The circadian hippocampus and its reprogramming in epilepsy: impact for chronotherapeutics

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Gene and protein expression displays circadian oscillations in numerous body organs. These oscillations can be disrupted in diseases, thus contributing to the disease pathology. Whether the molecular architecture of cortical brain regions oscillates daily and whether these oscillations are modified in brain disorders is less understood. We identified 1200 daily oscillating transcripts in the hippocampus of control mice. More transcripts (1600) were oscillating in experimental epilepsy, with only one fourth oscillating in both conditions. Proteomics confirmed these results. Metabolic activity and targets of antiepileptic drugs displayed different circadian regulation in control and epilepsy. Hence, the hippocampus, and perhaps other cortical regions, shows a daily remapping of its molecular landscape, which would enable different functioning modes during the night/day cycle. The impact of this remapping in brain pathologies needs to be taken into account not only to study their mechanisms, but also to design drug treatments and time their delivery.

Circadian rhythms regulate numerous brain functions (e.g. wakefulness, feeding, etc.) with 24-hour oscillations in most species. The core time keeping machinery is the suprachiasmatic nucleus (SCN). Its molecular architecture undergoes a daily remapping driven by transcriptional and translational feedback loops, thus allowing switching between different functional states [1,2]. Several studies suggest the existence of additional (ancillary) clocks in the brain outside the SCN [3]. Indeed, clock genes, including Per1, Per2, Bmal1, Cry1 and Cry2, exhibit rhythmic expression in a brain region- and gender-dependent manner [4,5]. Since these genes are involved in the regulation of transcription/translation of many other genes, brain regions outside the SCN may also undergo a complex daily remapping of their molecular architecture [6,7]. Such circadian regulation of neuronal circuits may enable appropriate

coordination between physiology and behavior, since learning and memory processes are regulated in a circadian manner [8,9]. In the hippocampus, a region critical for numerous learning and memory processes, synaptic responses [10], long term synaptic plasticity [11,12] and the memory-associated MAPK pathway [13] display circadian rhythmicity.

The first goal of this study is to provide the community with a resource listing of the genes and proteins undergoing circadian regulation in the mouse hippocampus. Such information is crucial not only for our understanding of hippocampal function, but also for a proper interpretation of already published data and for resolving discrepancies, since experiments performed at different times may occur within different molecular landscapes. The second goal of this study is to provide a similar resource in a mouse model of temporal lobe epilepsy (TLE), the most frequent form of epilepsy in adults. Several reasons motivate this choice. Alterations of circadian rhythms can lead to pathologies [14], and conversely, disruption of the circadian clock can have direct deleterious consequences [15,16], e.g. on sleep patterns [17]. In the liver, the circadian clock is reprogrammed by nutritional challenge, resulting in a different cycling of genes and proteins [18]. Since clock genes display different cycling behavior in experimental epilepsy [19], the circadian regulation of downstream genes may follow different rules in control and TLE conditions. This information is essential for a proper interpretation of studies comparing the levels of expression of genes and proteins, a standard experimental procedure to assess the reorganization of neuronal circuits in TLE (and in neurological disorders in general). It is also essential for chronotherapy (the proper timing of drug delivery) [20], as many pharmaceutical molecules target gene products showing circadian rhythmicity [21].

RESULTS

Circadian regulation of genes and proteins in the mouse hippocampus

Since the distribution of transcripts is heterogeneous along the septo-temporal axis of the hippocampus [22], we focused on its ventral part [23], which is most epileptogenic in human TLE and experimental models [24]. Using Affymetrix microarrays and cluster analysis, we identified 1256 transcripts oscillating in the ventral hippocampus of control mice (**Fig. 1a** and **Supplementary Table 1**). Hence, 10% of hippocampal genes are regulated in a circadian manner, as compared to 19% in the SCN [5]. Data from post mortem human hippocampus suggests that less genes (n=659) are oscillating [7]. Comparison with the latter study is difficult because investigating circadian rhythms requires a strict control of circadian conditions (e.g. no light exposure during the night), which could not be achieved in the human study.

Using cluster analysis and a false discovery rate < 0.01, we found 197 transcripts differentially expressed in at least one time point, which could be identified based on biological functions (**Fig. 1b**). When compared to subcortical structures (**Table 1**), we found a clear overlap of core clock genes involved in transcriptional and translational feedback loops in the SCN across all investigated brain regions (highlighted in green in **Table 1**). Oscillating core clock genes in the hippocampus included Per1-3, Cry1, Arnt1, Nr1d1-2, and Dbp (**Fig. 1c**, **Table 1**). Transcriptome analysis was confirmed with qPCR (**Supplementary Fig. 1**). Interestingly, a large set of oscillating genes was specific to the hippocampus (**Table 1**), such as Creb1 (**Fig. 2a**), which is involved in both synaptic plasticity and synchronization of circadian rhythms [25], demonstrating that circadian rhythmicity of genes is brain region-dependent.

The analysis of the heatmaps (**Supplementary Fig. 2**) revealed that gene oscillations were distributed in a bimodal manner in control mice, with either a very low or very high

oscillation amplitude (**Fig. 2b**). The majority of genes with high amplitude oscillations were phase advanced in comparison to the rest of the oscillatory transcripts (**Fig. 2b**).

Proteomic data enabled the analysis of 1,500 peptides. We found 170 peptides oscillating in controls (**Fig. 1e** and **Supplementary Table 2**), i.e. the same percentage (11%) as for gene transcripts. Nine proteins were oscillating in both proteomic and transcriptome datasets, which partly originates from the fact that 3% of peptides have a correspondence in the transcriptome dataset.

Together these results demonstrate that 10% of the gene/protein map in the hippocampus of control mice undergoes a continuous remapping during the night/day cycle. We then performed the same analysis in age-matched TLE mice in order to determine whether such circadian regulation was maintained in pathological conditions.

Reprogramming of the circadian regulation of genes and proteins in experimental TLE

In experimental TLE, the number of oscillating transcripts was increased by 30% as compared to control (1650 versus 1256, **Fig. 1a** and **Supplementary Table 3**). Remarkably, only 29% of the oscillating transcripts were common to both control and TLE conditions, demonstrating a reprogramming of the daily remapping of hippocampal genes. Cluster analysis clearly separated the different groups by time and function (**Fig. 1b**). The core clock genes all gained in oscillation amplitudes in TLE as compared to control (**Fig. 1c,d**). Many important circadian-related genes gained oscillatory activity in TLE, from which we highlighted Bhlhe40 and Bhlhe41 (**Fig. 1d, 2a**). These genes encode proteins that interact with Arnlt and compete for E-box binding sites upstream of Per1 and repress Clock/Bmal activation of Per1, hence controlling circadian rhythms

[25]. Increased oscillations of Bhlhe40 and Bhlhe41 may play a key role in the larger recruitment of oscillating transcripts in TLE. Although the mechanism of the reprogramming in TLE was outside the scope of this study, we identified a possible epigenetic mechanism. Runx1, a DNA binding regulator, gained statistical significance in TLE (**Fig. 2a**). Runx1 regulates Creb1, Cry1, Per1 and Per3, and has protein-protein interaction with two key histone deacetylases, Hdac1 and Hdac2. In keeping with this, proteomics revealed oscillatory activity for Hdac1 and Hdac2 in TLE (**Supplementary Table 4**). Finally, Hdac8 also gained oscillatory activity in TLE. Together, these results suggest the involvement of multiple epigenetic mechanisms in the reprogramming of the circadian regulation of hippocampal genes in TLE. The amplitudes of the oscillations were increased in TLE as compared to control, and genes with high amplitude oscillations were phase advanced as compared to the rest of the transcripts (**Fig. 2b** and **Supplementary Fig. 2**).

As for transcripts, the number of oscillating peptides was increased by 40% in TLE as compared to control (237 versus 170 peptides, Fig. 1E and table S4), with only 5% common to both experimental groups.

We conclude that the cycling of genes and proteins is very different in experimental TLE as compared to control, which makes comparing levels of expression, even at the same time point, more difficult.

Functional analysis

The enriched terms reported from DAVID bioinformatics for oscillating genes found in control condition alone, epileptic condition alone, and oscillating in both conditions for three different p-

values are listed in **Supplementary Tables 5-13**. Many biological pathways, including those linked to metabolism, showed circadian regulation in control and TLE, and specific alterations in TLE as revealed by KEGG pathways gene sets, Gene Ontology biological process, Gene Ontology metabolic function and REACTOME pathway database (**Supplementary Fig 3-14**, **Supplementary Table 14-25**).

In order to show how the resource we provide can be used to predict/test functional consequences, we focus, in this example, on metabolic pathways, which were altered in TLE. Metabolic activity was assessed *in vitro* in the ventral CA1 region of the hippocampus using NAD(P)H imaging in stratum radiatum during stimulation of Schaffer collaterals (**Fig. 3a**). Activation of hippocampal cells by Schaffer collateral stimulation results in characteristic changes in NAD(P)H fluorescence intensity: the initial 'dip' is followed by the 'overshoot' component both of which reflect enhanced oxidation and reduction of the pyridine nucleotides, respectively [26]. In similar experimental conditions, the NAD(P)H fluorescence overshoot amplitude is mainly related to the intensity of cytosolic glycolysis in both astrocytes and neurons [26]. In slices prepared at ZT4, glycolysis was considerably decreased in TLE as compared to control (**Fig. 3a**), as previously reported [27]. However, it was considerably increased in TLE in slices prepared at ZT8 (**Fig. 3a**), as compared to TLE at ZT4 and as compared to control at ZT8 (**Fig. 3a**). Interestingly, glycolysis was also different between ZT4 and ZT8 in control slices, suggesting a circadian control of metabolism in hippocampal neurons (**Fig. 3a**). In keeping with these results, there was a marked increase in the expression of the type 3 glucose transporter specifically at ZT8 in TLE (**Fig. 3b**). Hence, for a cellular process as fundamental as metabolism, different circadian functional modes characterize control and TLE conditions. Whether this is due to a reprogramming of the hippocampal clock remains to be determined.

The circadian rhythmicity can also be appreciated at the system level. Seizures are regulated in a circadian manner in human and experimental mesial TLE [28], a result we confirmed in our mouse model (**Fig. 3c**). One explanation could be that the daily remapping of the molecular landscape brings neuronal networks close to seizure threshold at specific time points [29]. In line with this scenario, we found different seizure susceptibility at different time points between control and TLE animals (**Supplementary Fig. 15**). This further exemplifies the fact that control and TLE animals are subject to different operating modes.

Consequences for antiepileptic drug targets and chronotherapy

Another possible use of such resource is for drug target design and chronotherapy. Many common drugs (e.g. for gastritis, chronic pain, asthma, and rheumatoid arthritis) target products of genes characterized by circadian rhythmicity [21]. We obtained information on drugs and genes from DrugBank database version 5.0.6 [30], which contains information about 8283 drugs including 62 drugs that exert antiepileptic and anticonvulsant effects. In the database, we found mammalian genes encoding 2230 drug targets, 35 drug carriers, 238 drug enzymes and 130 drug transporters. For the 62 antiepileptic/anticonvulsant drugs, we found genes encoding 102 drug targets, 1 drug carrier, 32 drug enzymes and 18 drug transporters.

Among the genes that oscillate in control and TLE animals (JTK_CYCLE adjusted $p < 0.05$), we found 24 and 71 drug targets, 2 and 2 drug carriers, 2 and 7 drug enzymes, and 2 and 9 drug transporters, respectively (**Table 2**). There was little overlap between control and experimental TLE datasets, further highlighting the necessity to take into account the reorganization of gene variations that is specific to experimental TLE. We obtained similar conclusions when looking at genes which expression changes (one-way ANOVA, FDR < 0.05)

in at least one time point in control and TLE animals. We found 20 and 62 drug targets, 2 and 0 drug carriers, 2 and 11 drug enzymes, and 2 and 7 drug transporters, respectively (**Table 2**). **Table 3** provides examples of oscillating and differentially expressed gene products controlled by antiepileptic and anticonvulsant drugs.

Finally, new classes of antiepileptic drugs targeting AMPA and NMDA receptors are being developed [31]. Remarkably, many of the corresponding genes of AMPA and NMDA subunits present in the database showed different expression patterns at specific time points in TLE as compared to control (**Fig. 3d, e**).

Together these results suggest that the efficacy of antiepileptic and anticonvulsant drugs is time-dependent. It is important to stress that drug efficacy testing must be performed in experimental epilepsy models as the time-dependent regulation of the drug targets are different in TLE and control conditions. The resource we provide can be used to assess such factor.

DISCUSSION

We conclude that hippocampal networks undergo a complex daily remapping at the gene and protein level. The number of oscillating genes and proteins is likely to be an underestimate as hippocampal samples were collected every four hours. The remapping may drive hippocampal networks into different functioning modes in a circadian-dependent manner to optimize information processing at specific time points. For example, the remapping may contribute to the circadian regulation of theta oscillations and place cell firing in the hippocampus [32,33], or, if a remapping also occurs in the cortex, to the circadian regulation of cortical excitability in humans [34]. Such oscillations could be a downstream consequence of those occurring in the SCN, and the

daily activation of various hormonal and neuromodulator pathways [8]. Alternatively, the clock could be intrinsic since some hippocampal genes continue to oscillate *ex vivo* [35]. Yet, the daily molecular remapping is important to consider for understanding hippocampal function. Since multiple other damped (secondary) circadian oscillators exist in the brain, each with specific phase properties [36], it is likely that a remapping also exists in other brain regions, each with a specific set of regulated genes and proteins. In addition, a similar resource should be provided for other hippocampal regions (like the dorsal hippocampus), since the molecular architecture of the hippocampus is not homogenous along its septo-temporal axis [22].

One major limitation of our approach is to lump all cell types from the different hippocampal subfields. Future studies should focus on cell-type specific analysis [37], a complex endeavor since it requires instantaneous "freezing" of cells and networks to stop the cycling process at specific times during the night and day cycle.

In epilepsy, we report a large reprogramming of the cycling behavior, with the possible involvement of epigenetic mechanisms [38,39]. It is not yet possible to determine whether this is a cause or consequence of seizures, altered sleep/wake cycles, or just a homeostatic mechanism. However, the important result is that the hippocampus uses a different functional regime in TLE as compared to control. This makes comparing genes and proteins from control and TLE tissues very difficult, as down or up-regulation could just sign different oscillating properties in both conditions (e.g. a phase shift). In fact, if two systems are under two different functioning modes, one can argue that they will have to be studied for themselves, rather than being compared to each other. Based on this novel information, it will be now important to indicate the circadian time a given animal was used in any experimental condition, and to take into consideration a possible reprogramming when studying neurological disorders. Indeed, we can propose that such

reprogramming may occur in most (if not all) neurological disorders [40]. This argument is even more crucial for chronotherapeutics [20], highlighting the necessity to take into account the fact that the expression of drug targets may display different expression time-dependent changes in pathologies as compared to controls.

The time of the day is thus a critical parameter to consider for the proper interpretation of molecular, physiological and behavioral studies, as the functional architecture of the hippocampus may be dynamically regulated in a time-dependent manner. Overall, the present findings have important implications for disease pathogenesis and therapy.

Figure 1. Circadian regulation of genes and proteins in the hippocampus and their reprogramming in epilepsy. (**a**) In control mice (n=4 per Zeitgeber Time – ZT), 1256 transcripts are oscillating. In TLE (n=4 per ZT), more transcripts are oscillating (1650). Only 474 are common to both conditions, showing a remodeling of the landscape of oscillating genes in TLE. (**b**) Right panel. Heatmap of 1105 mRNAs showing circadian regulation. 124 mRNAs were differentially expressed in at least one time point only in control animals, 908 mRNAs were differentially expressed only in TLE and 73 mRNAs were differentially expressed in both groups. Each column per time window represents an individual animal and each row represents an individual mRNA. Colors on the heatmap represent Z-score: higher – red, lower – blue. The hour of tissue collection is indicated below (ZT). The dendrogram obtained from hierarchical clustering is shown on the left side of the heatmap panel. Genes are ordered by clustering complete-linkage method together with Pearson correlation distance measure. Colors in the bar on the left side of the heatmap panel represent clusters obtained by cutting dendrogram at selected level heights to obtain nine groups. Black lines in the bar on the right side of the heatmap panel mark genes showing differences in expression between control or TLE animals based on one-way ANOVA (cut-off FDR < 0.1). Left top panel. Biological functions for each gene cluster, according to Gene Ontology vocabulary using DAVID. Only terms, which are represented by more than 5% of genes in a given cluster, are presented in the Table. Left bottom panel. Transcription factors with binding sites overrepresented in different gene clusters. (**c** and **d**) Oscillation patterns and amplitudes of core clock genes. Note the phase change and general increase in oscillation amplitude in TLE as compared to controls. (**e**) In control mice 170 peptides are oscillating, whilst 337 are oscillating in TLE. Only 11 peptides oscillate in both

conditions, indicating a reprogramming of the molecular daily remapping of the hippocampus in TLE.

Figure 2. Different oscillatory patterns of gene transcripts in control mice and their alterations in TLE. (**a**) Oscillatory patterns of genes, which may contribute to the reprogramming of the circadian hippocampal remapping in TLE. *Creb1* oscillates in both conditions. Key controllers of circadian rhythms, *Bhlhe40* and *Bhlhe41*, show increased oscillation amplitudes in TLE, which may contribute to the large recruitment of oscillating genes in TLE. *Runx1*, a DNA binding regulator, and *Hdac8*, a chromatin remodeler, gain statistically significant oscillation in TLE. *JunD*, which interacts with the AP-1 transcription factor complex and *Creb1* shows a 180° phase shift in TLE as compared to control. (**b**) Phase-Amplitude matrices. Most of the transcripts show high amplitude oscillations in TLE, whilst they are distributed in a bimodal manner in controls between low and high amplitude. The majority of high amplitude oscillatory transcripts are phase advanced as compared to the rest of the oscillatory transcripts, a property more pronounced in TLE.

Figure 3. Alteration of circadian regulation of metabolism and drug targets in TLE. (**A**) (**a**) Averaged NAD(P)H fluorescence changes induced by 10 Hz 30s electrical pulse train stimulation of Schafer collaterals (rectangle) imaged in *Stratum Radiatum* of the hippocampal slices of control and TLE mice. (**a**) **I.** Averaged NAD(P)H fluorescence recorded in TLE (yellow trace) and control (dark gray trace) slices prepared at ZT4. The mean amplitude of the NAD(P)H transient overshoot was significantly smaller in TLE than in control mice (TLE: 1.3±0.17% n=9, control: 3.5±0.5%, n=10, $p<0.01$, dashed arrows) suggesting reduced activity of

cytosolic glycolysis in TLE as compared with control. The decrease in NAD(P)H fluorescence dip amplitude in TLE did not reach statistical significance (TLE: -1.3±0.2%, control: -1.9±0.20%, p=0.2, dotted double-head arrows). **II.** There was no difference in NAD(P)H overshoot in slices prepared at ZT8 in TLE (red trace) and control (grey trace) mice (TLE: 4.1±0.4%, n=6, control: 4.6±0.9%, n=6, p=0.3). However, dip amplitudes were significantly different (TLE: -0.6±0.1%, control: -1.7±0.3%, $p<0.05$). A smaller dip indicates a reduced activity of oxidative phosphorylation or/and an increased activity of cytosolic glycolysis, which rapid onset produces a massive reduction of NAD^+ and masks NADH oxidation in mitochondria. Tthe time of slice preparation had also a significant impact on metabolic activity in both controls (**III**) and TLE (**IV**) conditions. In slices made at ZT8 (grey trace) from control animals, NAD(P)H overshoot amplitude was slightly but significantly larger than in slice made at ZT4 (4.6±0.9%, n=6 vs 3.5±0.5%, n=10, $p<0.05$). The mean amplitudes of the initial dips were similar at both time points (-1.9±0.2% vs -1.7±0,4, p=0.7, n=6). In TLE slices made at ZT8 (red trace) NAD(P)H fluorescence rise started 8±2 s earlier ($n>6$, $p<0.05$) and reached greater levels than in slice made at ZT4 (yellow trace). (**b**) The type 3 glucose transporter shows a different circadian regulation in control and TLE, with a specific significant upregulation at ZT15 in TLE. (**c**) Top. Circadian regulation of seizure incidence during the night and day cycle. The highest seizure probability is found around ZT15. Bottom. Two days after shifting the light/dark cycle by 8 hours in the animal facility, the temporal pattern of seizure incidence shifted accordingly. (**d** and **e)** Alterations of the temporal expression of genes encoding for NMDA and AMPA receptors subunits, respectively.

Table 1: List of genes showing a circadian regulation in control mice, in the hippocampus (Hip), suprachiasmatic nucleus (SCN), Cerebellum (Cer), Brain Stem (Bstm) and Hypothalamus (Hyp). If most core clock genes display circadian regulation in most structures, numerous genes oscillate specifically in the hippocampus.

Table 2: List of genes that oscillate (JTK_CYCLE adjusted $p < 0.05$) or that show changes in expression in at least one time point (one-way ANOVA, FDR < 0.05) in control animals and experimental TLE. Genes are separated in drug targets, carriers, enzymes and transporters. There is little overlap between the control and TLE conditions (common ones are underlined). The ABCC1 is not only transporter for *Phenobarbital* but also a drug target for Sulfinpyrazone and Biricodar dicitrate (in italics). Genes in Bold are shown in table 3.

Table 3: Genes that are drug target (T) or transporters (Tr), and that oscillate (JTK_CYCLE, adjusted p value < 0.05; OSC) or that are differentially expressed (one-way-ANOVA, adjusted p value < 0.05; DE) in control (CTR) or TLE animals. Information on drugs can be found in the Supplemental Material.

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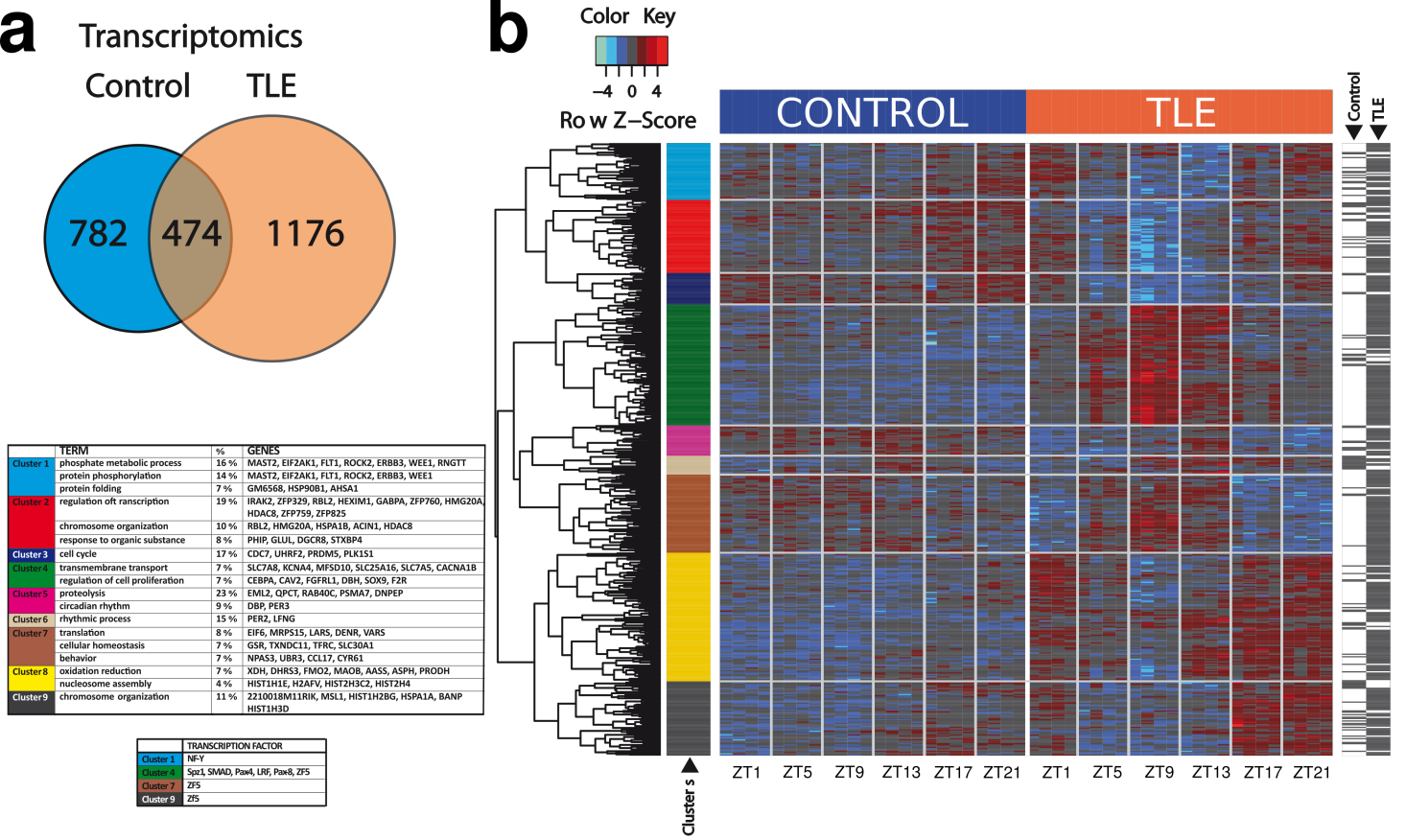
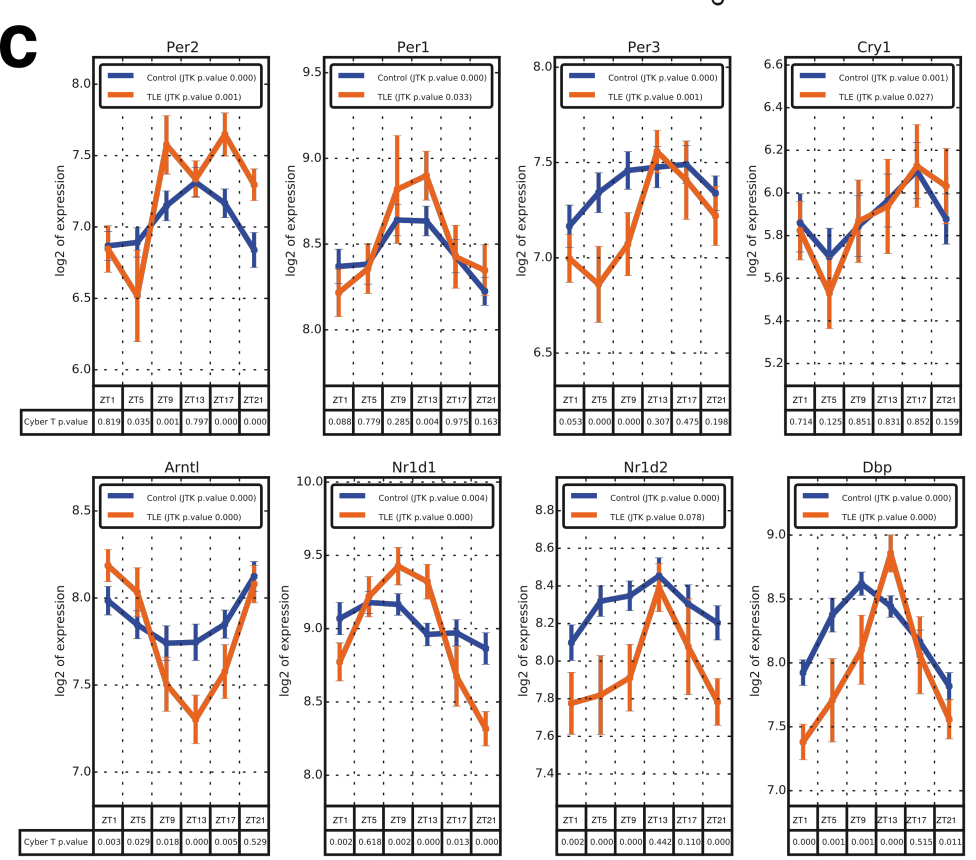


	TERM	%	GENES
Cluster 1	phosphate metabolic process	16 %	MAST2, EIF2AK1, FLT1, ROCK2, ERBB3, WEE1, RNGTT
	protein phosphorylation	14 %	MAST2, EIF2AK1, FLT1, ROCK2, ERBB3, WEE1
	protein folding	7 %	GM6568, HSP90B1, AHSA1
Cluster 2	regulation oft rancription	19 %	IRAK2, ZFP329, RBL2, HEXIM1, GABPA, ZFP760, HMG20A, HDAC8, ZFP759, ZFP825
	chromosome organization	10 %	RBL2, HMG20A, HSPA1B, ACIN1, HDAC8
	response to organic substance	8 %	PHIP, GLUL, DGCR8, STXBP4
Cluster 3	cell cycle	17 %	CDC7, UHRF2, PRDM5, PLK1S1
Cluster 4	transmembrane transport	7 %	SLC7A8, KCNA4, MFSD10, SLC25A16, SLC7A5, CACNA1B
	regulation of cell proliferation	7 %	CEBPA, CAV2, FGFRL1, DBH, SOX9, F2R
Cluster 5	proteolysis	23 %	EML2, QPCT, RAB40C, PSMA7, DNPEP
	circadian rhythm	9 %	DBP, PER3
Cluster 6	rhythmic process	15 %	PER2, LFNG
Cluster 7	translation	8 %	EIF6, MRPS15, LARS, DENR, VARS
	cellular homeostasis	7 %	GSR, TXNDC11, TFRC, SLC30A1
	behavior	7 %	NPAS3, UBR3, CCL17, CYR61
Cluster 8	oxidation reduction	7 %	XDH, DHRS3, FMO2, MAOB, AASS, ASPH, PRODH
	nucleosome assembly	4 %	HIST1H1E, H2AFV, HIST2H3C2, HIST2H4
Cluster 9	chromosome organization	11 %	2210018M11RIK, MSL1, HIST1H2BG, HSPA1A, BANP HIST1H3D

	TRANSCRIPTION FACTOR
Cluster 1	NF-Y
Cluster 4	Spz1, SMAD, Pax4, LRF, Pax8, ZF5
Cluster 7	ZF5
Cluster 9	ZF5



d

Gene	Control Amp	Epileptic Amp
Bhlhe40	0.2375081574	0.4140875868
Bhlhe41	0.3839730036	0.8064160334
Arntl	0.3834664913	0.8833480509
Hdac8	0.1094111846	0.4769890427
Runx1	0.1811503567	0.7019302037
Per2	0.4750034544	1.130855182
Cry1	0.4035340666	0.5957495958

