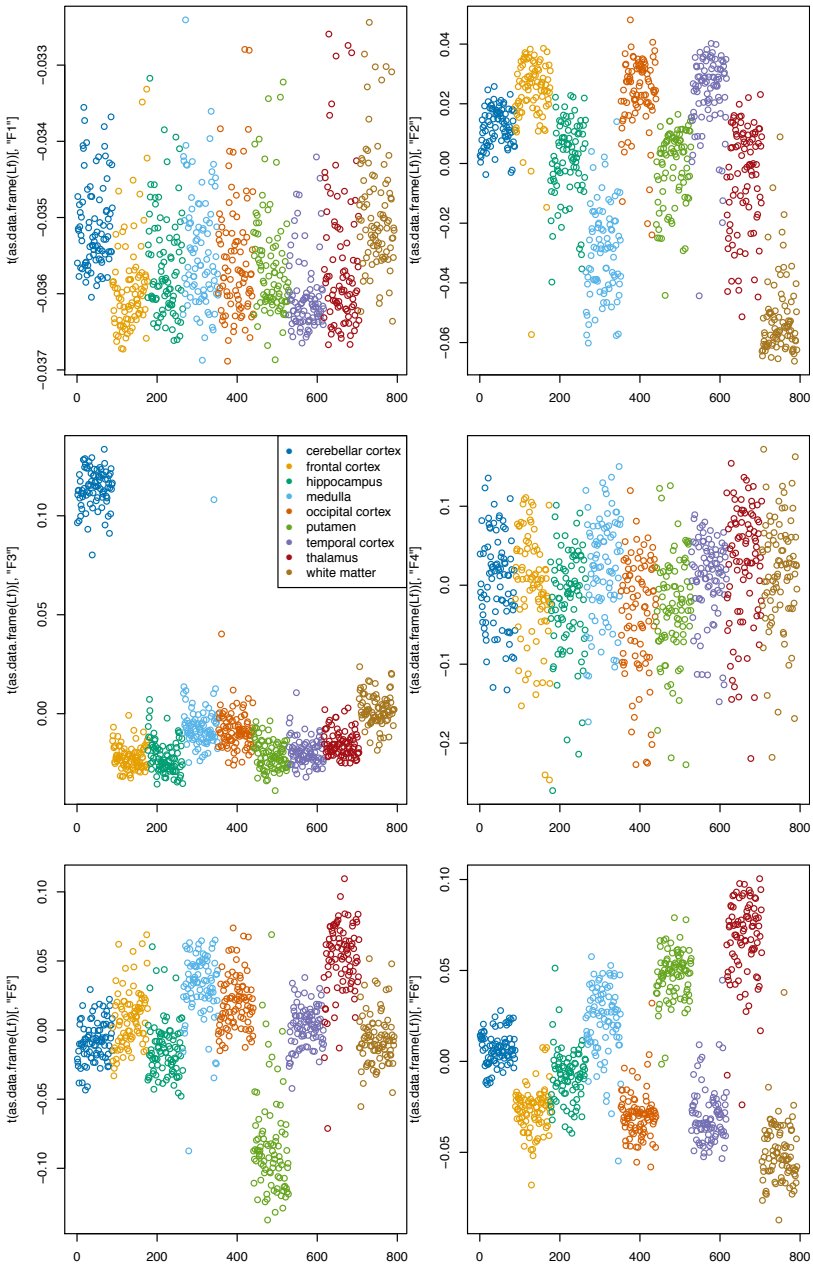
Supplementary Figures

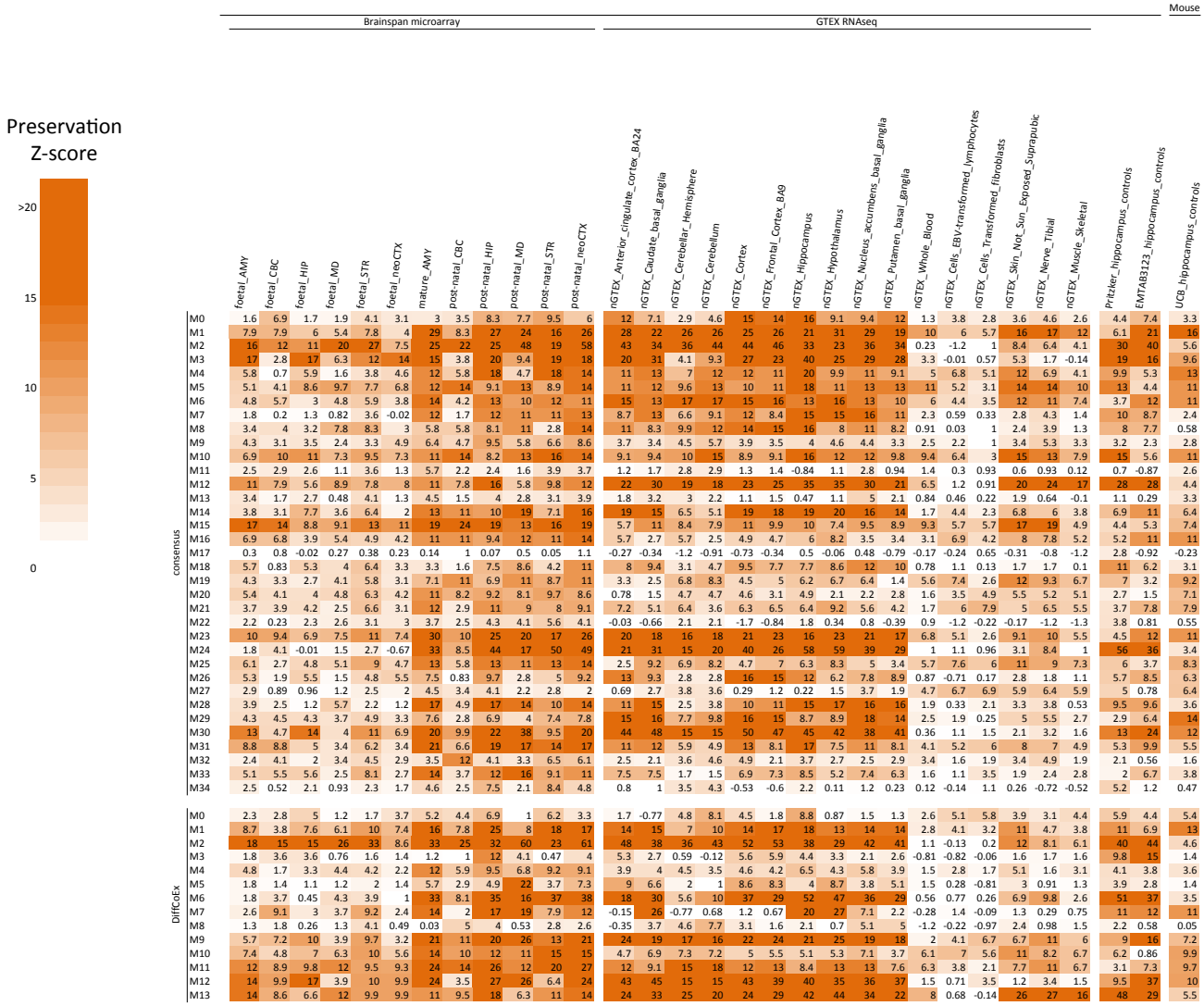
Supplementary Figure 1: Plots of the values for each sample for the 6 first hidden factors as defined using PEER.

The circles are colored depending on the brain region of the sample. The hidden factors F1 and F4 were selected, as their values didn't match the variability possibly due to brain regions.



Supplementary Figure 2: Heatmap of module preservation scores for modules identified in UKBEC in other expression datasets, across different brain regions, across pre-natal and post-natal life, in other non brain tissues, and in mouse hippocampus.

