Supplementary Text

Data processing and analysis

Adapter trimming was done with Trimmomatic (v 0.32) with default parameters. For mapping, we used Bowtie2. For paired-end reads, we used parameters as in Denny et al (2016)[1]. For single-end reads, no additional parameters were set. Picard was used for removing duplicates with *lenient* stringency level. For peak analysis, we tested three parameter sets with two peak calling mode, *broad* and *narrow*, as below:

1) Default parameters: shift 0, extsize 200, default FDR cutoff (0.01)
2) ENCODE parameters: shift -37, extsize 73, p-value cutoff (0.01)
3) BAMPE parameters: BAMPE mode for paired ends, default FDR cutoff (0.01)

Samples sequenced with single-end reads were excluded in BAMPE parameters. The number of peaks greatly varies across different parameters (**Figure S1**). Peak mode affected in the peak numbers to some degree. ENCODE parameters produced much higher number of peaks and showed different pattern to the number of reads. When we added the same level of FDR filtering, however, the trend in regard to the number of reads became consistent across different parameters.

RNA expression variability test of commonly accessible genes

We assigned the rank of mean expression, *r(gene)*, to the commonly accessible genes. Then we generated the control set by randomly selecting genes ranked closest to the genes within the commonly accessible gene set (e.g., *r(gene)+1* or *r(gene)-1*), excluding genes within the set. The direction of selecting the closest ranked gene was determined randomly. The Wilcoxon rank sum test was applied between the commonly accessible gene set and the control set.

Mouse brain sample description

Among various types of neurons in the CeA, somatostatin-positive neurons (SOM+) are long-range projection neurons and are one of the major populations of the CeA, whose synaptic plasticity plays a role in fear learning [2]. In stark contrast, SOM+ neurons in the cortex are local interneurons that have distinct functions and developmental origin compared with SOM+ neurons in the CeA [3, 4]. Interestingly, the Tyrosine Kinase-Type Cell Surface Receptor HER4 (*ErbB4*), which plays important roles in neuronal development and function, is largely excluded from SOM+ cortical neurons but is highly expressed in SOM+ CeA neurons [5, 6]. Therefore, SOM+ neurons in the CeA and those in the cortex are ideally suited to the test of epigenetic changes in the contexts of fear memory formation and the manipulation of ErbB4 content. Here we assayed global changes in chromatin accessibility in the SOM+ CeA neurons versus SOM+ cortical neurons in fear-conditioned mice and mice in which *Erbb4* is selectively deleted in SOM+ cells ($SOM^{Erbb4\text{-}KO}$ mice) that could lead to differentially regulated gene expression. For the purposes of the current analysis, this variation is matched between amygdala and cortex samples and we focus only on the top-level brain-region analysis within this paper.

Male and female mice bred onto the C57BL/6J background with the age of 2-3 months were used for the experiments. Fear conditioning procedures were performed following Penzo et al (2014) [7] with modifications; 2 tones during habituation and the shock intensity at 0.7 mA. Control mice were under the same condition except for foot shock.