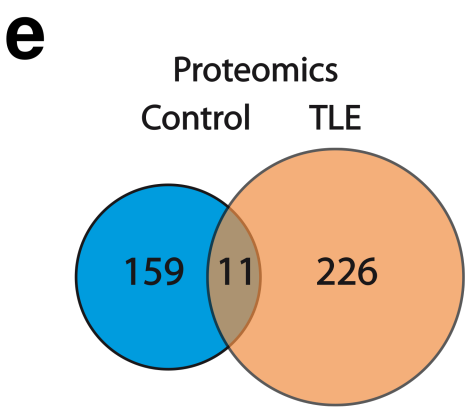
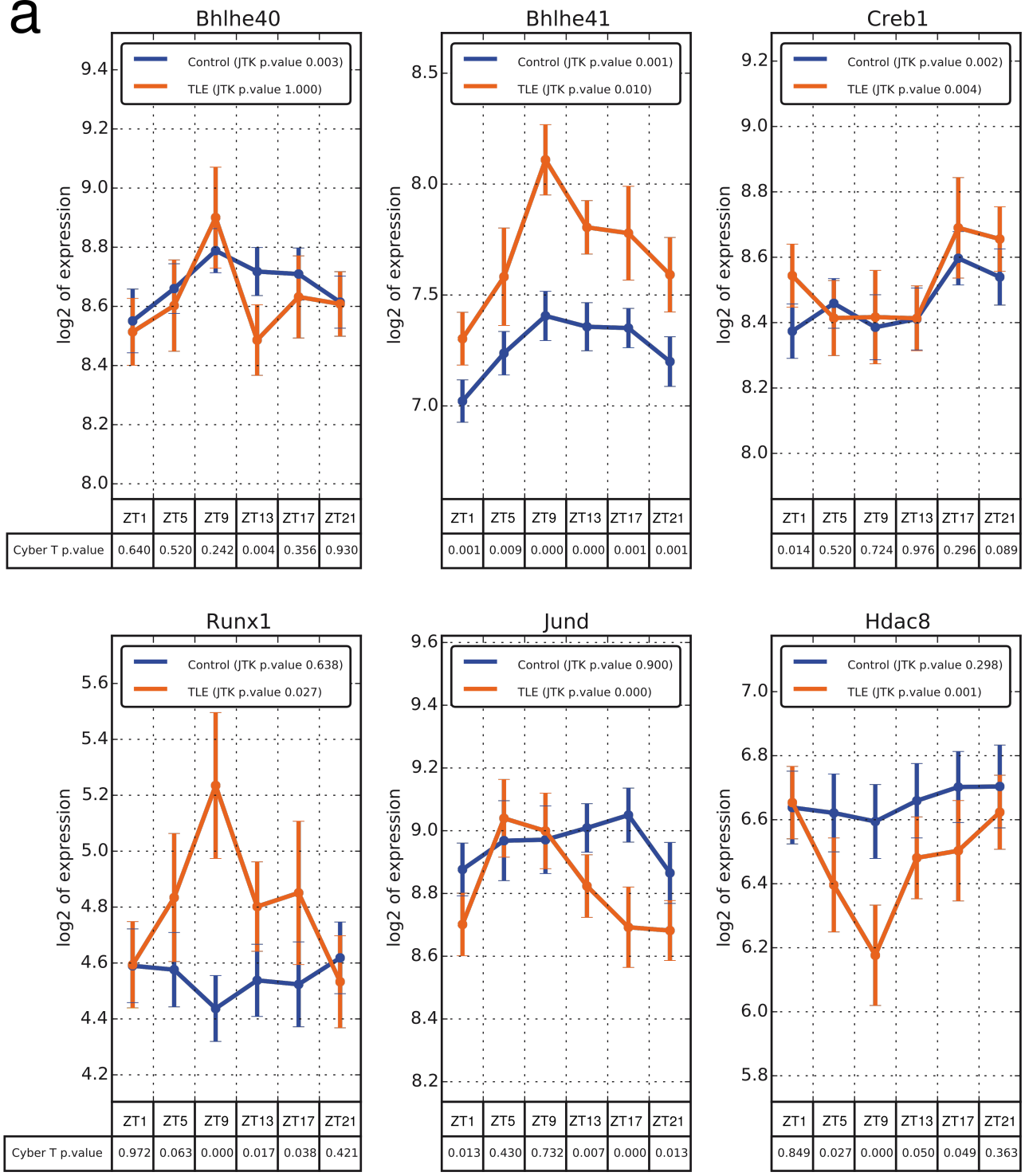


Figure 1

a


Bhlhe40
Control (JTK p.value 0.003)
TLE (JTK p.value 1.000)
log2 of expression
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
Cyber T p.value 0.640 0.520 0.242 0.004 0.356 0.930
Bhlhe41
Control (JTK p.value 0.001)
TLE (JTK p.value 0.010)
0.001 0.009 0.000 0.000 0.001 0.001
Creb1
Control (JTK p.value 0.002)
TLE (JTK p.value 0.004)
0.014 0.520 0.724 0.976 0.296 0.089
Runx1
Control (JTK p.value 0.638)
TLE (JTK p.value 0.027)
Cyber T p.value 0.972 0.063 0.000 0.017 0.038 0.421
Jund
Control (JTK p.value 0.900)
TLE (JTK p.value 0.000)
0.013 0.430 0.732 0.007 0.000 0.013
Hdac8
Control (JTK p.value 0.298)
TLE (JTK p.value 0.001)
0.849 0.027 0.000 0.050 0.049 0.363

b

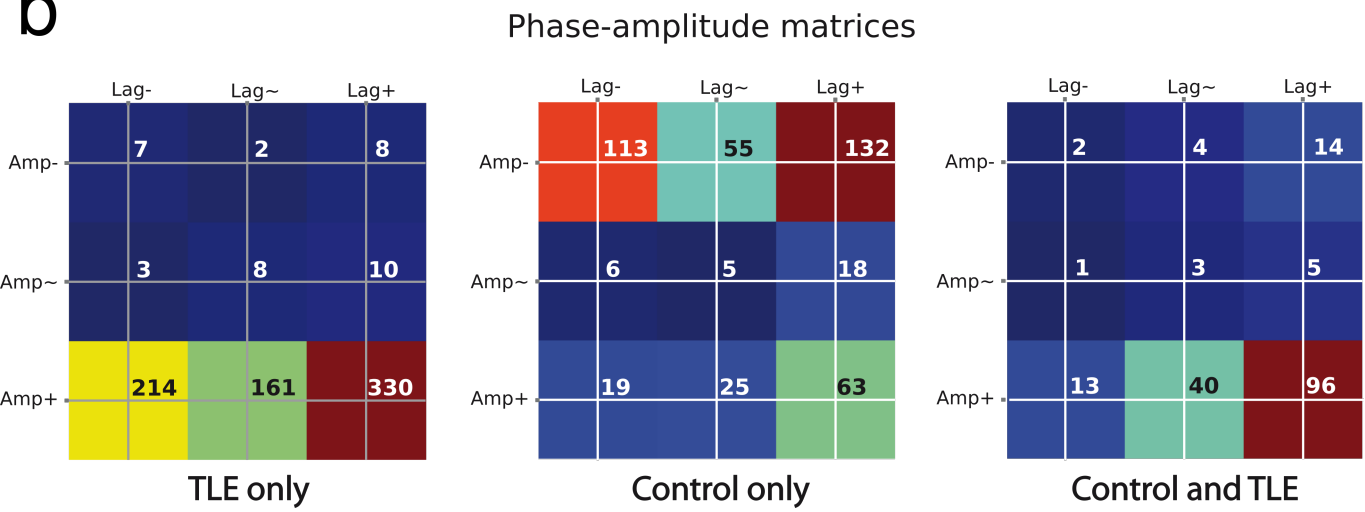

Phase-amplitude matrices
Lag- Lag~ Lag+
Amp- Amp~ Amp+
7 2 8
3 8 10
214 161 330
TLE only
113 55 132
6 5 18
19 25 63
Control only
2 4 14
1 3 5
13 40 96
Control and TLE

Figure 2

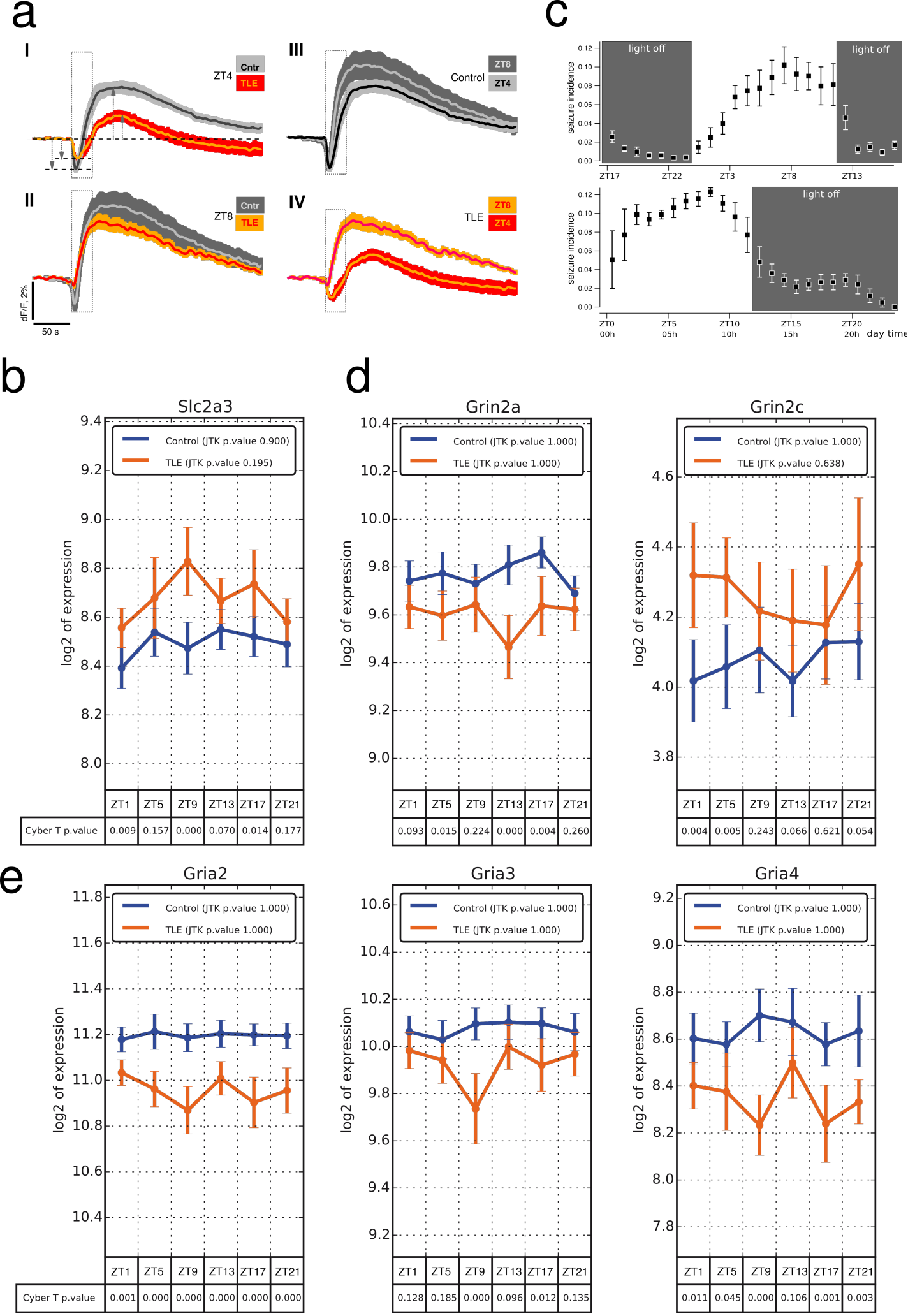

a
I
ZT4
Cntr
TLE
II
ZT8
Cntr
TLE
dF/F, 2%
50 s
III
Control
ZT8
ZT4
IV
TLE
ZT8
ZT4
c
light off
seizure incidence
ZT17
ZT22
ZT3
ZT8
ZT13
ZT0
00h
ZT5
05h
ZT10
10h
ZT15
15h
ZT20
20h
day time
b
Slc2a3
Control (JTK p.value 0.900)
TLE (JTK p.value 0.195)
log2 of expression
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
Cyber T p.value 0.009 0.157 0.000 0.070 0.014 0.177
d
Grin2a
Control (JTK p.value 1.000)
TLE (JTK p.value 1.000)
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
0.093 0.015 0.224 0.000 0.004 0.260
Grin2c
Control (JTK p.value 1.000)
TLE (JTK p.value 0.638)
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
0.004 0.005 0.243 0.066 0.621 0.054
e
Gria2
Control (JTK p.value 1.000)
TLE (JTK p.value 1.000)
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
Cyber T p.value 0.001 0.000 0.000 0.000 0.000 0.000
Gria3
Control (JTK p.value 1.000)
TLE (JTK p.value 1.000)
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
0.128 0.185 0.000 0.096 0.012 0.135
Gria4
Control (JTK p.value 1.000)
TLE (JTK p.value 1.000)
ZT1 ZT5 ZT9 ZT13 ZT17 ZT21
0.011 0.045 0.000 0.106 0.001 0.003

Figure 3

Gene	Hip	SCN	Cer	Bstm	Hyp
Dbp	0.0000	NA	0.0000	0.0000	0.0000
Hif3a	0.0000	0.1914	0.0001	0.0028	0.0057
1700084c01rik	0.0000	NA	1.0000	0.0002	0.0028
Folh1	0.0000	1.0000	0.0002	0.0001	0.0013
P4ha1	0.0000	0.0023	0.0112	0.0028	0.0080
Zbtb40	0.0000	NA	0.1654	0.0261	0.0001
Mfsd2a	0.0000	NA	0.0001	0.0035	0.0003
Cirbp	0.0000	0.0000	0.0139	0.0017	0.0004
Arntl	0.0000	0.0006	0.0000	0.0000	0.0000
0610040b10rik	0.0000	NA	0.0261	1.0000	1.0000
Prr5	0.0000	1.0000	0.0090	0.3962	1.0000
Per2	0.0000	0.0000	0.0000	0.0000	0.0000
Mertk	0.0000	1.0000	0.0570	0.0112	0.0003
Fabp7	0.0000	0.0000	0.0000	0.0000	0.0000
Fmo2	0.0000	NA	0.0000	0.0000	0.0000
Smox	0.0000	NA	0.0319	1.0000	1.0000
Sdf2l1	0.0000	NA	0.0687	0.0002	0.0000
Plekho2	0.0000	NA	1.0000	1.0000	1.0000
Rrp8	0.0000	NA	0.2692	0.0000	0.0071
Mmaa	0.0000	NA	0.2494	0.0004	0.0004
Sdc4	0.0000	0.0063	0.0045	0.0007	0.0002
1110002b05rik	0.0000	1.0000	1.0000	1.0000	1.0000
Gm129	0.0000	NA	0.0000	0.0000	0.0002
Per3	0.0000	0.7163	0.0000	0.0000	0.0000
Gpr139	0.0000	NA	1.0000	1.0000	1.0000
4933437f05rik	0.0000	NA	0.0521	0.0005	0.0015
H1f0	0.0000	0.0371	0.0035	0.0319	0.4932
Mrps6	0.0000	NA	NA	NA	NA
Kcnv1	0.0000	NA	0.2494	1.0000	0.3666
Mpzl1	0.0000	NA	0.1397	0.5695	0.0019
Rftn2	0.0000	NA	0.0139	0.3962	0.0057
Flt1	0.0000	1.0000	0.0035	0.0354	0.0010
Rtp1	0.0000	NA	1.0000	1.0000	1.0000
Lfng	0.0000	NA	0.0017	0.0002	0.0021
Hsp90b1	0.0000	NA	0.0001	0.0028	0.0004
Scg2	0.0000	1.0000	1.0000	0.6556	1.0000
Nmnat1	0.0000	NA	0.0319	1.0000	0.1654
Oaf	0.0000	NA	0.5695	1.0000	1.0000
Tsc22d3	0.0000	0.3071	0.0000	0.0000	0.0002
9430083a17rik	0.0000	NA	NA	NA	NA
9230110c19rik	0.0000	NA	0.6556	0.0987	0.9836
Sox2	0.0000	0.0964	0.0319	1.0000	0.4258
Loc100862610	0.0000	NA	NA	NA	NA
Pdia6	0.0000	0.0127	0.0472	0.0002	0.0000
Lpcat3	0.0000	0.9843	0.0570	0.0212	0.0009
Calr	0.0001	0.0551	0.0002	0.0000	0.0000
Slc2a1	0.0001	0.0063	0.0002	0.0017	0.1654
Ago3	0.0001	NA	0.3406	0.0000	0.0064
Zfp410	0.0001	NA	1.0000	0.5695	0.0004
Dio2	0.0001	NA	NA	NA	NA
Eid2	0.0001	NA	1.0000	0.1526	1.0000
Sft2d2	0.0001	NA	0.8616	1.0000	1.0000
Gabpa	0.0001	1.0000	0.0172	0.1397	0.0057
Bphl	0.0001	1.0000	1.0000	1.0000	1.0000
Ankrd13a	0.0001	NA	0.0071	0.0139	0.0001
Hyou1	0.0001	1.0000	0.0472	0.0028	0.4932
Rtp3	0.0001	NA	NA	NA	NA
Wdr78	0.0001	0.1914	0.9836	0.4595	0.0354
Slc38a2	0.0001	0.1622	0.3146	0.0000	0.0000
Loc100505262	0.0001	NA	NA	NA	NA
Tsga10	0.0001	NA	1.0000	0.0035	0.0521
Rasl10a	0.0001	NA	1.0000	0.5313	1.0000
Spry3	0.0001	NA	1.0000	1.0000	1.0000
Kirrel2	0.0001	NA	0.1526	0.0906	0.0319
Gm15453	0.0001	NA	NA	NA	NA
Per1	0.0001	0.0001	0.0007	0.0000	0.0000
Hspa5	0.0001	0.0007	0.0319	0.0002	0.0000
Xdh	0.0001	1.0000	0.0021	0.0687	0.1397
Hist2h4	0.0001	NA	1.0000	0.0172	0.2494
Traf4	0.0001	0.0246	1.0000	0.4932	1.0000
Tmem55a	0.0001	0.2249	0.4595	0.0002	0.0570
Hnrpdl	0.0001	0.0090	0.0987	0.0001	0.4932
Mmp14	0.0001	NA	0.0001	0.0000	0.0000
Hmg20a	0.0001	NA	0.9836	1.0000	0.5695
Cst3	0.0001	0.0667	0.0001	1.0000	0.0825
Kdr	0.0001	0.3568	0.0101	0.0011	0.0035
Atp10a	0.0001	NA	0.0001	0.0006	0.0035
Nop10	0.0001	0.0000	1.0000	1.0000	1.0000
Ormdl1	0.0001	0.0004	0.0388	1.0000	0.0290
Uba6	0.0002	NA	0.1654	0.0001	0.0172
Xbp1	0.0002	0.1622	0.0388	0.0045	0.1176
L3mbtl3	0.0002	NA	1.0000	0.0006	0.0090
Pllp	0.0002	NA	0.0003	0.0000	0.0000
Slco1c1	0.0002	NA	0.0139	1.0000	1.0000
Fam84a	0.0002	NA	1.0000	0.0172	0.0002
Gm10069	0.0002	NA	0.0354	0.2296	0.0051
Pid1	0.0002	NA	0.0388	0.1952	1.0000
Angptl4	0.0002	0.0303	1.0000	0.0430	0.0906
Prkab2	0.0002	NA	1.0000	1.0000	1.0000
Rasal2	0.0002	NA	1.0000	0.0057	1.0000
Opalin	0.0002	NA	0.0000	0.0000	0.0004
Upf2	0.0002	0.1622	1.0000	0.0045	0.1654
Tmc7	0.0002	NA	1.0000	0.6126	0.0987
Jhdm1d	0.0002	NA	0.0035	0.4932	0.0261
Cdk2ap2	0.0002	1.0000	1.0000	1.0000	0.2494
Arxes1	0.0002	NA	0.1397	1.0000	1.0000
Tbc1d4	0.0002	NA	0.9836	0.0629	1.0000
Ndufa1	0.0002	1.0000	1.0000	1.0000	1.0000
Zfp429	0.0002	NA	1.0000	1.0000	1.0000
Glul	0.0002	0.1914	0.4595	1.0000	0.0388
Gm14025	0.0003	NA	NA	NA	NA
Srrt	0.0003	0.0101	0.0261	0.0000	0.0017
Spats1	0.0003	NA	1.0000	1.0000	1.0000
Prtg	0.0003	NA	0.6556	1.0000	1.0000
Cables1	0.0003	NA	0.0001	0.0000	0.0687
B230206f22rik	0.0003	NA	NA	NA	NA
Osbp2	0.0003	NA	1.0000	1.0000	1.0000
Rit1	0.0003	0.0246	1.0000	1.0000	1.0000
Cacna1i	0.0003	NA	1.0000	0.3666	1.0000

Type of action	Oscillating genes Control	Oscillating genes TLE	Expression change Control	Expression change TLE
Target	ADAM10, BPHL, **CACNA1I**, CALR, CRBN, FLT1, FOLH1, GLUL, HSP90B1, HSPA5, IGF1R, KDR, MERTK, MMAA, MMP14, NDUFA1, NDUFA6, NMNAT1, NPEPPS, P4HA1, PRKAB2, RAB8B, SMOX, XDH	***ABCC1***, ACAN, ADRBK1, ADSSL1, AFG3L2, AKT2, ALAS1, ALDH6A1, ALKBH3, ANO1, APRT, BCL2, CD52, CTSK, CYB5R3, CYSLTR2, DDAH2, DHPS, DNPEP, EDNRB, F2R, FASN, FPGS, GARS, GLS, GLUL, GPT2, GRIK5, GRM7, GSR, HCN2, HDAC6, HDAC8, HIF1AN, HRH3, IMPG2, LARS, MAPT, MERTK, MLLT4, MMAA, MMP14, MTRR, NDUFA10, NFKBIA, PDE7A, PFN1, PIK3CA, PRKAB1, PSMA4, PSMA7, PSMB7, PTPRS, QPCT, RAB8B, RNGTT, RPL19, RPS6KA4, RYR2, SGPL1, SHMT1, SLC15A2, SLC16A3, SLC6A9, SLC7A8, STMN4, SULT2B1, TSTA3, TUBD1, VARS, WEE1	ADAM10, BRAF, CALR, CXCR4, FLT1, FOLH1, GLUL, HSP90B1, HSPA5, MERTK, MMAA, NDUFA1, NDUFA6, NFKBIA, P4HA1, PRKAB2, SLC16A1, SMOX, TOP1, XDH	AASS, ***ABCC1***, ADSSL1, AGT, AKT2, ALDH6A1, ALDH7A1, AMT, APRT, ASPH, CACNA1B, CALR, CD44, CYB5R3, CYSLTR2, DBH, DDAH2, DDX6, DHPS, DHRS3, DNPEP, F2R, **GABRA3**, GLUL, GPT2, GSR, GSTM5, HDAC6, HDAC8, HIF1AN, HSP90B1, HSPA5, HSPB1, IMPG2, KCNA4, LARS, **MAOB**, MERTK, MLLT4, MMAA, NCOA5, NDUFA10, NFKBIA, P4HA1, PAICS, PDE7A, PDK4, PRKAB1, PRODH, PSMA7, PTPRS, QPCT, RB1, RNGTT, ROCK2, SERPINF2, SHMT1, SLC7A8, SULT2B1, TUBD1, VARS, WEE1
Carrier	FABP7, SLC2A1	FABP5, SLC2A1	FABP7, SLC2A1	
Enzyme	GLUG, XDH	APRT, FPGS, GLS, GLUL, GSR, HIF1AN, VARS	GLUL, XDH	APRT, CHKA, DBH, GLUL, GSR, HIF1AN, MAOB, PRODH, SRM, TGM1, VARS
Transporter	SLC2A1, **SLCO1C1**	**ABCC1**, ABCC5, SLC15A2, SLC16A3, SLC2A1, SLC2A9, SLC7A5, SLC7A8, TFRC	**SLC16A1**, SLC2A1	**ABCC1**, ABCC5, SLC14A1, SLC2A9, SLC7A5, SLC7A8, TFRC

Table 2

Gene symbol	Function	OSC	DE	Animals	Anticonvulsant drug names
ABCC1	Tr	+	+	TLE	Phenobarbital
CACNA1B	T	-	+	TLE	Gabapentin, levetiracetam
CACNA1I	T	+	-	CTR	Paramethadione, zonisamide, flunarizine
GABRA3	T	-	+	TLE	Meprobamate, metharbital, thiopental, primidone, diazepam, methylphenobarbital, estazolam, fludiazepam, nitrazepam
MAOB	T	-	+	TLE	Zonisamide
SLC16A1	Tr	-	+	CTR	Valproic Acid
SLCO1C1	Tr	+	-	CTR	Phenytoin

Table 3

Note

All the data will be made publicly available on the Circadiomics [1,2] web portal at http://circadiomics.igb.uci.edu/ upon acceptance of the manuscript.

Supplementary Materials

Materials and methods

Animals

All experiments were performed on FVB adult male mice following Inserm procedures. Twenty four control and twenty four TLE mice were used for transcriptomics and proteomics. They were kept in a special in house animal facility with a strict control of light and temperature conditions (beginning of the light phase at 7:30 and beginning of the night phase at 19:30). A red light, which does not disrupt circadian rhythmicity, was present during the night phase to allow researchers to manipulate the animals. During the night phase, no external light could enter the room when opening the door. Mice were housed in groups of four to five to enable social interaction. Cages had enriched environment. Throughout the experimental procedure, the same researcher took care of the animals at the same time of the day to limit external stressful factors. Animals were anesthetized with isoflurane in the animal facility and four of them killed every four hours (six time points).

The brain was quickly extracted and the hippocampus removed in modified ice cold ACSF. Right (for transcriptome analysis) and left (for proteomics) hippocampi were separated into their ventral and dorsal parts and quickly frozen. Only the ventral parts were used here. The average time between decapitation and sample freezing was 90s per mice to limit any degradation of gene products and proteins. All tissue collection was performed during a single 24h period. The collection of the hippocampal tissue from the four mice per time window was performed in less than 10 minutes.

Model of epilepsy

Adult FVB mice were injected with methylscopolamine (1 mg/kg i.p.) 30 min before the pilocarpine injections. Pilocarpine was repeatedly injected (100 mg/kg i.p.), every twenty minutes, until status epilepticus (SE) was observed [3]. After 90 min of SE, we injected diazepam (10 mg/kg i.p.) to stop SE. All mice then received 0.5 ml NaCl (0.9%) subcutaneously, and again in the evening. During the following days, if required, mice were fed with a syringe.

24/7 EEG monitoring

Ten mice were implanted with a telemetry probe (ETA F10, (Data Science International [DSI], St Paul, MN). The stereotaxic surgery was performed under ketamine (100mg/kg) / xylazine (10mg/kg) anesthesia. Lidocaine was used locally. Temperature, heart rate, and breathing rate were continuously monitored during the surgical procedure (MouseOx®Plus). A recording skull screw was secured above the hippocampal CA1 region (-1.8mm posterior, +1.8mm lateral), and a reference skull screw was secured above the cerebellum. The leads of the telemetry probe (Data Science International [DSI], St Paul, MN) were wrapped around the recording and reference screws, and screws were all encased in dental cement. The probe body containing the battery was placed subcutaneously in the back of the mice. Animals were allowed 7 days postsurgical recovery before any further experimental procedures were conducted. Electroencephalographic (EEG) recordings were performed continuously until the end of the experimental protocol. Seizures were automatically detected with DSI software (adjusting for frequency and amplitude) using low detection values. This led to numerous false positives (mostly movement artifacts), which were manually removed after double-checking by a trained technician and clinical epileptologist. Complete EEG recordings were

fully visually inspected. No false negatives were detected (i.e., the semi-automated procedure insured the detection of all seizures).

All pilocarpine-treated mice developed spontaneous seizures.

Animal care and handling

We kept 6 mice (control or epileptic) per cage, with enriched environment. We found that keeping epileptic mice together (as opposed to one mouse per cage) dramatically changed their behavior. They recovered faster from status epilepticus. They could be easily handled, denoting a lack of stress. When epileptic mice are housed in individual cages, they are extremely nervous and it is very difficult to handle them. Here, we removed a confounding stress factor linked to the lack of social interaction, as reported in rats [4].

Seizure threshold tests with pentylenetetrazole (PTZ)

Seizure threshold was determined in individual male FVB mice by the timed intravenous pentylenetetrazole (PTZ) test as described previously [5], in a total of 57 naive and 55 epileptic mice. Epilepsy was induced by pilocarpine [3], and seizure thresholds were determined 7-9 weeks after SE, when all mice had developed epilepsy. Groups of 8–20 mice were used per threshold determination. PTZ infusion was stopped at the first seizure, and seizure threshold was calculated in mg PTZ per kg body weight based on the infusion time needed to induce this seizure endpoint [5]. PTZ thresholds were determined every 4 hours during the light and dark phase. The maximum number of threshold determinations was limited to 3 per animal with 7 days in between (repeated seizure threshold tests do not alter the threshold if an interval of at least 48 h lies within the determinations) [5-7]. Additionally, we performed two PTZ seizure threshold determinations at the same time-point (ZT11:30) to compare PTZ

thresholds at the beginning and at the end of the experiment, demonstrating the reproducibility of the method.

Data were analyzed by using the Prism5 software from GraphPad (La Jolla, CA, USA). Thresholds of control and SE animals were analyzed separately using one-way analysis of variance (ANOVA) and Bonferroni post tests and combined by using a two-way ANOVA with Student's *t*-tests as post hoc analysis. All tests were used two-sided; a $P < 0.05$ was considered significant.

RNA isolation and microarray hybridization. RNA isolation and microarray hybridization was performed as previously described [8]. The isolation of total RNA was performed using the miRNeasy Mini kit (QIAGEN, # 217004) according to the manufacturer's instructions. The sample quality was determined using a NanoDrop 2000 spectrophotometer (Thermo, Fisher Scientific) and Agilent 2100 Bioanalyzer. GeneChip® Mouse Gene 2.1 ST arrays (Affymetrix, Santa Clara, CA, # 902120) were used for mRNA profiling. One hundred nanograms of total mRNA was used for cDNA synthesis using the Ambion WT Expression Kit (Life Technologies, # 4411974). Hybridization, washing and scanning were conducted according to Affymetrix guidelines for the GeneAtlas™ instrument.

