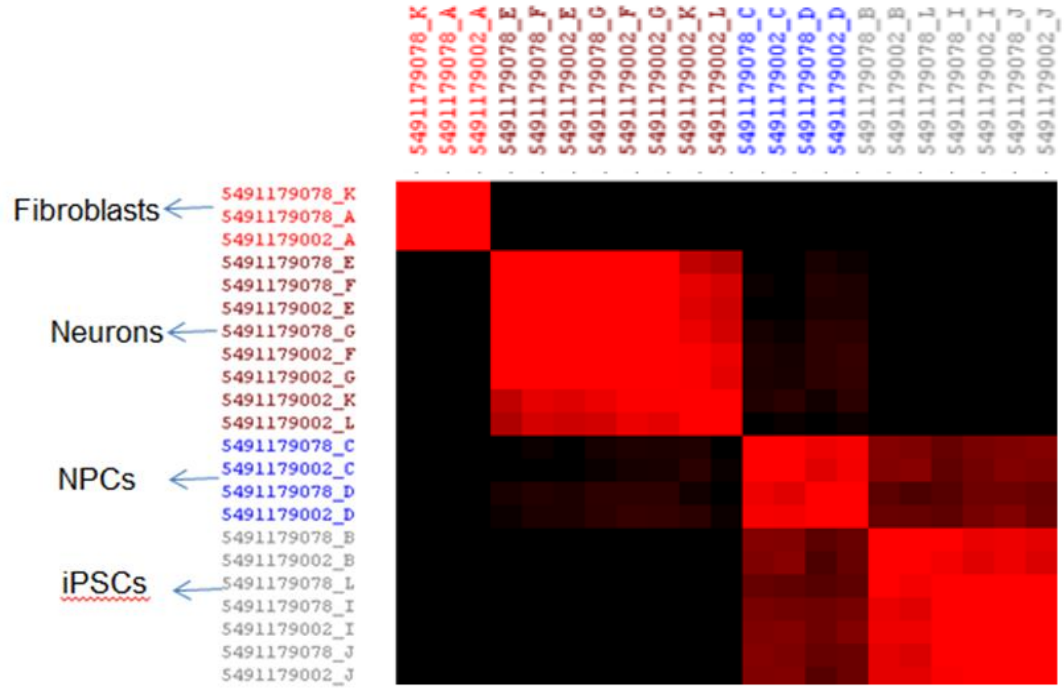
Sodium valproate rescues expression of *TRANK1* in iPSC-derived neural cells that carry a genetic variant associated with serious mental illness

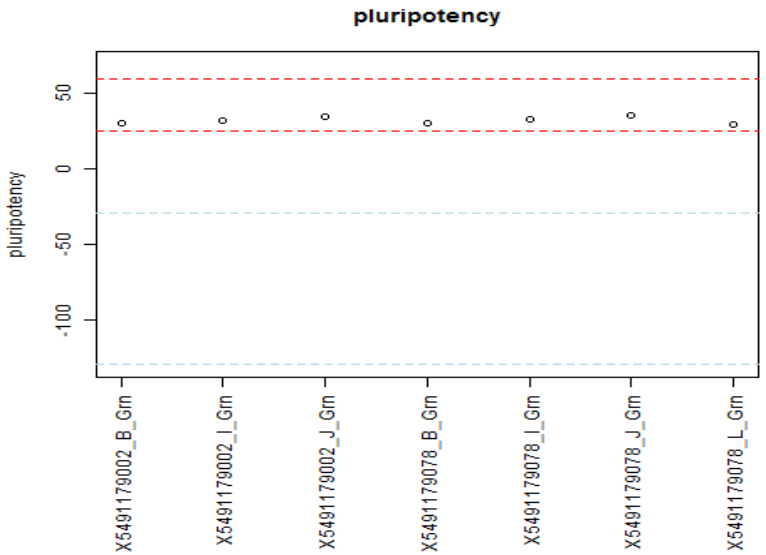
Jiang et al.

Supplementary figures: S1 to S10, tables: S1-S8

a



b



c

Analyzed Files

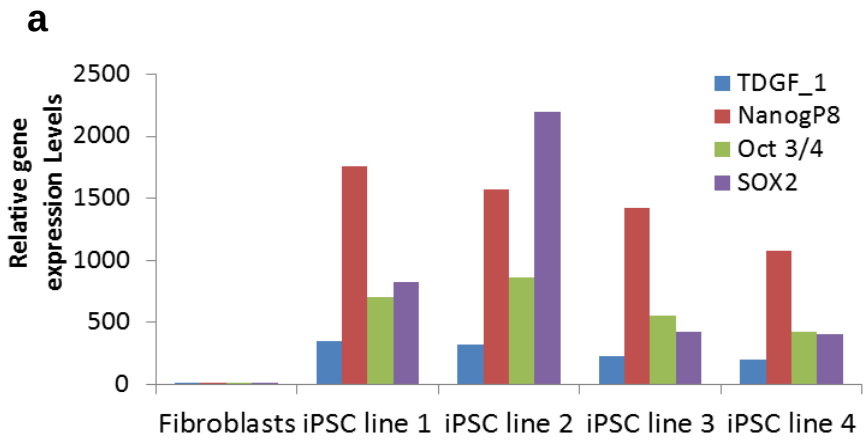
File Name	Pluri Raw	Pluri Logit P	Novelty	Novelty Logit P	PluriTest Result
X5491179002_B_Grn	30.158	1	1.452	0.016	Pass
X5491179002_I_Grn	32.439	1	1.136	0.001	Pass
X5491179002_J_Grn	34.704	1	1.207	0.001	Pass
X5491179078_B_Grn	30.437	1	1.426	0.012	Pass
X5491179078_I_Grn	33.069	1	1.196	0.001	Pass
X5491179078_J_Grn	35.941	1	1.198	0.001	Pass
X5491179078_L_Grn	29.33	1	1.478	0.02	Pass

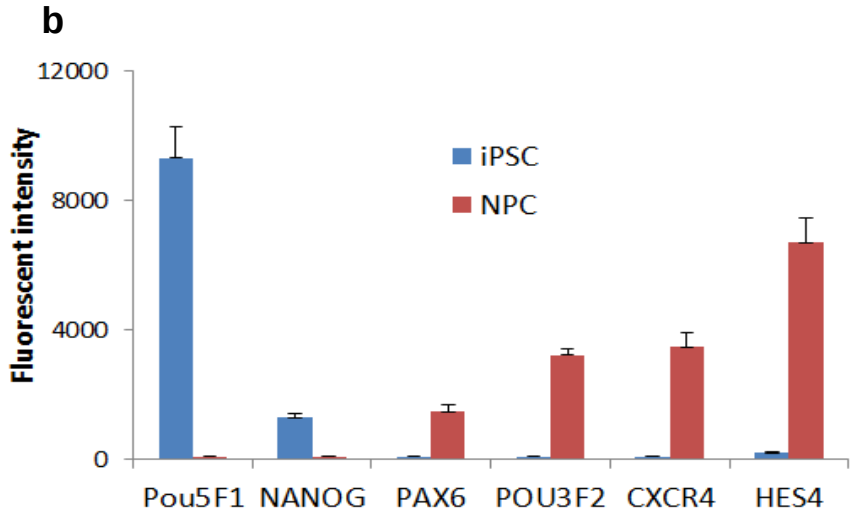
Figure S1. Multidimensional data model for assessing iPSCs and their neuronal derivatives. a, Principal component analysis of fibroblasts (3 samples in red), iPSC(7 samples in gray) and their neural derivatives NPCs (4 samples in blue) and neurons (8 samples in purple). **b**, **c**, Model-Based Multi Class Pluripotency Score (PluriTest). **b**, The lines in the plot indicated empirically determined thresholds for defining normal pluripotent lines. Score above blue lines indicate those scores that we have observed in approximately 95 percent of the pluripotent cells. All 7 iPSC lines in this chip were all above blue line. **c**, Pluripotency analyses data showed all 7 iPSC lines in this chip passed PluriTest with P<0.05

Global gene expression profiles demonstrated that fibroblasts, iPSCs, iPSC-derived neural progenitor cells (NPC), and neurons formed distinct clusters, as expected (Figure S2A). All studied iPSC lines exhibited gene expression profiles typical of pluripotent stem cells (Figure S2B, Figure S2C).