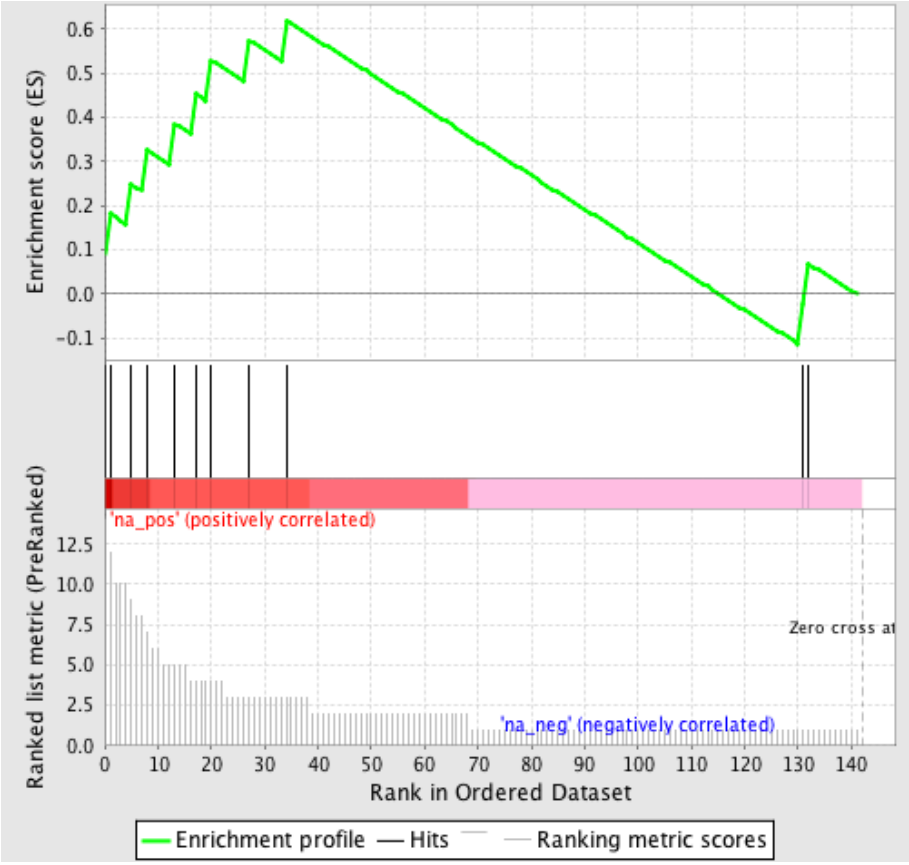
Module conservation was assessed using the $Z_{summary}$ value [31], which quantifies the degree of module preservation between gene expression datasets. Moderate preservation of co-expression is indicated by a $z_{summary}$ score of >5) and strong preservation by a $Z_{summary}$ score >10.