Quantitative PCR. Reverse transcription for individual qPCRs was carried out using 250 ng of total RNA and the High-Capacity Reverse Transcription Kit (# 4368814, Life Technologies) according to the manufacturer's instruction. Quantitative PCRs were run on the ABI 79OOHT Fast Real-Time PCR instrument (Applied Biosystems). Gene expression analysis was conducted using a relative standard curve method with glyceraldehyde-3-phosphate dehydrogenase (Gapdh) to normalise the expression levels of target genes. All reactions were performed in triplicates.

Bioinformatic analysis. Analysis of microarrays was performed using R/Bioconductor (R Core Team, 2014; www.bioconductor.org). All microarrays were normalized with the Robust Multi-array Average (RMA) algorithm using oligo package (version 1.28.3) [9]. Background value of intensity of probes was defined as median value of the intensity of antigenomic probes. The intensity of genomic probes below the background intensity was corrected to this background value. Probes with intensity greater than background value in less than four samples were removed from analysis. Only probes that corresponded to a single gene were selected for further analysis.

JTK_Cycle and BIO_CYCLE were used to identify oscillating genes at three p-value thresholds [10]. Gene lists for transcripts oscillating at each p-value in the control condition alone, the TLE condition alone, or both conditions were identified for further analysis. Cyber-T was used to identify differentially expressed timepoints between control and TLE conditions for each animal [11]. Cyber-T p-values found for each time point for core clock genes are reported (Figure 2C). Proteomic data for both control and TLE conditions was also analyzed by JTK_Cycle to identify rhythmic proteins. All transcriptome data is available for search on Circadiomics along with JTK_Cycle and BIO_CYCLE results [1].

Genes, which expression level differed between time points according to one-way ANOVA analysis performed separately for control and epileptic animals are presented on the heatmap (Figure 1). Differences were considered as significant for adjusted p-value < 0.5 – or 0.01 – depending on our final decision (FDR – Benjamini & Hochberg (BH) correction). Genes were ordered by clustering complete-linkage method together with Pearson correlation distance measure. Nine gene clusters highlighted on the heatmap were obtained by cutting dendrogram the selected level of the dendrogram. Functional analysis for Biological Function Go Terms was performed using MF FAT Chart option with default settings in DAVID with

(http://david.abcc.ncifcrf.gov; [12,13]). Transcription factor binding sites overrepresented in promoters within clusters were detected with gProfiler (http://biit.cs.ut.ee/gprofiler/; [14,15]) with custom background defined as genes detected in the experiment to reveal the functional and regulatory groups presented in the data.

Further transcription factor binding site enrichment analysis was performed using MotifMap [16,17] and CHiP-seq datasets provided by UCSC Encode project [18]. Transcription factor binding sites identified by MotifMap were found both 10 KB upstream and 2 KB downstream of transcription start sites (TSS) for all genes in each of the differentially expressed gene lists for all pair-wise comparisons. The motifs identified were found with a BBLS conservation score of greater than or equal to 1.0 and an FDR of less than 0.25. CHiP-seq datasets were used to locate experimentally identified binding site locations within the same interval around the TSS for differentially expressed genes. Only the 90th percentile of CHiP-seq peaks were used from each dataset provided by UCSC Encode. A Fisher's exact test was performed separately using the full background list of motifs from MotifMap and all target genes from the CHiP-seq datasets to compute the statistical likelihood of over representation in promotor regions.

Proteomics

Protein extraction:

All steps of the protein extraction were performed on ice or at 4°C. Isolated hippocampal tissue was homogenized in lysis buffer containing 20 mM triethylammonium bicarbonate (TEAB, Fluka), 5 % sodium deoxycholate (SDC, Sigma-Aldrich) and 1 tablet of protease inhibitor (Roche). Homogenates were boiled for 3 minutes and subsequently sonicated three times for 10 s, each time paused for 30 s.

Samples were centrifuged to pellet tissue debris and the protein concentration in the supernatant was measured with a BCA protein assay (Pierce) using bovine serum albumin as standard.

Protein Digestion:

Dithiotreitol (DTT) was added to 200 µg of the global protein fraction up to a final concentration of 20 mM DTT in the solution. Samples were incubated for 20 min at 55°C and then centrifuged for 1 minute at 10000xg (20 °C). The supernatant was transferred to filter devices (10kDa MWCO, VWR) and filled up with digestion buffer (DB) containing 20 mM TEAB and 0.5 % SDC. Next, the samples were centrifuged for 10 minutes at 10000xg (20°C), the flow-through was discarded and 100 µl of 40 mM Indoacetamide (IAA) in DB was added to the filter devices followed by a 20 min incubation at room temperature in darkness. Afterwards samples were washed twice with DB and trypsin solved in DB was added to yield a protein to trypsin ratio of 100:1. Samples were incubated over night at 37°C. Filter devices were centrifuged for 20 minutes at 10000xg (20° C) and the flow-through was collected. Residual peptides were removed by another centrifugation step with DB. The flow-throughs of one sample were combined and first an equal volume of ethyl acetate and subsequently trifluoreoacetic acid (TFA, final concentration 0.5%) was added. The solution was mixed and centrifuged for 2 minutes at 14000xg (20° C). The upper layer was discarded and 250 µl of acetate ethyl was added, followed by centrifugation. The upper layer was discarded again and the aqueous phase was collected for further procession.

Isobaric labeling and peptide fractionation

Peptides were vacuum concentrated and labeled with amine-reactive, 6-plex tandem mass tag reagents (Thermo Fisher Scientific, Bremen, Germany) according to manufacturer's instructions. The labeling reaction was quenched by addition of 5% hydroxylamine. Labeled peptides were pooled and desalted on Oasis HLB cartridges (Waters GmbH, Eschborn, Germany). Eluates containing 70% acetonitrile, 0.1% formic acid (FA) were dried and fractionated to 24 fractions by isoelectric point with an Offgel fractionator according to manufacturer's recommendations (Agilent Technologies, Waldbronn, Germany). Peptide fractions were dried and stored at -20°C.

LC-MS analysis

Peptides were dissolved in 8 µl 0.1% trifluoroacetic acid. 1.5 µl were injected onto a C18 trap column (20 mm length, 100 µm inner diameter) coupled to a C18 analytical column (200 mm length, 75 µm inner diameter), made in house with 1.9 µm ReproSil-Pur 120 C18-AQ particles (Dr. Maisch, Ammerbuch, Germany). Solvent A was 0.1% formic acid. Peptides were separated during a linear gradient from 4% to 40% solvent B (90% ACN, 0.1% formic acid) within 90 min. The nanoHPLC was coupled online to an LTQ Orbitrap Velos mass spectrometer (Thermo Fisher Scientific). Peptide ions between 330 and 1800 m/z were scanned in the Orbitrap detector with a resolution of 30,000 (maximum fill time 400 ms, AGC target 10^6, lock mass 371.0318 Da). The 20 most intense precursor ions (threshold intensity 5000) were subjected to higher energy collision induced dissociation (HCD) and fragments also analyzed in the Orbitrap. Fragmented peptide ions were excluded from repeat analysis for 15 s. Raw data processing and analyses of database searches were performed with Proteome Discoverer software 1.4.1.12 (Thermo Fisher Scientific). Peptide identification was done with an in house Mascot server version 2.4.1 (Matrix Science Ltd, London, UK). MS2 data (including a-series ions) were searched against mouse sequences from SwissProt (release

2014_01). Precursor Ion m/z tolerance was 10 ppm, fragment ion tolerance 20 mmu. Tryptic peptides were searched with up to two missed cleavages. Low scoring spectrum matches were searched again with semitryptic specificity with up to one missed cleavage. Oxidation (Met), acetylation (protein N-terminus), and TMTsixplex (on Lys and N-terminus) were set as dynamic modifications, carbamidomethylation (Cys), was set as static modification. Mascot results from searches against SwissProt were sent to the percolator algorithm [19] version 2.04 as implemented in Proteome Discoverer. Only proteins with two peptides (maximum FDR 1%) were considered identified.

***In vitro* experiments**

Tissue slice preparation. Mice were anaesthetized with isoflurane and decapitated at ZT11 or ZT15. The brain was rapidly removed from the skull and placed in the ice-cold ACSF as above. The ACSF solution consisted of (in mmol/L): NaCl 126, KCl 3.50, NaH2PO4 1.25, NaHCO3 25, CaCl2 2.00, MgCl2 1.30, and dextrose 5, pH 7.4. ACSF was aerated with 95% O2/5% CO2 gas mixture. Slices of ventral hippocampus (350 µm) were cut as described [20], using a tissue slicer (Leica VT 1200s, Leica Microsystem, Germany). The ice-cold (< 6°C) cutting solution consisted of (in mmol/L): K-gluconate 140, HEPES 10, Na-gluconate 15, EGTA 0.2, NaCl 4, pH adjusted to 7.2 with KOH. Slices were then immediately transferred to a multi-section, dual-side perfusion holding chamber with constantly circulating ACSF and allowed to recover for 2h at room temperature (22°C-24°C). Slices were then transferred to a recording chamber continuously superfused with ACSF (flow rate 7ml/min, warmed at 30–31°C) with access to both slice sides.

Synaptic stimulation and field potential recordings. Schaffer collaterals were stimulated using a DS2A isolated stimulator (Digitimer Ltd, UK) with a bipolar metal electrode.

Stimulus current was adjusted using single pulses (100-300 µA, 200µs, 0.15 Hz) to induce a local field potential (LFP) of about 60% of maximal amplitude. LFPs were recorded using glass microelectrodes filled with ASCF, placed in stratum pyramidale and connected to an EXT-02F/2 amplifier (NPI Electronic GmbH, Germany). Synaptic stimulation consisting of a stimulus train (200µs pulses) at 10 Hz lasting 30s was used to trigger metabolic response.

NAD(P)H fluorescence imaging. NAD(P)H and NADH have similar optical properties, therefore it is expected that NAD(P)H may contribute to the total autofluorescence signal. Because the cellular NADP/ NAD(P)H pool is about one order of magnitude lower than the NAD/NADH pool, in the present study we assume that short-term variations of experimentally detected NAD(P)H responses account for variations in NADH (see discussion in [21]). Changes in NAD(P)H fluorescence in hippocampal slices were monitored using a 290–370 nm excitation filter and a 420 nm long-pass filter for the emission (Omega Optical, Brattleboro, VT). The light source was the pE-2 illuminator (CoolLed, UK) equipped with 365 nm LED. Slices were epi-illuminated and imaged through a Nikon upright microscope (FN1, Eclipse) with 4x/0.10 Nikon Plan objective. Images were acquired using a 16-bit Pixelfly CCD camera (PCO AG, Germany). Because of a low level of fluorescence emission, NAD(P)H images were acquired every 600-800 ms as 4x4 binned images (effective spatial resolution of 348x260 pixels). The exposure time was adjusted to obtain baseline fluorescence intensity between 2000 and 3000 optical intensity levels. Fluorescence intensity changes in stratum radiatum near the site of LFP recording were measured in 3 regions of interest ~1mm distant from the stimulation electrode tip using ImageJ software (NIH, USA). Data were expressed as the percentage changes in fluorescence over a baseline [(ΔF/F) • 100]. Signal analysis was performed using IgorPro software (WaveMetrics, Inc, OR, USA).

Statistical analysis and signal processing. NAD(P)H dip and overshoot amplitudes were expressed as means ±SEM. Normality was rejected by Shapiro-Wilk normality test; therefore we used non-parametric Wilcoxon rank sum test. The level of significance was set at $p<0.05$.

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Author contributions

AG, AMB GB and JAM performed experiments, and analyzed data. AB, AI, KJD, NG, SB, SJ, SS and WL performed experiments, analyzed data and wrote the manuscript. AB, KL, PB and PSC supervised aspects of the project and wrote the manuscript. CB conceived and managed the project, performed experiments, analyzed data and wrote the manuscript.

figure S1. Changes in expression levels of selected genes in the ventral hippocampus of TLE and control animals. Panel A shows results for clock genes, panel B is dedicated for selected channels genes. Top rows show microarray data, whilst bottom rows show qPCR results. In the qPCR analysis GAPDH was used as an internal control and all values represent the mRNA level of the gene of interest normalised to the GAPDH mRNA level. Results are represented as means ± SD (n=4 in each group for each time-point in TLE and control animals). Note the correspondence between microarray and qPCR data. Panel C shows the correlation between qPCR and microarray data calculated using Spearman correlation. Rho and p-values are shown on the graph. Yellow circles represent epileptic animals and blue triangles represent control animals. Symbols indicate # results of the one-way ANOVA analysis, * $p<0.05$, ** $p<0.01$ of unpaired t-test with Welch's correction, ooo $p<0.001$, oo $p<0.01$, o $p<0.05$.

figure S2. Heatmaps of oscillating genes in both conditions (top), control only (middle) and epileptic (TLE) only (bottom). JTK algorithm [10] was used to estimate gene oscillations. A gene was considered as significantly oscillating if Benjamani-Hochberg q-value was less then 0.05. Genes were ordered according to phase. The treatment groups are color-coded: blue for controls and orange for TLE. The panels on the left side of the heatmaps show which genes are enriched in neurons (blue), oligodendrocytes (green), and astrocytes (coral). Cell type enrichment is based on data obtained from [22].

figures S3 to figure S8. Differences in up- or down-regulation of gene sets for Gene Ontology Molecular Function (GO_MF, S3), Cellular Component (GO_CC, S4) and Biological Process (GO_BP, S5), as well as for biological pathways based on BIOCARTA (S6), KEGG (S7) and REACTOME (S8). Gene Sets were obtained from Molecular Signatures Database v5.0

(http://software.broadinstitute.org/gsea/msigdb/index.jsp) and used in Gene Set Enrichment Analysis (http://software.broadinstitute.org/gsea/index.jsp). For GSEA, we used a ranking based on score -log10(pvalue) * sign (fold change). We calculated p-values comparing two consecutive time points with t-test in control and epileptic animals separately (e.g. when comparing ZT3 and ZT7, we used ZT3 as our reference time point). All values can be found in corresponding tables S14 to S19. A large wealth of information is available to evaluate the circadian regulation of different pathways in controls and their modification in TLE. For example, based on GO_MF, there is a down-regulation of voltage-gated channels at ZT3 in controls, but at ZT19 in TLE; whilst anion channel activity is specifically up-regulated at ZT7 in TLE.

figures S9 to figure S14. As figure S3 to S8, but here the analysis was done to compare differences between control and TLE animals at each time point. All values can be found in corresponding tables S20 to S25. This data is particularly useful to identify which pathways are modified in TLE at specific time points. For example, there is an up-regulation of glucose metabolism at ZT19 and a down-regulation of pyruvate metabolism at ZT3 and ZT7 in TLE.

figure S15. Thresholds of control mice did not differ significantly, whereas thresholds of TLE animals were significantly lower at ZT23.30 and ZT3.30 than during day-time represented by ZT11.30 (one way ANOVA P=0.0171, post hoc Bonferroni P<0.05). Both groups and time-points were compared using a two-way ANOVA, which revealed significant differences between the two groups at the time-points ZT11.30 and ZT23:30 (two-way ANOVA, followed by unpaired t-test *P<0.05;**P<0.01).

Tables S1 to S4. Results of transcriptome (S1) and proteome (S2) analyses for control and TLE (S3 and S4) animals, respectively.

Tables S5 to S13. Enriched terms reported from DAVID bioinformatics for oscillating genes found in control condition alone, epileptic condition alone, and oscillating in both conditions for 0.05 (S5 to S7), 0.01 (S8 to S10) and 0.001 (S11 to S13) p-values, respectively.

Tables S14 to S25. Raw data corresponding to figures S3 to S14 for Gene Ontology Molecular Function (GO_MF), Cellular Component (GO_CC), Biological Process (GO_BP), BIOCARTA, KEGG and REACTOME.

Additional information about drugs:

Sulfinpyrazone (DB01138) - A uricosuric drug that is used to reduce the serum urate levels in gout therapy. It lacks anti-inflammatory, analgesic, and diuretic properties. [PubChem] INDICATION: For the treatment of gout and gouty arthritis.

Biricodar dicitrate (DB04851) - The pipecolinate derivative biricodar (VX-710) is a clinically applicable modulator of P-glycoprotein (Pgp) and multidrug resistance protein (MRP-1). INDICATION: Administered intravenously, biricodar dicitrate is to be used in combination with cancer chemotherapy agents.

Antiepileptic and Anticonvulsant drugs:

Diazepam (DB00829) - A benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnesic properties and a long duration of action. Its actions are mediated by enhancement of gamma-aminobutyric acid activity. It is used in the treatment of severe anxiety disorders, as a hypnotic in the short-term management of insomnia, as a sedative and premedicant, as an anticonvulsant, and in the management of alcohol withdrawal syndrome. (From Martindale, The Extra Pharmacopoeia, 30th ed, p589) INDICATION: Used in the treatment of severe anxiety disorders, as a hypnotic in the short-term management of insomnia, as a sedative and premedicant, as an anticonvulsant, and in the management of alcohol withdrawal syndrome.

Estazolam (DB01215) - A benzodiazepine with anticonvulsant, hypnotic, and muscle relaxant properties. It has been shown in some cases to be more potent than diazepam or nitrazepam. [PubChem] INDICATION: For the short-term management of insomnia

characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

Fludiazepam (DB01567) - Fludiazepam is a drug which is a benzodiazepine derivative. It possesses anxiolytic, anticonvulsant, sedative and skeletal muscle relaxant properties. It is a scheduled drug in the U.S., but is approved for use in Japan. INDICATION: Used for the short-term treatment of anxiety disorders.

Flunarizine (DB04841) - Flunarizine is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity.
It is effective in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo of central and peripheral origin, and as an
adjuvant in the therapy of epilepsy. INDICATION: Used in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo of central
and peripheral origin, and as an adjuvant in the therapy of epilepsy.

Gabapentin (DB00996) - Gabapentin (brand name Neurontin) is a medication originally developed for the treatment of epilepsy. Presently, gabapentin is widely used to relieve pain, especially neuropathic pain. Gabapentin is well tolerated in most patients, has a relatively mild side-effect profile, and passes through the body unmetabolized. INDICATION: For the management of postherpetic neuralgia in adults and as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy.

Levetiracetam (DB01202) - Levetiracetam is an anticonvulsant medication used to treat epilepsy. Levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. Levetiracetam binds to the synaptic vesicle protein SV2A, which is thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to synaptic vesicle protein SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. INDICATION: Used as adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.

Meprobamate (DB00371) - A carbamate with hypnotic, sedative, and some muscle relaxant properties, although in therapeutic doses reduction of anxiety rather than a direct effect may be responsible for muscle relaxation. Meprobamate has been reported to have anticonvulsant actions against petit mal seizures, but not against grand mal seizures (which may be exacerbated). It is used in the treatment of anxiety disorders, and also for the short-term management of insomnia but has largely been superseded by the benzodiazepines. (From Martindale, The Extra Pharmacopoeia, 30th ed, p603) Meprobamate is a controlled substance in the U.S. INDICATION: For the management of anxiety disorders or for the short-term relief of the symptoms of anxiety.

Metharbital (DB00463) - Metharbital was patented in 1905 by Emil Fischer working for Merck. It was marketed as Gemonil by Abbott Laboratories. It is a barbiturate anticonvulsant, used in the treatment of epilepsy. It has similar properties to phenobarbital [Wikipedia]. INDICATION: Metharbital is used for the treatment of epilepsy.

Methylphenobarbital (DB00849) - A barbiturate that is metabolized to phenobarbital. It has been used for similar purposes, especially in epilepsy, but there is no evidence mephobarbital offers any advantage over phenobarbital. [PubChem] INDICATION: For the relief of anxiety, tension, and apprehension, also used as an anticonvulsant for the treatment of epilepsy.

Nitrazepam (DB01595) - A benzodiazepine derivative used as an anticonvulsant and hypnotic. INDICATION: Used to treat short-term sleeping problems (insomnia), such as difficulty falling asleep, frequent awakenings during the night, and early-morning awakening.

Paramethadione (DB00617) - Paramethadione is an anticonvulsant in the oxazolidinedione class. It is associated with fetal trimethadione syndrome, which is also known as paramethadione syndrome. INDICATION: Used for the control of absence (petit mal) seizures that are refractory to treatment with other medications.

Phenobarbital (DB01174) - A barbituric acid derivative that acts as a nonselective central nervous system depressant. It promotes binding to inhibitory gamma-aminobutyric acid subtype receptors, and modulates chloride currents through receptor channels.
It also inhibits glutamate induced depolarizations. [PubChem]. INDICATION: For the treatment of all types of seizures except absence seizures.

Phenytoin (DB00252) - An anticonvulsant that is used in a wide variety of seizures. It is also an anti-arrhythmic and a muscle relaxant. The mechanism of therapeutic action is not clear, although several cellular actions have been described including effects on ion channels, active transport, and general membrane stabilization. The mechanism of its muscle relaxant effect appears to involve a reduction in the sensitivity of muscle spindles to stretch. Phenytoin has

been proposed for several other therapeutic uses, but its use has been limited by its many adverse effects and interactions with other drugs. [PubChem]. INDICATION: For the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

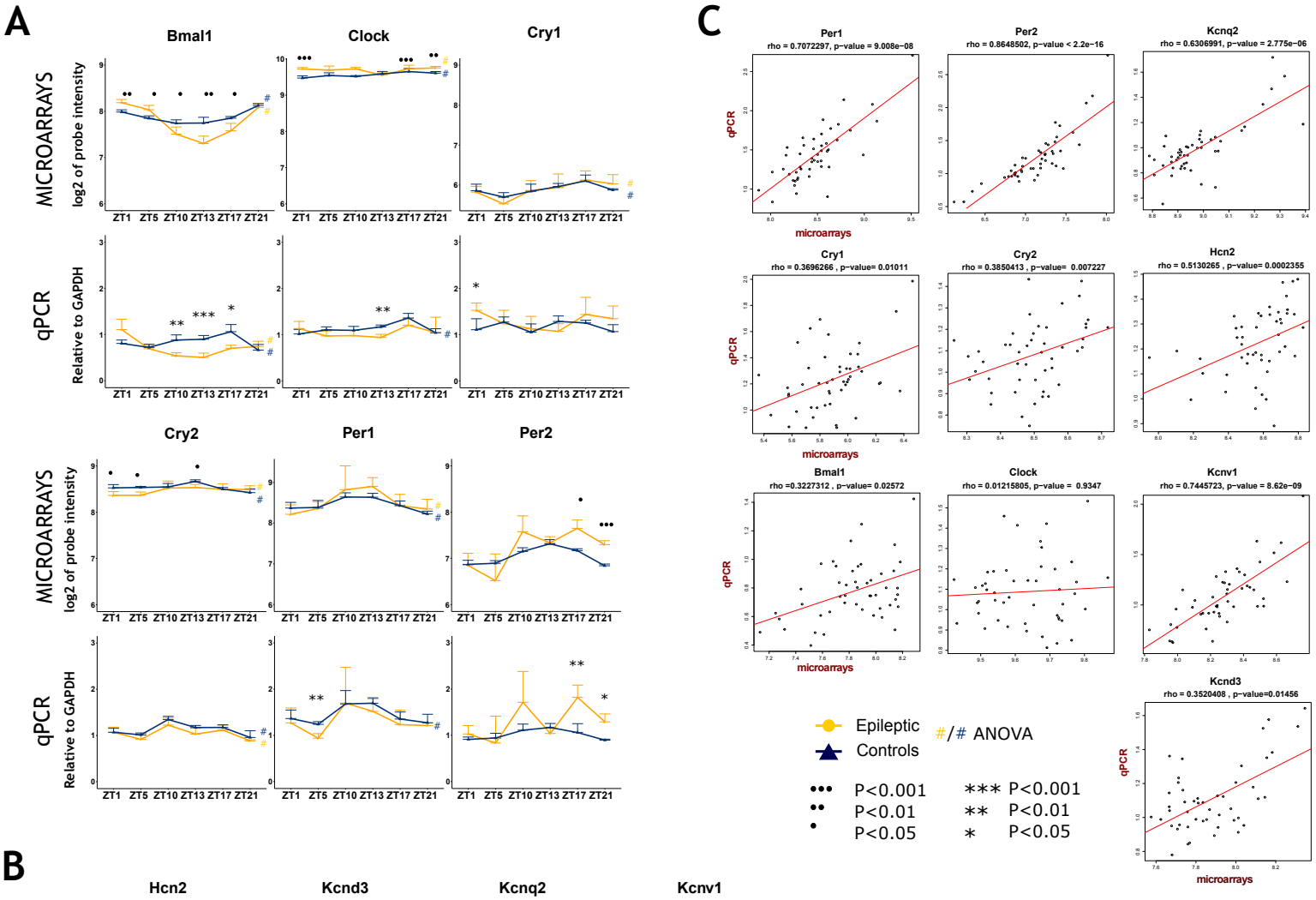
Primidone (DB00794) - An antiepileptic agent related to the barbiturates; it is partly metabolized to phenobarbital in the body and owes some of its actions to this metabolite. Adverse effects are reported to be more frequent than with phenobarbital. (From Martindale, The Extra Pharmacopoeia, 30th ed, p309) INDICATION: For the treatment of epilepsy

Thiopental (DB00599) - A barbiturate that is administered intravenously for the induction of general anesthesia or for the production of complete anesthesia of short duration. It is also used for hypnosis and for the control of convulsive states. It has been used in neurosurgical patients to reduce increased intracranial pressure. It does not produce any excitation but has poor analgesic and muscle relaxant properties. Small doses have been shown to be anti-analgesic and lower the pain threshold. (From Martindale, The Extra Pharmacopoeia, 30th ed, p920) INDICATION: For use as the sole anesthetic agent for brief (15 minute) procedures, for induction of anesthesia prior to administration of other anesthetic agents, to supplement regional anesthesia, to provide hypnosis during balanced anesthesia with other agents for analgesia or muscle relaxation, for the control of convulsive states during or following inhalation anesthesia or local anesthesia, in neurosurgical patients with increased intracranial pressure, and for narcoanalysis and narcosynthesis in psychiatric disorders.

Valproic Acid (DB00313) - Valproic acid, supplied as the sodium salt valproate semisodium or divalproex sodium, is a fatty acid with anticonvulsant properties used in the treatment of

epilepsy. The mechanisms of its therapeutic actions are not well understood. It may act by increasing gamma-aminobutyric acid levels in the brain or by altering the properties of voltage dependent sodium channels. Typically supplied in the sodium salt form (CAS number: 76584-70-8). Valproic Acid is also a histone deacetylase inhibitor and is under investigation for treatment of HIV and various cancers. INDICATION: For treatment and management of seizure disorders, mania, and prophylactic treatment of migraine headache. In epileptics, valproic acid is used to control absence seizures, tonic-clonic seizures (grand mal), complex partial seizures, and the seizures associated with Lennox-Gastaut syndrome.

Zonisamide (DB00909) - Zonisamide is a sulfonamide anticonvulsant approved for use as an adjunctive therapy in adults with partial-onset seizures. Zonisamide may be a carbonic anhydrase inhibitor although this is not one of the primary mechanisms of action. Zonisamide may act by blocking repetitive firing of voltage-gated sodium channels leading to a reduction of T-type calcium channel currents, or by binding allosterically to GABA receptors. This latter action may inhibit the uptake of the inhibitory neurotransmitter GABA while enhancing the uptake of the excitatory neurotransmitter glutamate. INDICATION: For use as adjunctive treatment of partial seizures in adults with epilepsy.