Key

Samples	Sample ID
5491179002_A	GM23476
5491179002_B	GM23240
5491179002_C	CN4
5491179002_D	CN5
5491179002_E	GM05990_6weeks
5491179002_F	NL1_6weeks
5491179002_G	GM05990_3weeks
5491179002_H	NL1_3weeks
5491179002_I	CN1
5491179002_J	CN2
5491179002_K	GM05990_3weeks
5491179002_L	NL1_3weeks
5491179078_A	10593
5491179078_B	GM05990
5491179078_C	GM23476
5491179078_D	GM23240
5491179078_E	GM23476_6weeks
5491179078_F	GM23240_6weeks
5491179078_G	GM23476_3weeks
5491179078_H	GM23240_3weeks
5491179078_I	CN4
5491179078_J	CN5
5491179078_K	GM05990
5491179078_L	Cell stage





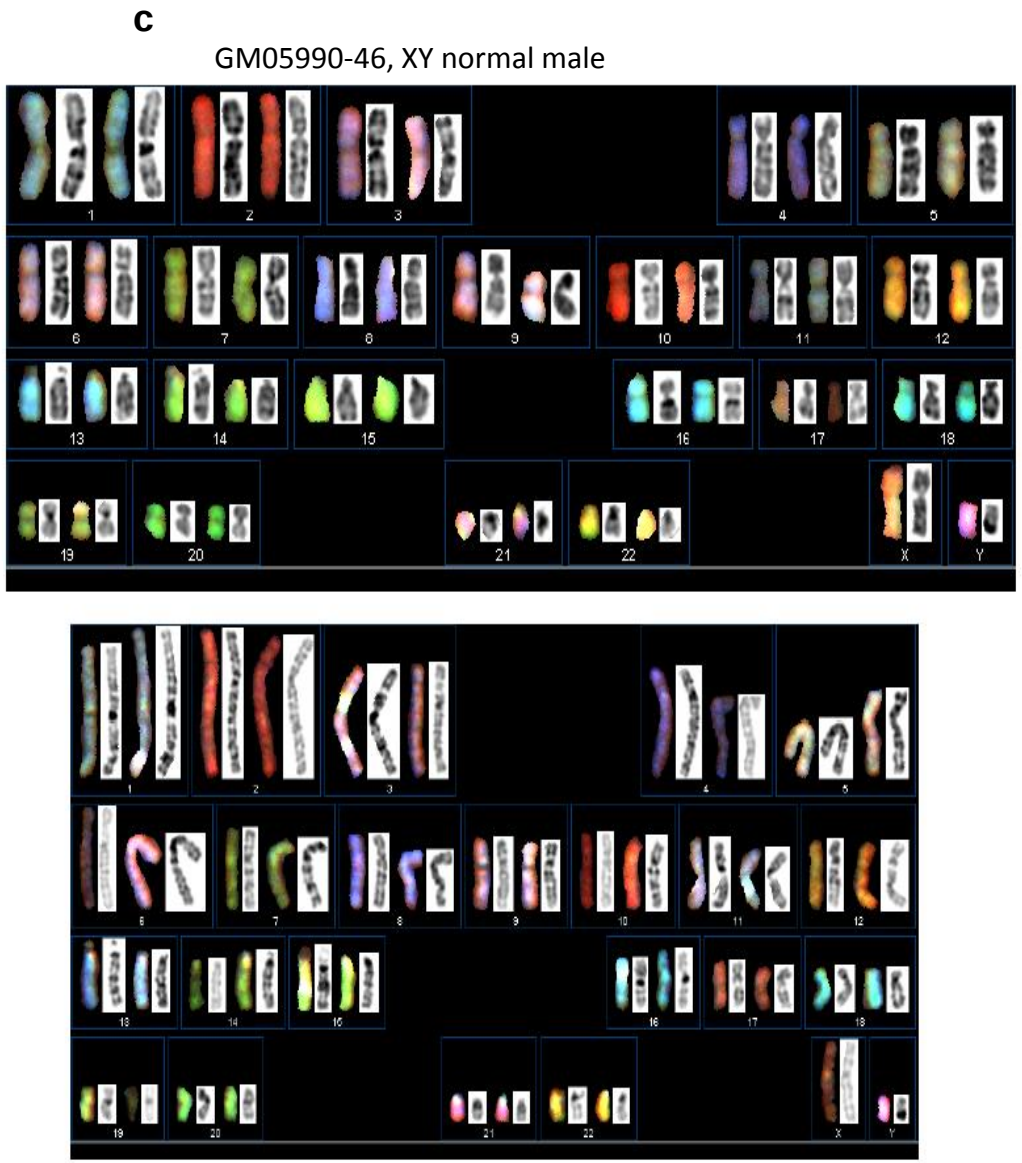
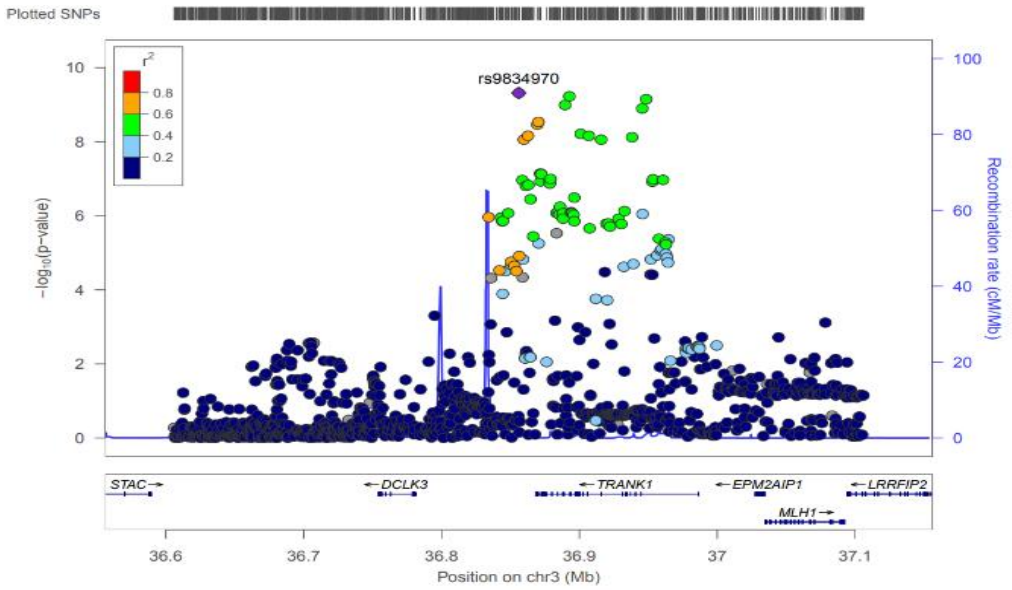


Figure S2. a, qRT-PCR analysis of gene expression on selected pluripotency markers (TDGF-1, OCT4, Nanog and Sox2) in fibroblasts and iPSC lines. **b**, Comparison analysis of gene expression of the selected pluripotency and NPC markers in iPSC and NPC lines from gene expression microarray. **c**, Chromosome-specific fluorescence in-situ hybridization showed that iPSC lines maintained the normal human karyotype.
Real-time polymerase chain reaction (RT-PCR) assays in all iPSC lines demonstrated 100- to 2000-fold increased expression of pluripotency markers relative to the original fibroblasts (Figure S3A). All iPSC lines maintained a normal human karyotype (Figure S3B).
To confirm a neural lineage of NPC lines, quantitative real time-PCR (qRT–PCR) analysis was carried out for several established NPC marker genes. As expected, the pluripotency-associated genes *NANOG* and *POU5F1* (encoding OCT4) were down-regulated in NPCs, while *PAX6* and *POU3F2, CXCR4, HES4* were markedly upregulated (Figure S2C).