Preparation of nuclei from brain tissue

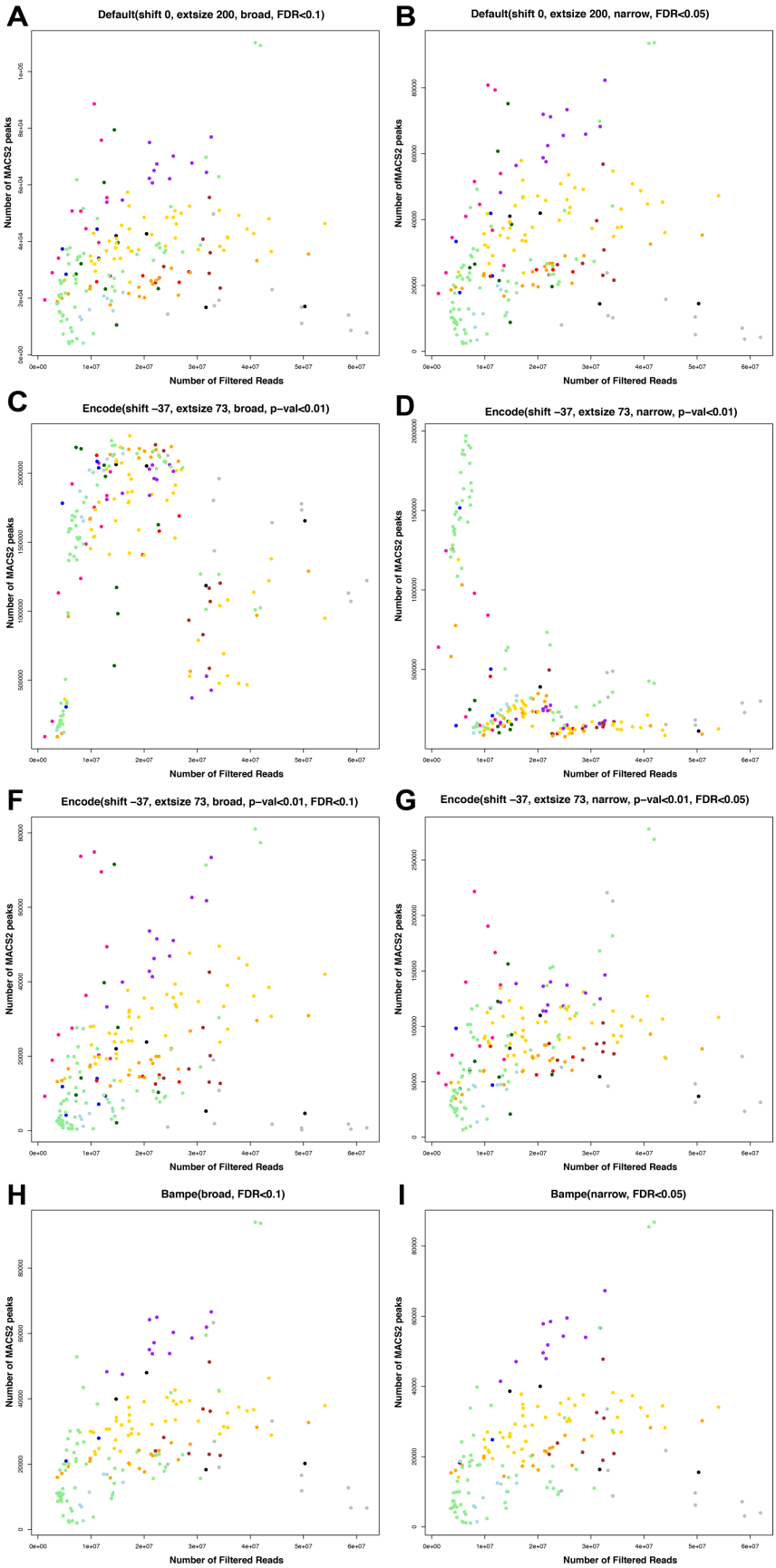
24 hours after fear conditioning, animals were deeply anesthetized and rapidly decapitated. Brains were dissected and sectioned at 500mm on ice in a stainless steel brain matrix (EMS 69090-C). PFC or CeA was microdissected in ice-cold PBS with 1x protease inhibitors (Roche) under a stereomicroscope. The tissue was resuspended in 500µl homogenization buffer containing 300mM sucrose, 60mM KCl, 15mM NaCl, 15mM Tris-HCl, 5mM MgCl2, 0.1mM EGTA, 1 mM DTT, 0.1mM PMSF and 1x protease inhibitors, EDTA-free (Roche), and disrupted using a cordless pestle motor homogenize tissue with 4 bursts of 5 seconds. Nuclei were prepared by a seven minute detergent lysis with the addition of IGEPAL CA-630 (Sigma) to a final concentration of 0.2%, followed by pelleting at 1500rcf and gentle resuspension in PBS containing 2% FBS for FACS sorting. Nuclei were filtered through 40 mm cell strainers and NucBlue was added to $SOM^{Erbb4\text{-}KO}$ nuclei, while $SOM^{H2B\text{-}GFP}$ were gated on GFP. Nuclei were sorted into technical replicates of 50,000 nuclei and immediately proceeded to the ATAC-seq transposition reaction.