A
Bmal1
Clock
Cry1
MICROARRAYS
log2 of probe intensity
qPCR
Relative to GAPDH
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Per1
Per2
ZT1 ZT5 ZT10 ZT13 ZT17 ZT21
C
Per1
rho = 0.7072297, p−value = 9.008e−08
Per2
rho = 0.8648502, p−value < 2.2e−16
Kcnq2
rho = 0.6306991, p−value = 2.775e−06
Cry1
rho = 0.3696266 , p−value= 0.01011
Cry2
rho = 0.3850413 , p−value= 0.007227
Hcn2
rho = 0.5130265 , p−value= 0.0002355
Bmal1
rho =0.3227312 , p−value= 0.02572
Clock
rho = 0.01215805, p−value = 0.9347
Kcnv1
rho = 0.7445723, p−value = 8.62e−09
Kcnd3
rho = 0.3520408 , p−value=0.01456
qPCR
microarrays
Epileptic
Controls
#/# ANOVA
P<0.001
P<0.01
P<0.05
*** P<0.001
** P<0.01
* P<0.05

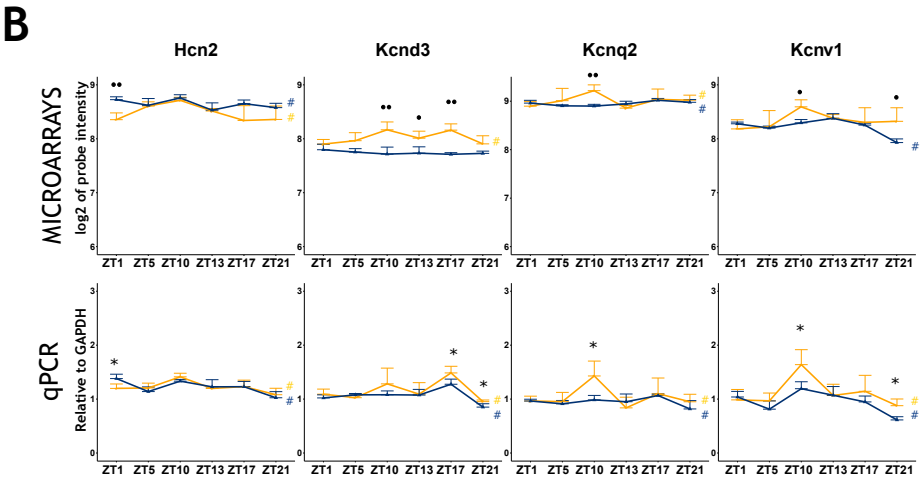
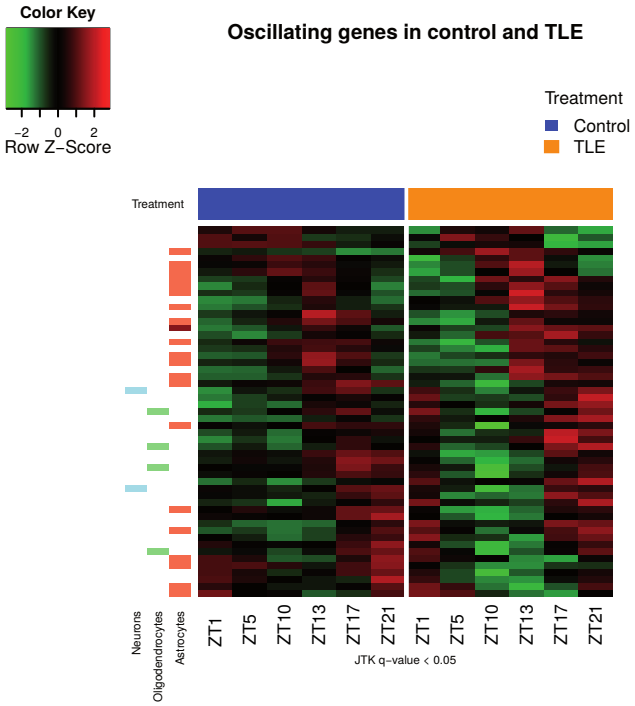
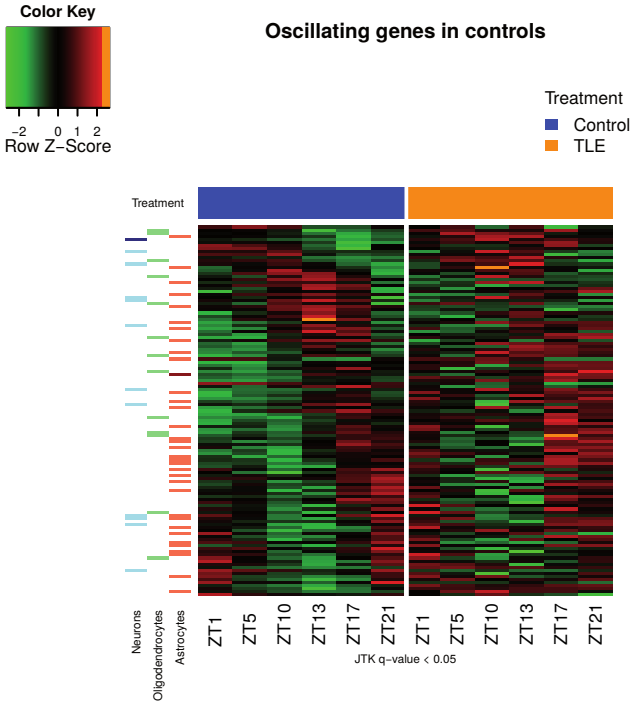

B
Hcn2
Kcnd3
Kcnq2
Kcnv1
MICROARRAYS
log2 of probe intensity
qPCR
Relative to GAPDH
ZT1 ZT5 ZT10 ZT13 ZT17 ZT21

figure S1


Color Key
−2 0 2
Row Z−Score
Oscillating genes in control and TLE
Treatment
Control
TLE
Treatment
Neurons
Oligodendrocytes
Astrocytes
ZT1 ZT5 ZT10 ZT13 ZT17 ZT21 ZT1 ZT5 ZT10 ZT13 ZT17 ZT21
JTK q−value < 0.05


Color Key
−2 0 1 2
Row Z−Score
Oscillating genes in controls
Treatment
Control
TLE
Treatment
Neurons
Oligodendrocytes
Astrocytes
ZT1 ZT5 ZT10 ZT13 ZT17 ZT21 ZT1 ZT5 ZT10 ZT13 ZT17 ZT21
JTK q−value < 0.05

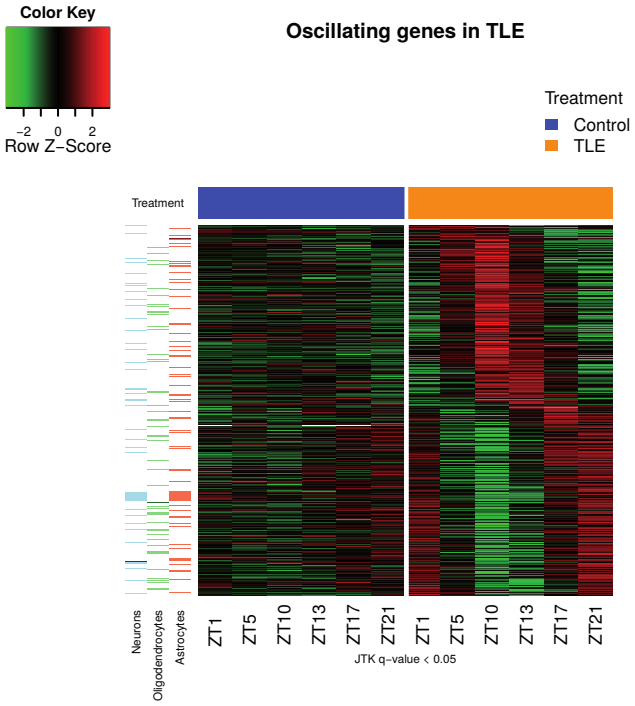

Color Key
−2 0 2
Row Z−Score
Oscillating genes in TLE
Treatment
Control
TLE
Treatment
Neurons
Oligodendrocytes
Astrocytes
ZT1 ZT5 ZT10 ZT13 ZT17 ZT21 ZT1 ZT5 ZT10 ZT13 ZT17 ZT21
JTK q−value < 0.05

figure S2

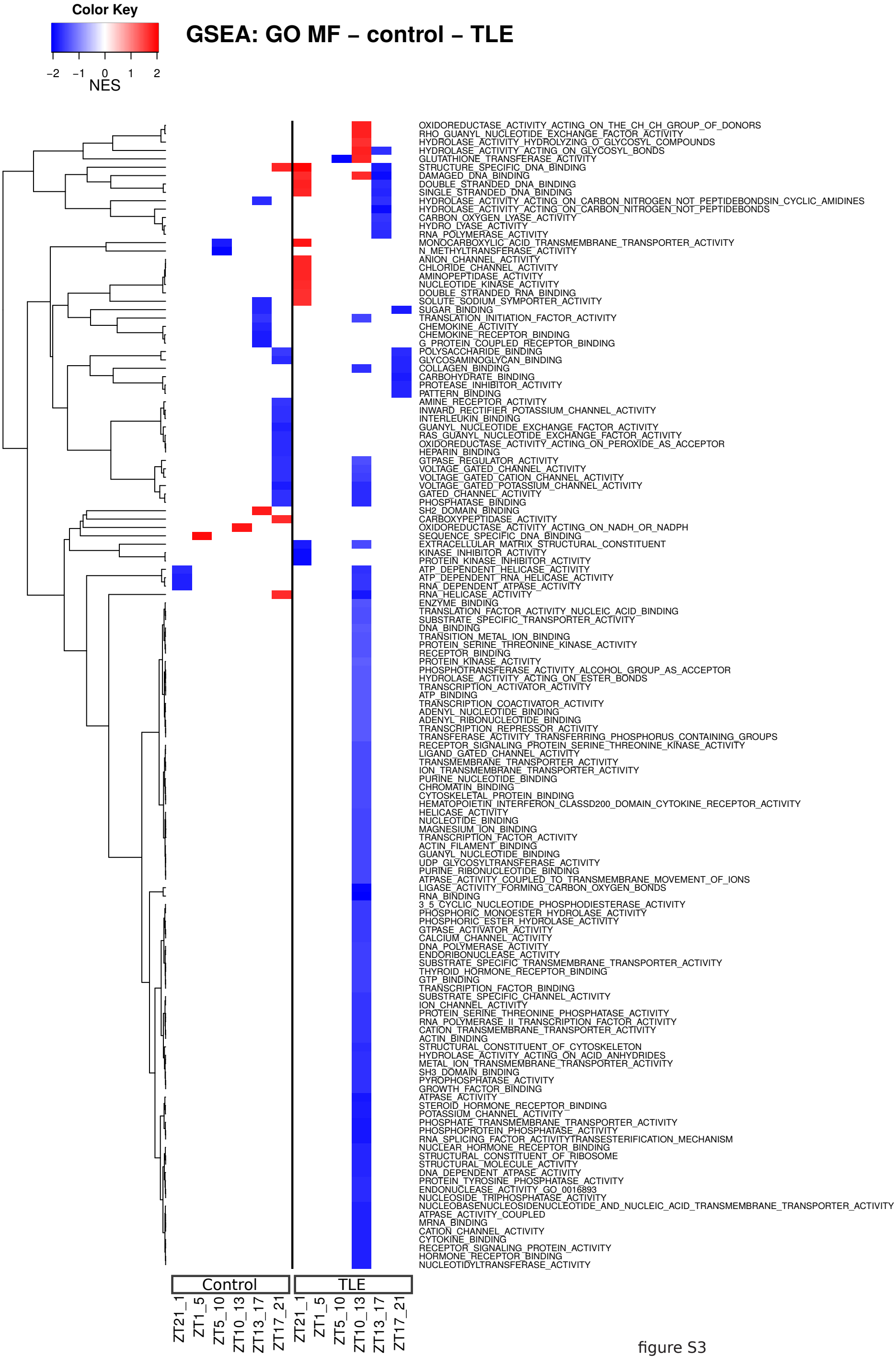

Color Key
−2 −1 0 1 2
NES
GSEA: GO MF – control – TLE
OXIDOREDUCTASE_ACTIVITY_ACTING_ON_THE_CH_CH_GROUP_OF_DONORS
RHO_GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
HYDROLASE_ACTIVITY_HYDROLYZING_O_GLYCOSYL_COMPOUNDS
HYDROLASE_ACTIVITY_ACTING_ON_GLYCOSYL_BONDS
GLUTATHIONE_TRANSFERASE_ACTIVITY
STRUCTURE_SPECIFIC_DNA_BINDING
DAMAGED_DNA_BINDING
DOUBLE_STRANDED_DNA_BINDING
SINGLE_STRANDED_DNA_BINDING
HYDROLASE_ACTIVITY_ACTING_ON_CARBON_NITROGEN_NOT_PEPTIDEBONDSIN_CYCLIC_AMIDINES
HYDROLASE_ACTIVITY_ACTING_ON_CARBON_NITROGEN_NOT_PEPTIDEBONDS
CARBON_OXYGEN_LYASE_ACTIVITY
HYDRO_LYASE_ACTIVITY
RNA_POLYMERASE_ACTIVITY
MONOCARBOXYLIC_ACID_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
N_METHYLTRANSFERASE_ACTIVITY
ANION_CHANNEL_ACTIVITY
CHLORIDE_CHANNEL_ACTIVITY
AMINOPEPTIDASE_ACTIVITY
NUCLEOTIDE_KINASE_ACTIVITY
DOUBLE_STRANDED_RNA_BINDING
SOLUTE_SODIUM_SYMPORTER_ACTIVITY
SUGAR_BINDING
TRANSLATION_INITIATION_FACTOR_ACTIVITY
CHEMOKINE_ACTIVITY
CHEMOKINE_RECEPTOR_BINDING
G_PROTEIN_COUPLED_RECEPTOR_BINDING
POLYSACCHARIDE_BINDING
GLYCOSAMINOGLYCAN_BINDING
COLLAGEN_BINDING
CARBOHYDRATE_BINDING
PROTEASE_INHIBITOR_ACTIVITY
PATTERN_BINDING
AMINE_RECEPTOR_ACTIVITY
INWARD_RECTIFIER_POTASSIUM_CHANNEL_ACTIVITY
INTERLEUKIN_BINDING
GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
RAS_GUANYL_NUCLEOTIDE_EXCHANGE_FACTOR_ACTIVITY
OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PEROXIDE_AS_ACCEPTOR
HEPARIN_BINDING
GTPASE_REGULATOR_ACTIVITY
VOLTAGE_GATED_CHANNEL_ACTIVITY
VOLTAGE_GATED_CATION_CHANNEL_ACTIVITY
VOLTAGE_GATED_POTASSIUM_CHANNEL_ACTIVITY
GATED_CHANNEL_ACTIVITY
PHOSPHATASE_BINDING
SH2_DOMAIN_BINDING
CARBOXYPEPTIDASE_ACTIVITY
OXIDOREDUCTASE_ACTIVITY_ACTING_ON_NADH_OR_NADPH
SEQUENCE_SPECIFIC_DNA_BINDING
EXTRACELLULAR_MATRIX_STRUCTURAL_CONSTITUENT
KINASE_INHIBITOR_ACTIVITY
PROTEIN_KINASE_INHIBITOR_ACTIVITY
ATP_DEPENDENT_HELICASE_ACTIVITY
ATP_DEPENDENT_RNA_HELICASE_ACTIVITY
RNA_DEPENDENT_ATPASE_ACTIVITY
RNA_HELICASE_ACTIVITY
ENZYME_BINDING
TRANSLATION_FACTOR_ACTIVITY_NUCLEIC_ACID_BINDING
SUBSTRATE_SPECIFIC_TRANSPORTER_ACTIVITY
DNA_BINDING
TRANSITION_METAL_ION_BINDING
PROTEIN_SERINE_THREONINE_KINASE_ACTIVITY
RECEPTOR_BINDING
PROTEIN_KINASE_ACTIVITY
PHOSPHOTRANSFERASE_ACTIVITY_ALCOHOL_GROUP_AS_ACCEPTOR
HYDROLASE_ACTIVITY_ACTING_ON_ESTER_BONDS
TRANSCRIPTION_ACTIVATOR_ACTIVITY
ATP_BINDING
TRANSCRIPTION_COACTIVATOR_ACTIVITY
ADENYL_NUCLEOTIDE_BINDING
ADENYL_RIBONUCLEOTIDE_BINDING
TRANSCRIPTION_REPRESSOR_ACTIVITY
TRANSFERASE_ACTIVITY_TRANSFERRING_PHOSPHORUS_CONTAINING_GROUPS
RECEPTOR_SIGNALING_PROTEIN_SERINE_THREONINE_KINASE_ACTIVITY
LIGAND_GATED_CHANNEL_ACTIVITY
TRANSMEMBRANE_TRANSPORTER_ACTIVITY
ION_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
PURINE_NUCLEOTIDE_BINDING
CHROMATIN_BINDING
CYTOSKELETAL_PROTEIN_BINDING
HEMATOPOIETIN_INTERFERON_CLASSD200_DOMAIN_CYTOKINE_RECEPTOR_ACTIVITY
HELICASE_ACTIVITY
NUCLEOTIDE_BINDING
MAGNESIUM_ION_BINDING
TRANSCRIPTION_FACTOR_ACTIVITY
ACTIN_FILAMENT_BINDING
GUANYL_NUCLEOTIDE_BINDING
UDP_GLYCOSYLTRANSFERASE_ACTIVITY
PURINE_RIBONUCLEOTIDE_BINDING
ATPASE_ACTIVITY_COUPLED_TO_TRANSMEMBRANE_MOVEMENT_OF_IONS
LIGASE_ACTIVITY_FORMING_CARBON_OXYGEN_BONDS
RNA_BINDING
3_5_CYCLIC_NUCLEOTIDE_PHOSPHODIESTERASE_ACTIVITY
PHOSPHORIC_MONOESTER_HYDROLASE_ACTIVITY
PHOSPHORIC_ESTER_HYDROLASE_ACTIVITY
GTPASE_ACTIVATOR_ACTIVITY
CALCIUM_CHANNEL_ACTIVITY
DNA_POLYMERASE_ACTIVITY
ENDORIBONUCLEASE_ACTIVITY
SUBSTRATE_SPECIFIC_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
THYROID_HORMONE_RECEPTOR_BINDING
GTP_BINDING
TRANSCRIPTION_FACTOR_BINDING
SUBSTRATE_SPECIFIC_CHANNEL_ACTIVITY
ION_CHANNEL_ACTIVITY
PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY
RNA_POLYMERASE_II_TRANSCRIPTION_FACTOR_ACTIVITY
CATION_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
ACTIN_BINDING
STRUCTURAL_CONSTITUENT_OF_CYTOSKELETON
HYDROLASE_ACTIVITY_ACTING_ON_ACID_ANHYDRIDES
METAL_ION_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
SH3_DOMAIN_BINDING
PYROPHOSPHATASE_ACTIVITY
GROWTH_FACTOR_BINDING
ATPASE_ACTIVITY
STEROID_HORMONE_RECEPTOR_BINDING
POTASSIUM_CHANNEL_ACTIVITY
PHOSPHATE_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
PHOSPHOPROTEIN_PHOSPHATASE_ACTIVITY
RNA_SPLICING_FACTOR_ACTIVITYTRANSESTERIFICATION_MECHANISM
NUCLEAR_HORMONE_RECEPTOR_BINDING
STRUCTURAL_CONSTITUENT_OF_RIBOSOME
STRUCTURAL_MOLECULE_ACTIVITY
DNA_DEPENDENT_ATPASE_ACTIVITY
PROTEIN_TYROSINE_PHOSPHATASE_ACTIVITY
ENDONUCLEASE_ACTIVITY_GO_0016893
NUCLEOSIDE_TRIPHOSPHATASE_ACTIVITY
NUCLEOBASENUCLEOSIDENUCLEOTIDE_AND_NUCLEIC_ACID_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
ATPASE_ACTIVITY_COUPLED
MRNA_BINDING
CATION_CHANNEL_ACTIVITY
CYTOKINE_BINDING
RECEPTOR_SIGNALING_PROTEIN_ACTIVITY
HORMONE_RECEPTOR_BINDING
NUCLEOTIDYLTRANSFERASE_ACTIVITY
Control
TLE
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21

figure S3

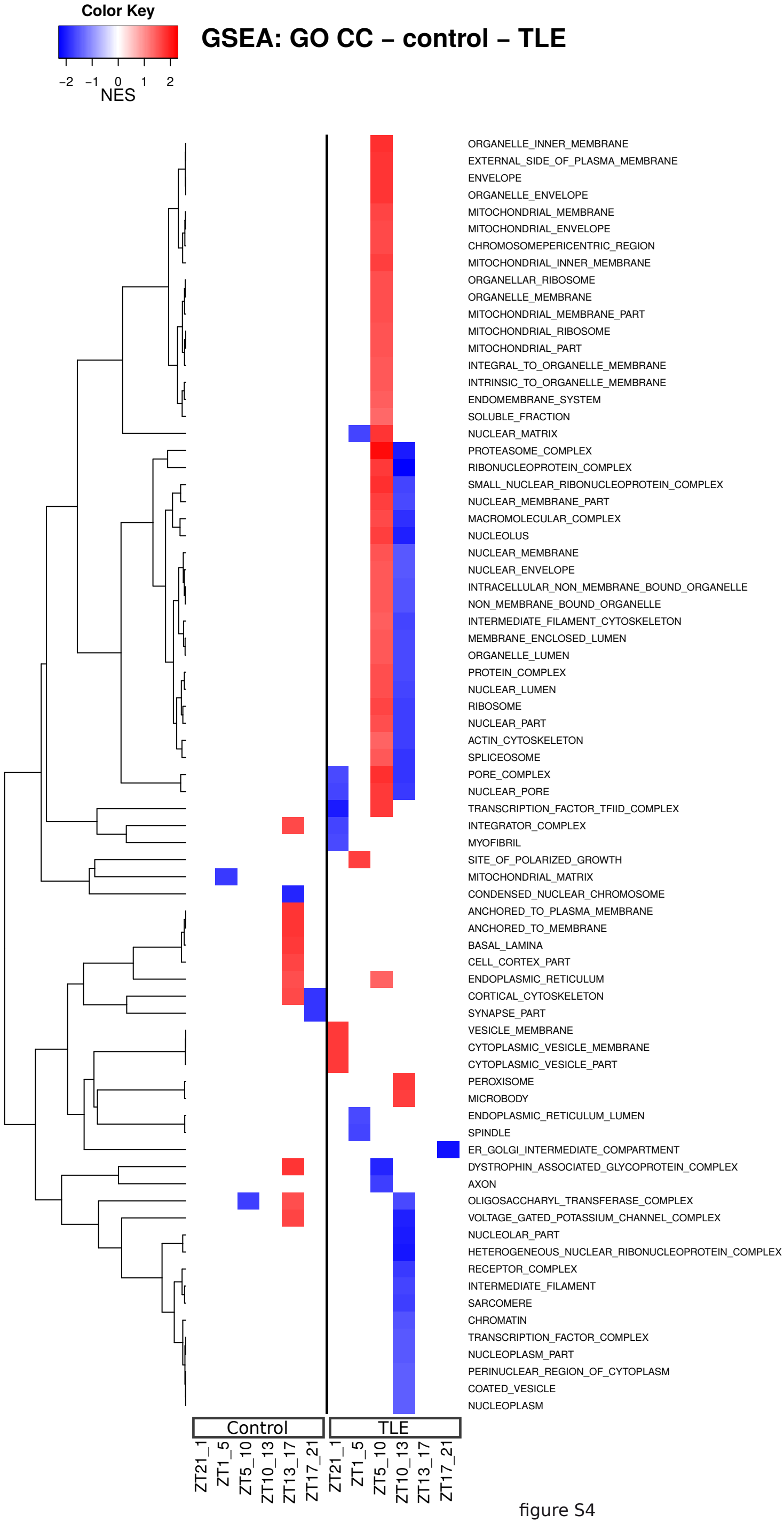
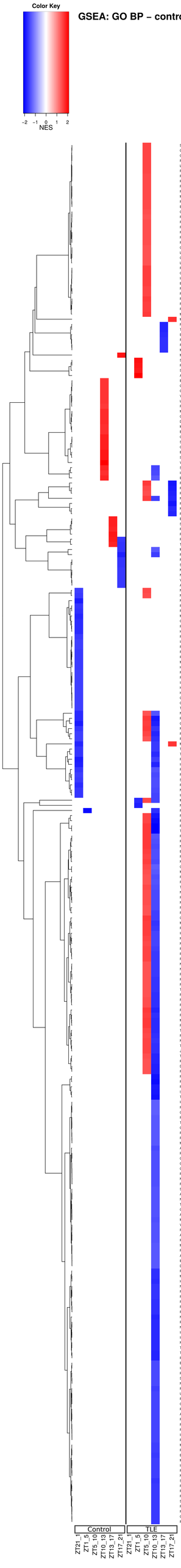

Color Key
−2 −1 0 1 2
NES
GSEA: GO CC – control – TLE
ORGANELLE_INNER_MEMBRANE
EXTERNAL_SIDE_OF_PLASMA_MEMBRANE
ENVELOPE
ORGANELLE_ENVELOPE
MITOCHONDRIAL_MEMBRANE
MITOCHONDRIAL_ENVELOPE
CHROMOSOMEPERICENTRIC_REGION
MITOCHONDRIAL_INNER_MEMBRANE
ORGANELLAR_RIBOSOME
ORGANELLE_MEMBRANE
MITOCHONDRIAL_MEMBRANE_PART
MITOCHONDRIAL_RIBOSOME
MITOCHONDRIAL_PART
INTEGRAL_TO_ORGANELLE_MEMBRANE
INTRINSIC_TO_ORGANELLE_MEMBRANE
ENDOMEMBRANE_SYSTEM
SOLUBLE_FRACTION
NUCLEAR_MATRIX
PROTEASOME_COMPLEX
RIBONUCLEOPROTEIN_COMPLEX
SMALL_NUCLEAR_RIBONUCLEOPROTEIN_COMPLEX
NUCLEAR_MEMBRANE_PART
MACROMOLECULAR_COMPLEX
NUCLEOLUS
NUCLEAR_MEMBRANE
NUCLEAR_ENVELOPE
INTRACELLULAR_NON_MEMBRANE_BOUND_ORGANELLE
NON_MEMBRANE_BOUND_ORGANELLE
INTERMEDIATE_FILAMENT_CYTOSKELETON
MEMBRANE_ENCLOSED_LUMEN
ORGANELLE_LUMEN
PROTEIN_COMPLEX
NUCLEAR_LUMEN
RIBOSOME
NUCLEAR_PART
ACTIN_CYTOSKELETON
SPLICEOSOME
PORE_COMPLEX
NUCLEAR_PORE
TRANSCRIPTION_FACTOR_TFIID_COMPLEX
INTEGRATOR_COMPLEX
MYOFIBRIL
SITE_OF_POLARIZED_GROWTH
MITOCHONDRIAL_MATRIX
CONDENSED_NUCLEAR_CHROMOSOME
ANCHORED_TO_PLASMA_MEMBRANE
ANCHORED_TO_MEMBRANE
BASAL_LAMINA
CELL_CORTEX_PART
ENDOPLASMIC_RETICULUM
CORTICAL_CYTOSKELETON
SYNAPSE_PART
VESICLE_MEMBRANE
CYTOPLASMIC_VESICLE_MEMBRANE
CYTOPLASMIC_VESICLE_PART
PEROXISOME
MICROBODY
ENDOPLASMIC_RETICULUM_LUMEN
SPINDLE
ER_GOLGI_INTERMEDIATE_COMPARTMENT
DYSTROPHIN_ASSOCIATED_GLYCOPROTEIN_COMPLEX
AXON
OLIGOSACCHARYL_TRANSFERASE_COMPLEX
VOLTAGE_GATED_POTASSIUM_CHANNEL_COMPLEX
NUCLEOLAR_PART
HETEROGENEOUS_NUCLEAR_RIBONUCLEOPROTEIN_COMPLEX
RECEPTOR_COMPLEX
INTERMEDIATE_FILAMENT
SARCOMERE
CHROMATIN
TRANSCRIPTION_FACTOR_COMPLEX
NUCLEOPLASM_PART
PERINUCLEAR_REGION_OF_CYTOPLASM
COATED_VESICLE
NUCLEOPLASM
Control
TLE
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21