Unconditional



Conditional on rs9834970

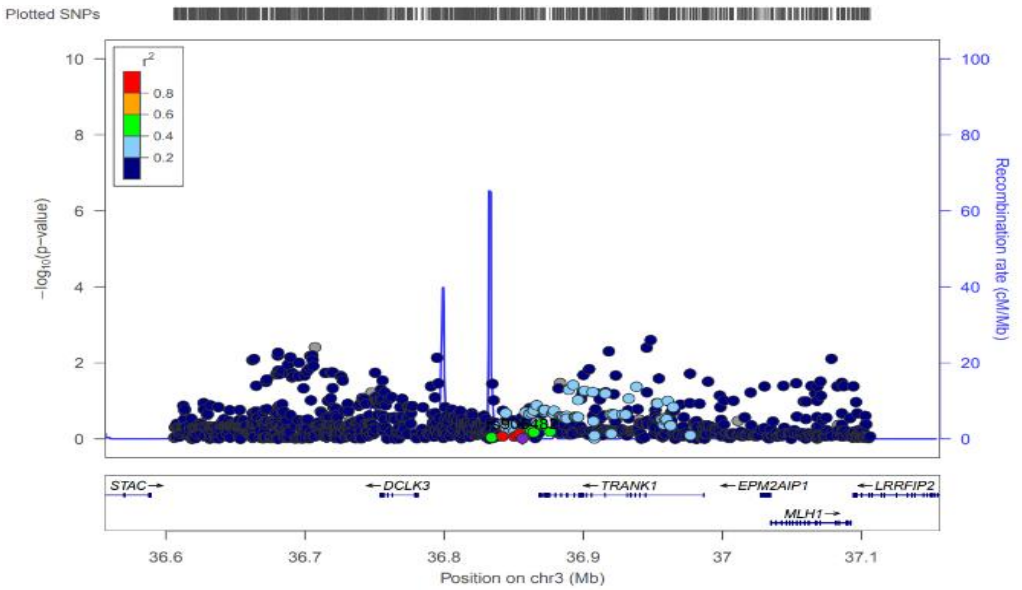


Figure S3. Conditional analysis of genetic association signals in the TRANK1 locus. Unconditional analysis performed in a large case-control sample (Hou et al 2017) supports genome-wide significant association with bipolar disorder.
As expected, rs9834970 yielded the most significant result (p=4.83E-10, n=25,877). Analysis was then repeated using the approximate conditional analysis method implemented in GCTA. https://www.ncbi.nlm.nih.gov/pubmed/22426310.
The results show no significant association between bipolar disorder and any remaining SNPs in the region. This demonstrates that rs9834970, or SNPs in very strong linkage disequilibrium with it, fully accounts for the
association signal at this locus. Graphical representations were generated using LocusZoom (LocusZoom: regional visualization of genome-wide association scan results R.J. Pruim, R.P. Welch, et al., Bioinformatics (2010)

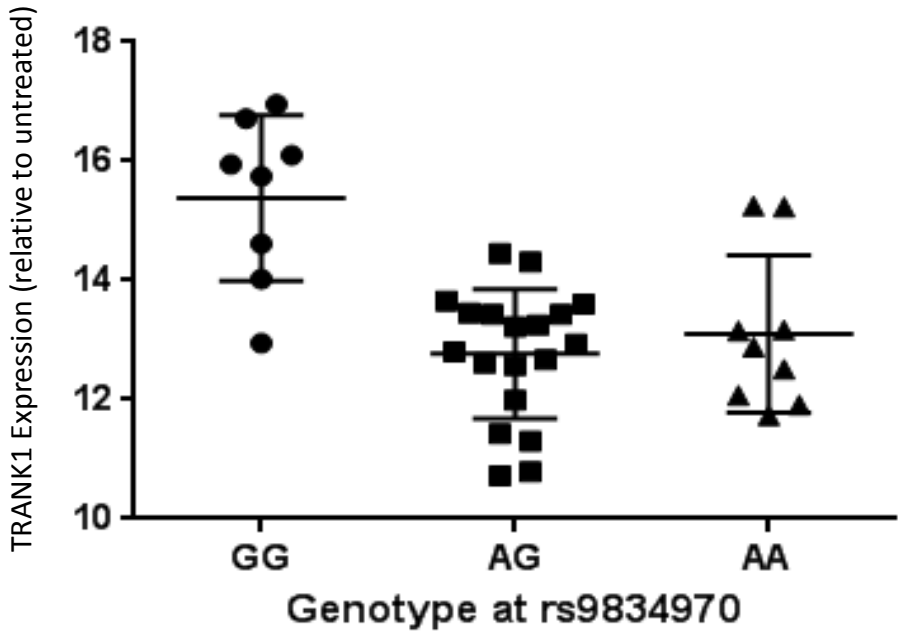


Figure S4. Genotypic effects of rs9834970 on *TRANK1* gene expression at baseline in iPSC, the results were seen in iPSCs, where homozygous risk-allele carriers (GG genotype) showed significantly lower baseline *TRANK1* expression than AA homozygotes ($p<0.0001$).

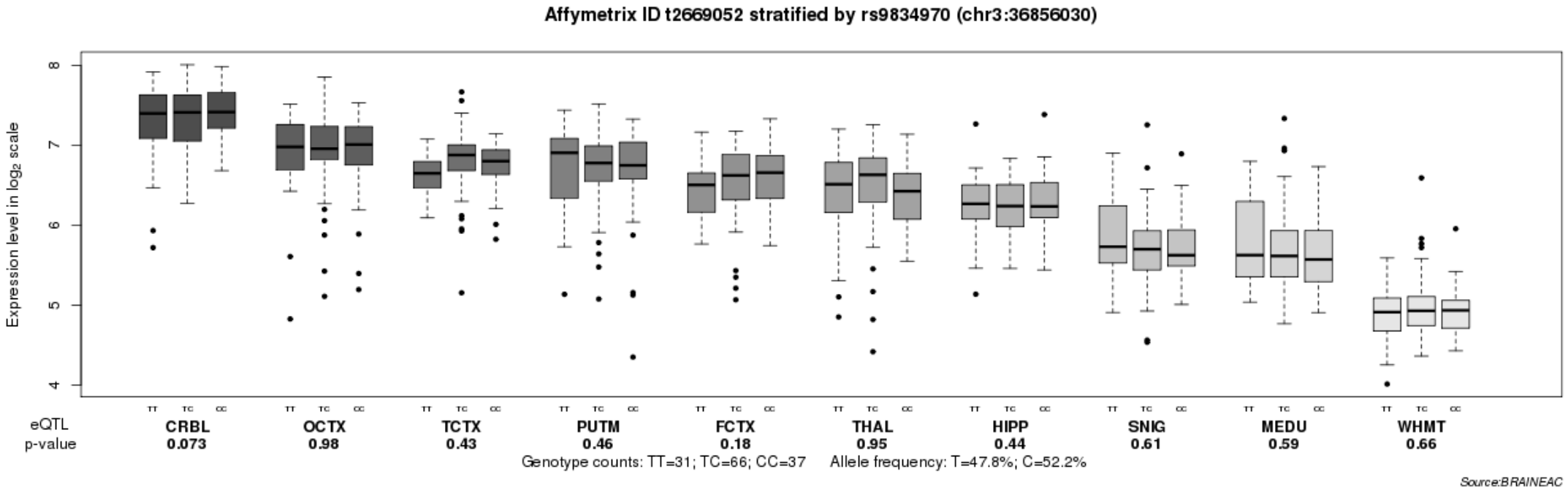


Figure S5. TRANK1 expression (Winsorized mean over probe sets) in 10 postmortem human brain regions, stratified by genotype at rs9834970. Source: www.braineac.org. These results suggest that rs9834970 either does not affect expression of *TRANK1* in mature brain tissue or exerts cell-type specific effects that cannot be easily detected in heterogeneous brain tissues.