consensus	M0	1.6	6.9	1.7	1.9	4.1	3.1	3	3.5	8.3	7.7	9.5	6	12	7.1	2.9	4.6	15	14	16	9.1	9.4	12	1.3	3.8	2.8	3.6	4.6	2.6	4.4	7.4	3.3
	M1	7.9	7.9	6	5.4	7.8	4	29	8.3	27	24	16	26	28	22	26	26	25	26	21	31	29	19	10	6	5.7	16	17	12	6.1	21	16
	M2	16	12	11	20	27	7.5	25	22	25	48	19	58	43	34	36	44	44	46	33	23	36	34	0.23	-1.2	1	8.4	6.4	4.1	30	40	5.6
	M3	17	2.8	17	6.3	12	14	15	3.8	20	9.4	19	18	20	31	4.1	9.3	27	23	40	25	29	28	3.3	-0.01	0.57	5.3	1.7	-0.14	19	16	9.6
	M4	5.8	0.7	5.9	1.6	3.8	4.6	12	5.8	18	4.7	18	14	11	13	7	12	12	11	20	9.9	11	9.1	5	6.8	5.1	12	6.9	4.1	9.9	5.3	13
	M5	5.1	4.1	8.6	9.7	7.7	6.8	12	14	9.1	13	8.9	14	11	12	9.6	13	10	11	18	11	13	13	11	5.2	3.1	14	14	10	13	4.4	11
	M6	4.8	5.7	3	4.8	5.9	3.8	14	4.2	13	10	12	11	15	13	17	17	15	16	13	16	13	10	6	4.4	3.5	12	11	7.4	3.7	12	11
	M7	1.8	0.2	1.3	0.82	3.6	-0.02	12	1.7	12	11	11	13	8.7	13	6.6	9.1	12	8.4	15	15	16	11	2.3	0.59	0.33	2.8	4.3	1.4	10	8.7	2.4
	M8	3.4	4	3.2	7.8	8.3	3	5.8	5.8	8.1	11	2.8	14	11	8.3	9.9	12	14	15	16	8	11	8.2	0.91	0.03	1	2.4	3.9	1.3	8	7.7	0.58
	M9	4.3	3.1	3.5	2.4	3.3	4.9	6.4	4.7	9.5	5.8	6.6	8.6	3.7	3.4	4.5	5.7	3.9	3.5	4	4.6	4.4	3.3	2.5	2.2	1	3.4	5.3	3.3	3.2	2.3	2.8
	M10	6.9	10	11	7.3	9.5	7.3	11	14	8.2	13	16	14	9.1	9.4	10	15	8.9	9.1	16	12	12	9.8	9.4	6.4	3	15	13	7.9	15	5.6	11
	M11	2.5	2.9	2.6	1.1	3.6	1.3	5.7	2.2	2.4	1.6	3.9	3.7	1.2	1.7	2.8	2.9	1.3	1.4	-0.84	1.1	2.8	0.94	1.4	0.3	0.93	0.6	0.93	0.12	0.7	-0.87	2.6
	M12	11	7.9	5.6	8.9	7.8	8	11	7.8	16	5.8	9.8	12	22	30	19	18	23	25	35	35	30	21	6.5	1.2	0.91	20	24	17	28	28	4.4
	M13	3.4	1.7	2.7	0.48	4.1	1.3	4.5	1.5	4	2.8	3.1	3.9	1.8	3.2	3	2.2	1.1	1.5	0.47	1.1	5	2.1	0.84	0.46	0.22	1.9	0.64	-0.1	1.1	0.29	3.3
	M14	3.8	3.1	7.7	3.6	6.4	2	13	11	10	19	7.1	16	19	15	6.5	5.1	19	18	19	20	16	14	1.7	4.4	2.3	6.8	6	3.8	6.9	11	6.4
	M15	17	14	8.8	9.1	13	11	19	24	19	13	16	19	5.7	11	8.4	7.9	11	9.9	10	7.4	9.5	8.9	9.3	5.7	5.7	17	19	4.9	4.4	5.3	7.4
	M16	6.9	6.8	3.9	5.4	4.9	4.2	11	11	9.4	12	11	14	5.7	2.7	5.7	2.5	4.9	4.7	6	8.2	3.5	3.4	3.1	6.9	4.2	8	7.8	5.2	5.2	11	11