figure S4


Color Key
GSEA: GO BP – control – TLE
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NES
STEROID_BIOSYNTHETIC_PROCESS
CELL_CYCLE_PROCESS
CELL_CYCLE_GO_0007049
POSITIVE_REGULATION_OF_IMMUNE_RESPONSE
LEUKOCYTE_MIGRATION
POSITIVE_REGULATION_OF_PHOSPHATE_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_PROTEIN_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_PHOSPHORYLATION
REGULATION_OF_CYTOKINE_BIOSYNTHETIC_PROCESS
POSITIVE_REGULATION_OF_IMMUNE_SYSTEM_PROCESS
MITOTIC_CELL_CYCLE_CHECKPOINT
POSITIVE_REGULATION_OF_CELLULAR_PROTEIN_METABOLIC_PROCESS
ECTODERM_DEVELOPMENT
CARBOXYLIC_ACID_TRANSPORT
REGULATION_OF_IMMUNE_SYSTEM_PROCESS
REGULATION_OF_PROTEIN_MODIFICATION_PROCESS
REGULATION_OF_CYCLIN_DEPENDENT_PROTEIN_KINASE_ACTIVITY
RESPONSE_TO_EXTRACELLULAR_STIMULUS
RESPONSE_TO_NUTRIENT_LEVELS
POSITIVE_REGULATION_OF_BINDING
ORGANIC_ACID_TRANSPORT
LEUKOCYTE_ACTIVATION
CELL_CYCLE_CHECKPOINT_GO_0000075
LIPID_BIOSYNTHETIC_PROCESS
POSITIVE_REGULATION_OF_CYTOKINE_BIOSYNTHETIC_PROCESS
CELL_CYCLE_PHASE
INDUCTION_OF_APOPTOSIS_BY_EXTRACELLULAR_SIGNALS
EPIDERMIS_DEVELOPMENT
REGULATION_OF_PROTEIN_SECRETION
REGULATION_OF_INTERFERON_GAMMA_BIOSYNTHETIC_PROCESS
REGULATION_OF_MITOTIC_CELL_CYCLE
POSITIVE_REGULATION_OF_PROTEIN_AMINO_ACID_PHOSPHORYLATION
REGULATION_OF_PHOSPHORYLATION
M_PHASE
MEIOTIC_RECOMBINATION
REGULATION_OF_T_CELL_PROLIFERATION
T_CELL_PROLIFERATION
BIOPOLYMER_BIOSYNTHETIC_PROCESS
POSITIVE_REGULATION_OF_T_CELL_PROLIFERATION
RESPONSE_TO_ORGANIC_SUBSTANCE
MITOCHONDRIAL_MEMBRANE_ORGANIZATION_AND_BIOGENESIS
MEIOTIC_CELL_CYCLE
SPHINGOLIPID_METABOLIC_PROCESS
PROTEIN_AMINO_ACID_ADP_BIOSYLATION
SPHINGOLIPID_METABOLIC_PROCESS
AMINE_TRANSPORT
ENERGY_DERIVATION_BY_OXIDATION_OF_ORGANIC_COMPOUNDS
GLIOGENESIS
COENZYME_METABOLIC_PROCESS
VACUOLAR_TRANSPORT
LYSOSOMAL_TRANSPORT
RESPONSE_TO_HEAT
MEMBRANE_ORGANIZATION_AND_BIOGENESIS
GOLGI_VESICLE_TRANSPORT
DI___TRI_VALENT_INORGANIC_CATION_TRANSPORT
MEIOSIS_I
ER_TO_GOLGI_VESICLE_MEDIATED_TRANSPORT
CALCIUM_ION_TRANSPORT
SECRETION_BY_CELL
CELLULAR_LOCALIZATION
ENDOSOME_TRANSPORT
SECRETORY_PATHWAY
VESICLE_MEDIATED_TRANSPORT
S_PHASE_OF_MITOTIC_CELL_CYCLE
INTRACELLULAR_TRANSPORT
ESTABLISHMENT_OF_CELLULAR_LOCALIZATION
REGULATION_OF_PROTEIN_IMPORT_INTO_NUCLEUS
REGULATION_OF_NUCLEOCYTOPLASMIC_TRANSPORT
REGULATION_OF_INTRACELLULAR_TRANSPORT
NUCLEAR_IMPORT
RESPONSE_TO_CARBOHYDRATE_STIMULUS
NEGATIVE_REGULATION_OF_SECRETION
REGULATION_OF_NEURON_APOPTOSIS
ENZYME_LINKED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY
SULFUR_COMPOUND_BIOSYNTHETIC_PROCESS
REGULATION_OF_CELLULAR_COMPONENT_SIZE
REGULATION_OF_TRANSFORMING_GROWTH_FACTOR_BETA_RECEPTOR_SIGNALING_PATHWAY
PROTEOGLYCAN_BIOSYNTHETIC_PROCESS
TRANSMEMBRANE_RECEPTOR_PROTEIN_TYROSINE_KINASE_SIGNALING_PATHWAY
MUSCLE_DEVELOPMENT
REGULATION_OF_ACTION_POTENTIAL
REGULATION_OF_CYTOSKELETON_ORGANIZATION_AND_BIOGENESIS
SULFUR_METABOLIC_PROCESS
NERVOUS_SYSTEM_DEVELOPMENT
NEURON_DEVELOPMENT
VACUOLE_ORGANIZATION_AND_BIOGENESIS
ACTIN_FILAMENT_BUNDLE_FORMATION
NEGATIVE_REGULATION_OF_RNA_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_TRANSCRIPTION_DNA_DEPENDENT
N_TERMINAL_PROTEIN_AMINO_ACID_MODIFICATION
PROTEIN_OLIGOMERIZATION
RESPONSE_TO_HYPOXIA
MYELOID_CELL_DIFFERENTIATION
CYTOSKELETON_DEPENDENT_INTRACELLULAR_TRANSPORT
PROTEIN_FOLDING
HOMEOSTASIS_OF_NUMBER_OF_CELLS
PROTEIN_CATABOLIC_PROCESS
INSULIN_RECEPTOR_SIGNALING_PATHWAY
POSITIVE_REGULATION_OF_EPITHELIAL_CELL_PROLIFERATION
POSITIVE_REGULATION_OF_CELL_DIFFERENTIATION
POSITIVE_REGULATION_OF_MAPKKK_CASCADE
MICROTUBULE_BASED_MOVEMENT
HEMOPOIESIS
REGULATION_OF_CELL_MORPHOGENESIS
RESPONSE_TO_VIRUS
IMMUNE_SYSTEM_DEVELOPMENT
HEMOPOIETIC_OR_LYMPHOID_ORGAN_DEVELOPMENT
HEME_BIOSYNTHETIC_PROCESS
CELLULAR_PROTEIN_CATABOLIC_PROCESS
CELL_CYCLE_ARREST_GO_0007050
TRANSITION_METAL_ION_TRANSPORT
NEGATIVE_REGULATION_OF_CELL_CYCLE
RNA_PROCESSING
G1_S_TRANSITION_OF_MITOTIC_CELL_CYCLE
NEGATIVE_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
RNA_METABOLIC_PROCESS
PEPTIDYL_AMINO_ACID_MODIFICATION
MRNA_METABOLIC_PROCESS
TRANSCRIPTION_INITIATION
TRANSCRIPTION_INITIATION_FROM_RNA_POLYMERASE_II_PROMOTER
REGULATION_OF_CELL_GROWTH
INDUCTION_OF_APOPTOSIS_BY_INTRACELLULAR_SIGNALS
REGULATION_OF_CELL_CYCLE
RESPONSE_TO_BIOTIC_STIMULUS
STEROID_HORMONE_RECEPTOR_SIGNALING_PATHWAY
REGULATION_OF_GROWTH
NEGATIVE_REGULATION_OF_GROWTH
INTRACELLULAR_RECEPTOR_MEDIATED_SIGNALING_PATHWAY
MRNA_PROCESSING_GO_0006397
NEGATIVE_REGULATION_OF_CELLULAR_PROTEIN_METABOLIC_PROCESS
REGULATION_OF_TRANSLATIONAL_INITIATION
RNA_SPLICING
PROTEIN_RNA_COMPLEX_ASSEMBLY
RIBONUCLEOPROTEIN_COMPLEX_BIOGENESIS_AND_ASSEMBLY
TRNA_METABOLIC_PROCESS
REGULATION_OF_BINDING
REGULATION_OF_DNA_BINDING
NEGATIVE_REGULATION_OF_METABOLIC_PROCESS
BIOSYNTHETIC_PROCESS
PROTEIN_IMPORT
NEGATIVE_REGULATION_OF_CELLULAR_METABOLIC_PROCESS
CELL_PROLIFERATION_GO_0008283
MULTI_ORGANISM_PROCESS
RNA_SPLICING,VIA_TRANSESTERIFICATION_REACTIONS
REGULATION_OF_MOLECULAR_FUNCTION
TISSUE_DEVELOPMENT
NEGATIVE_REGULATION_OF_CELLULAR_PROCESS
REGULATION_OF_PROTEIN_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_BIOLOGICAL_PROCESS
REGULATION_OF_PROTEIN_KINASE_ACTIVITY
POSITIVE_REGULATION_OF_SIGNAL_TRANSDUCTION
CELLULAR_BIOSYNTHETIC_PROCESS
MACROMOLECULE_BIOSYNTHETIC_PROCESS
POSITIVE_REGULATION_OF_BIOLOGICAL_PROCESS
INTERPHASE
NEGATIVE_REGULATION_OF_TRANSCRIPTION
NEGATIVE_REGULATION_OF_NUCLEOBASE|NUCLEOSIDE|NUCLEOTIDE_AND_NUCLEIC_ACID_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_RESPONSE_TO_STIMULUS
POSITIVE_REGULATION_OF_CELLULAR_PROCESS
RRNA_METABOLIC_PROCESS
NUCLEAR_TRANSPORT
NUCLEOCYTOPLASMIC_TRANSPORT
REGULATION_OF_MAP_KINASE_ACTIVITY
REGULATION_OF_GENE_EXPRESSION
RNA_BIOSYNTHETIC_PROCESS
TRANSCRIPTION_DNA_DEPENDENT
REGULATION_OF_NUCLEOBASE|NUCLEOSIDE|NUCLEOTIDE_AND_NUCLEIC_ACID_METABOLIC_PROCESS
REGULATION_OF_CELLULAR_METABOLIC_PROCESS
REGULATION_OF_TRANSCRIPTION
RRNA_PROCESSING
REGULATION_OF_SIGNAL_TRANSDUCTION
MAPKKK_CASCADE_GO_0000165
RIBOSOME_BIOGENESIS_AND_ASSEMBLY
TRANSCRIPTION
REGULATION_OF_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_BINDING
TRICARBOXYLIC_ACID_CYCLE_INTERMEDIATE_METABOLIC_PROCESS
JAK_STAT_CASCADE
TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
PROTEIN_AMINO_ACID_DEPHOSPHORYLATION
DEPHOSPHORYLATION
REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
PROTEIN_KINASE_CASCADE
REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_CASCADE
POSITIVE_REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_CASCADE
I_KAPPAB_KINASE_NF_KAPPAB_CASCADE
TRANSLATION
IMMUNE_RESPONSE
REGULATION_OF_BIOLOGICAL_QUALITY
ORGAN_MORPHOGENESIS
PROTEIN_LOCALIZATION
TRANSPORT
ORGAN_DEVELOPMENT
REGULATION_OF_RESPONSE_TO_STIMULUS
REGULATION_OF_CATALYTIC_ACTIVITY
MACROMOLECULE_LOCALIZATION
ANGIOGENESIS
PEPTIDYL_TYROSINE_MODIFICATION
CATION_TRANSPORT
CELL_MIGRATION
CARBOHYDRATE_BIOSYNTHETIC_PROCESS
PROGRAMMED_CELL_DEATH
NEGATIVE_REGULATION_OF_APOPTOSIS
REGULATION_OF_KINASE_ACTIVITY
SYSTEM_DEVELOPMENT
ANOMOGENESIS
NEGATIVE_REGULATION_OF_PROGRAMMED_CELL_DEATH
TRANSFORMING_GROWTH_FACTOR_BETA_RECEPTOR_SIGNALING_PATHWAY
GROWTH
APOPTOSIS_GO
MONOVALENT_INORGANIC_CATION_TRANSPORT
VASCULATURE_DEVELOPMENT
RESPONSE_TO_STRESS
ACTIN_CYTOSKELETON_ORGANIZATION_AND_BIOGENESIS
PROTEIN_TRANSPORT
MULTICELLULAR_ORGANISMAL_DEVELOPMENT
REGULATION_OF_CELLULAR_PROTEIN_METABOLIC_PROCESS
ACTIN_FILAMENT_BASED_PROCESS
ESTABLISHMENT_OF_PROTEIN_LOCALIZATION
DEFENSE_RESPONSE
POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS
MYOBLAST_DIFFERENTIATION
ICOSANOID_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_SIGNAL_TRANSDUCTION
REGULATION_OF_RNA_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_TRANSCRIPTIONDNA_DEPENDENT
RESPONSE_TO_WOUNDING
POSITIVE_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
POTASSIUM_ION_TRANSPORT
NEGATIVE_REGULATION_OF_TRANSCRIPTION_FACTOR_ACTIVITY
POSITIVE_REGULATION_OF_TRANSCRIPTION
NEGATIVE_REGULATION_OF_DNA_BINDING
INACTIVATION_OF_MAPK_ACTIVITY
INFLAMMATORY_RESPONSE
NEGATIVE_REGULATION_OF_CELL_MIGRATION
TRNA_PROCESSING
TRANSLATIONAL_INITIATION
POSITIVE_REGULATION_OF_NUCLEOBASE|NUCLEOSIDE|NUCLEOTIDE_AND_NUCLEIC_ACID_METABOLIC_PROCESS
EMBRYO_IMPLANTATION
INTRACELLULAR_PROTEIN_TRANSPORT
POSITIVE_REGULATION_OF_CELL_PROLIFERATION
SKELETAL_MUSCLE_DEVELOPMENT
NEGATIVE_REGULATION_OF_TRANSFERASE_ACTIVITY
PROTEIN_TARGETING
UBIQUITIN_CYCLE
PEPTIDYL_TYROSINE_PHOSPHORYLATION
CELL_DEVELOPMENT
PROTEIN_MODIFICATION_PROCESS
ANATOMICAL_STRUCTURE_FORMATION
RESPONSE_TO_EXTERNAL_STIMULUS
PHOSPHORYLATION
REGULATION_OF_TRANSFERASE_ACTIVITY
INTRACELLULAR_SIGNALING_CASCADE
PROTEIN_AMINO_ACID_PHOSPHORYLATION
MRNA_SPLICE_SITE_SELECTION
POSITIVE_REGULATION_OF_METABOLIC_PROCESS
BIOPOLYMER_MODIFICATION
METAL_ION_TRANSPORT
INTERPHASE_OF_MITOTIC_CELL_CYCLE
PROTEIN_IMPORT_INTO_NUCLEUS
NEGATIVE_REGULATION_OF_MAP_KINASE_ACTIVITY
S_PHASE
REGULATION_OF_GENE_SPECIFIC_TRANSCRIPTION
POSITIVE_REGULATION_OF_CELLULAR_METABOLIC_PROCESS
RHYTHMIC_PROCESS
SPLICEOSOME_ASSEMBLY
REGULATION_OF_TRANSLATION
REGULATION_OF_TRANSCRIPTIONDNA_DEPENDENT
CIRCADIAN_RHYTHM
POST_TRANSLATIONAL_PROTEIN_MODIFICATION
Control
TLE
ZT2_1
ZT5_10
ZT10_13
ZT13_17
ZT17_24
ZT2_1
ZT5_10
ZT10_13
ZT13_17
ZT17_24

figure S5

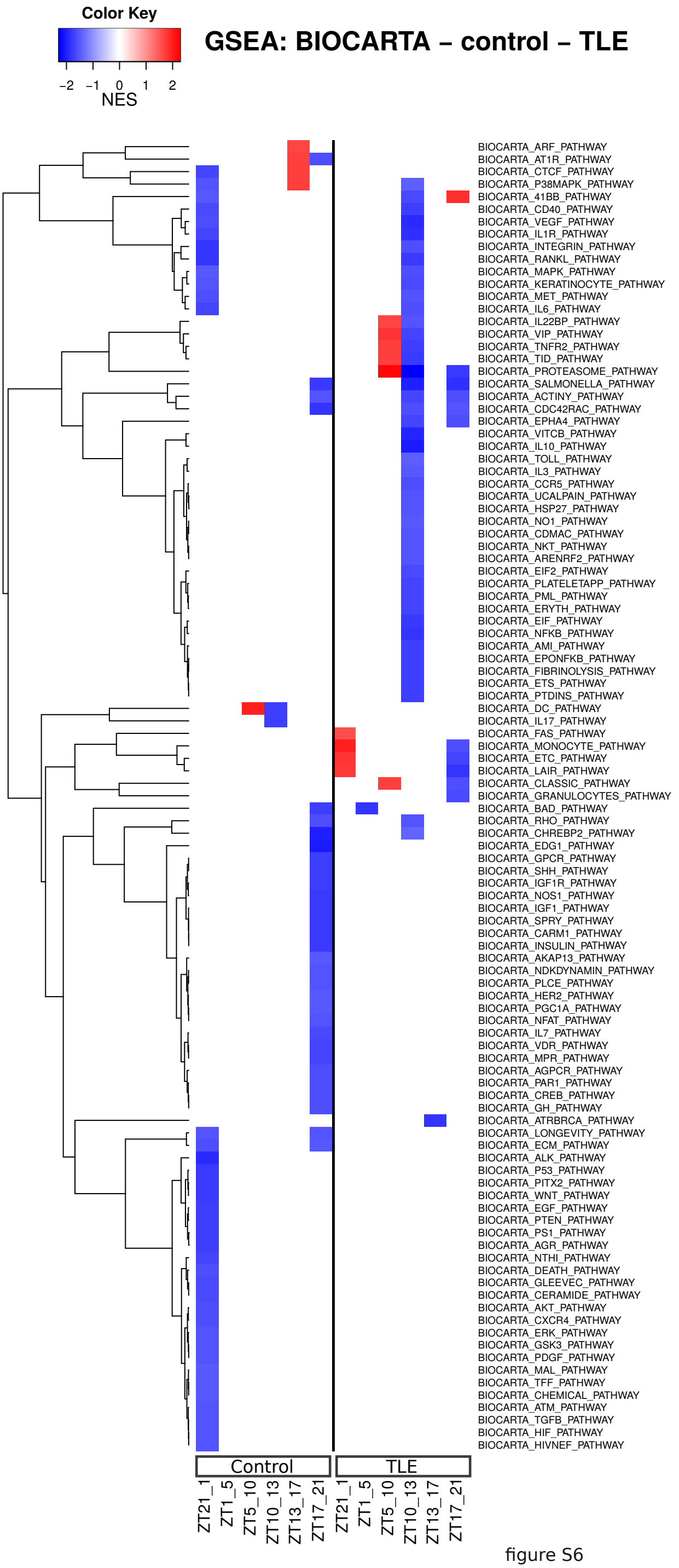
Color Key
−2 −1 0 1 2
NES
GSEA: BIOCARTA – control – TLE
BIOCARTA_ARF_PATHWAY
BIOCARTA_AT1R_PATHWAY
BIOCARTA_CTCF_PATHWAY
BIOCARTA_P38MAPK_PATHWAY
BIOCARTA_41BB_PATHWAY
BIOCARTA_CD40_PATHWAY
BIOCARTA_VEGF_PATHWAY
BIOCARTA_IL1R_PATHWAY
BIOCARTA_INTEGRIN_PATHWAY
BIOCARTA_RANKL_PATHWAY
BIOCARTA_MAPK_PATHWAY
BIOCARTA_KERATINOCYTE_PATHWAY
BIOCARTA_MET_PATHWAY
BIOCARTA_IL6_PATHWAY
BIOCARTA_IL22BP_PATHWAY
BIOCARTA_VIP_PATHWAY
BIOCARTA_TNFR2_PATHWAY
BIOCARTA_TID_PATHWAY
BIOCARTA_PROTEASOME_PATHWAY
BIOCARTA_SALMONELLA_PATHWAY
BIOCARTA_ACTINY_PATHWAY
BIOCARTA_CDC42RAC_PATHWAY
BIOCARTA_EPHA4_PATHWAY
BIOCARTA_VITCB_PATHWAY
BIOCARTA_IL10_PATHWAY
BIOCARTA_TOLL_PATHWAY
BIOCARTA_IL3_PATHWAY
BIOCARTA_CCR5_PATHWAY
BIOCARTA_UCALPAIN_PATHWAY
BIOCARTA_HSP27_PATHWAY
BIOCARTA_NO1_PATHWAY
BIOCARTA_CDMAC_PATHWAY
BIOCARTA_NKT_PATHWAY
BIOCARTA_ARENRF2_PATHWAY
BIOCARTA_EIF2_PATHWAY
BIOCARTA_PLATELETAPP_PATHWAY
BIOCARTA_PML_PATHWAY
BIOCARTA_ERYTH_PATHWAY
BIOCARTA_EIF_PATHWAY
BIOCARTA_NFKB_PATHWAY
BIOCARTA_AMI_PATHWAY
BIOCARTA_EPONFKB_PATHWAY
BIOCARTA_FIBRINOLYSIS_PATHWAY
BIOCARTA_ETS_PATHWAY
BIOCARTA_PTDINS_PATHWAY
BIOCARTA_DC_PATHWAY
BIOCARTA_IL17_PATHWAY
BIOCARTA_FAS_PATHWAY
BIOCARTA_MONOCYTE_PATHWAY
BIOCARTA_ETC_PATHWAY
BIOCARTA_LAIR_PATHWAY
BIOCARTA_CLASSIC_PATHWAY
BIOCARTA_GRANULOCYTES_PATHWAY
BIOCARTA_BAD_PATHWAY
BIOCARTA_RHO_PATHWAY
BIOCARTA_CHREBP2_PATHWAY
BIOCARTA_EDG1_PATHWAY
BIOCARTA_GPCR_PATHWAY
BIOCARTA_SHH_PATHWAY
BIOCARTA_IGF1R_PATHWAY
BIOCARTA_NOS1_PATHWAY
BIOCARTA_IGF1_PATHWAY
BIOCARTA_SPRY_PATHWAY
BIOCARTA_CARM1_PATHWAY
BIOCARTA_INSULIN_PATHWAY
BIOCARTA_AKAP13_PATHWAY
BIOCARTA_NDKDYNAMIN_PATHWAY
BIOCARTA_PLCE_PATHWAY
BIOCARTA_HER2_PATHWAY
BIOCARTA_PGC1A_PATHWAY
BIOCARTA_NFAT_PATHWAY
BIOCARTA_IL7_PATHWAY
BIOCARTA_VDR_PATHWAY
BIOCARTA_MPR_PATHWAY
BIOCARTA_AGPCR_PATHWAY
BIOCARTA_PAR1_PATHWAY
BIOCARTA_CREB_PATHWAY
BIOCARTA_GH_PATHWAY
BIOCARTA_ATRBRCA_PATHWAY
BIOCARTA_LONGEVITY_PATHWAY
BIOCARTA_ECM_PATHWAY
BIOCARTA_ALK_PATHWAY
BIOCARTA_P53_PATHWAY
BIOCARTA_PITX2_PATHWAY
BIOCARTA_WNT_PATHWAY
BIOCARTA_EGF_PATHWAY
BIOCARTA_PTEN_PATHWAY
BIOCARTA_PS1_PATHWAY
BIOCARTA_AGR_PATHWAY
BIOCARTA_NTHI_PATHWAY
BIOCARTA_DEATH_PATHWAY
BIOCARTA_GLEEVEC_PATHWAY
BIOCARTA_CERAMIDE_PATHWAY
BIOCARTA_AKT_PATHWAY
BIOCARTA_CXCR4_PATHWAY
BIOCARTA_ERK_PATHWAY
BIOCARTA_GSK3_PATHWAY
BIOCARTA_PDGF_PATHWAY
BIOCARTA_MAL_PATHWAY
BIOCARTA_TFF_PATHWAY
BIOCARTA_CHEMICAL_PATHWAY
BIOCARTA_ATM_PATHWAY
BIOCARTA_TGFB_PATHWAY
BIOCARTA_HIF_PATHWAY
BIOCARTA_HIVNEF_PATHWAY
Control
TLE
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21

figure S6

Color Key
−2
0
1
2
NES
GSEA: KEGG – control – TLE
KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM
KEGG_CITRATE_CYCLE_TCA_CYCLE
KEGG_SNARE_INTERACTIONS_IN_VESICULAR_TRANSPORT
KEGG_ONE_CARBON_POOL_BY_FOLATE
KEGG_GLYOXYLATE_AND_DICARBOXYLATE_METABOLISM
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_BIOSYNTHESIS
KEGG_BUTANOATE_METABOLISM
KEGG_GLUTATHIONE_METABOLISM
KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS
KEGG_LYSOSOME
KEGG_ABC_TRANSPORTERS
KEGG_OTHER_GLYCAN_DEGRADATION
KEGG_PEROXISOME
KEGG_PYRUVATE_METABOLISM
KEGG_LIMONENE_AND_PINENE_DEGRADATION
KEGG_HOMOLOGOUS_RECOMBINATION
KEGG_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS
KEGG_PYRIMIDINE_METABOLISM
KEGG_PROPANOATE_METABOLISM
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION
KEGG_FATTY_ACID_METABOLISM
KEGG_DRUG_METABOLISM_CYTOCHROME_P450
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450
KEGG_HISTIDINE_METABOLISM
KEGG_GLYCOSAMINOGLYCAN_DEGRADATION
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION
KEGG_SPLICEOSOME
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION
KEGG_PROTEASOME
KEGG_HUNTINGTONS_DISEASE
KEGG_TAURINE_AND_HYPOTAURINE_METABOLISM
KEGG_CIRCADIAN_RHYTHM_MAMMAL
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS
KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY
KEGG_P53_SIGNALING_PATHWAY
KEGG_STEROID_BIOSYNTHESIS
KEGG_VIBRIO_CHOLERAE_INFECTION
KEGG_ALZHEIMERS_DISEASE
KEGG_GLYCOLYSIS_GLUCONEOGENESIS
KEGG_PARKINSONS_DISEASE
KEGG_TYROSINE_METABOLISM
KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM
KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM
KEGG_OXIDATIVE_PHOSPHORYLATION
KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG
KEGG_RNA_POLYMERASE
KEGG_ASTHMA
KEGG_PPAR_SIGNALING_PATHWAY
KEGG_BETA_ALANINE_METABOLISM
KEGG_O_GLYCAN_BIOSYNTHESIS
KEGG_N_GLYCAN_BIOSYNTHESIS
KEGG_CELL_ADHESION_MOLECULES_CAMS
KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_CHONDROITIN_SULFATE
KEGG_AXON_GUIDANCE
KEGG_ERBB_SIGNALING_PATHWAY
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM
KEGG_INSULIN_SIGNALING_PATHWAY
KEGG_TYPE_II_DIABETES_MELLITUS
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_KERATAN_SULFATE
KEGG_MELANOMA
KEGG_LONG_TERM_POTENTIATION
KEGG_NON_SMALL_CELL_LUNG_CANCER
KEGG_ADHERENS_JUNCTION
KEGG_GLIOMA
KEGG_RIG_I_LIKE_RECEPTOR_SIGNALING_PATHWAY
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
KEGG_PROTEIN_EXPORT
KEGG_JAK_STAT_SIGNALING_PATHWAY
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON
KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY
KEGG_RIBOSOME
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES
KEGG_CARDIAC_MUSCLE_CONTRACTION
KEGG_LEISHMANIA_INFECTION
KEGG_ACUTE_MYELOID_LEUKEMIA
KEGG_PRION_DISEASES
KEGG_ECM_RECEPTOR_INTERACTION
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM
KEGG_MAPK_SIGNALING_PATHWAY
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS
KEGG_AMYOTROPHIC_LATERAL_SCLEROSIS_ALS
KEGG_RNA_DEGRADATION
KEGG_VEGF_SIGNALING_PATHWAY
KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY
KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY
KEGG_TGF_BETA_SIGNALING_PATHWAY
KEGG_CHRONIC_MYELOID_LEUKEMIA
KEGG_PROSTATE_CANCER
KEGG_FOCAL_ADHESION
KEGG_ENDOCYTOSIS
KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION
KEGG_CHEMOKINE_SIGNALING_PATHWAY
KEGG_PATHWAYS_IN_CANCER
KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC
KEGG_DILATED_CARDIOMYOPATHY
KEGG_SMALL_CELL_LUNG_CANCER
KEGG_NOTCH_SIGNALING_PATHWAY
KEGG_RENAL_CELL_CARCINOMA
KEGG_BLADDER_CANCER
KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS
KEGG_ENDOMETRIAL_CANCER
KEGG_EPITHELIAL_CELL_SIGNALING_IN_HELICOBACTER_PYLORI_INFECTION
KEGG_APOPTOSIS
KEGG_WNT_SIGNALING_PATHWAY
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY
KEGG_PANCREATIC_CANCER
KEGG_CELL_CYCLE
KEGG_HEDGEHOG_SIGNALING_PATHWAY
KEGG_BASAL_CELL_CARCINOMA
KEGG_INOSITOL_PHOSPHATE_METABOLISM
KEGG_GNRH_SIGNALING_PATHWAY
KEGG_ARGININE_AND_PROLINE_METABOLISM
KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION
KEGG_COLORECTAL_CANCER
Control
TLE
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21
ZT21_1
ZT1_5
ZT5_10
ZT10_13
ZT13_17
ZT17_21

