAACCT P12: GACTCACTCCTTCTTGGCATCT	chr7:23286092
P13: GGTGGTGTGTGCCTGTAGT P14: TTCATGTAATGTAAAGCGAATAATG	chr7: 23288603
P15: GGTGAAGTCCCGTCCCTACT P16: GCTCATCAATGTGCCATTCT	chr7: 23297260

Primer pairs next to restriction sites were used to evaluate digestion efficiency (Pc and P_R, P1 and P2, P3 and P4, P5 and P6, P7 and P8, P9 and P10, P11 and P12, P13 and P14, P15 and P16). The constant primer (Pc) paired with P2, P4, P6, P8, P10, P12, P14, P16 were used in 3C analysis. The following primers in *GAPDH* were used in loading control assessment (F: ACAGTCCATGCCATCACTGCC, R: CCTGCTTCACCACCTTCTTG). Pc: constant primer.

Supplementary Table 3. Regulatory motifs altered on rs2069837

Position Weight Matrix ID (Library from Kheradpour and Kellis, 2013)	**Strand**	**Ref**	**Alt**	**Match on:** **Ref:** TAAGTATCTACTGTGTGCCAGGCACTTTAAATAAATATTGTGTCTAATCTTCAAAACAA **Alt:** TAAGTATCTACTGTGTGCCAGGCACTTTAGATAAATATTGTGTCTAATCTTCAAAACAA
Arid3a_2	+	11.6	6.1	NNNNTTRATYAAWHNHN
Arid5a	-	11.5	10.5	DNYHBHAATATTRB
Fox	-	16	12.4	WAARYAAAYAWWV
Foxa_known1	-	12.9	10.2	HWRWRYAAAYA
Foxa_known4	-	14.7	10.6	WRARYAAAYAWKNMV
Foxd3	-	12.8	8.5	RAAHMAAYAWWY
Foxf1	-	14.1	10.1	YRHAYAAACAHNB
Foxi1	-	11.6	7.4	WAWRYAAAYAHVH
Foxj1_1	-	11.9	-0	TAAACAAACAHWD
Foxj2_1	-	14.5	12.7	HHNHMRRYAAAYAHHNNW
Foxl1_1	-	14.8	13.8	DHDVHATAAAYAHDDN
HDAC2_disc2	+	11.9	10.4	WRRGYMAAYA
Hlx1	-	11.4	8.1	DRTAWTYAAWTADKD
Mef2_known5	+	6.9	-5	HSTGTTRCTAWAAATAGAWHMN
Nkx6-2	-	11.8	10.8	RWRDTAAWTABB
TATA_known1	+	12	9.1	NHDWWWTWWAWWWDRN
TATA_known3	+	10.8	11.3	KATAAATW

Ref: reference allele; Alt: alternative allele; values in the table are log-odds scores of position weight matrices (PWMs). S = C or G, W = A or T, R = A or G, Y = C or T, K = G or T, M = A or C, N = any base pair.

Supplementary Table 4. Predicted binding proteins in the rs2069837 locus using CIS-BP database

Name	Motif ID	Family	Sequence	From	To	Direction	Score Allele A	Score Allele G
ARID3	M0106_1.02	ARID/BRIGHT	AAATAAATA	7	15	R	8.04	-
FOXA	M6241_1.02	Forkhead	TAAATAAATA	6	15	F	14.932	13.313
FOXD	M6241_1.02	Forkhead	TAAATAAATA	6	15	F	14.932	13.313
FOXI	M6241_1.02	Forkhead	TAAATAAATA	6	15	F	14.932	13.313
FOXJ	M6241_1.02	Forkhead	TAAATAAATA	6	15	F	14.932	13.313
FOXL	M6241_1.02	Forkhead	TAAATAAATA	6	15	F	14.932	13.313
MEF2	M6340_1.02	MADS box	ACTTTAAATAAATA	2	15	F	10.525	-
GATA	M3314_1.02	GATA	TTTAGATAAATAT	4	16	F	-	8.627

F**:** forward; “From” and “to” mean the position of the sequence CACTTTAA/GATAAATAT which matched the corresponding motif; The “score” evaluates each position in the sequence with all PWMs, using a standard log odds scoring method (Nat Biotechnol. 2011;29(6):480-3.).