	M17	0.3	0.8	-0.02	0.27	0.38	0.23	0.14	1	0.07	0.5	0.05	1.1	-0.27	-0.34	-1.2	-0.91	-0.73	-0.34	0.5	-0.06	0.48	-0.79	-0.17	-0.24	0.65	-0.31	-0.8	-1.2	2.8	-0.92	-0.23
	M18	5.7	0.83	5.3	4	6.4	3.3	3.3	1.6	7.5	8.6	4.2	11	8	9.4	3.1	4.7	9.5	7.7	7.7	8.6	12	10	0.78	1.1	0.13	1.7	1.7	0.1	11	6.2	3.1
	M19	4.3	3.3	2.7	4.1	5.8	3.1	7.1	11	6.9	11	8.7	11	3.3	2.5	6.8	8.3	4.5	5	6.2	6.7	6.4	1.4	5.6	7.4	2.6	12	9.3	6.7	7	3.2	9.2
	M20	5.4	4.1	4	4.8	6.3	4.2	11	8.2	9.2	8.1	9.7	8.6	0.78	1.5	4.7	4.7	4.6	3.1	4.9	2.1	2.2	2.8	1.6	3.5	4.9	5.5	5.2	5.1	2.7	1.5	7.1
	M21	3.7	3.9	4.2	2.5	6.6	3.1	12	2.9	11	9	8	9.1	7.2	5.1	6.4	3.6	6.3	6.5	6.4	9.2	5.6	4.2	1.7	6	7.9	5	6.5	5.5	3.7	7.8	7.9
	M22	2.2	0.23	2.3	2.6	3.1	3	3.7	2.5	4.3	4.1	5.6	4.1	-0.03	-0.66	2.1	2.1	-1.7	-0.84	1.8	0.34	0.8	-0.39	0.9	-1.2	-0.22	-0.17	-1.2	-1.3	3.8	0.81	0.55
	M23	10	9.4	6.9	7.5	11	7.4	30	10	25	20	17	26	20	18	16	18	21	23	16	23	21	17	6.8	5.1	2.6	9.1	10	5.5	4.5	12	11
	M24	1.8	4.1	-0.01	1.5	2.7	-0.67	33	8.5	44	17	50	49	21	31	15	20	40	26	58	59	39	29	1	1.1	0.96	3.1	8.4	1	56	36	3.4
	M25	6.1	2.7	4.8	5.1	9	4.7	13	5.8	13	11	13	14	2.5	9.2	6.9	8.2	4.7	7	6.3	8.3	5	3.4	5.7	7.6	6	11	9	7.3	6	3.7	8.3
	M26	5.3	1.9	5.5	1.5	4.8	5.5	7.5	0.83	9.7	2.8	5	9.2	13	9.3	2.8	2.8	16	15	12	6.2	7.8	8.9	0.87	-0.71	0.17	2.8	1.8	1.1	5.7	8.5	6.3
	M27	2.9	0.89	0.96	1.2	2.5	2	4.5	3.4	4.1	2.2	2.8	2	0.69	2.7	3.8	3.6	0.29	1.2	0.22	1.5	3.7	1.9	4.7	6.7	6.9	5.9	6.4	5.9	5	0.78	6.4
	M28	3.9	2.5	1.2	5.7	2.2	1.2	17	4.9	17	14	10	14	11	15	2.5	3.8	10	11	15	17	16	16	1.9	0.33	2.1	3.3	3.8	0.53	9.5	9.6	3.6
	M29	4.3	4.5	4.3	3.7	4.9	3.3	7.6	2.8	6.9	4	7.4	7.8	15	16	7.7	9.8	16	15	8.7	8.9	18	14	2.5	1.9	0.25	5	5.5	2.7	2.9	6.4	14
	M30	13	4.7	14	4	11	6.9	20	9.9	22	38	9.5	20	44	48	15	15	50	47	45	42	38	41	0.36	1.1	1.5	2.1	3.2	1.6	13	24	12
	M31	8.8	8.8	5	3.4	6.2	3.4	21	6.6	19	17	14	17	11	12	5.9	4.9	13	8.1	17	7.5	11	8.1	4.1	5.2	6	8	7	4.9	5.3	9.9	5.5
	M32	2.4	4.1	2	3.4	4.5	2.9	3.5	12	4.1	3.3	6.5	6.1	2.5	2.1	3.6	4.6	4.9	2.1	3.7	2.7	2.5	2.9	3.4	1.6	1.9	3.4	4.9	1.9	2.1	0.56	1.6