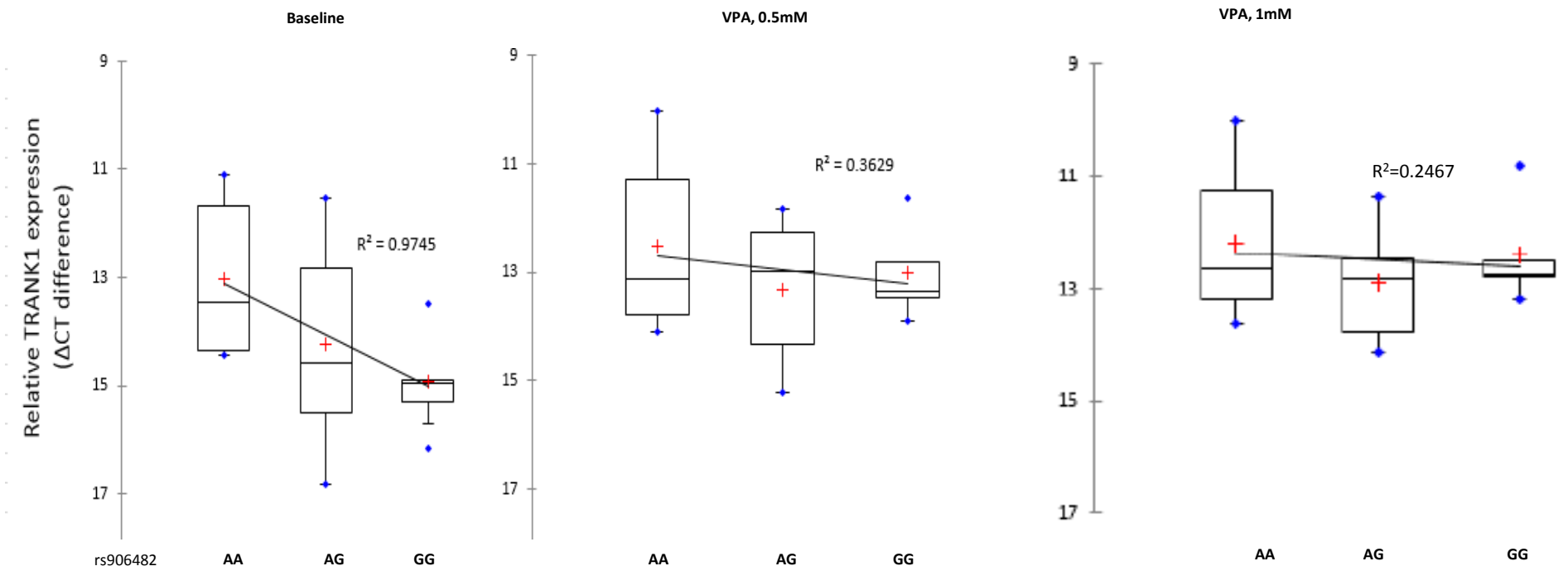


Figure S6. Genotypic effects of rs906482 on *TRANK1* gene expression in NPCs at baseline and after 72 h of VPA treatment. Cell lines carring the risk allele (AG or GG genotype at rs906482) showed significantly lower baseline TRANK1 expression than AA. VPA also rescued *TRANK1* expression in carriers of the G-allele at rs906842. Values are expressed as mean relative ΔCT difference ± S.E.M. Comparisons: baseline, GG vs AA, $p<0.0001$; baseline, GG vs AG, $p<0.05$; baseline, GG vs VPA 0.5 mM, GG, $p<0.05$; baseline GG vs VPA 1 mM, GG, $p<0.01$. n =3 for GG carries; n = 3 for AA carries; n =5 for AG carries.

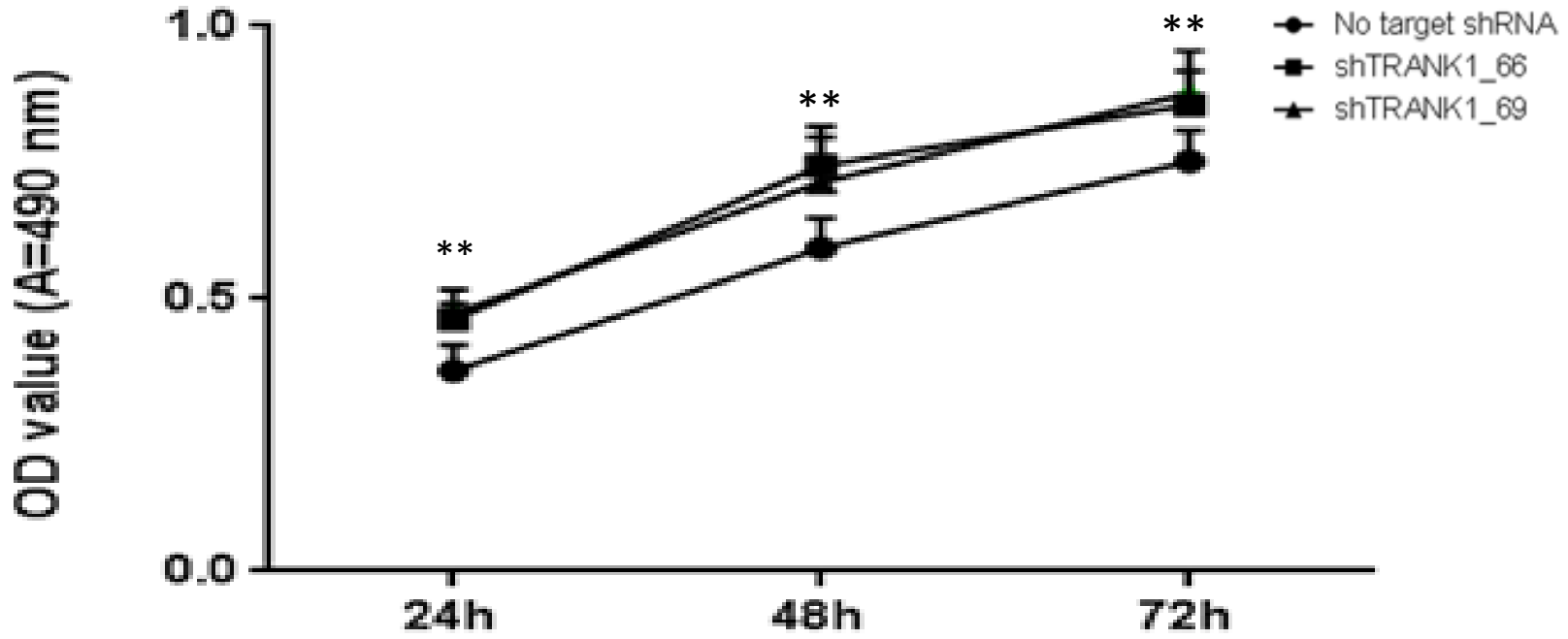


Figure S7 Knockdown of *TRANK1* promoted growthmand proliferation of HeLa cells
To study the effect of *TRANK1* knockdown on the proliferation of HeLa cells, growth curves of cells in the no target shRNA control, shRNA TRANK1 _66, and shRNA TRANK1_69 were determined by using the MTT assay. After the expression of *TRANK1* was inhibited, cell proliferation was significantly increased in the knockdown lines within 2 or 3 days compared with that in the no-target scramble control group. **p<0.001