figure S7

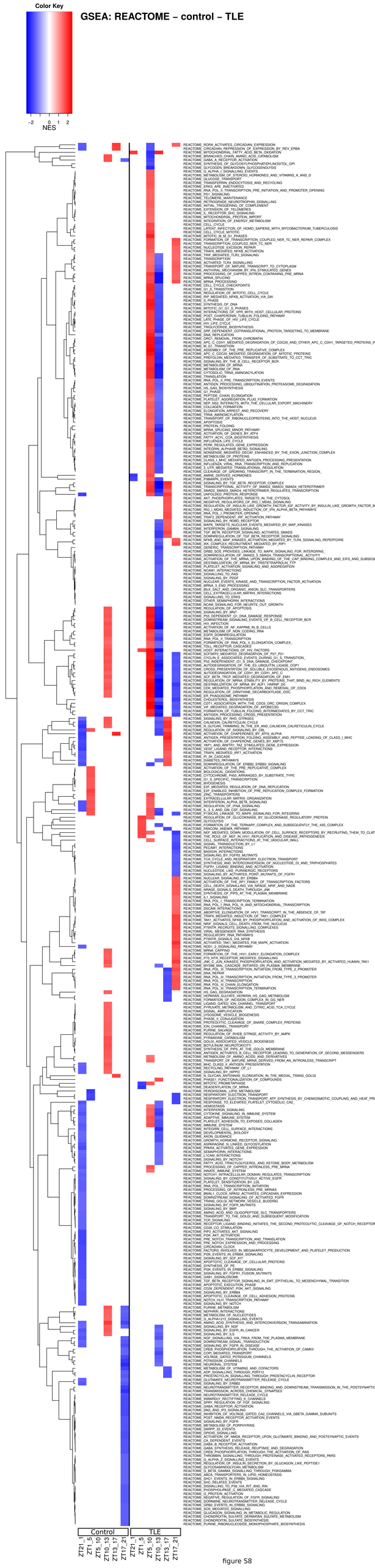
Color Key
GSEA: REACTOME – control – TLE
−2
0
1
2
NES
REACTOME_RORA_ACTIVATES_CIRCADIAN_EXPRESSION
REACTOME_CIRCADIAN_REPRESSION_OF_EXPRESSION_BY_REV_ERBA
REACTOME_MITOCHONDRIAL_FATTY_ACID_BETA_OXIDATION
REACTOME_BRANCHED_CHAIN_AMINO_ACID_CATABOLISM
REACTOME_GABA_A_RECEPTOR_ACTIVATION
REACTOME_SYNTHESIS_OF_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI
REACTOME_GLYCOGEN_BREAKDOWN_GLYCOGENOLYSIS
REACTOME_G_ALPHA_I_SIGNALLING_EVENTS
REACTOME_SYNTHESIS_OF_VITAMIN_D_AND_ITS_HORMONES_AND_VITAMINS_A_AND_D
REACTOME_GLUCOSE_TRANSPORT
REACTOME_TRANSFERRIN_ENDOCYTOSIS_AND_RECYCLING
REACTOME_ERKS_ARE_INACTIVATED
REACTOME_RNA_POL_II_TRANSCRIPTION_PRE_INITIATION_AND_PROMOTER_OPENING
REACTOME_PD1_SIGNALING
REACTOME_TELOMERE_MAINTENANCE
REACTOME_RETROGRADE_NEUROTROPHIN_SIGNALLING
REACTOME_INITIAL_TRIGGERING_OF_COMPLEMENT
REACTOME_ZIP_ZTP_ZTR_FAMILY_MEMBERS
REACTOME_IL_RECEPTOR_SHC_SIGNALING
REACTOME_MITOCHONDRIAL_PROTEIN_IMPORT
REACTOME_INTEGRATION_OF_ENERGY_METABOLISM
REACTOME_CELL_CYCLE
REACTOME_LATENT_INFECTION_OF_HOMO_SAPIENS_WITH_MYCOBACTERIUM_TUBERCULOSIS
REACTOME_CELL_CYCLE_MITOTIC
REACTOME_MITOTIC_M_M_G1_PHASES
REACTOME_FORMATION_OF_TRANSCRIPTION_COUPLED_NER_TC_NER_REPAIR_COMPLEX
REACTOME_DEACTIVATION_OF_THE_BETA_CATENIN_TCF_NER_TC_NER
REACTOME_NUCLEOTIDE_EXCISION_REPAIR
REACTOME_TRAF6_MEDIATED_NFKB_ACTIVATION
REACTOME_TRIF_MEDIATED_TLR3_SIGNALING
REACTOME_TRANSCRIPTION
REACTOME_ACTIVATED_TLR4_SIGNALLING
REACTOME_TRANSPORT_OF_MATURE_TRANSCRIPT_TO_CYTOPLASM
REACTOME_ANTIVIRAL_MECHANISM_BY_IFN_STIMULATED_GENES
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA
REACTOME_MEIOTICS
REACTOME_MRNA_PROCESSING
REACTOME_CELL_CYCLE_CHECKPOINTS
REACTOME_G1_S_TRANSITION
REACTOME_REGULATION_OF_MITOTIC_CELL_CYCLE
REACTOME_RIP_MEDIATED_NFKB_ACTIVATION_VIA_DAI
REACTOME_S_PHASE
REACTOME_SYNTHESIS_OF_DNA
REACTOME_MITOTIC_G1_G1_S_PHASES
REACTOME_HIV_INFECTION_PRE_WITH_HOST_CELLULAR_PROTEINS
REACTOME_POST_CHAPERONIN_TUBULIN_FOLDING_PATHWAY
REACTOME_LATE_PHASE_OF_HIV_LIFE_CYCLE
REACTOME_HIV_LIFE_CYCLE
REACTOME_TRIGLYCERIDE_BIOSYNTHESIS
REACTOME_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE
REACTOME_DNA_REPLICATION
REACTOME_DRC1_REMOVAL_FROM_CHROMATIN
REACTOME_APC_C_CDH1_MEDIATED_DEGRADATION_OF_CDC20_AND_OTHER_APC_C_CDH1_TARGETED_PROTEINS_IN_LATE_MITOSIS_EARLY_G1
REACTOME_DNA_REPAIR
REACTOME_ASSEMBLY_OF_THE_PRE_REPLICATIVE_COMPLEX
REACTOME_APC_C_CDC20_MEDIATED_DEGRADATION_OF_MITOTIC_PROTEINS
REACTOME_PREFOLDIN_MEDIATED_TRANSFER_OF_SUBSTRATE_TO_CCT_TRIC
REACTOME_SIGNALING_BY_THE_B_CELL_RECEPTOR_BCR
REACTOME_METABOLISM_OF_MRNA
REACTOME_METABOLISM_OF_RNA
REACTOME_CYTOSOLIC_TRNA_AMINOACYLATION
REACTOME_TRANSLATION
REACTOME_HIV_INFECTION_PRE_WITH_CELLULAR_PROTEINS
REACTOME_ANTIGEN_PROCESSING_UBIQUITINATION_PROTEASOME_DEGRADATION
REACTOME_HS_GAG_BIOSYNTHESIS
REACTOME_G1_PHASE
REACTOME_PEPTIDE_CHAIN_ELONGATION
REACTOME_PLATELET_AGGREGATION_PLUG_FORMATION
REACTOME_NEP_NS2_INTERACTS_WITH_THE_CELLULAR_EXPORT_MACHINERY
REACTOME_COLLAGEN_FORMATION
REACTOME_ELONGATION_ARREST_AND_RECOVERY
REACTOME_TRNA_AMINOACYLATION
REACTOME_TRANSPORT_OF_RIBONUCLEOPROTEINS_INTO_THE_HOST_NUCLEUS
REACTOME_APOPTOSIS
REACTOME_PROTEIN_FOLDING
REACTOME_MRNA_SPLICING_MINOR_PATHWAY
REACTOME_ACTIVATION_OF_GENES_BY_ATF4
REACTOME_FATTY_ACYL_COA_BIOSYNTHESIS
REACTOME_INFLUENZA_LIFE_CYCLE
REACTOME_PERK_REGULATED_GENE_EXPRESSION
REACTOME_NONSENSE_MEDIATED_DECAY_NMD_SIGNALING
REACTOME_NONSENSE_MEDIATED_DECAY_ENHANCED_BY_THE_EXON_JUNCTION_COMPLEX
REACTOME_METABOLISM_OF_PROTEINS
REACTOME_CLASS_I_MHC_MEDIATED_ANTIGEN_PROCESSING_PRESENTATION
REACTOME_INFLUENZA_VIRAL_RNA_TRANSCRIPTION_AND_REPLICATION
REACTOME_3_UTR_MEDIATED_TRANSLATIONAL_REGULATION
REACTOME_CLEAVAGE_OF_GROWING_TRANSCRIPT_IN_THE_TERMINATION_REGION_
REACTOME_AMINE_DERIVED_HORMONES
REACTOME_PSMAPK_EVENTS
REACTOME_SIGNALING_BY_TGF_BETA_RECEPTOR_COMPLEX
REACTOME_TRANSCRIPTIONAL_ACTIVITY_OF_SMAD2_SMAD3_SMAD4_HETEROTRIMER
REACTOME_SMAD2_SMAD3_SMAD4_HETEROTRIMER_REGULATES_TRANSCRIPTION
REACTOME_UNFOLDED_PROTEIN_RESPONSE
REACTOME_AKT_PHOSPHORYLATES_TARGETS_IN_THE_CYTOSOL
REACTOME_NEGATIVE_REGULATORS_OF_RIG_I_MDA5_SIGNALING
REACTOME_REGULATION_OF_INSULIN_LIKE_GROWTH_FACTOR_IGF_ACTIVITY_BY_INSULIN_LIKE_GROWTH_FACTOR_BINDING_PROTEINS_IGFBPS
REACTOME_RIG_I_MDA5_MEDIATED_INDUCTION_OF_IFN_ALPHA_BETA_PATHWAYS
REACTOME_RNA_POL_I_PROMOTER_OPENING
REACTOME_ERK_MAPK_TARGETS_NUCLEAR_EVENTS_MEDIATED_BY_MAP_KINASES
REACTOME_SIGNALING_BY_ROBO_RECEPTOR_
REACTOME_MAPK_TARGETS_NUCLEAR_EVENTS_MEDIATED_BY_MAP_KINASES
REACTOME_INTERFERON_GAMMA_SIGNALING
REACTOME_TGF_BETA_RECEPTOR_SIGNALING_ACTIVATES_SMAD3
REACTOME_DOWNREGULATION_OF_TGF_BETA_RECEPTOR_SIGNALING
REACTOME_NFKB_AND_MAP_KINASES_ACTIVATION_MEDIATED_BY_TLR4_SIGNALING_REPERTOIRE
REACTOME_IKK_COMPLEX_RECRUITMENT_MEDIATED_BY_RIP1
REACTOME_GENERIC_TRANSCRIPTION_PATHWAY
REACTOME_SFRS_BCS_PROVIDES_TRANSLOCASE_A_MAPK_SIGNALING_FOR_INTERGRINS_
REACTOME_DOWNREGULATION_OF_SMAD2_SMAD4_TRANSCRIPTIONAL_ACTIVITY
REACTOME_STABILIZATION_OF_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S
REACTOME_DESTABILIZATION_OF_MRNA_BY_TRISTETRAPROLIN_TTP
REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION
REACTOME_NCAM1_INTERACTIONS
REACTOME_SIGNALLING_TO_RAS
REACTOME_SIGNALING_BY_PDGF
REACTOME_NUCLEAR_EVENTS_KINASE_AND_TRANSCRIPTION_FACTOR_ACTIVATION
REACTOME_MRNA_3_END_PROCESSING
REACTOME_BILE_SALT_AND_ORGANIC_ANION_SLC_TRANSPORTERS
REACTOME_ECM_PROTEOGLYCANS_MATRIX_INTERACTIONS
REACTOME_SIGNALLING_TO_ERKS
REACTOME_OTHER_SEMAPHORIN_INTERACTIONS
REACTOME_NCAM_SIGNALING_FOR_NEURITE_OUT_GROWTH
REACTOME_REGULATION_OF_APOPTOSIS
REACTOME_SIGNALING_BY_WNT
REACTOME_P53_DEPENDENT_G1_DNA_DAMAGE_RESPONSE
REACTOME_DOWNSTREAM_SIGNALING_EVENTS_OF_B_CELL_RECEPTOR_BCR
REACTOME_HIV_INFECTION
REACTOME_ACTIVATION_OF_NF_KAPPAB_IN_B_CELLS
REACTOME_METABOLISM_OF_NON_CODING_RNA
REACTOME_EGFR_DOWNREGULATION
REACTOME_RNA_POL_II_TRANSCRIPTION
REACTOME_FORMATION_OF_RNA_POL_II_ELONGATION_COMPLEX_
REACTOME_TOLL_RECEPTOR_CASCADES
REACTOME_HOST_INTERACTIONS_OF_HIV_FACTORS
REACTOME_SCF(SKP1_MEDIATED_DEGRADATION_OF_P27_P21
REACTOME_CYCLIN_E_ASSOCIATED_EVENTS_DURING_G1_S_TRANSITION_
REACTOME_G2_PHASE_DNA_DAMAGE_CHECKPOINT_DNA_DAMAGE_CHECKPOINT_
REACTOME_AUTODEGRADATION_OF_THE_E3_UBIQUITIN_LIGASE_COP1
REACTOME_CROSS_PRESENTATION_OF_SOLUBLE_EXOGENOUS_ANTIGENS_ENDOSOMES
REACTOME_AUTODEGRADATION_OF_CDH1_BY_CDH1_APC_C
REACTOME_SCF_BETA_TRCP_MEDIATED_DEGRADATION_OF_EMI1
REACTOME_REGULATION_OF_MRNA_STABILITY_BY_PROTEINS_THAT_BIND_AU_RICH_ELEMENTS
REACTOME_DESTABILIZATION_OF_MRNA_BY_AUF1_HNRNP_D0
REACTOME_CDK_MEDIATED_PHOSPHORYLATION_AND_REMOVAL_OF_CDC6
REACTOME_REGULATION_OF_ORNITHINE_DECARBOXYLASE_ODC
REACTOME_CELL_CYCLE_PROBE
REACTOME_CHOLESTEROL_BIOSYNTHESIS
REACTOME_CDT1_ASSOCIATION_WITH_THE_CDC6_ORC_ORIGIN_COMPLEX
REACTOME_VIF_MEDIATED_DEGRADATION_OF_APOBEC3G
REACTOME_FORMATION_OF_TUBULIN_FOLDING_INTERMEDIATES_BY_CCT_TRIC
REACTOME_ANTIGEN_PROCESSING_CROSS_PRESENTATION
REACTOME_SIGNALING_BY_RHO_GTPASES
REACTOME_CALNEXIN_CALRETICULIN_CYCLE
REACTOME_N_GLYCAN_TRIMMING_IN_THE_ER_AND_CALNEXIN_CALRETICULIN_CYCLE
REACTOME_ER_QUALITY_CONTROL_COMPONENTS_OF_CBL
REACTOME_ACTIVATION_OF_CHAPERONES_BY_ATF6_ALPHA
REACTOME_ANTIGEN_PRESENTATION_FOLDING_ASSEMBLY_AND_PEPTIDE_LOADING_OF_CLASS_I_MHC
REACTOME_ACTIVATION_OF_CHAPERONE_GENES_BY_XBP1S
REACTOME_YAP1_AND_WWTR1_TAZ_STIMULATED_GENE_EXPRESSION
REACTOME_VEGF_LIGAND_RECEPTOR_INTERACTIONS
REACTOME_TRAF6_MEDIATED_IRF7_ACTIVATION
REACTOME_PI_3K_CASCADE
REACTOME_DOWNSTREAM_TCR_SIGNALING
REACTOME_SIGNALING_BY_THE_CIRCADIAN_CLOCK_ERBB2_ERBB3_SIGNALING
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX
REACTOME_BIOLOGICAL_OXIDATIONS
REACTOME_CYTOCHROME_P450_ARRANGED_BY_SUBSTRATE_TYPE
REACTOME_G1_S_SPECIFIC_TRANSCRIPTION
REACTOME_MYOGENESIS
REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION
REACTOME_E2F_ENABLED_INHIBITION_OF_PRE_REPLICATION_COMPLEX_FORMATION
REACTOME_DNA_TRANSLOCATIONS
REACTOME_ERKS_ARE_INACTIVATED
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING
REACTOME_REGULATION_OF_IFNA_SIGNALING
REACTOME_IL_3_5_AND_GM_CSF_SIGNALING
REACTOME_P130CAS_LINKAGE_TO_MAPK_SIGNALING_FOR_INTEGRINS
REACTOME_REGULATION_OF_GLUCOKINASE_BY_GLUCOKINASE_REGULATORY_PROTEIN
REACTOME_GLYCOLYSIS
REACTOME_FORMATION_OF_THE_TERNARY_COMPLEX_AND_SUBSEQUENTLY_THE_43S_COMPLEX
REACTOME_NANOG_GENES_ACTIVATE_MRNA
REACTOME_ARF6_MEDIATES_DOWN_MODULATION_OF_CELL_SURFACE_RECEPTORS_BY_RECRUITING_THEM_TO_CLATHRIN_ADAPTERS
REACTOME_THE_INOLE_OF_NEF_IN_HIV1_REPLICATION_AND_DISEASE_PATHOGENESIS
REACTOME_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL
REACTOME_SIGNAL_TRANSDUCTION_BY_L1
REACTOME_PECAM1_INTERACTIONS
REACTOME_SASGN_INTERACTIONS
REACTOME_SIGNALING_BY_FGFR3_MUTANTS
REACTOME_TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT
REACTOME_SYNTHESIS_AND_INTERCONVERSION_OF_NUCLEOTIDE_DI_AND_TRIPHOSPHATES
REACTOME_ACTIVATION_OF_BAX_AND_TRUNCATED_BID
REACTOME_NUCLEOTIDE_LIKE_PURINERGIC_RECEPTORS
REACTOME_SIGNALING_BY_ACTIVATED_POINT_MUTANTS_OF_FGFR1
REACTOME_NUCLEAR_SIGNALING_BY_ERBB4
REACTOME_ACTIVATION_OF_THE_AP1_FAMILY_OF_TRANSCRIPTION_FACTORS
REACTOME_CELL_DEATH_SIGNALLING_VIA_NRAGE_NRIF_AND_NADE
REACTOME_NRAGE_SIGNALS_DEATH_THROUGH_JNK
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_PLASMA_MEMBRANE
REACTOME_S1_SIGNALING
REACTOME_RNA_POL_I_RNA_TRANSCRIPTION_TERMINATION
REACTOME_RNA_POL_I_RNA_POL_III_AND_MITOCHONDRIAL_TRANSCRIPTION
REACTOME_DSCAM_INTERACTIONS
REACTOME_ABORTIVE_ELONGATION_OF_HIV1_TRANSCRIPT_IN_THE_ABSENCE_OF_TAT
REACTOME_TRAF6_MEDIATED_INDUCTION_OF_TAK1_COMPLEX
REACTOME_TAK1_ACTIVATES_NFKB_BY_PHOSPHORYLATION_AND_ACTIVATION_OF_IKKS_COMPLEX
REACTOME_NRIF_SIGNALS_CELL_DEATH_FROM_THE_NUCLEUS
REACTOME_PTINTR_RECRUITS_SIGNALLING_COMPLEXES
REACTOME_VIRAL_MESSENGER_RNA_SYNTHESIS
REACTOME_SIGNALING_BY_PDGF_MUTANTS
REACTOME_PTINTR_DISNALS_VIA_NFKB
REACTOME_ACTIVATED_TAK1_MEDIATES_P38_MAPK_ACTIVATION
REACTOME_NOD1_2_SIGNALING_PATHWAY
REACTOME_MRNA_CAPPING
REACTOME_FORMATION_OF_THE_HIV1_EARLY_ELONGATION_COMPLEX
REACTOME_P75_NTR_RECEPTOR_MEDIATED_SIGNALLING
REACTOME_JNK_C_JUN_KINASES_PHOSPHORYLATION_AND_ACTIVATION_MEDIATED_BY_ACTIVATED_HUMAN_TAK1
REACTOME_MYD88_MAL_CASCADE_INITIATED_ON_PLASMA_MEMBRANE
REACTOME_RNA_POL_II_TRANSCRIPTION_INITIATION_FROM_TYPE_2_PROMOTER
REACTOME_DNA_REPAIR
REACTOME_RNA_POL_III_TRANSCRIPTION_INITIATION_FROM_TYPE_3_PROMOTER
REACTOME_RNA_POL_III_TRANSCRIPTION
REACTOME_RNA_POL_III_CHAIN_ELONGATION
REACTOME_RNA_POL_III_TRANSCRIPTION_TERMINATION
REACTOME_HS_GAG_DEGRADATION
REACTOME_HEPARAN_SULFATE_HEPARIN_HS_GAG_METABOLISM
REACTOME_FORMATION_OF_INCISION_COMPLEX_IN_GG_NER
REACTOME_SLC_MEDIATED_TRANSMEMBRANE_TRANSPORT
REACTOME_PYRUVATE_METABOLISM_AND_CITRIC_ACID_TCA_CYCLE
REACTOME_SIGNAL_AMPLIFICATION
REACTOME_LYSOSOME_VESICLE_BIOGENESIS
REACTOME_PHASE_II_CONJUGATION
REACTOME_PROTEOLYTIC_CLEAVAGE_OF_SNARE_COMPLEX_PROTEINS
REACTOME_ION_CHANNEL_TRANSPORT
REACTOME_PURINE_SALVAGE
REACTOME_REGULATION_OF_RHEB_GTPASE_ACTIVITY_BY_AMPK
REACTOME_SIGNALING_BY_NOTCH1
REACTOME_GOLGI_ASSOCIATED_VESICLE_BIOGENESIS
REACTOME_BOTULINUM_NEUROTOXICITY
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_GOLGI_MEMBRANE
REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS
REACTOME_METABOLISM_OF_AMINO_ACIDS_AND_DERIVATIVES
REACTOME_TRANSPORT_OF_MATURE_MRNA_DERIVED_FROM_AN_INTRONLESS_TRANSCRIPT
REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION
REACTOME_RECYCLING_PATHWAY_OF_L1
REACTOME_SIGNALING_BY_NOTCH
REACTOME_N_GLYCAN_ANTENNAE_ELONGATION_IN_THE_MEDIAL_TRANS_GOLGI
REACTOME_PHASE1_FUNCTIONALIZATION_OF_COMPOUNDS
REACTOME_MITOTIC_PROMETAPHASE
REACTOME_DEADENYLATION_OF_MRNA
REACTOME_PEROXISOMAL_LIPID_METABOLISM
REACTOME_RESPIRATORY_ELECTRON_TRANSPORT
REACTOME_RESPIRATORY_ELECTRON_TRANSPORT_ATP_SYNTHESIS_BY_CHEMIOSMOTIC_COUPLING_AND_HEAT_PRODUCTION_BY_UNCOUPLING_PROTEINS_
REACTOME_RESPONSE_TO_ELEVATED_PLATELET_CYTOSOLIC_CA2_
REACTOME_SIGNALING_BY_ERK
REACTOME_INTERFERON_SIGNALING
REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM
REACTOME_ADAPTIVE_IMMUNE_SYSTEM
REACTOME_PLATELET_ADHESION_TO_EXPOSED_COLLAGEN
REACTOME_IMMUNE_SYSTEM
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS
REACTOME_DEVELOPMENTAL_BIOLOGY
REACTOME_AXON_GUIDANCE
REACTOME_ADENOSINE_RECEPTOR_SIGNALING
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION
REACTOME_PPARA_ACTIVATES_GENE_EXPRESSION
REACTOME_SEMAPHORIN_INTERACTIONS
REACTOME_L1CAM_INTERACTIONS
REACTOME_SIGNALING_BY_NOTCH1
REACTOME_FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM
REACTOME_PROCESSING_OF_CAPPED_INTRONLESS_PRE_MRNA
REACTOME_INNATE_IMMUNE_SYSTEM
REACTOME_PPAR_ALPHA_ACTIVATION_DOMAIN_REGULATES_TRANSCRIPTION
REACTOME_SIGNALING_BY_CONSTITUTIVELY_ACTIVE_EGFR
REACTOME_PLATELET_SENSITIZATION_BY_LDL
REACTOME_RNA_POL_I_TRANSCRIPTION_INITIATION
REACTOME_PROCESSING_OF_INTRONLESS_PRE_MRNAS
REACTOME_BMAL1_CLOCK_NPAS2_ACTIVATES_CIRCADIAN_EXPRESSION
REACTOME_DOWNSTREAM_SIGNALING_OF_ACTIVATED_FGFR
REACTOME_TRANS_GOLGI_NETWORK_VESICLE_BUDDING
REACTOME_SIGNALING_BY_FGFR_MUTANTS
REACTOME_SIGNALING_BY_ERK
REACTOME_AMINO_ACID_AND_OLIGOPEPTIDE_SLC_TRANSPORTERS
REACTOME_TRANSPORT_TO_THE_GOLGI_AND_SUBSEQUENT_MODIFICATION
REACTOME_TCR_SIGNALING
REACTOME_RECEPTOR_LIGAND_BINDING_INITIATES_THE_SECOND_PROTEOLYTIC_CLEAVAGE_OF_NOTCH_RECEPTOR
REACTOME_CD28_CO_STIMULATION
REACTOME_PIP3_ACTIVATES_AKT_SIGNALING
REACTOME_PI3K_AKT_ACTIVATION
REACTOME_PRE_NOTCH_TRANSCRIPTION_AND_TRANSLATION
REACTOME_PRE_NOTCH_EXPRESSION_AND_PROCESSING
REACTOME_CIRCADIAN_CLOCK
REACTOME_FACTORS_INVOLVED_IN_MEGAKARYOCYTE_DEVELOPMENT_AND_PLATELET_PRODUCTION
REACTOME_PI3K_EVENTS_IN_ERBB4_SIGNALING
REACTOME_SIGNALING_BY_SCF_KIT
REACTOME_APOPTOTIC_CLEAVAGE_OF_CELLULAR_PROTEINS
REACTOME_SYNTHESIS_OF_PE
REACTOME_PI3K_EVENTS_IN_ERBB2_SIGNALING
REACTOME_SIGNALING_BY_FGFR1_FUSION_MUTANTS
REACTOME_SIGNALING_BY_BMP
REACTOME_TGF_BETA_RECEPTOR_SIGNALING_IN_EMT_EPITHELIAL_TO_MESENCHYMAL_TRANSITION
REACTOME_APOPTOTIC_EXECUTION_PHASE
REACTOME_CD28_DEPENDENT_PI3K_AKT_SIGNALING
REACTOME_SIGNALING_BY_ERBB4
REACTOME_APOPTOTIC_CLEAVAGE_OF_CELL_ADHESION_PROTEINS
REACTOME_NOTCH_HLH_TRANSCRIPTION_PATHWAY
REACTOME_SIGNALING_BY_NOTCH
REACTOME_PURINE_METABOLISM
REACTOME_DEGRADATION_PATHWAYS
REACTOME_METABOLISM_OF_NUCLEOTIDES
REACTOME_G_ALPHA(12/13)_SIGNALLING_EVENTS
REACTOME_AMINO_ACID_SYNTHESIS_AND_INTERCONVERSION_TRANSAMINATION
REACTOME_SIGNALLING_BY_NGF
REACTOME_SIGNALING_BY_EGFR_IN_CANCER
REACTOME_SIGNALING_BY_ILS
REACTOME_NGF_SIGNALING_VIA_TRKA_FROM_THE_PLASMA_MEMBRANE
REACTOME_DOWNSTREAM_SIGNAL_TRANSDUCTION
REACTOME_CREB_PHOSPHORYLATION_BY_PKA
REACTOME_CREB_PHOSPHORYLATION_THROUGH_THE_ACTIVATION_OF_CAMKII
REACTOME_COPI_MEDIATED_TRANSPORT
REACTOME_VOLTAGE_GATED_POTASSIUM_CHANNELS
REACTOME_POTASSIUM_CHANNELS
REACTOME_NEURONAL_SYSTEM
REACTOME_METABOLISM_OF_VITAMINS_AND_COFACTORS
REACTOME_ADP_SIGNALLING_THROUGH_P2RY12
REACTOME_PROSTACYCLIN_SIGNALLING_THROUGH_PROSTACYCLIN_RECEPTOR
REACTOME_NEUROTRANSMITTER_RECEPTOR_BINDING_AND_DOWNSTREAM_TRANSMISSION_IN_THE_POSTSYNAPTIC_CELL
REACTOME_TRANSMISSION_ACROSS_CHEMICAL_SYNAPSES
REACTOME_NEUROTRANSMITTER_RELEASE_CYCLE
REACTOME_INWARDLY_RECTIFYING_K_CHANNELS
REACTOME_SPRY_REGULATION_OF_FGF_SIGNALING
REACTOME_GABA_RECEPTOR_ACTIVATION
REACTOME_DAG_AND_IP3_SIGNALING
REACTOME_ADENOSINE_POTASSIUM_GATED_CAQ_CHANNELS_VIA_GBETA_GAMMA_SUBUNITS
REACTOME_POST_NMDA_RECEPTOR_ACTIVATION_EVENTS
REACTOME_SIGNALING_BY_FGFR
REACTOME_METABOLISM_OF_PORPHYRINS
REACTOME_DARPP_32_EVENTS
REACTOME_OPIOID_SIGNALLING
REACTOME_ACTIVATION_OF_NMDA_RECEPTOR_UPON_GLUTAMATE_BINDING_AND_POSTSYNAPTIC_EVENTS
REACTOME_CA_DEPENDENT_EVENTS
REACTOME_GABA_B_RECEPTOR_ACTIVATION
REACTOME_CREB_PHOSPHORYLATION_THROUGH_THE_MAPK_AND_RAS_DEGRADATION
REACTOME_CREB_PHOSPHORYLATION_THROUGH_THE_ACTIVATION_OF_RAS
REACTOME_THROMBIN_SIGNALLING_THROUGH_PROTEINASE_ACTIVATED_RECEPTORS_PARS
REACTOME_G_ALPHA_Z_SIGNALLING_EVENTS
REACTOME_REGULATION_OF_INSULIN_SECRETION_BY_GLUCAGON_LIKE_PEPTIDE1
REACTOME_GLYCOSAMINOGLYCAN_METABOLISM
REACTOME_G_BETA_GAMMA_SIGNALLING_THROUGH_PI3KGAMMA
REACTOME_ABCA_TRANSPORTERS_IN_LIPID_HOMEOSTASIS
REACTOME_SHC1_EVENTS_IN_ERBB4_SIGNALING
REACTOME_SHC_RELATED_EVENTS
REACTOME_SIGNALING_BY_PDGF_PDGFR_FGF_AND_TEN
REACTOME_SOS_MEDIATED_SIGNALLING
REACTOME_GLUCAGON_SIGNALING_IN_METABOLIC_REGULATION
REACTOME_CHONDROITIN_SULFATE_DERMATAN_SULFATE_METABOLISM
REACTOME_CHONDROITIN_SULFATE_BIOSYNTHESIS
REACTOME_PURINE_RIBONUCLEOSIDE_MONOPHOSPHATE_BIOSYNTHESIS
Control
TLE
Z121_1
Z11_5
Z15_10
Z10_13
Z13_17
Z117_20

figure S8

Color Key
−2 −1 0 1 2
NES
GSEA: GO MF
NEUTRAL_AMINO_ACID_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
ACTIVE_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
AMINE_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
SULFOTRANSFERASE_ACTIVITY
AMINO_ACID_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
PHOSPHATASE_INHIBITOR_ACTIVITY
TRANSFERASE_ACTIVITY_TRANSFERRING_HEXOSYL_GROUPS
CARBOXYLIC_ACID_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
ORGANIC_ACID_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
ANTIGEN_BINDING
ACETYLGALACTOSAMINYLTRANSFERASE_ACTIVITY
PHOSPHOLIPASE_C_ACTIVITY
INOSITOL_OR_PHOSPHATIDYLINOSITOL_PHOSPHODIESTERASE_ACTIVITY
MANNOSYLTRANSFERASE_ACTIVITY
RECEPTOR_ACTIVITY
TRANSMEMBRANE_RECEPTOR_ACTIVITY
NEUROTRANSMITTER_RECEPTOR_ACTIVITY
COFACTOR_TRANSPORTER_ACTIVITY
MONOOXYGENASE_ACTIVITY
LOW_DENSITY_LIPOPROTEIN_BINDING
SECRETIN_LIKE_RECEPTOR_ACTIVITY
PHOSPHATASE_BINDING
TRANSITION_METAL_ION_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
HISTONE_METHYLTRANSFERASE_ACTIVITY
COLLAGEN_BINDING
RECEPTOR_SIGNALING_PROTEIN_ACTIVITY
LIPOPROTEIN_BINDING
GROWTH_FACTOR_BINDING
ZINC_ION_BINDING
HYDROLASE_ACTIVITY_ACTING_ON_ESTER_BONDS
INTERLEUKIN_RECEPTOR_ACTIVITY
INORGANIC_ANION_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
RNA_POLYMERASE_ACTIVITY
INTERLEUKIN_BINDING
EXTRACELLULAR_LIGAND_GATED_ION_CHANNEL_ACTIVITY
PEPTIDE_BINDING
NUCLEOTIDYLTRANSFERASE_ACTIVITY
EXCITATORY_EXTRACELLULAR_LIGAND_GATED_ION_CHANNEL_ACTIVITY
SUBSTRATE_SPECIFIC_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
PHOSPHOPROTEIN_PHOSPHATASE_ACTIVITY
PHOSPHORIC_ESTER_HYDROLASE_ACTIVITY
PROTEIN_SERINE_THREONINE_PHOSPHATASE_ACTIVITY
PHOSPHATASE_REGULATOR_ACTIVITY
SUBSTRATE_SPECIFIC_TRANSPORTER_ACTIVITY
TRANSMEMBRANE_TRANSPORTER_ACTIVITY
HEMATOPOIETIN_INTERFERON_CLASSD200_DOMAIN_CYTOKINE_RECEPTOR_ACTIVITY
PHOSPHORIC_MONOESTER_HYDROLASE_ACTIVITY
PHOSPHATE_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
SIGNAL_SEQUENCE_BINDING
CYTOKINE_BINDING
INOSITOL_OR_PHOSPHATIDYLINOSITOL_KINASE_ACTIVITY
HYDROLASE_ACTIVITY_ACTING_ON_ACID_ANHYDRIDES
CYCLASE_ACTIVITY
NUCLEOSIDE_TRIPHOSPHATASE_ACTIVITY
TUBULIN_BINDING
PYROPHOSPHATASE_ACTIVITY
ATP_DEPENDENT_RNA_HELICASE_ACTIVITY
ATP_DEPENDENT_HELICASE_ACTIVITY
RNA_HELICASE_ACTIVITY
MICROTUBULE_BINDING
CYTOSKELETAL_PROTEIN_BINDING
RNA_DEPENDENT_ATPASE_ACTIVITY
DOUBLE_STRANDED_DNA_BINDING
STRUCTURE_SPECIFIC_DNA_BINDING
DAMAGED_DNA_BINDING
DNA_DEPENDENT_ATPASE_ACTIVITY
ATP_DEPENDENT_DNA_HELICASE_ACTIVITY
SINGLE_STRANDED_DNA_BINDING
UNFOLDED_PROTEIN_BINDING
TRANSLATION_INITIATION_FACTOR_ACTIVITY
TRANSLATION_REGULATOR_ACTIVITY
TRANSLATION_FACTOR_ACTIVITY_NUCLEIC_ACID_BINDING
MICROTUBULE_MOTOR_ACTIVITY
IONOTROPIC_GLUTAMATE_RECEPTOR_ACTIVITY
HEMATOPOIETIN_INTERFERON_CLASSD200_DOMAIN_CYTOKINE_RECEPTOR_BINDING
CARBOHYDRATE_KINASE_ACTIVITY
DNA_HELICASE_ACTIVITY
ATPASE_ACTIVITY_COUPLED
CALCIUM_CHANNEL_ACTIVITY
RAS_GTPASE_BINDING
GLUTAMATE_RECEPTOR_ACTIVITY
HELICASE_ACTIVITY
ATPASE_ACTIVITY
MOTOR_ACTIVITY
ZT1
ZT5
ZT10
ZT13
ZT17
ZT21