	M33	5.1	5.5	5.6	2.5	8.1	2.7	14	3.7	12	16	9.1	11	7.5	7.5	1.7	1.5	6.9	7.3	8.5	5.2	7.4	6.3	1.6	1.1	3.5	1.9	2.4	2.8	2	6.7	3.8
	M34	2.5	0.52	2.1	0.93	2.3	1.7	4.6	2.5	7.5	2.1	8.4	4.8	0.8	1	3.5	4.3	-0.53	-0.6	2.2	0.11	1.2	0.23	0.12	-0.14	1.1	0.26	-0.72	-0.52	5.2	1.2	0.47
DiffCoEx	M0	2.3	2.8	5	1.2	1.7	3.7	5.2	4.4	6.9	1	6.2	3.3	1.7	-0.77	4.8	8.1	4.5	1.8	8.8	0.87	1.5	1.3	2.6	5.1	5.8	3.9	3.1	4.4	5.9	4.4	5.4
	M1	8.7	3.8	7.6	6.1	10	7.4	16	7.8	25	8	18	17	14	15	7	10	14	17	18	13	14	14	2.8	4.1	3.2	11	4.7	3.8	11	6.9	13
	M2	18	15	15	26	33	8.6	33	25	32	60	23	61	48	38	36	43	52	53	38	29	42	41	1.1	-0.13	0.2	12	8.1	6.1	40	44	4.6
	M3	1.8	3.6	3.6	0.76	1.6	1.4	1.2	1	12	4.1	0.47	4	5.3	2.7	0.59	-0.12	5.6	5.9	4.4	3.3	2.1	2.6	-0.81	-0.82	-0.06	1.6	1.7	1.6	9.8	15	1.4
	M4	4.8	1.7	3.3	4.4	4.2	2.2	12	5.9	9.5	6.8	9.2	9.1	3.9	4	4.5	3.5	4.6	4.2	6.5	4.3	5.8	3.9	1.5	2.8	1.7	5.1	1.6	3.1	4.1	3.8	3.6
	M5	1.8	1.4	1.1	1.2	2	1.4	5.7	2.9	4.9	22	3.7	7.3	9	6.6	2	1	8.6	8.3	4	8.7	3.8	5.1	1.5	0.28	-0.81	3	0.91	1.3	3.9	2.8	1.4
	M6	1.8	3.7	0.45	4.3	3.9	1	33	8.1	35	16	37	38	18	30	5.6	10	37	29	52	47	36	29	0.56	0.77	0.26	6.9	9.8	2.6	51	37	3.5
	M7	2.6	9.1	3	3.7	9.2	2.4	14	2	17	19	7.9	12	-0.15	26	-0.77	0.68	1.2	0.67	20	27	7.1	2.2	-0.28	1.4	-0.09	1.3	0.29	0.75	11	12	11
	M8	1.3	1.8	0.26	1.3	4.1	0.49	0.03	5	4	0.53	2.8	2.6	-0.35	3.7	4.6	7.7	3.1	1.6	2.1	0.7	5.1	5	-1.2	-0.22	-0.97	2.4	0.98	1.5	2.2	0.58	0.05
	M9	5.7	7.2	10	3.9	9.7	3.2	21	11	20	26	13	21	24	19	17	16	22	24	21	25	19	18	2	4.1	6.7	6.7	11	6	9	16	7.2
	M10	7.4	4.8	7	6.3	10	5.6	14	10	12	11	15	15	4.7	6.9	7.3	7.2	5	5.5	5.1	5.3	7.1	3.7	6.1	7	5.6	11	8.2	6.7	6.2	0.86	9.9
	M11	12	8.9	9.8	12	9.5	9.3	24	14	26	12	20	27	12	9.1	15	18	12	13	8.4	13	13	7.6	6.3	3.8	2.1	7.7	11	6.7	3.1	7.3	9.7
	M12	14	9.9	17	3.9	10	9.9	24	3.5	27	26	6.4	24	43	45	15	15	43	39	40	35	36	37	1.5	0.71	3.5	1.2	3.4	1.5	9.5	37	10
	M13	14	8.6	6.6	12	9.9	9.9	11	9.5	18	6.3	11	14	24	33	25	20	24	29	42	44	34	22	8	0.68	-0.14	26	27	16	48	29	5.5