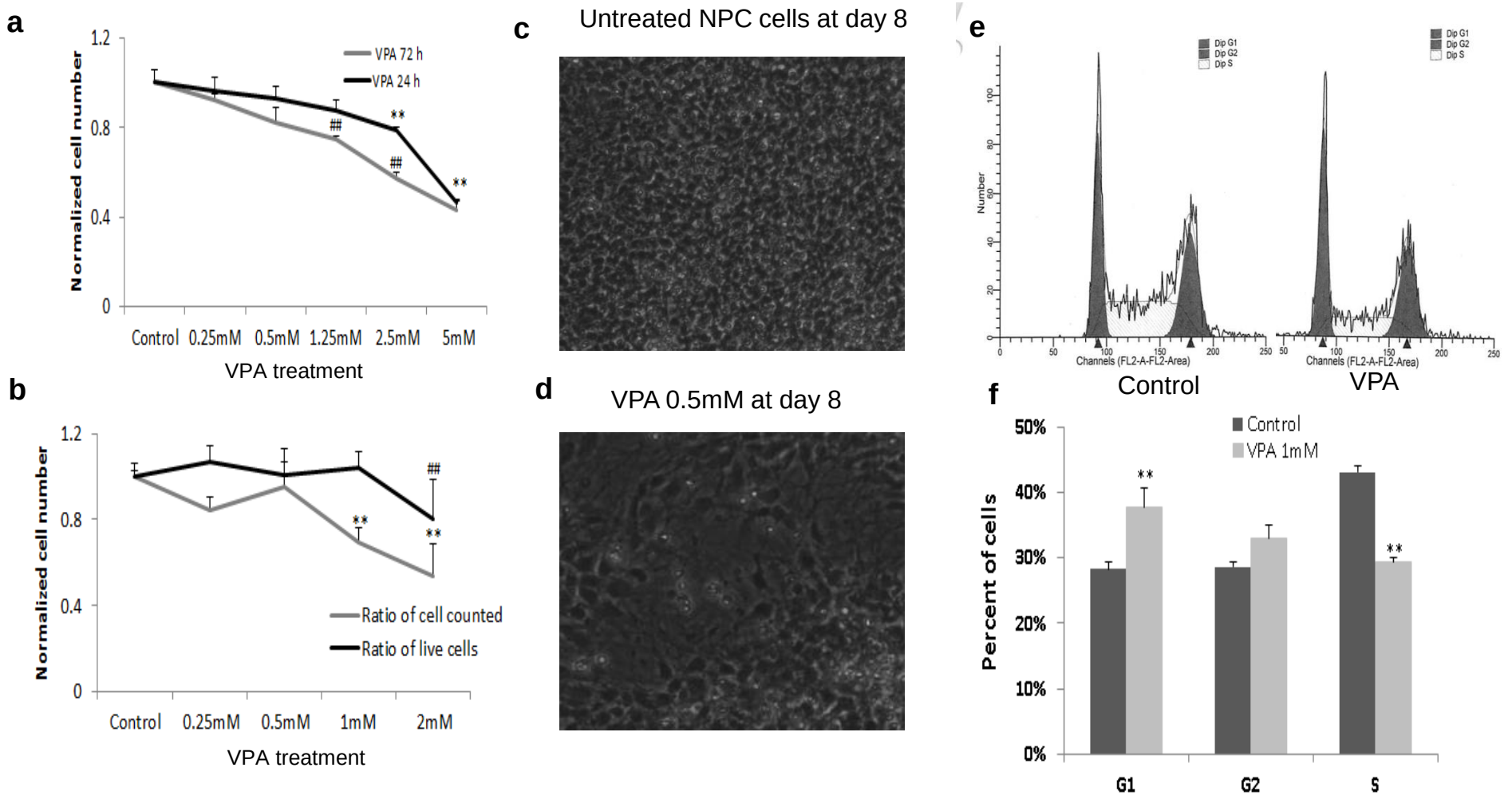


Figure S8. Effects of VPA on cell cycle, proliferation, and death in iPSC derived neural progenitor cells. **a-b**, NPC cells were treated with VPA (0, 0.25, 0.5, 1, 2mM) for 72 hours, a, Dose dependent effects of VPA on cell numbers after 72h treatment. b, Fractions of surviving cells were counted for each condition. Representative phase-contrast images (10x) of NPC cells after eight days of culture in 6-well plates in NPC expansion medium. **c**, Untreated control. **d**, After seven days of treatment with 0.5 mM VPA, NPCs were plated at low density. Cell density was significant lower in the VPA-treated than the untreated group, suggesting that VPA inhibits cell proliferation. Neural progenitor cells were treated with 1 mM VPA for 24 hours, then harvested, fixed, and stained with propidium iodide before analysis by flow cytometry. **e**, Typical flow cytometric patterns for control and VPA-treated cells. **f**, The graph shows the percentage of G1, G2, and S phase cells between untreated and VPA treated cells. Treatment with VPA did not increase cell death, but increase the fraction of cells in G1 and G2 and significantly reduced S phase cells. The graph shows changes in the cell cycle distribution as assessed by DNA flow cytometric analysis.

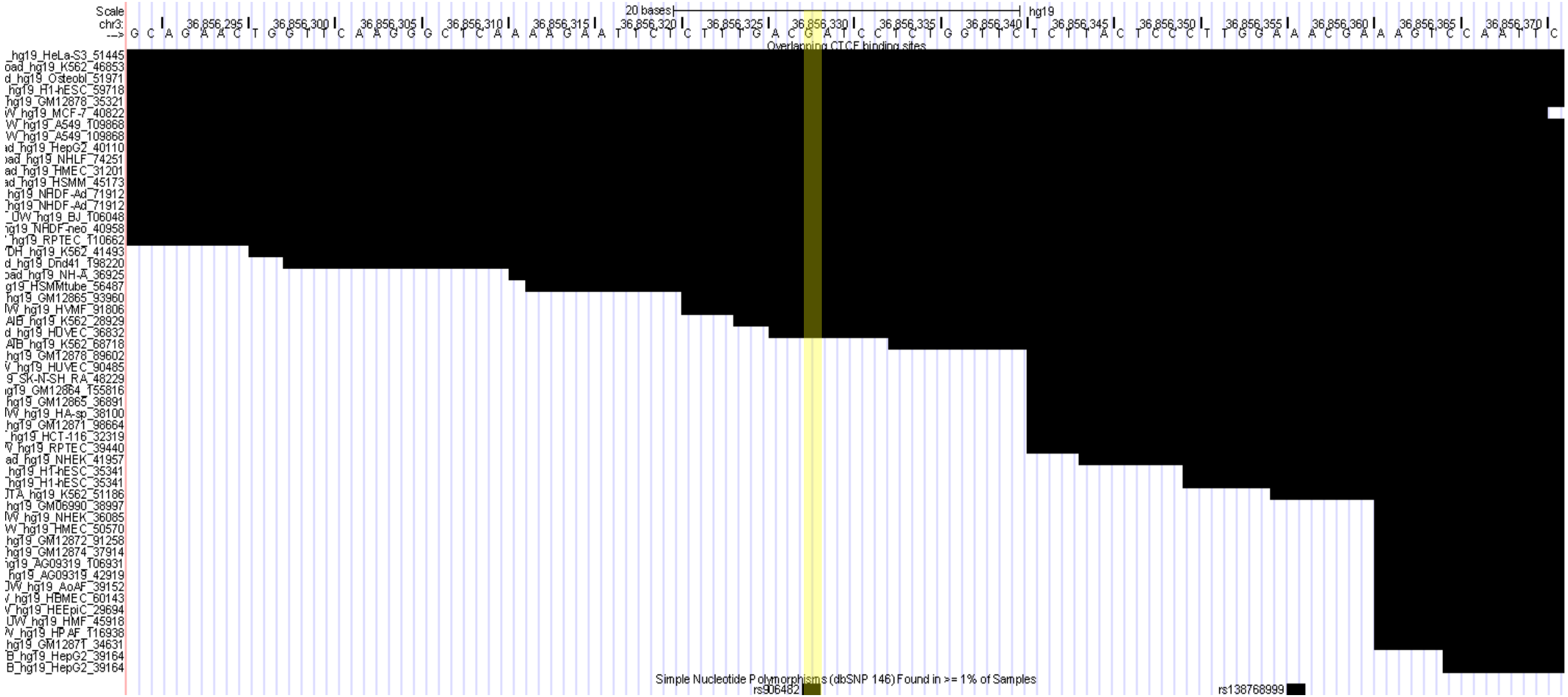


Figure S9. CTCF binding sites overlapping rs906482. Binding sites were experimentally verified by ChipSeq in various cell lines. ENCODE data was summarized by (http://insulatordb.uthsc.edu), and depicted in UCSC Human Genome Browser (hg19).