ATAC-seq library preparation

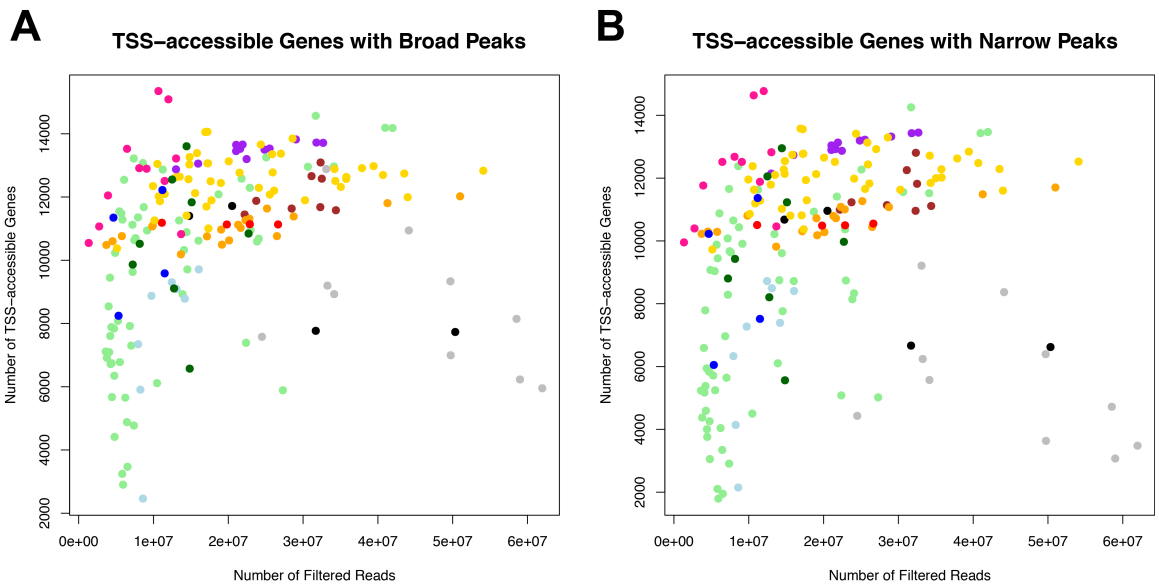
For each library, 50,000 sorted nuclei were resuspended in Transposition Reaction Mix then incubated at 37° C. Using Qiagen MinElute Kit we purified 50uL reaction volume. Transposed DNA were stored at -20C. We used the primers in Buenrostro et al (2013) for library construction. ATAC-seq library quality was assessed on an agarose gel with 1X SYBR Gold to view banding. Libraries were quantified by both Bioanalyzer High Sensitivity Chips and the KAPA Illumina Library Quantification kit.

1. Denny SK, Yang D, Chuang C-H, Brady JJ, Lim JS, Grüner BM, Chiou S-H, Schep AN, Baral J, Hamard C, et al: **Nfib Promotes Metastasis through a Widespread Increase in Chromatin Accessibility.** *Cell* 2016, **166:**328-342.
2. Li H, Penzo MA, Taniguchi H, Kopec CD, Huang ZJ, Li B: **Experience-dependent modification of a central amygdala fear circuit.** *Nat Neurosci* 2013, **16:**332-339.
3. Kepecs A, Fishell G: **Interneuron cell types are fit to function.** *Nature* 2014, **505:**318-326.
4. Wamsley B, Fishell G: **Genetic and activity-dependent mechanisms underlying interneuron diversity.** *Nat Rev Neurosci* 2017, **18:**299-309.
5. Ahrens S, Jaramillo S, Yu K, Ghosh S, Hwang GR, Paik R, Lai C, He M, Huang ZJ, Li B: **ErbB4 regulation of a thalamic reticular nucleus circuit for sensory selection.** *Nat Neurosci* 2015, **18:**104-111.
6. Neddens J, Buonanno A: **Expression of the neuregulin receptor ErbB4 in the brain of the rhesus monkey (Macaca mulatta).** *PLoS One* 2011, **6:**e27337.