Supplementary Table 5. Binding proteins observed with mass spectrometry. The list is filtered to include only proteins detected using data included in Supplementary Tables 3 and 4 (See Methods).

Family/protein	Protein name	Coverage	Unique Peptides	MW [kDa]	PSMs (unlabeled)	PSMs (Mutated)	PSMs (Allele A)	PSMs (Allele G)
ARID	Arid3A	25.29	6	62.9	1	1	7	5
	Arid3B	19.25	8	60.6	1	3	9	5
Fox	FOXJ3	20.25	7	68.9	2	6	10	5
	FOXA1	46.39	9	49.1	0	8	16	12
MEF2	MEF2A	7.49	1	54.8	0	0	**3**	**0**
	MEF2C	7.61	1	51.2	0	0	**3**	**0**
	MEF2D	8.06	2	55.9	0	0	**4**	**0**
GATA	GATA1	26.92	6	42.7	1	4	**2**	**8**
	GATA2	27.39	8	50	2	3	**2**	**12**
TAF	TAF1	4.64	7	212.5	1	5	1	3
	TAF4	14.74	8	110	2	7	3	4
HDAC	HDAC2	56.35	14	55.3	2	19	19	15
	HDAC5	25.70	6	121.9	0	4	**3**	**0**
	HDAC7	61.61	14	102.9	4	20	19	20

PSMs: peptide spectrum matches; MW: molecular weight; ARID: AT-rich interaction domain containing (ARID) family; Fox: forkhead box family; MEF2: myocyte enhancer factor-2; TAF: TATA box binding protein associated factor; HDAC: Histone deacetylase.

Supplementary Table 6. Binding proteins detected by mass spectrometry that also participate in chromatin looping

Family/protein	Protein name	Coverage	Unique Peptides	MW [kDa]	PSMs (unlabeled)	PSMs (Mutated)	PSMs (Allele A)	PSMs (Allele G)
CTCF	CTCF	41.67	22	82.7	3	16	12	11
Cohesin complex	SMC1A	62.53	81	143.1	2	66	52	66
	SMC3	61.54	79	141.5	4	63	61	64
	RAD21	63.07	30	71.6	2	20	15	26
	STAG1	14.78	10	144.3	3	7	8	6
	STAG2	39.88	30	141.2	5	23	25	19

PSMs: peptide spectrum matches; MW: molecular weight; CTCF: CCCTC-binding factor.

Supplementary Table 7. Annotation analysis of the genes interacting with rs2069837 using DNase hypersensitivity data

Category	Term	Count	%	P-Value	Genes
GOTERM_BP_DIRECT	GO:0045765~regulation of angiogenesis	2	16.6	0.015	*IL6, GPNMB*
GOTERM_BP_DIRECT	GO:1901215~negative regulation of neuron death	2	16.6	0.018	*IL6, GPNMB*
GOTERM_BP_DIRECT	GO:0070374~positive regulation of ERK1 and ERK2 cascade	2	16.6	0.080	*IL6, GPNMB*
GOTERM_MF_DIRECT	GO:0005515~protein binding	8	66.6	0.045	*KLHL7, IL6, TOMM7, MALSU1, IGF2BP3, NUPL2, GPNMB, FAM126A*

Supplementary Table 8. Demographic information of the healthy subjects using in this study

Sample	Gender	Ethnicity	Age	Genotype of rs2069837
1	Female	Hispanic	22	AA
3	Female	Caucasian	22	AA
4	Male	Caucasian	23	AA
5	Female	Caucasian	25	AA
6	Female	Caucasian	52	AA
7	Female	Caucasian	53	AA
2	Female	Caucasian	64	AA
8	Female	Hispanic	20	AG
9	Female	Caucasian	22	AG
10	Male	N/A	22	AG
11	Female	Caucasian	25	AG
12	Female	Caucasian	54	AG
13	Female	Caucasian	56	AG
14	Female	Caucasian	64	AG