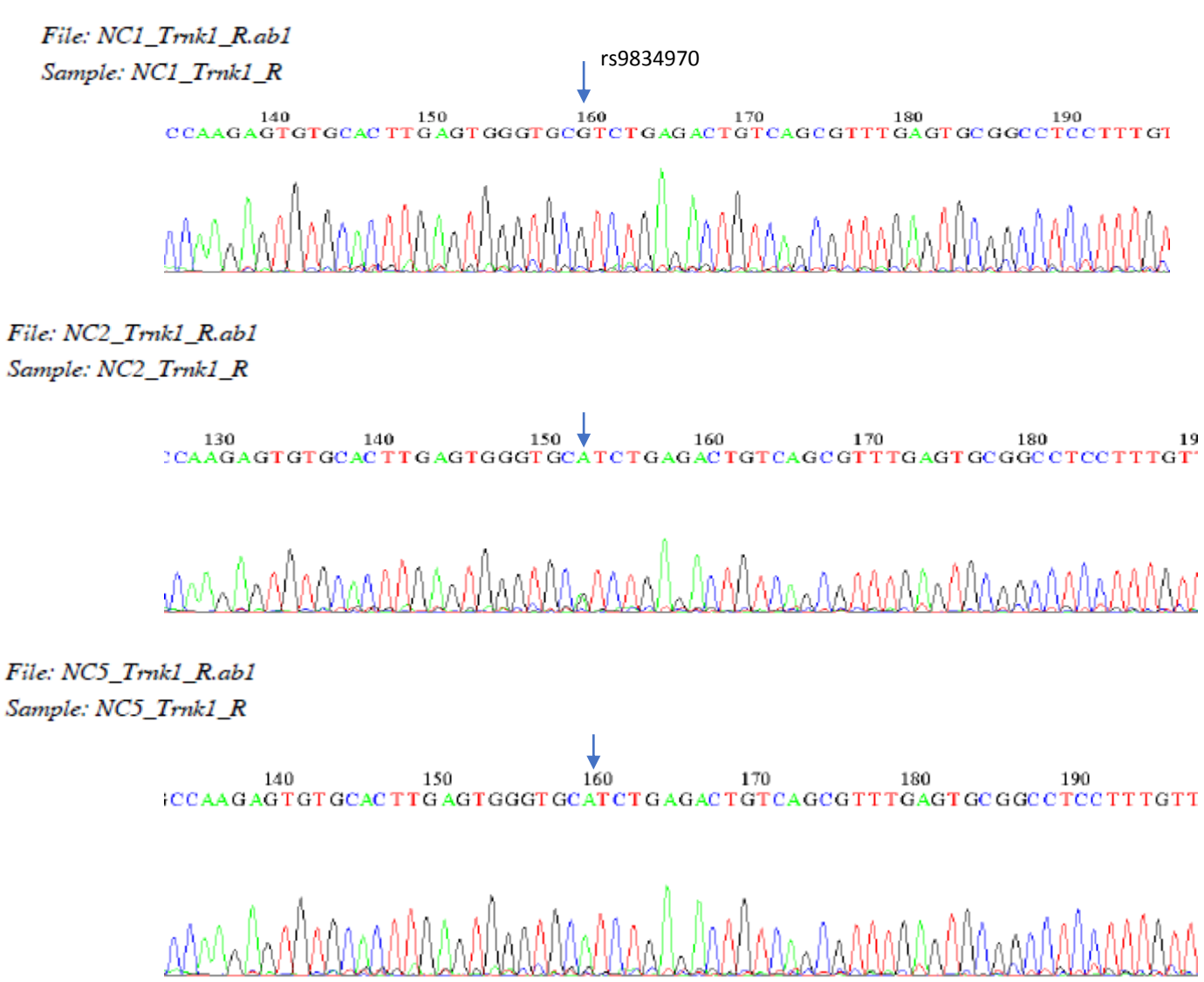


Figure S10. Representative Sanger sequences flanking rs9834970 in DNA from NPC lines with known genotypes AA, GG, and AG. 400 bp flanking rs9834970 was Sanger-sequenced at Macrogen. All samples showed the expected genotypes at rs9834970. No additional variants were detected.

Table S1 . Genes identified as significantly differentially expressed (P<0.05) with >1.75 fold change in TRANK1 shRNA knockdown HeLa cells vs no target control cells.

Symbol	Fold change	Symbol	Fold change	Symbol	Fold change
ANKRD1	6.63	SPINT2	2.03	LOC1001331	1.76
GDF15	4.79	PTHLH	2.03	SPANXA2	1.76
ALPK2	4.60	GPNMB	2.02	STS-1	1.76
OLR1	4.22	LOC643031	2.02	C5orf46	1.76
SERPINE1	4.22	F2R	2.01	SEMA3C	1.75
CPA4	4.11	BDKRB1	2.01	TIMP3	1.75
DKK1	4.11	PFKFB4	1.98	KRT13	1.75
ACTG2	3.86	C9orf169	1.98	EPHA2	1.75
F3	3.83	LEPREL1	1.98	PSMB8	-1.75
F3	3.68	TNNC1	1.98	FAM89A	-1.75
MFAP5	3.37	PTHLH	1.97	SOX18	-1.76
ARHGDIB	3.13	SH3KBP1	1.97	HCP5	-1.76
IL7R	3.05	SERPINB7	1.97	ADAMTS8	-1.76
PTGES	2.97	KRT17P3	1.97	CNTNAP1	-1.77
IL7R	2.96	PSG4	1.97	SOBP	-1.77
NRG1	2.80	DAAM1	1.97	LOC728635	-1.78
BMP4	2.77	S100P	1.97	C14orf147	-1.78
CLIC3	2.74	FAM176A	1.95	CDC42EP4	-1.79
TUFT1	2.74	ANTXR2	1.93	CD83	-1.79
UTS2	2.67	JAG1	1.93	C14orf142	-1.79
NTN4	2.65	PLAC8	1.93	B3GNT1	-1.79
GLS	2.61	EMP1	1.91	DYNLT3	-1.80
NT5E	2.60	LBH	1.90	CA12	-1.80
NGF	2.59	ARID3A	1.90	TNFSF10	-1.80
KRT14	2.56	LOC651397	1.90	FAM89A	-1.82
TNFSF9	2.55	BIRC3	1.89	GAL	-1.82
PRAGMIN	2.53	ACTA2	1.89	SMARCA4	-1.83
THBS1	2.49	MEGF6	1.89	DAPL1	-1.83
CLDN1	2.47	SCG5	1.89	SCD	-1.83
CNN1	2.42	PHLDB2	1.89	LPCAT3	-1.84
GPRC5A	2.42	NEXN	1.87	CCL2	-1.84
LOC10012	2.41	C1orf133	1.87	CD74	-1.86
LOC65051	2.37	TPM2	1.86	BACE2	-1.86
TMEM166	2.35	RIPK4	1.86	PDX1	-1.88
42067	2.34	FLNB	1.86	CYP27B1	-1.90
TGFA	2.31	DKFZp761P0	1.86	HLA-F	-1.91
CDKN1A	2.30	FNDC3B	1.86	NR4A2	-1.91
SLCO2A1	2.29	LOC652683	1.85	TAP1	-1.91
FOLR1	2.29	CCND1	1.85	IGFBP5	-1.95
LOC64555	2.28	PDE2A	1.84	KCNG1	-1.95

DCN	2.26	TMEM156	1.84	IGFBP5	-1.95
CRYAB	2.25	TPM1	1.83	INSIG1	-1.96
MFGE8	2.24	ZDHHC11	1.83	HLA-H	-1.96
TGFA	2.23	HIST1H4H	1.83	NR4A2	-1.96
PDGFC	2.21	DCBLD1	1.83	KCNIP3	-1.98
ELFN2	2.20	SC5DL	1.82	RHBDL3	-1.98
IL11	2.19	PRKAG2	1.82	LMNB1	-1.99
AFAP1L2	2.18	TEK	1.82	LPIN1	-2.02
PLAC8	2.17	AKR1B10	1.82	OAF	-2.05
MOBKL2B	2.16	FTH1	1.82	PCSK9	-2.06
PHLDB2	2.16	C9orf3	1.81	IFIT2	-2.06
LOC64476(	2.16	KRT80	1.81	HLA-A29.1	-2.09
CDA	2.16	LOC653110	1.81	TPR	-2.17
TRQ1	2.16	OPTN	1.81	COL15A1	-2.17
IGFBP3	2.14	ITGA5	1.80	OASL	-2.18
GPR1	2.12	CAV1	1.80	SREBF1	-2.20
CACNG6	2.12	TBC1D2	1.80	TMOD1	-2.25
SYT11	2.11	KRT80	1.80	TCN1	-2.27
SLC35F3	2.11	SH3KBP1	1.79	PSMB8	-2.27
ENC1	2.11	GPR64	1.79	IFITM1	-2.34
FOLR1	2.10	FAM176A	1.79	FOS	-2.37
UTS2	2.10	TGFBR2	1.79	HLA-B	-2.38
	2.09	AADACL1	1.79	PSMB8	-2.39
KRT16	2.09	GLIPR1	1.78	NR2F1	-2.40
SUSD2	2.08	RASGRP1	1.78	FOSB	-2.40
IGFBP3	2.07	FRMD6	1.78	SREBF1	-2.43
CAV1	2.07	YIPF5	1.78	ECEL1	-2.56
CDK6	2.07	ABLIM3	1.77	NEU4	-2.75
EDN1	2.04	SPANXB2	1.77	PCOLCE	-2.79
LUM	2.03	LOC442597	1.77	C13orf15	-3.00
CD70	2.03	FAM133A	1.77	CA9	-3.28
		HDAC1	1.76	MIR1974	-3.79

Table S2. Gene enrichment analysis of genes differentially expressed after *TRANK1* shRNA knockdown in HeLa cells.