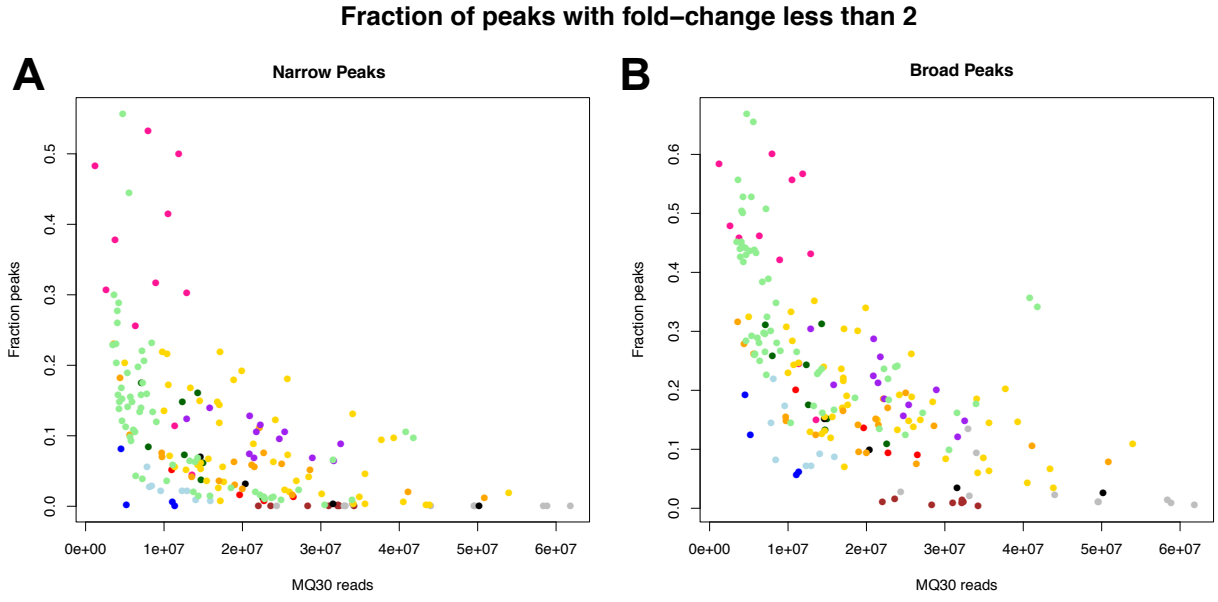
7. Penzo MA, Robert V, Li B: **Fear conditioning potentiates synaptic transmission onto long-range projection neurons in the lateral subdivision of central amygdala.** *J Neurosci* 2014, **34:**2432-2437.


A
Default(shift 0, extsize 200, broad, FDR<0.1)
B
Default(shift 0, extsize 200, narrow, FDR<0.05)
C
Encode(shift −37, extsize 73, broad, p−val<0.01)
D
Encode(shift −37, extsize 73, narrow, p−val<0.01)
F
Encode(shift −37, extsize 73, broad, p−val<0.01, FDR<0.1)
G
Encode(shift −37, extsize 73, narrow, p−val<0.01, FDR<0.05)
H
Bampe(broad, FDR<0.1)
I
Bampe(narrow, FDR<0.05)
Number of MACS2 peaks
Number of Filtered Reads

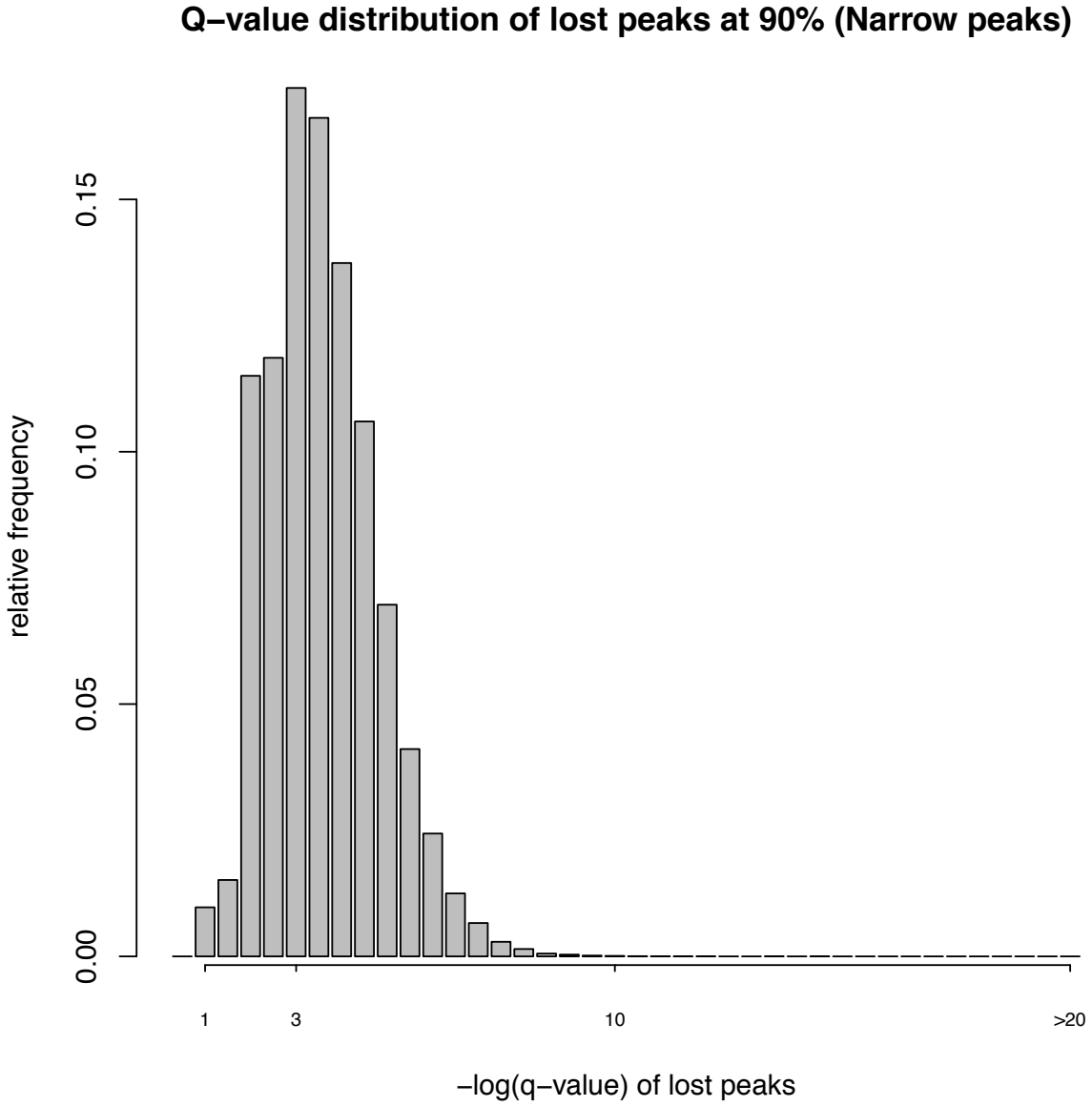
S1 Figure. Number of peaks vs. number of filtered reads. MACS2 peaks are generated under **(A,B)** default parameter setting with broad and narrow mode, **(C,D)** ENCODE parameters with p-value cutoff only, **(E,F)** ENCODE parameters with the default q-value restrictions (0.1 for broad, 0.05 for narrow), and **(H,I)** BAMPE parameters.