figure S9

Color Key
−2 −1 0 1 2
NES
GSEA: GO CC
INTRINSIC_TO_GOLGI_MEMBRANE
EXTERNAL_SIDE_OF_PLASMA_MEMBRANE
ORGANELLE_ENVELOPE
ENVELOPE
VOLTAGE_GATED_POTASSIUM_CHANNEL_COMPLEX
INTEGRAL_TO_GOLGI_MEMBRANE
MEDIATOR_COMPLEX
LEADING_EDGE
COLLAGEN
CLATHRIN_COATED_VESICLE
NUCLEAR_ENVELOPE
NUCLEAR_MEMBRANE
CELL_FRACTION
ER_GOLGI_INTERMEDIATE_COMPARTMENT
NUCLEAR_PORE
ENDOMEMBRANE_SYSTEM
NUCLEAR_MEMBRANE_PART
PORE_COMPLEX
ENDOPLASMIC_RETICULUM
ENDOSOME
TRANSPORT_VESICLE
ORGANELLE_MEMBRANE
RECEPTOR_COMPLEX
INTEGRAL_TO_PLASMA_MEMBRANE
INTRINSIC_TO_PLASMA_MEMBRANE
INTEGRAL_TO_ORGANELLE_MEMBRANE
ENDOPLASMIC_RETICULUM_MEMBRANE
INTRINSIC_TO_ORGANELLE_MEMBRANE
ENDOPLASMIC_RETICULUM_PART
EARLY_ENDOSOME
MEMBRANE_FRACTION
NUCLEAR_ENVELOPE_ENDOPLASMIC_RETICULUM_NETWORK
RNA_POLYMERASE_COMPLEX
NUCLEAR_DNA_DIRECTED_RNA_POLYMERASE_COMPLEX
DNA_DIRECTED_RNA_POLYMERASE_COMPLEX
VACUOLE
DNA_DIRECTED_RNA_POLYMERASEII_CORE_COMPLEX
LYTIC_VACUOLE
LYSOSOME
INSOLUBLE_FRACTION
KINESIN_COMPLEX
MICROTUBULE_ASSOCIATED_COMPLEX
MITOCHONDRIAL_OUTER_MEMBRANE
HETEROGENEOUS_NUCLEAR_RIBONUCLEOPROTEIN_COMPLEX
RIBONUCLEOPROTEIN_COMPLEX
DYSTROPHIN_ASSOCIATED_GLYCOPROTEIN_COMPLEX
MICROTUBULE_CYTOSKELETON
UBIQUITIN_LIGASE_COMPLEX
CYTOSKELETAL_PART
PROTON_TRANSPORTING_TWO_SECTOR_ATPASE_COMPLEX
U12_DEPENDENT_SPLICEOSOME
ZT1
ZT5
ZT10
ZT13
ZT17
ZT21

figure S10

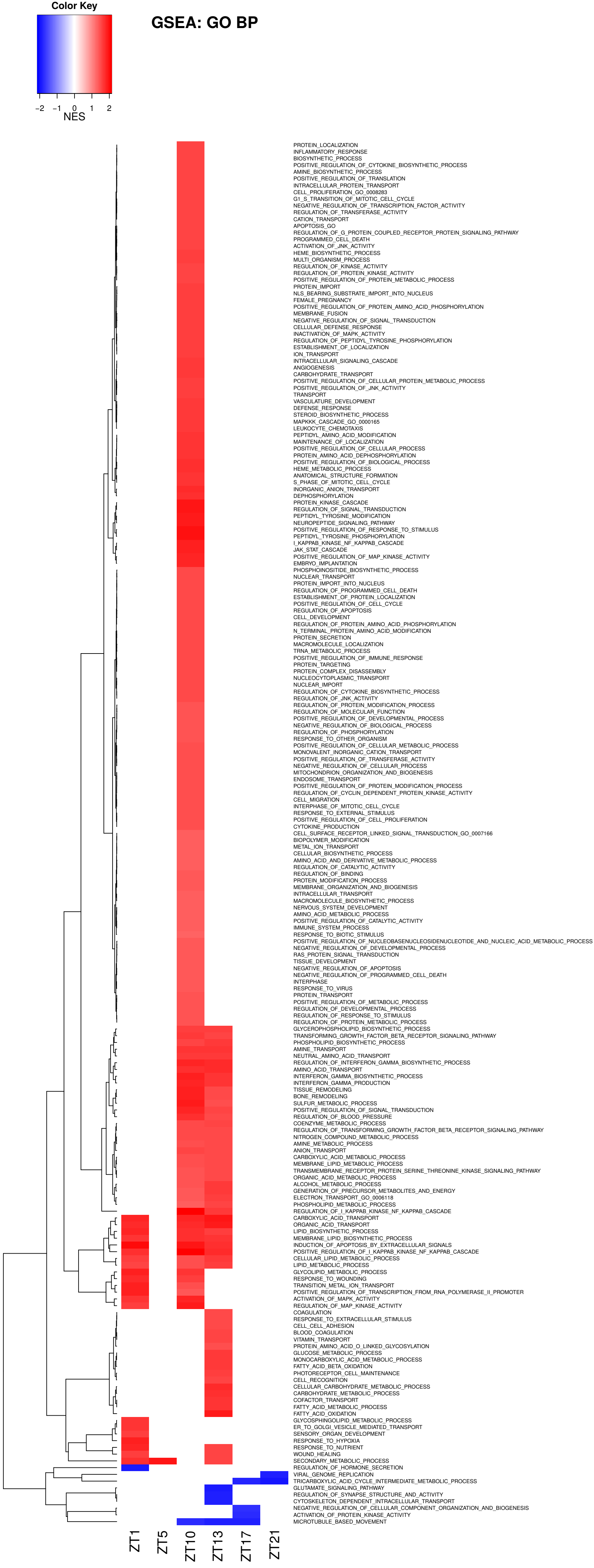
Color Key
−2 −1 0 1 2
NES
GSEA: GO BP
PROTEIN_LOCALIZATION
INFLAMMATORY_RESPONSE
BIOSYNTHETIC_PROCESS
POSITIVE_REGULATION_OF_CYTOKINE_BIOSYNTHETIC_PROCESS
AMINE_BIOSYNTHETIC_PROCESS
POSITIVE_REGULATION_OF_TRANSLATION
INTRACELLULAR_PROTEIN_TRANSPORT
CELL_PROLIFERATION_GO_0008283
G1_S_TRANSITION_OF_MITOTIC_CELL_CYCLE
NEGATIVE_REGULATION_OF_TRANSCRIPTION_FACTOR_ACTIVITY
REGULATION_OF_TRANSFERASE_ACTIVITY
CATION_TRANSPORT
APOPTOSIS_GO
REGULATION_OF_G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY
PROGRAMMED_CELL_DEATH
ACTIVATION_OF_JNK_ACTIVITY
HEME_BIOSYNTHETIC_PROCESS
MULTI_ORGANISM_PROCESS
REGULATION_OF_KINASE_ACTIVITY
REGULATION_OF_PROTEIN_KINASE_ACTIVITY
POSITIVE_REGULATION_OF_PROTEIN_METABOLIC_PROCESS
PROTEIN_IMPORT
NLS_BEARING_SUBSTRATE_IMPORT_INTO_NUCLEUS
FEMALE_PREGNANCY
POSITIVE_REGULATION_OF_PROTEIN_AMINO_ACID_PHOSPHORYLATION
MEMBRANE_FUSION
NEGATIVE_REGULATION_OF_SIGNAL_TRANSDUCTION
CELLULAR_DEFENSE_RESPONSE
INACTIVATION_OF_MAPK_ACTIVITY
REGULATION_OF_PEPTIDYL_TYROSINE_PHOSPHORYLATION
ESTABLISHMENT_OF_LOCALIZATION
ION_TRANSPORT
INTRACELLULAR_SIGNALING_CASCADE
ANGIOGENESIS
CARBOHYDRATE_TRANSPORT
POSITIVE_REGULATION_OF_CELLULAR_PROTEIN_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_JNK_ACTIVITY
TRANSPORT
VASCULATURE_DEVELOPMENT
DEFENSE_RESPONSE
STEROID_BIOSYNTHETIC_PROCESS
MAPKKK_CASCADE_GO_0000165
LEUKOCYTE_CHEMOTAXIS
PEPTIDYL_AMINO_ACID_MODIFICATION
MAINTENANCE_OF_LOCALIZATION
POSITIVE_REGULATION_OF_CELLULAR_PROCESS
PROTEIN_AMINO_ACID_DEPHOSPHORYLATION
POSITIVE_REGULATION_OF_BIOLOGICAL_PROCESS
HEME_METABOLIC_PROCESS
ANATOMICAL_STRUCTURE_FORMATION
S_PHASE_OF_MITOTIC_CELL_CYCLE
INORGANIC_ANION_TRANSPORT
DEPHOSPHORYLATION
PROTEIN_KINASE_CASCADE
REGULATION_OF_SIGNAL_TRANSDUCTION
PEPTIDYL_TYROSINE_MODIFICATION
NEUROPEPTIDE_SIGNALING_PATHWAY
POSITIVE_REGULATION_OF_RESPONSE_TO_STIMULUS
PEPTIDYL_TYROSINE_PHOSPHORYLATION
I_KAPPAB_KINASE_NF_KAPPAB_CASCADE
JAK_STAT_CASCADE
POSITIVE_REGULATION_OF_MAP_KINASE_ACTIVITY
EMBRYO_IMPLANTATION
PHOSPHOINOSITIDE_BIOSYNTHETIC_PROCESS
NUCLEAR_TRANSPORT
PROTEIN_IMPORT_INTO_NUCLEUS
REGULATION_OF_PROGRAMMED_CELL_DEATH
ESTABLISHMENT_OF_PROTEIN_LOCALIZATION
POSITIVE_REGULATION_OF_CELL_CYCLE
REGULATION_OF_APOPTOSIS
CELL_DEVELOPMENT
REGULATION_OF_PROTEIN_AMINO_ACID_PHOSPHORYLATION
N_TERMINAL_PROTEIN_AMINO_ACID_MODIFICATION
PROTEIN_SECRETION
MACROMOLECULE_LOCALIZATION
TRNA_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_IMMUNE_RESPONSE
PROTEIN_TARGETING
PROTEIN_COMPLEX_DISASSEMBLY
NUCLEOCYTOPLASMIC_TRANSPORT
NUCLEAR_IMPORT
REGULATION_OF_CYTOKINE_BIOSYNTHETIC_PROCESS
REGULATION_OF_JNK_ACTIVITY
REGULATION_OF_PROTEIN_MODIFICATION_PROCESS
REGULATION_OF_MOLECULAR_FUNCTION
POSITIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS
NEGATIVE_REGULATION_OF_BIOLOGICAL_PROCESS
REGULATION_OF_PHOSPHORYLATION
RESPONSE_TO_OTHER_ORGANISM
POSITIVE_REGULATION_OF_CELLULAR_METABOLIC_PROCESS
MONOVALENT_INORGANIC_CATION_TRANSPORT
POSITIVE_REGULATION_OF_TRANSFERASE_ACTIVITY
NEGATIVE_REGULATION_OF_CELLULAR_PROCESS
MITOCHONDRION_ORGANIZATION_AND_BIOGENESIS
ENDOSOME_TRANSPORT
POSITIVE_REGULATION_OF_PROTEIN_MODIFICATION_PROCESS
REGULATION_OF_CYCLIN_DEPENDENT_PROTEIN_KINASE_ACTIVITY
CELL_MIGRATION
INTERPHASE_OF_MITOTIC_CELL_CYCLE
RESPONSE_TO_EXTERNAL_STIMULUS
POSITIVE_REGULATION_OF_CELL_PROLIFERATION
CYTOKINE_PRODUCTION
CELL_SURFACE_RECEPTOR_LINKED_SIGNAL_TRANSDUCTION_GO_0007166
BIOPOLYMER_MODIFICATION
METAL_ION_TRANSPORT
CELLULAR_BIOSYNTHETIC_PROCESS
AMINO_ACID_AND_DERIVATIVE_METABOLIC_PROCESS
REGULATION_OF_CATALYTIC_ACTIVITY
REGULATION_OF_BINDING
PROTEIN_MODIFICATION_PROCESS
MEMBRANE_ORGANIZATION_AND_BIOGENESIS
INTRACELLULAR_TRANSPORT
MACROMOLECULE_BIOSYNTHETIC_PROCESS
NERVOUS_SYSTEM_DEVELOPMENT
AMINO_ACID_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_CATALYTIC_ACTIVITY
IMMUNE_SYSTEM_PROCESS
RESPONSE_TO_BIOTIC_STIMULUS
POSITIVE_REGULATION_OF_NUCLEOBASENUCLEOSIDENUCLEOTIDE_AND_NUCLEIC_ACID_METABOLIC_PROCESS
NEGATIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS
RAS_PROTEIN_SIGNAL_TRANSDUCTION
TISSUE_DEVELOPMENT
NEGATIVE_REGULATION_OF_APOPTOSIS
NEGATIVE_REGULATION_OF_PROGRAMMED_CELL_DEATH
INTERPHASE
RESPONSE_TO_VIRUS
PROTEIN_TRANSPORT
POSITIVE_REGULATION_OF_METABOLIC_PROCESS
REGULATION_OF_DEVELOPMENTAL_PROCESS
REGULATION_OF_RESPONSE_TO_STIMULUS
REGULATION_OF_PROTEIN_METABOLIC_PROCESS
GLYCEROPHOSPHOLIPID_BIOSYNTHETIC_PROCESS
TRANSFORMING_GROWTH_FACTOR_BETA_RECEPTOR_SIGNALING_PATHWAY
PHOSPHOLIPID_BIOSYNTHETIC_PROCESS
AMINE_TRANSPORT
NEUTRAL_AMINO_ACID_TRANSPORT
REGULATION_OF_INTERFERON_GAMMA_BIOSYNTHETIC_PROCESS
AMINO_ACID_TRANSPORT
INTERFERON_GAMMA_BIOSYNTHETIC_PROCESS
INTERFERON_GAMMA_PRODUCTION
TISSUE_REMODELING
BONE_REMODELING
SULFUR_METABOLIC_PROCESS
POSITIVE_REGULATION_OF_SIGNAL_TRANSDUCTION
REGULATION_OF_BLOOD_PRESSURE
COENZYME_METABOLIC_PROCESS
REGULATION_OF_TRANSFORMING_GROWTH_FACTOR_BETA_RECEPTOR_SIGNALING_PATHWAY
NITROGEN_COMPOUND_METABOLIC_PROCESS
AMINE_METABOLIC_PROCESS
ANION_TRANSPORT
CARBOXYLIC_ACID_METABOLIC_PROCESS
MEMBRANE_LIPID_METABOLIC_PROCESS
TRANSMEMBRANE_RECEPTOR_PROTEIN_SERINE_THREONINE_KINASE_SIGNALING_PATHWAY
ORGANIC_ACID_METABOLIC_PROCESS
ALCOHOL_METABOLIC_PROCESS
GENERATION_OF_PRECURSOR_METABOLITES_AND_ENERGY
ELECTRON_TRANSPORT_GO_0006118
PHOSPHOLIPID_METABOLIC_PROCESS
REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_CASCADE
CARBOXYLIC_ACID_TRANSPORT
ORGANIC_ACID_TRANSPORT
LIPID_BIOSYNTHETIC_PROCESS
MEMBRANE_LIPID_BIOSYNTHETIC_PROCESS
INDUCTION_OF_APOPTOSIS_BY_EXTRACELLULAR_SIGNALS
POSITIVE_REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_CASCADE
CELLULAR_LIPID_METABOLIC_PROCESS
LIPID_METABOLIC_PROCESS
GLYCOLIPID_METABOLIC_PROCESS
RESPONSE_TO_WOUNDING
TRANSITION_METAL_ION_TRANSPORT
POSITIVE_REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER
ACTIVATION_OF_MAPK_ACTIVITY
REGULATION_OF_MAP_KINASE_ACTIVITY
COAGULATION
RESPONSE_TO_EXTRACELLULAR_STIMULUS
CELL_CELL_ADHESION
BLOOD_COAGULATION
VITAMIN_TRANSPORT
PROTEIN_AMINO_ACID_O_LINKED_GLYCOSYLATION
GLUCOSE_METABOLIC_PROCESS
MONOCARBOXYLIC_ACID_METABOLIC_PROCESS
FATTY_ACID_BETA_OXIDATION
PHOTORECEPTOR_CELL_MAINTENANCE
CELL_RECOGNITION
CELLULAR_CARBOHYDRATE_METABOLIC_PROCESS
CARBOHYDRATE_METABOLIC_PROCESS
COFACTOR_TRANSPORT
FATTY_ACID_METABOLIC_PROCESS
FATTY_ACID_OXIDATION
GLYCOSPHINGOLIPID_METABOLIC_PROCESS
ER_TO_GOLGI_VESICLE_MEDIATED_TRANSPORT
SENSORY_ORGAN_DEVELOPMENT
RESPONSE_TO_HYPOXIA
RESPONSE_TO_NUTRIENT
WOUND_HEALING
SECONDARY_METABOLIC_PROCESS
REGULATION_OF_HORMONE_SECRETION
VIRAL_GENOME_REPLICATION
TRICARBOXYLIC_ACID_CYCLE_INTERMEDIATE_METABOLIC_PROCESS
GLUTAMATE_SIGNALING_PATHWAY
REGULATION_OF_SYNAPSE_STRUCTURE_AND_ACTIVITY
CYTOSKELETON_DEPENDENT_INTRACELLULAR_TRANSPORT
NEGATIVE_REGULATION_OF_CELLULAR_COMPONENT_ORGANIZATION_AND_BIOGENESIS
ACTIVATION_OF_PROTEIN_KINASE_ACTIVITY
MICROTUBULE_BASED_MOVEMENT
ZT1
ZT5
ZT10
ZT13
ZT17
ZT21

figure S11

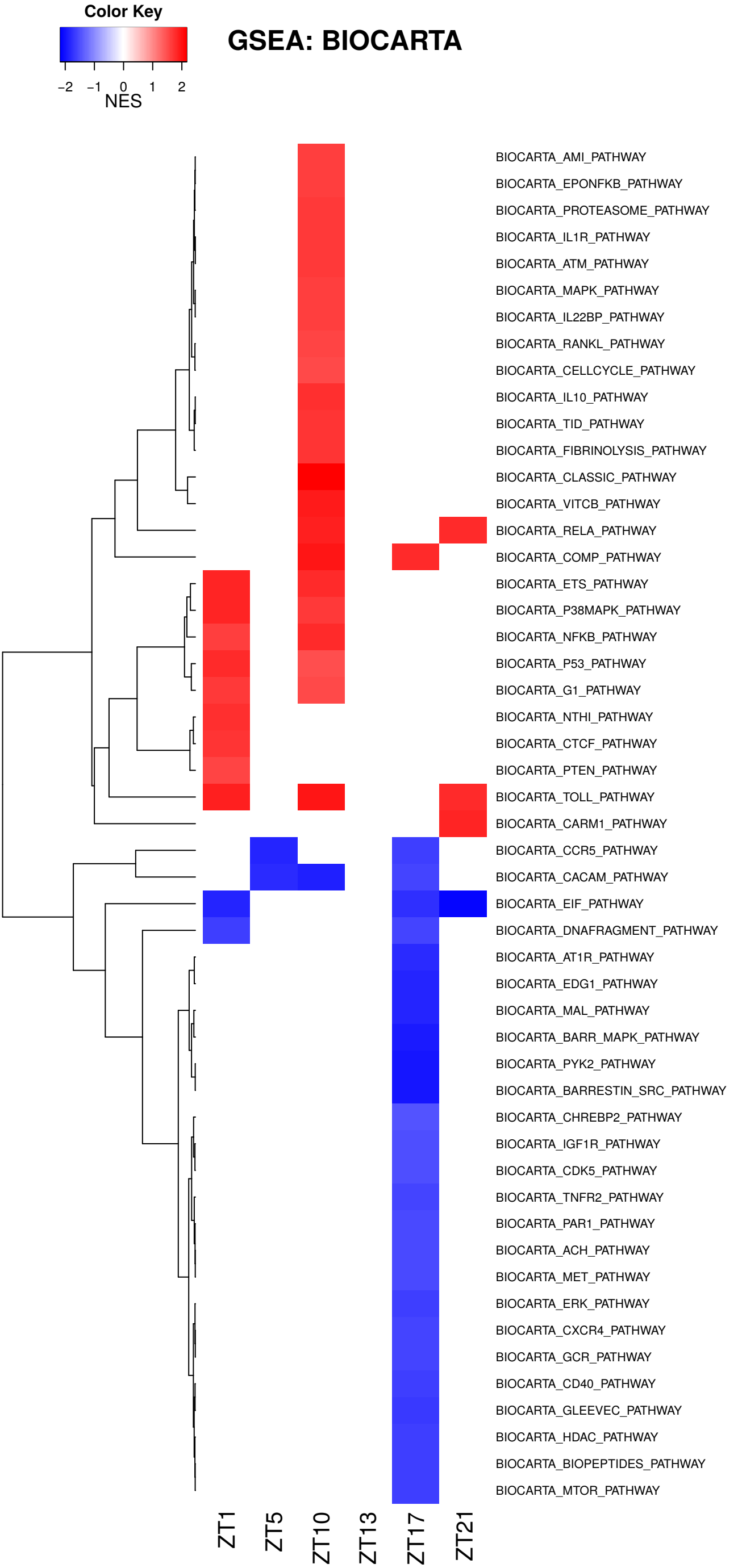
Color Key
−2
−1
0
1
2
NES
GSEA: BIOCARTA
BIOCARTA_AMI_PATHWAY
BIOCARTA_EPONFKB_PATHWAY
BIOCARTA_PROTEASOME_PATHWAY
BIOCARTA_IL1R_PATHWAY
BIOCARTA_ATM_PATHWAY
BIOCARTA_MAPK_PATHWAY
BIOCARTA_IL22BP_PATHWAY
BIOCARTA_RANKL_PATHWAY
BIOCARTA_CELLCYCLE_PATHWAY
BIOCARTA_IL10_PATHWAY
BIOCARTA_TID_PATHWAY
BIOCARTA_FIBRINOLYSIS_PATHWAY
BIOCARTA_CLASSIC_PATHWAY
BIOCARTA_VITCB_PATHWAY
BIOCARTA_RELA_PATHWAY
BIOCARTA_COMP_PATHWAY
BIOCARTA_ETS_PATHWAY
BIOCARTA_P38MAPK_PATHWAY
BIOCARTA_NFKB_PATHWAY
BIOCARTA_P53_PATHWAY
BIOCARTA_G1_PATHWAY
BIOCARTA_NTHI_PATHWAY
BIOCARTA_CTCF_PATHWAY
BIOCARTA_PTEN_PATHWAY
BIOCARTA_TOLL_PATHWAY
BIOCARTA_CARM1_PATHWAY
BIOCARTA_CCR5_PATHWAY
BIOCARTA_CACAM_PATHWAY
BIOCARTA_EIF_PATHWAY
BIOCARTA_DNAFRAGMENT_PATHWAY
BIOCARTA_AT1R_PATHWAY
BIOCARTA_EDG1_PATHWAY
BIOCARTA_MAL_PATHWAY
BIOCARTA_BARR_MAPK_PATHWAY
BIOCARTA_PYK2_PATHWAY
BIOCARTA_BARRESTIN_SRC_PATHWAY
BIOCARTA_CHREBP2_PATHWAY
BIOCARTA_IGF1R_PATHWAY
BIOCARTA_CDK5_PATHWAY
BIOCARTA_TNFR2_PATHWAY
BIOCARTA_PAR1_PATHWAY
BIOCARTA_ACH_PATHWAY
BIOCARTA_MET_PATHWAY
BIOCARTA_ERK_PATHWAY
BIOCARTA_CXCR4_PATHWAY
BIOCARTA_GCR_PATHWAY
BIOCARTA_CD40_PATHWAY
BIOCARTA_GLEEVEC_PATHWAY
BIOCARTA_HDAC_PATHWAY
BIOCARTA_BIOPEPTIDES_PATHWAY
BIOCARTA_MTOR_PATHWAY
ZT1
ZT5
ZT10
ZT13
ZT17
ZT21

figure S12

Color Key
−2 −1 0 1 2
NES
GSEA: KEGG
KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GLOBO_SERIES
KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS
KEGG_MELANOMA
KEGG_PATHWAYS_IN_CANCER
KEGG_TGF_BETA_SIGNALING_PATHWAY
KEGG_ACUTE_MYELOID_LEUKEMIA
KEGG_NOTCH_SIGNALING_PATHWAY
KEGG_PANCREATIC_CANCER
KEGG_CELL_ADHESION_MOLECULES_CAMS
KEGG_PYRIMIDINE_METABOLISM
KEGG_JAK_STAT_SIGNALING_PATHWAY
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY
KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION
KEGG_WNT_SIGNALING_PATHWAY
KEGG_PROSTATE_CANCER
KEGG_ETHER_LIPID_METABOLISM
KEGG_RETINOL_METABOLISM
KEGG_PEROXISOME
KEGG_ABC_TRANSPORTERS
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450
KEGG_GLYCOSAMINOGLYCAN_DEGRADATION
KEGG_DRUG_METABOLISM_CYTOCHROME_P450
KEGG_TYROSINE_METABOLISM
KEGG_RNA_POLYMERASE
KEGG_GLUTATHIONE_METABOLISM
KEGG_ADHERENS_JUNCTION
KEGG_PURINE_METABOLISM
KEGG_SULFUR_METABOLISM
KEGG_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS
KEGG_SPHINGOLIPID_METABOLISM
KEGG_OTHER_GLYCAN_DEGRADATION
KEGG_LYSOSOME
KEGG_P53_SIGNALING_PATHWAY
KEGG_GLYCEROPHOSPHOLIPID_METABOLISM
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES
KEGG_APOPTOSIS
KEGG_MAPK_SIGNALING_PATHWAY
KEGG_SMALL_CELL_LUNG_CANCER
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON
KEGG_CHRONIC_MYELOID_LEUKEMIA
KEGG_FOCAL_ADHESION
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
KEGG_LEISHMANIA_INFECTION
KEGG_SNARE_INTERACTIONS_IN_VESICULAR_TRANSPORT
KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY
KEGG_ECM_RECEPTOR_INTERACTION
KEGG_PROTEIN_EXPORT
KEGG_PORPHYRIN_AND_CHLOROPHYLL_METABOLISM
KEGG_PROTEASOME
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM
KEGG_HUNTINGTONS_DISEASE
KEGG_STEROID_BIOSYNTHESIS
KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM
KEGG_N_GLYCAN_BIOSYNTHESIS
KEGG_OLFACTORY_TRANSDUCTION
KEGG_ASCORBATE_AND_ALDARATE_METABOLISM
KEGG_PROPANOATE_METABOLISM
KEGG_BUTANOATE_METABOLISM
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION
KEGG_FATTY_ACID_METABOLISM
KEGG_VIRAL_MYOCARDITIS
KEGG_CARDIAC_MUSCLE_CONTRACTION
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS
KEGG_PYRUVATE_METABOLISM
KEGG_GLYOXYLATE_AND_DICARBOXYLATE_METABOLISM
KEGG_CITRATE_CYCLE_TCA_CYCLE
KEGG_ALZHEIMERS_DISEASE
KEGG_OXIDATIVE_PHOSPHORYLATION
KEGG_PARKINSONS_DISEASE
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS
KEGG_LONG_TERM_DEPRESSION
KEGG_ENDOMETRIAL_CANCER
KEGG_GNRH_SIGNALING_PATHWAY
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION
KEGG_LIMONENE_AND_PINENE_DEGRADATION
KEGG_NON_SMALL_CELL_LUNG_CANCER
KEGG_ONE_CARBON_POOL_BY_FOLATE
KEGG_ERBB_SIGNALING_PATHWAY
KEGG_GLIOMA
KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION
KEGG_SPLICEOSOME
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION
KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS
KEGG_OOCYTE_MEIOSIS
KEGG_GAP_JUNCTION
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY
KEGG_LONG_TERM_POTENTIATION
ZT1
ZT5
ZT10
ZT13
ZT17
ZT21