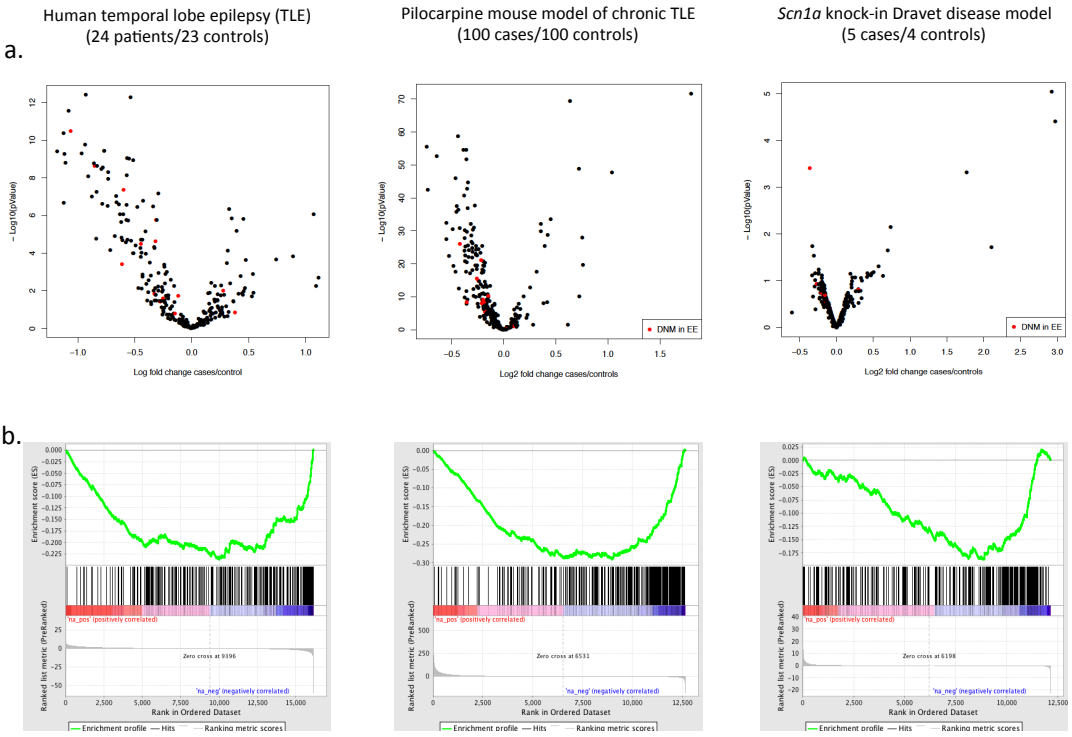
Supplementary Figure 3: Gene Set Enrichment Analysis (GSEA) plot of non synonymous *de novo* mutations (nsDNM) in patients ascertained for epileptic encephalopathy (EE) for genes coding for proteins with higher degree in the M30 protein-protein interaction (PPI) network.