GO ACCESSION	GO Term	p-value	corrected p-value	Gene Counts
GO:0005576	extracellular region	1.19E-08	1.85E-04	43
GO:0005102	receptor binding	8.38E-08	6.54E-04	25
GO:0050896	response to stimulus	5.10E-07	0.001989609	77
GO:0032502	developmental process	4.06E-07	0.001989609	49
GO:0042127	regulation of cell proliferation	9.64E-07	0.003011155	19
GO:0023052	signaling	2.98E-06	0.006652566	63
GO:0048856	anatomical structure development	4.64E-06	0.008177349	39
GO:0002376	immune system process	4.71E-06	0.008177349	23
GO:0007275	multicellular organismal development	6.55E-06	0.009181970	43
GO:0032879	regulation of localization	6.10E-06	0.009181970	17
GO:0048731	system development	8.11E-06	0.009744492	35

Table S3 . Genes identified as significantly differentially expressed (P<0.05) w fold change in 0.5 mM VPA treatment for 72 h in neural progenitor cells

Symbol	Fold change	Symbol	Fold change	Symbol	Fold change
Sep3/	-1.65	H2AFJ	1.60	OKL38	-1.97
Sep3/	-1.75	HERPUD1	-1.53	OLFML2A	-3.03
ACCN2	-2.31	HERPUD1	-1.66	OSBPL10	-1.78
ACLY	-1.67	HIST1H2BD	1.71	PAG1	-1.51
ACSL4	-1.58	HLA-A	1.52	PAK2	-1.51
ACSS2	-1.51	HLA-B	1.71	PARM1	-1.59
ACSS2	-1.52	HNRNPA2B1	-1.56	PIK4CA	-1.59
ADAM11	-2.10	HOMER2	-1.53	PLCG1	-1.52
AFAP1	-1.57	HSPA12A	-1.88	PLEKHA4	-1.68
AGRN	-1.55	IARS	-1.53	PLP1	-1.52
ALCAM	-1.95	ID2	1.67	PMP22	-1.50
ANK2	-1.60	IDI1	-1.59	PPFIBP2	1.53
ARAP3	1.62	IFI6	2.03	PPP1R15A	-1.50
ASAP1	-1.53	IFI6	1.89	PREX1	-1.54
ASNS	-1.71	INA	-1.74	PRKCA	-1.63
ASNS	-1.85	INHBE	-2.00	PRRG1	-1.59
ATF4	-1.55	INSM1	-1.83	PRRX1	1.78
ATP6V1G2	-1.67	ISL1	-1.65	PTBP2	-1.50
ATP9A	-1.60	ITFG2	-1.50	PTMA	-1.85
BMP7	1.89	ITGB5	1.60	PTPRD	-1.56
BRSK2	-1.62	JAG2	-1.50	RAB6A	-1.59
BSN	-1.53	KCNQ2	-1.58	RAB6B	-1.67
C12orf51	-1.60	KIAA0182	-1.51	RAPGEF6	-1.60
C14orf132	-1.70	KIAA0363	-1.58	RBP1	-1.55
C17orf96	1.52	KIAA1211	-1.55	RCAN1	-1.55
C7orf16	-1.63	KIF1A	-1.62	REC8	2.09
C9orf171	1.61	KIF21A	-1.59	REC8	1.63
CACNA1H	-1.51	KLHL35	-1.76	REEP1	-1.81
CACNA2D2	-1.53	LCOR	-1.60	RGMB	-1.54
CASP3	-1.59	LCOR	-1.68	RHBDL3	-1.80
CDC2L2	1.51	LGALS1	1.95	RIMS3	-1.61
CDKN1A	-1.74	LMO3	1.52	RNU1-3	-1.85
CDKN2D	-1.83	LOC10012806	-1.56	RNU1-5	-1.76
CDO1	-1.52	LOC10012806	-1.64	RNU1A3	-1.85
CDO1	-1.55	LOC10012825	-1.50	RNU1G2	-1.71
CEBPB	-1.87	LOC10012902	-1.56	RNU4ATAC	-1.71
CENTA1	-1.75	LOC10012965	-1.52	RPLP1	-1.55
CHGB	-1.59	LOC10013120	-1.53	RTN1	-1.91
CHRNA3	-1.61	LOC10013213	-1.61	RTN1	-2.15
CLASP2	-1.66	LOC10013229	-1.56	RTN4	-1.87
CLEC2D	1.83	LOC10013356	1.57	RUFY3	-1.80

CNTN2	-1.76	LOC143543	-1.61	SCG2	-1.51
CNTNAP1	-1.59	LOC148430	-1.91	SCRN1	1.63
CNTNAP3B	1.52	LOC157627	-1.85	SEL1L3	1.65
COL4A6	2.01	LOC387763	-1.80	SESN1	-1.53
COL6A2	1.79	LOC389342	-1.51	SFRP2	1.62
CORO1C	-1.63	LOC392285	-1.50	SH3PXD2A	-1.53
CREB5	-1.58	LOC401720	-1.51	SILV	-1.58
CRYZ	2.11	LOC440063	-2.49	SLC15A3	-1.52
CYP51A1	-1.50	LOC441506	-1.50	SLC15A4	-1.64
CYR61	1.65	LOC441763	1.82	SLC7A5	-1.91
DACH2	-1.62	LOC644029	-1.51	SLIT2	1.52
DCLK1	-1.62	LOC644131	-1.54	SLITRK1	-1.53
DCTN1	-1.57	LOC644422	1.57	SNORA12	1.51
DCTN1	-1.67	LOC644914	-1.51	SNORD80	-1.62
DCX	-1.54	LOC645138	-1.53	SOST	-1.69
DDIT3	-1.77	LOC645979	-1.52	SOX8	-1.56
DDIT4	-1.67	LOC647673	-1.51	SPOCK1	1.83
DDX17	-1.61	LOC649679	-1.60	SPRY1	2.18
DLX1	2.13	LOC650494	1.51	SPRY1	2.05
DRD4	1.65	LOC653752	1.54	SPTAN1	-1.57
DUS3L	-1.56	LOC654194	1.51	SRRM4	-1.51
EBF1	-1.57	LOC727821	-1.54	STARD7	-1.69
EBF3	-1.80	LOC728590	-1.62	STMN2	-1.53
EFHD1	1.62	LOC728715	-1.51	STMN2	-1.57
EGR2	1.75	LOC728734	-1.55	STMN4	-1.70
ELAVL2	-1.51	LOC728843	-1.55	STS-1	1.51
ELAVL3	-1.54	LOC728855	1.56	SULF1	2.15
ELAVL3	-1.55	LOC729208	-1.51	SYT4	-1.63
ELAVL4	-1.59	LOC730525	2.03	TACC2	-1.55
EMX2OS	1.67	LRP4	1.55	TAGLN3	-1.89
EPB41L3	-1.97	LSS	-1.59	TGFBI	1.99
F12	1.62	LUM	1.54	TGFBR2	-1.85
FABP5L2	-1.58	LY6H	-1.74	TGFBR2	-1.96
FABP7	1.79	MAP1A	-1.52	TGFBR3	-1.81
FAM102B	-1.59	MAP4	-1.97	TMEFF2	-1.96
FAM190B	-1.51	MAPK12	-1.53	TNC	1.54
FBLN2	1.65	MAPT	-1.91	TNRC4	-1.75
FBLN2	1.59	MAST1	-1.55	TP53INP2	-1.74
FGF13	-1.53	MDGA1	-1.79	TPBG	1.57
FHL2	1.62	MEIS2	-1.68	TPD52L1	1.57
FLJ46906	1.51	MEX3B	-1.62	TPM2	1.50
FNDC5	-1.68	MFAP2	1.76	TRAPPC6B	-1.51
FRZB	1.66	MGC3032	-1.52	TRIB3	-2.00
FTHL12	-1.60	MGC40489	-1.52	TRIL	1.61
FTHL2	-1.61	MIAT	-1.65	TSC22D3	-1.55
FTHL8	-1.51	MMRN1	1.69	TSPO	1.69
G3BP1	-1.55	MTHFD1L	-1.79	TUBA1C	1.69