figure S13

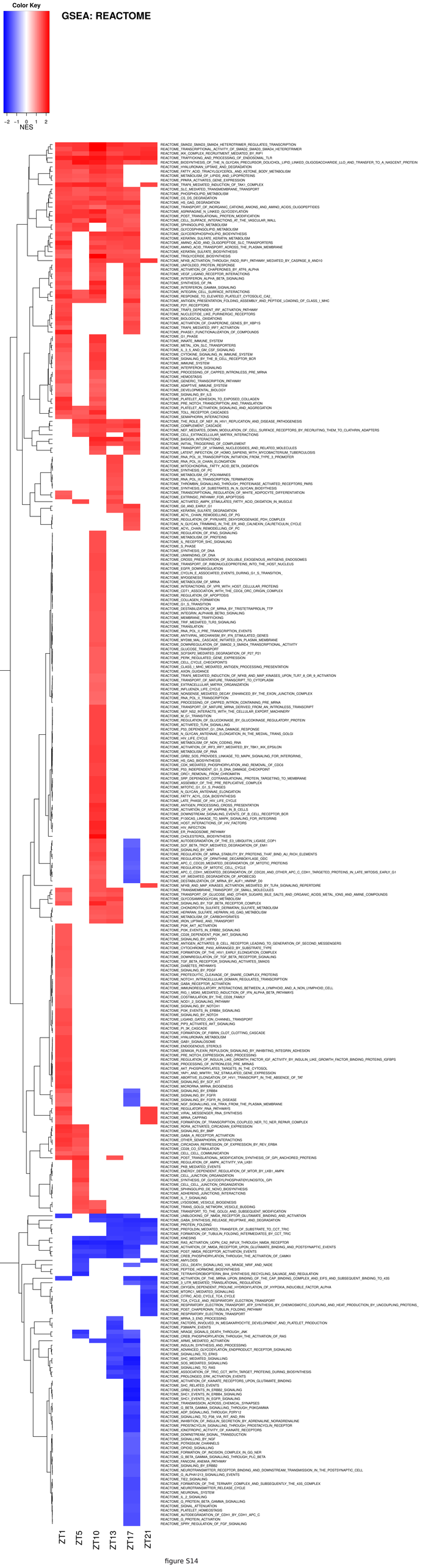
Color Key
−2 −1 0 1 2
NES
GSEA: REACTOME
REACTOME_SMAD2_SMAD3_SMAD4_HETEROTRIMER_REGULATES_TRANSCRIPTION
REACTOME_TRANSCRIPTIONAL_ACTIVITY_OF_SMAD2_SMAD3_SMAD4_HETEROTRIMER
REACTOME_IKK_COMPLEX_RECRUITMENT_MEDIATED_BY_RIP1
REACTOME_TRAF1FICIONO_AND_PROCESSING_OF_ENDOSOMAL_TLR
REACTOME_BIOSYNTHESIS_OF_THE_N_GLYCAN_PRECURSOR_DOLICHOL_LPID_LINKED_OLIGOSACCHARIDE_LLO_AND_TRANSFER_TO_A_NASCENT_PROTEIN
REACTOME_HYALURONAN_UPTAKE_AND_DEGRADATION
REACTOME_FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM
REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS
REACTOME_PPARA_ACTIVATES_GENE_EXPRESSION
REACTOME_TRAF6_MEDIATED_INDUCTION_OF_TAK1_COMPLEX
REACTOME_SLC_MEDIATED_TRANSMEMBRANE_TRANSPORT
REACTOME_PHOSPHOLIPID_METABOLISM
REACTOME_CS_DS_DEGRADATION
REACTOME_HS_GAG_DEGRADATION
REACTOME_TRANSPORT_OF_INORGANIC_CATIONS_ANIONS_AND_AMINO_ACIDS_OLIGOPEPTIDES
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION
REACTOME_POST_TRANSLATIONAL_PROTEIN_MODIFICATION
REACTOME_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL
REACTOME_SPHINGOLIPID_METABOLISM
REACTOME_GLYCOSPHINGOLIPID_METABOLISM
REACTOME_GLYCEROPHOSPHOLIPID_BIOSYNTHESIS
REACTOME_KERATAN_SULFATE_KERATN_METABOLISM
REACTOME_AMINO_ACID_AND_OLIGOPEPTIDE_SLC_TRANSPORTERS
REACTOME_AMINO_ACID_TRANSPORT_ACROSS_THE_PLASMA_MEMBRANE
REACTOME_KERATAN_SULFATE_BIOSYNTHESIS
REACTOME_TRIGLYCERIDE_BIOSYNTHESIS
REACTOME_NFKB_ACTIVATION_THROUGH_FADD_RIP1_PATHWAY_MEDIATED_BY_CASPASE_8_AND10
REACTOME_UNFOLDED_PROTEIN_RESPONSE
REACTOME_ACTIVATION_OF_CHAPERONES_BY_ATF6_ALPHA
REACTOME_VEGF_LIGAND_RECEPTOR_INTERACTIONS
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING
REACTOME_SYNTHESIS_OF_PA
REACTOME_INTERFERON_GAMMA_SIGNALING
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS
REACTOME_RESPONSE_TO_ELEVATED_PLATELET_CYTOSOLIC_CA2_
REACTOME_ANTIGEN_PRESENTATION_FOLDING_ASSEMBLY_AND_PEPTIDE_LOADING_OF_CLASS_I_MHC
REACTOME_P2Y_RECEPTORS
REACTOME_TRAF3_DEPENDENT_IRF_ACTIVATION_PATHWAY
REACTOME_NUCLEOTIDE_LIKE_PURINERGIC_RECEPTORS
REACTOME_BIOLOGICAL_OXIDATIONS
REACTOME_ACTIVATION_OF_CHAPERONE_GENES_BY_XBP1S
REACTOME_TRAF6_MEDIATED_IRF7_ACTIVATION
REACTOME_PHASE1_FUNCTIONALIZATION_OF_COMPOUNDS
REACTOME_G1_PHASE
REACTOME_INNATE_IMMUNE_SYSTEM
REACTOME_METAL_ION_SLC_TRANSPORTERS
REACTOME_IL_3_5_AND_GM_CSF_SIGNALING
REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM
REACTOME_SIGNALING_BY_THE_B_CELL_RECEPTOR_BCR
REACTOME_IMMUNE_SYSTEM
REACTOME_INTERFERON_SIGNALING
REACTOME_PROCESSING_OF_CAPPED_INTRONLESS_PRE_MRNA
REACTOME_HEMOSTASIS
REACTOME_GENERIC_TRANSCRIPTION_PATHWAY
REACTOME_ADAPTIVE_IMMUNE_SYSTEM
REACTOME_DEVELOPMENTAL_BIOLOGY
REACTOME_SIGNALING_BY_ILS
REACTOME_PLATELET_ADHESION_TO_EXPOSED_COLLAGEN
REACTOME_PRE_NOTCH_TRANSCRIPTION_AND_TRANSLATION
REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION
REACTOME_TOLL_RECEPTOR_CASCADES
REACTOME_SEMAPHORIN_INTERACTIONS
REACTOME_THE_ROLE_OF_NEF_IN_HIV1_REPLICATION_AND_DISEASE_PATHOGENESIS
REACTOME_COMPLEMENT_CASCADE
REACTOME_NEF_MEDIATES_DOWN_MODULATION_OF_CELL_SURFACE_RECEPTORS_BY_RECRUITING_THEM_TO_CLATHRIN_ADAPTERS
REACTOME_CELL_EXTRACELLULAR_MATRIX_INTERACTIONS
REACTOME_BASIGIN_INTERACTIONS
REACTOME_INITIAL_TRIGGERING_OF_COMPLEMENT
REACTOME_TRANSPORT_OF_VITAMINS_NUCLEOSIDES_AND_RELATED_MOLECULES
REACTOME_LATENT_INFECTION_OF_HOMO_SAPIENS_WITH_MYCOBACTERIUM_TUBERCULOSIS
REACTOME_RNA_POL_III_TRANSCRIPTION_INITIATION_FROM_TYPE_3_PROMOTER
REACTOME_RNA_POL_III_CHAIN_ELONGATION
REACTOME_MITOCHONDRIAL_FATTY_ACID_BETA_OXIDATION
REACTOME_SYNTHESIS_OF_PC
REACTOME_METABOLISM_OF_POLYAMINES
REACTOME_RNA_POL_III_TRANSCRIPTION_TERMINATION
REACTOME_THROMBIN_SIGNALLING_THROUGH_PROTEINASE_ACTIVATED_RECEPTORS_PARS
REACTOME_SYNTHESIS_OF_SUBSTRATES_IN_N_GLYCAN_BIOSYTHESIS
REACTOME_TRANSCRIPTIONAL_REGULATION_OF_WHITE_ADIPOCYTE_DIFFERENTIATION
REACTOME_EXTRINSIC_PATHWAY_FOR_APOPTOSIS
REACTOME_ACTIVATED_AMPK_STIMULATES_FATTY_ACID_OXIDATION_IN_MUSCLE
REACTOME_G0_AND_EARLY_G1
REACTOME_KERATAN_SULFATE_DEGRADATION
REACTOME_ACYL_CHAIN_REMODELLING_OF_PG
REACTOME_REGULATION_OF_PYRUVATE_DEHYDROGENASE_PDH_COMPLEX
REACTOME_N_GLYCAN_TRIMMING_IN_THE_ER_AND_CALNEXIN_CALRETICULIN_CYCLE
REACTOME_ACYL_CHAIN_REMODELLING_OF_PC
REACTOME_REGULATION_OF_IFNG_SIGNALING
REACTOME_METABOLISM_OF_PROTEINS
REACTOME_IL_RECEPTOR_SHC_SIGNALING
REACTOME_S_PHASE
REACTOME_SYNTHESIS_OF_DNA
REACTOME_UNWINDING_OF_DNA
REACTOME_CROSS_PRESENTATION_OF_SOLUBLE_EXOGENOUS_ANTIGENS_ENDOSOMES
REACTOME_TRANSPORT_OF_RIBONUCLEOPROTEINS_INTO_THE_HOST_NUCLEUS
REACTOME_EGFR_DOWNREGULATION
REACTOME_CYCLIN_E_ASSOCIATED_EVENTS_DURING_G1_S_TRANSITION_
REACTOME_MYOGENESIS
REACTOME_METABOLISM_OF_MRNA
REACTOME_INTERACTIONS_OF_VPR_WITH_HOST_CELLULAR_PROTEINS
REACTOME_CDT1_ASSOCIATION_WITH_THE_CDC6_ORC_ORIGIN_COMPLEX
REACTOME_REGULATION_OF_APOPTOSIS
REACTOME_COLLAGEN_FORMATION
REACTOME_G1_S_TRANSITION
REACTOME_DESTABILIZATION_OF_MRNA_BY_TRISTETRAPROLIN_TTP
REACTOME_INTEGRIN_ALPHAIIB_BETA3_SIGNALING
REACTOME_MEMBRANE_TRAFFICKING
REACTOME_TRIF_MEDIATED_TLR3_SIGNALING
REACTOME_TRANSLATION
REACTOME_RNA_POL_II_PRE_TRANSCRIPTION_EVENTS
REACTOME_ANTIVIRAL_MECHANISM_BY_IFN_STIMULATED_GENES
REACTOME_MYD88_MAL_CASCADE_INITIATED_ON_PLASMA_MEMBRANE
REACTOME_DOWNREGULATION_OF_SMAD2_3_SMAD4_TRANSCRIPTIONAL_ACTIVITY
REACTOME_GLUCOSE_TRANSPORT
REACTOME_SCF5KP2_MEDIATED_DEGRADATION_OF_P27_P21
REACTOME_PERK_REGULATED_GENE_EXPRESSION
REACTOME_CELL_CYCLE_CHECKPOINTS
REACTOME_CLASS_I_MHC_MEDIATED_ANTIGEN_PROCESSING_PRESENTATION
REACTOME_AXON_GUIDANCE
REACTOME_TRAF6_MEDIATED_INDUCTION_OF_NFKB_AND_MAP_KINASES_UPON_TLR7_8_OR_9_ACTIVATION
REACTOME_TRANSPORT_OF_MATURE_TRANSCRIPT_TO_CYTOPLASM
REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION
REACTOME_INFLUENZA_LIFE_CYCLE
REACTOME_NONSENSE_MEDIATED_DECAY_ENHANCED_BY_THE_EXON_JUNCTION_COMPLEX
REACTOME_RNA_POL_II_TRANSCRIPTION
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA
REACTOME_TRANSPORT_OF_MATURE_MRNA_DERIVED_FROM_AN_INTRONLESS_TRANSCRIPT
REACTOME_NEP_NS2_INTERACTS_WITH_THE_CELLULAR_EXPORT_MACHINERY
REACTOME_M_G1_TRANSITION
REACTOME_REGULATION_OF_GLUCOKINASE_BY_GLUCOKINASE_REGULATORY_PROTEIN
REACTOME_ACTIVATED_TLR4_SIGNALLING
REACTOME_P53_DEPENDENT_G1_DNA_DAMAGE_RESPONSE
REACTOME_N_GLYCAN_ANTENNAE_ELONGATION_IN_THE_MEDIAL_TRANS_GOLGI
REACTOME_HIV_LIFE_CYCLE
REACTOME_METABOLISM_OF_NON_CODING_RNA
REACTOME_ACTIVATION_OF_IRF3_IRF7_MEDIATED_BY_TBK1_IKK_EPSILON
REACTOME_METABOLISM_OF_RNA
REACTOME_GRB2_SOS_PROVIDES_LINKAGE_TO_MAPK_SIGNALING_FOR_INTERGRINS_
REACTOME_HS_GAG_BIOSYNTHESIS
REACTOME_CDK_MEDIATED_PHOSPHORYLATION_AND_REMOVAL_OF_CDC6
REACTOME_P53_INDEPENDENT_G1_S_DNA_DAMAGE_CHECKPOINT
REACTOME_ORC1_REMOVAL_FROM_CHROMATIN
REACTOME_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE
REACTOME_ASSEMBLY_OF_THE_PRE_REPLICATIVE_COMPLEX
REACTOME_MITOTIC_G1_G1_S_PHASES
REACTOME_N_GLYCAN_ANTENNAE_ELONGATION
REACTOME_FATTY_ACYL_COA_BIOSYNTHESIS
REACTOME_LATE_PHASE_OF_HIV_LIFE_CYCLE
REACTOME_ANTIGEN_PROCESSING_CROSS_PRESENTATION
REACTOME_ACTIVATION_OF_NF_KAPPAB_IN_B_CELLS
REACTOME_DOWNSTREAM_SIGNALING_EVENTS_OF_B_CELL_RECEPTOR_BCR
REACTOME_P130CAS_LINKAGE_TO_MAPK_SIGNALING_FOR_INTEGRINS
REACTOME_HOST_INTERACTIONS_OF_HIV_FACTORS
REACTOME_HIV_INFECTION
REACTOME_ER_PHAGOSOME_PATHWAY
REACTOME_CHOLESTEROL_BIOSYNTHESIS
REACTOME_AUTODEGRADATION_OF_THE_E3_UBIQUITIN_LIGASE_COP1
REACTOME_SCF_BETA_TRCP_MEDIATED_DEGRADATION_OF_EMI1
REACTOME_SIGNALING_BY_WNT
REACTOME_REGULATION_OF_MRNA_STABILITY_BY_PROTEINS_THAT_BIND_AU_RICH_ELEMENTS
REACTOME_REGULATION_OF_ORNITHINE_DECARBOXYLASE_ODC
REACTOME_APC_C_CDC20_MEDIATED_DEGRADATION_OF_MITOTIC_PROTEINS
REACTOME_REGULATION_OF_MITOTIC_CELL_CYCLE
REACTOME_APC_C_CDH1_MEDIATED_DEGRADATION_OF_CDC20_AND_OTHER_APC_C_CDH1_TARGETED_PROTEINS_IN_LATE_MITOSIS_EARLY_G1
REACTOME_VIF_MEDIATED_DEGRADATION_OF_APOBEC3G
REACTOME_DESTABILIZATION_OF_MRNA_BY_AUF1_HNRNP_D0
REACTOME_NFKB_AND_MAP_KINASES_ACTIVATION_MEDIATED_BY_TLR4_SIGNALING_REPERTOIRE
REACTOME_TRANSMEMBRANE_TRANSPORT_OF_SMALL_MOLECULES
REACTOME_TRANSPORT_OF_GLUCOSE_AND_OTHER_SUGARS_BILE_SALTS_AND_ORGANIC_ACIDS_METAL_IONS_AND_AMINE_COMPOUNDS
REACTOME_GLYCOSAMINOGLYCAN_METABOLISM
REACTOME_SIGNALING_BY_TGF_BETA_RECEPTOR_COMPLEX
REACTOME_CHONDROITIN_SULFATE_DERMATAN_SULFATE_METABOLISM
REACTOME_HEPARAN_SULFATE_HEPARIN_HS_GAG_METABOLISM
REACTOME_METABOLISM_OF_CARBOHYDRATES
REACTOME_IRON_UPTAKE_AND_TRANSPORT
REACTOME_PI3K_AKT_ACTIVATION
REACTOME_PI3K_EVENTS_IN_ERBB2_SIGNALING
REACTOME_CD28_DEPENDENT_PI3K_AKT_SIGNALING
REACTOME_SIGNALING_BY_HIPPO
REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS
REACTOME_CYTOCHROME_P450_ARRANGED_BY_SUBSTRATE_TYPE
REACTOME_FORMATION_OF_THE_HIV1_EARLY_ELONGATION_COMPLEX
REACTOME_DOWNREGULATION_OF_TGF_BETA_RECEPTOR_SIGNALING
REACTOME_TGF_BETA_RECEPTOR_SIGNALING_ACTIVATES_SMAD3
REACTOME_DIABETES_PATHWAYS
REACTOME_SIGNALING_BY_PDGF
REACTOME_PROTEOLYTIC_CLEAVAGE_OF_SNARE_COMPLEX_PROTEINS
REACTOME_NOTCH1_INTRACELLULAR_DOMAIN_REGULATES_TRANSCRIPTION
REACTOME_GABA_RECEPTOR_ACTIVATION
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL
REACTOME_RIG_I_MDA5_MEDIATED_INDUCTION_OF_IFN_ALPHA_BETA_PATHWAYS
REACTOME_COSTIMULATION_BY_THE_CD28_FAMILY
REACTOME_NOD1_2_SIGNALING_PATHWAY
REACTOME_SIGNALING_BY_NOTCH1
REACTOME_PI3K_EVENTS_IN_ERBB4_SIGNALING
REACTOME_SIGNALING_BY_NOTCH
REACTOME_LIGAND_GATED_ION_CHANNEL_TRANSPORT
REACTOME_PIP3_ACTIVATES_AKT_SIGNALING
REACTOME_PI_3K_CASCADE
REACTOME_FORMATION_OF_FIBRIN_CLOT_CLOTTING_CASCADE
REACTOME_HYALURONAN_METABOLISM
REACTOME_GABA_SIGNALOSOME
REACTOME_ENDOGENOUS_STEROLS
REACTOME_SEMA3A_PLEXIN_REPULSION_SIGNALING_BY_INHIBITING_INTEGRIN_ADHESION
REACTOME_PRE_NOTCH_EXPRESSION_AND_PROCESSING
REACTOME_REGULATION_OF_INSULIN_LIKE_GROWTH_FACTOR_IGF_ACTIVITY_BY_INSULIN_LIKE_GROWTH_FACTOR_BINDING_PROTEINS_IGFBPS
REACTOME_PROCESSING_OF_INTRONLESS_PRE_MRNAS
REACTOME_AKT_PHOSPHORYLATES_TARGETS_IN_THE_CYTOSOL
REACTOME_VIFH_AND_WWTR1_TAZ_STIMULATED_GENE_EXPRESSION
REACTOME_ABORTIVE_ELONGATION_OF_HIV1_TRANSCRIPT_IN_THE_ABSENCE_OF_TAT
REACTOME_SIGNALING_BY_SCF_KIT
REACTOME_MICRORNA_MRNA_BIOGENESIS
REACTOME_SIGNALING_BY_ERBB4
REACTOME_SIGNALING_BY_FGFR
REACTOME_SIGNALING_BY_FGFR_IN_DISEASE
REACTOME_NGF_SIGNALLING_VIA_TRKA_FROM_THE_PLASMA_MEMBRANE
REACTOME_REGULATORY_RNA_PATHWAYS
REACTOME_VIRAL_MESSENGER_RNA_SYNTHESIS
REACTOME_MRNA_CAPPING
REACTOME_FORMATION_OF_TRANSCRIPTION_COUPLED_NER_TC_NER_REPAIR_COMPLEX
REACTOME_RORA_ACTIVATES_CIRCADIAN_EXPRESSION
REACTOME_SIGNALING_BY_BMP
REACTOME_GABA_A_RECEPTOR_ACTIVATION
REACTOME_OTHER_SEMAPHORIN_INTERACTIONS
REACTOME_CIRCADIAN_REPRESSION_OF_EXPRESSION_BY_REV_ERBA
REACTOME_CD28_CO_STIMULATION
REACTOME_CELL_CELL_COMMUNICATION
REACTOME_POST_TRANSLATIONAL_MODIFICATION_SYNTHESIS_OF_GPI_ANCHORED_PROTEINS
REACTOME_REGULATION_OF_AMPK_ACTIVITY_VIA_LKB1
REACTOME_PKB_MEDIATED_EVENTS
REACTOME_ENERGY_DEPENDENT_REGULATION_OF_MTOR_BY_LKB1_AMPK
REACTOME_CELL_JUNCTION_ORGANIZATION
REACTOME_SYNTHESIS_OF_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI
REACTOME_CELL_CELL_JUNCTION_ORGANIZATION
REACTOME_SPHINGOLIPID_DE_NOVO_BIOSYNTHESIS
REACTOME_ADHERENS_JUNCTIONS_INTERACTIONS
REACTOME_IL_7_SIGNALING
REACTOME_LYSOSOME_VESICLE_BIOGENESIS
REACTOME_TRANS_GOLGI_NETWORK_VESICLE_BUDDING
REACTOME_TRANSPORT_TO_THE_GOLGI_AND_SUBSEQUENT_MODIFICATION
REACTOME_UNBLOCKING_OF_NMDA_RECEPTOR_GLUTAMATE_BINDING_AND_ACTIVATION
REACTOME_GABA_SYNTHESIS_RELEASE_REUPTAKE_AND_DEGRADATION
REACTOME_PROTEIN_FOLDING
REACTOME_PREFOLDIN_MEDIATED_TRANSFER_OF_SUBSTRATE_TO_CCT_TRIC
REACTOME_FORMATION_OF_TUBULIN_FOLDING_INTERMEDIATES_BY_CCT_TRIC
REACTOME_KINESINS
REACTOME_RAS_ACTIVATION_UOPN_CA2_INFLUX_THROUGH_NMDA_RECEPTOR
REACTOME_ACTIVATION_OF_NMDA_RECEPTOR_UPON_GLUTAMATE_BINDING_AND_POSTSYNAPTIC_EVENTS
REACTOME_POST_NMDA_RECEPTOR_ACTIVATION_EVENTS
REACTOME_CREB_PHOSPHORYLATION_THROUGH_THE_ACTIVATION_OF_CAMKII
REACTOME_AMYLOIDS
REACTOME_CELL_DEATH_SIGNALLING_VIA_NRAGE_NRIF_AND_NADE
REACTOME_PEPTIDE_HORMONE_BIOSYNTHESIS
REACTOME_TETRAHYDROBIOPTERIN_BH4_SYNTHESIS_RECYCLING_SALVAGE_AND_REGULATION
REACTOME_ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S
REACTOME_3_UTR_MEDIATED_TRANSLATIONAL_REGULATION
REACTOME_OXYGEN_DEPENDENT_PROLINE_HYDROXYLATION_OF_HYPOXIA_INDUCIBLE_FACTOR_ALPHA
REACTOME_MTORC1_MEDIATED_SIGNALLING
REACTOME_CITRIC_ACID_CYCLE_TCA_CYCLE
REACTOME_TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT
REACTOME_RESPIRATORY_ELECTRON_TRANSPORT_ATP_SYNTHESIS_BY_CHEMIOSMOTIC_COUPLING_AND_HEAT_PRODUCTION_BY_UNCOUPLING_PROTEINS_
REACTOME_POST_CHAPERONIN_TUBULIN_FOLDING_PATHWAY
REACTOME_RESPIRATORY_ELECTRON_TRANSPORT
REACTOME_MRNA_3_END_PROCESSING
REACTOME_FACTORS_INVOLVED_IN_MEGAKARYOCYTE_DEVELOPMENT_AND_PLATELET_PRODUCTION
REACTOME_P38MAPK_EVENTS
REACTOME_NRAGE_SIGNALS_DEATH_THROUGH_JNK
REACTOME_CREB_PHOSPHORYLATION_THROUGH_THE_ACTIVATION_OF_RAS
REACTOME_ARMS_MEDIATED_ACTIVATION
REACTOME_INSULIN_SYNTHESIS_AND_PROCESSING
REACTOME_ADVANCED_GLYCOSYLATION_ENDPRODUCT_RECEPTOR_SIGNALING
REACTOME_SIGNALLING_TO_ERKS
REACTOME_SHC_MEDIATED_SIGNALLING
REACTOME_SOS_MEDIATED_SIGNALLING
REACTOME_SIGNALLING_TO_RAS
REACTOME_ASSOCIATION_OF_TRIC_CCT_WITH_TARGET_PROTEINS_DURING_BIOSYNTHESIS
REACTOME_PROLONGED_ERK_ACTIVATION_EVENTS
REACTOME_ACTIVATION_OF_KAINATE_RECEPTORS_UPON_GLUTAMATE_BINDING
REACTOME_SHC_RELATED_EVENTS
REACTOME_GRB2_EVENTS_IN_ERBB2_SIGNALING
REACTOME_SHC1_EVENTS_IN_ERBB4_SIGNALING
REACTOME_SHC1_EVENTS_IN_EGFR_SIGNALING
REACTOME_TRANSMISSION_ACROSS_CHEMICAL_SYNAPSES
REACTOME_G_BETA_GAMMA_SIGNALLING_THROUGH_PI3KGAMMA
REACTOME_ADP_SIGNALLING_THROUGH_P2RY12
REACTOME_SIGNALLING_TO_P38_VIA_RIT_AND_RIN
REACTOME_INHIBITION_OF_INSULIN_SECRETION_BY_ADRENALINE_NORADRENALINE
REACTOME_PROSTACYCLIN_SIGNALLING_THROUGH_PROSTACYCLIN_RECEPTOR
REACTOME_IONOTROPIC_ACTIVITY_OF_KAINATE_RECEPTORS
REACTOME_DOWNSTREAM_SIGNAL_TRANSDUCTION
REACTOME_SIGNALLING_BY_NGF
REACTOME_POTASSIUM_CHANNELS
REACTOME_OPIOID_SIGNALLING
REACTOME_FORMATION_OF_INCISION_COMPLEX_IN_GG_NER
REACTOME_G_BETA_GAMMA_SIGNALLING_THROUGH_PLC_BETA
REACTOME_FANCONI_ANEMIA_PATHWAY
REACTOME_SIGNALING_BY_ERBB2
REACTOME_NEUROTRANSMITTER_RECEPTOR_BINDING_AND_DOWNSTREAM_TRANSMISSION_IN_THE_POSTSYNAPTIC_CELL
REACTOME_G_ALPHA1213_SIGNALLING_EVENTS
REACTOME_TIE2_SIGNALING
REACTOME_FORMATION_OF_THE_TERNARY_COMPLEX_AND_SUBSEQUENTLY_THE_43S_COMPLEX
REACTOME_NEUROTRANSMITTER_RELEASE_CYCLE
REACTOME_NEURONAL_SYSTEM
REACTOME_IL_2_SIGNALING
REACTOME_G_PROTEIN_BETA_GAMMA_SIGNALLING
REACTOME_SIGNAL_ATTENUATION
REACTOME_PLATELET_HOMEOSTASIS
REACTOME_AUTODEGRADATION_OF_CDH1_BY_CDH1_APC_C
REACTOME_G_PROTEIN_ACTIVATION
REACTOME_SPRY_REGULATION_OF_FGF_SIGNALING
ZT1
ZT5
ZT10
ZT13
ZT17
ZT21

figure S14

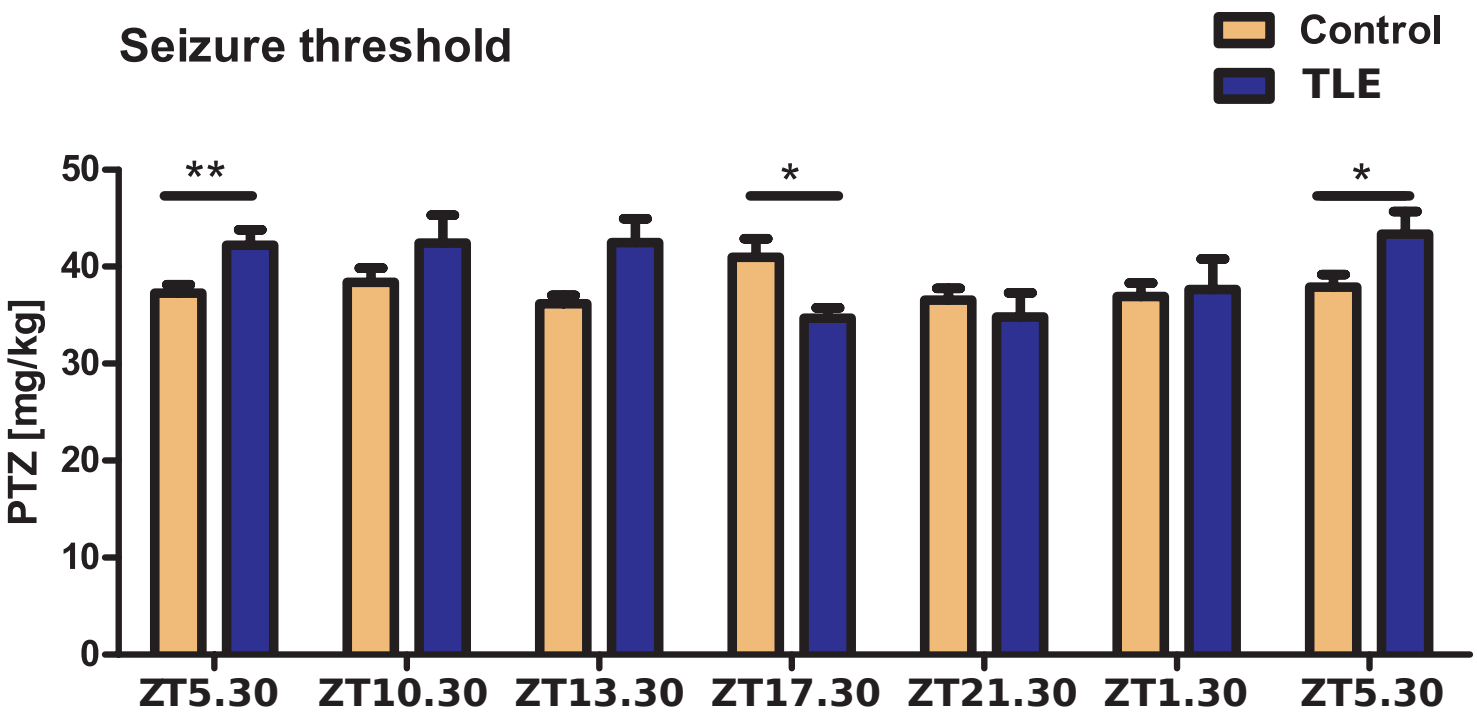
Seizure threshold
Control
TLE
PTZ [mg/kg]
50
40
30
20
10
0
**
*
*
ZT5.30
ZT10.30
ZT13.30
ZT17.30
ZT21.30
ZT1.30
ZT5.30

figure S15