The GSEA was performed ranking genes according to the number of intra-modular PPI and showed significant enrichment (Normalized Enrichment Score NES: 2.4, FDR q-value: 0.0013).



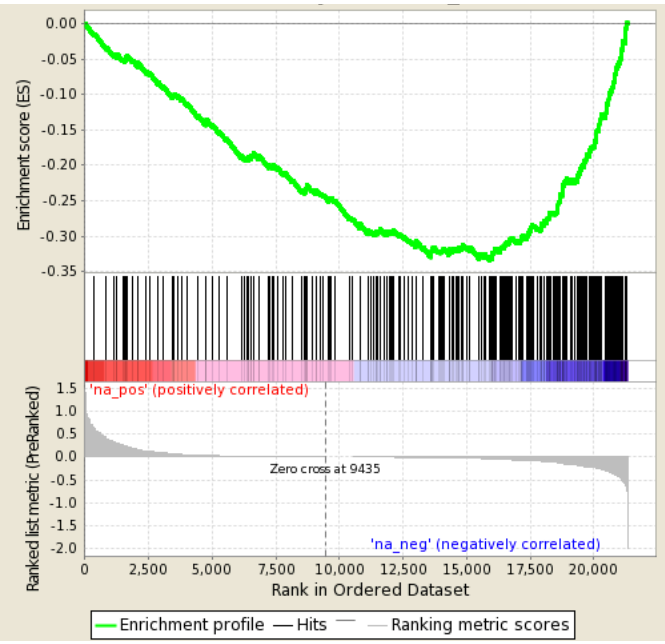
Supplementary Figure 4: Differential expression analysis of M30 genes in epileptic hippocampus in three epilepsies.