GAB2	-1.66	MTHFD2	-1.64	TUBB2A	-1.57
GABBR2	-1.62	MTHFD2	-1.68	TUBB4	-1.50
GALNT12	1.51	MUC1	-1.50	TUBB4Q	-1.62
GAP43	-1.62	MVD	-1.53	TXNRD1	-1.52
GCNT1	1.62	MYT1	-1.80	TXNRD1	-1.56
GDI1	-1.53	NDRG4	-1.59	VEGFB	1.52
GDPD5	-1.56	NEFM	-1.51	WARS	-1.63
GJA1	1.59	NPIP	-1.65	WARS	-1.69
GNG2	-1.81	NQO1	-1.94	XBP1	-1.51
GPC3	1.75	NRG1	-1.54	XBP1	-1.61
GPC4	2.10	NRP1	-1.56	YARS	-1.61
GRM2	-2.18	NSBP1	1.53	YWHAG	-1.60
GRTP1	1.50	OCIAD2	1.66	YWHAG	-1.65
				ZMAT3	-1.51

Table S4. Gene enrichment analysis of genes differentially expressed after VPA treatment in IPSC-derived neural progenitor cells

GO ACCESSION	GO Term	p-value	corrected p-value	Gene Counts
GO:0007399	nervous system development	1.30E-14	2.14E-10	41
GO:0048869	cellular developmental process	3.73E-12	3.08E-08	46
GO:0030154	cell differentiation	6.23E-12	3.42E-08	45
GO:0022008	neurogenesis	3.99E-11	1.31E-07	24
GO:0048856	anatomical structure development	6.86E-11	1.63E-07	59
GO:0048699	generation of neurons	6.94E-11	1.63E-07	23
GO:0032502	developmental process	1.76E-09	3.23E-06	65
GO:0051128	regulation of cellular component organization	1.97E-07	2.95E-04	20
GO:0048523	negative regulation of cellular process	2.60E-07	3.56E-04	39
GO:0030182	neuron differentiation	3.70E-07	4.47E-04	16
GO:0040008	regulation of growth	3.91E-07	4.47E-04	14
GO:0010975	regulation of neuron projection development	1.11E-06	9.15E-04	7
GO:0045664	regulation of neuron differentiation	3.36E-06	2.13E-03	8
GO:0050770	regulation of axonogenesis	8.03E-06	4.59E-03	6

Table S5. Cell lines used in present study

ID	Donor status	rs9834970 genotype	Source	Reprogramming method	iPSC		NPC		Neurons		Astrocytes		Gender
					Lithium	VPA	Lithium	VPA	Lithium	VPA	Lithium	VPA	
CN1	Healthy	GG	NHLBI Core	Lenti	-	-	+	+	-	-	-	-	M
CN2	Healthy	AG	NHLBI Core	Lenti	+	+	+	+	-	-	-	-	F
CN3	Healthy	AG	NHLBI Core	Lenti	+	+	+	+	-	-	-	-	F
CN4	Healthy	AG	NHLBI Core	Lenti	+	+	+	+	+	+	+	+	M
CN5	Healthy	AA	NHLBI Core	Lenti	-	-	+	+	+	+	+	+	F
NL1	Healthy	AG	CRM	Lenti	+	+	+	+	-	-	-	-	M
NL5	Healthy	AG	CRM	Lenti	-	-	+	+	-	-	-	-	M
GM23476	Healthy	GG	Coriell	Lenti	-	-	+	+	-	-	-	-	F
GM05990	Bipolar disorder	AA	Coriell	Lenti	-	-	+	+	+	+	+	+	M
10593	Bipolar disorder	GG	HGB	Sendai	-	-	+	+	+	+	+	+	F
GM23240	Spinomuscular Atrophy I	AA	Coriell	Lenti	-	-	+	+	-	-	-	-	M

Table S6. Sequences of selected oligonucleotides for quantitative RT-PCR assays

Gene	Forward primer	Reverse primer
GAPDH(human)	gctctctgctcctcctgttc	acgaccaaatccgttgactc
GAPDH(rat)	agctggtcatcaatgggaaa	atttgatgttagcfgggatcg
ACTB(human)	attggcaatgagcggttc	cgtggatgccacaggact
ACTB(rat)	cccgcgagtacaaccttct	cgtcatccatggcgaact
TRANK1(human)	gccaagaggagctttttgaa	gggaagggtcttagtctttagca
TRANK1(rat)	tccatgtttactgggagaaagc	ccaaccttctctttggcaag
HDAC1(human)	cggtgctggacatatgagac	tggtccaaagtattcaaagtagtca
HDAC1(rat)	tttgagttctgtcagttgtccac	cttcttcgcatggtgcag
HDAC2(human)	tgaaggagaaggaggtcgaa	tcttcaattctagctttctttgctc
HDAC2(rat)	cgctgactccctctctggt	tcactacttctacacatttagcgtga
OCT3/4	tgccgtgaaactggagaag	gcttggcaaattgttcgagt
SOX2	caacagaggctgcagaacag	cctttcttccctccttcattc
Nanog	tctccaacatcctgaacctca	ttgctattcttcggccagtt
TDGF-1	agatggcccgcttctctta	gagatggacgagcaaattcc

Table S7. Sequences of the TRANK1-specific shRNAs used in this study

shRNAs	Sequence
sh RNA for TRANK1_66	5'-CCGGTACTGATTCTGAGGCTTATAACTCGAGTTATAAGCCTCAGAATCAGTATTTTTG-3'
sh RNA for TRANK1_69	5'-CCGGTTGGCTGGCAGGCCTTATAAGCTCGAGCTTATAAGGCCTGCCAGCCAATTTTTG-3'
sh RNA for no target control	5'-CCGGCAACAAGATGAAGAGCACCAACTCGAGTTGGTGCTCTTCATCTTGTTGTTTTT-3'

Table S8. Sequences of specific and non-specific CTCF probes and of rs906482 A/G oligonucleotide probes used in EMSA assays.

EMSA_rs906482_A_allele_Fw	5'Biotin CTCTTTGACGATCCTCTGGTTCTCTTACTCCC 3'
EMSA_rs906482_A_allele_Rev	5' GGGAGTAAGAGAACCAGAGGATCGTCAAAGAG 3'
EMSA_rs906482_G_allele_Fw	5' Biotin CTCTTTGACAATCCTCTGGTTCTCTTACTCCC
EMSA_rs906482_G_allele_Rev	5'GGGAGTAAGAGAACCAGAGGATTGTCAAAGAG3'
CTCF consense probe_allele_Fw	5'CCCCCAGGGATGTAATTACGTCCCTCCCCCGCTAGGGGGCAGCAG-3'
CTCF consense probe_allele_Rw	5'CTGCTGCCCCCTAGCGGGGGAGGGACGTAATTACATCCCTGGGGG-3'
No specific competitor_allele_Fw	5'TGGCCAGGGCCGCGCCGTGGCGGGGCCAGGGCGCGGGGCT-3"
No specific competitor_allele_Rw	5'AGCCCCGCGCCCTGGCCCCGCCACGGCGCGGCCCTGGCCA-3'