a. "Volcano plot' of statistical significance against fold change between cases and controls. Each dot represents one gene of M30. Red dots are genes with non synonymous *de novo* mutation (DNM) in patients ascertained for EE. b. GSEA plots showing significant enrichment of M30 in down-regulated genes in epileptic hippocampus in all three epilepsies (human TLE: NES=-4.51, P <10^{-5}; pilocarpine TLE mouse model: NES=-5.83, P <10^{-5}; Dravet model: NES=-3.69, P <10^{-5}).



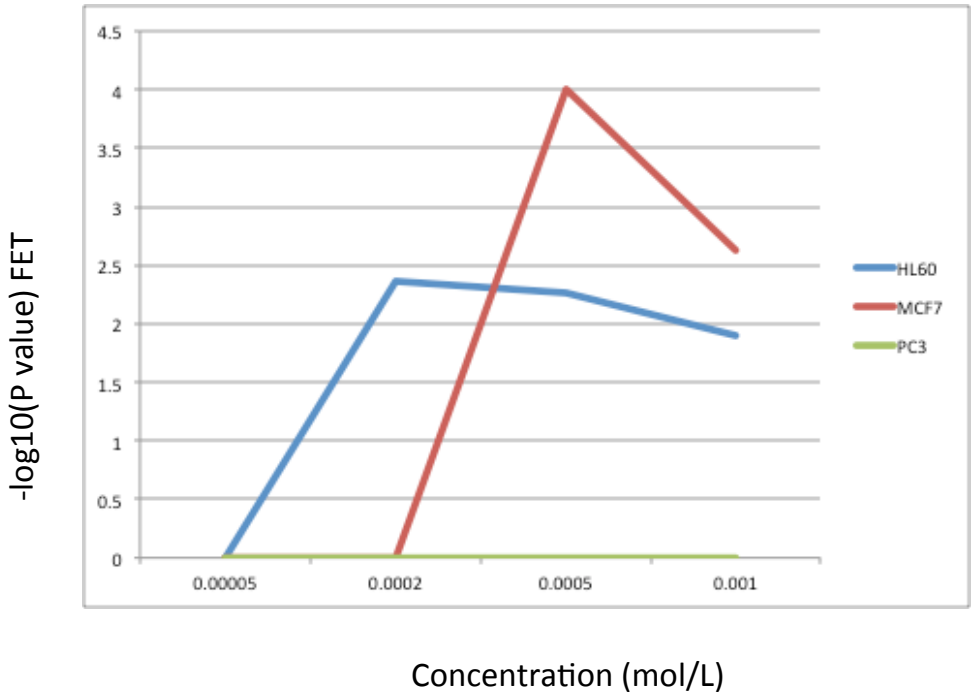
Supplementary Figure 5: GSEA plot of M30 for genes anti-correlated to seizure frequency in the pilocarpine mouse model of chronic TLE.

The GSEA was performed ranking genes according to their Spearman correlation coefficient with frequency of seizures weighted by significance and showed enrichment of M30 in genes anti-correlated to seizure frequency (NES=-6.68, $P < 10^{-4}$).



Supplementary Figure 6: Dose effect on significance of enrichment of M30 for genes significantly upregulated by valproic acid.

FET= Fisher Exact Test



Supplementary Figure 7: Mapped M30 genes which are up or down regulated by valproic acid.

Log2 fold change in a gene's expression on the x-axis plotted against – log10 pvalue of differential expression on the Y. Genes to the left of zero are down-regulated by the drug, and genes to the right are upregulated. Genes significantly differentially expressed (DE) at FDR <10% are highlighted in red.