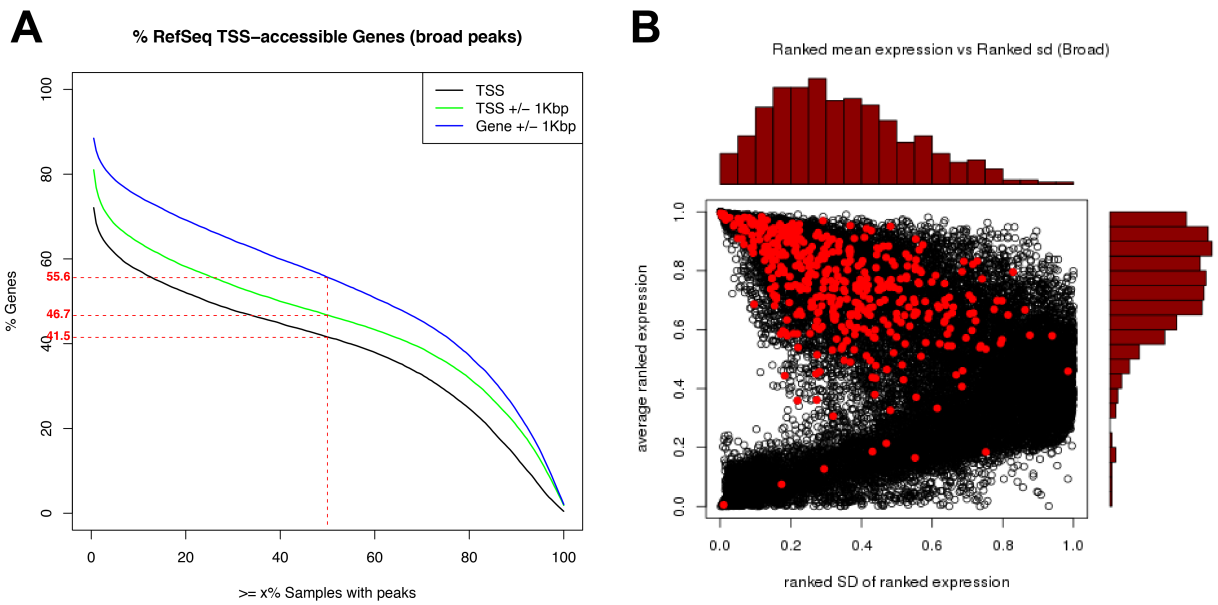
S2 Figure. Number of TSS-accessible genes vs. number of filtered reads. Each color represents each study. Left panel is generated from *broad* peaks and right panel is from *narrow* peaks.



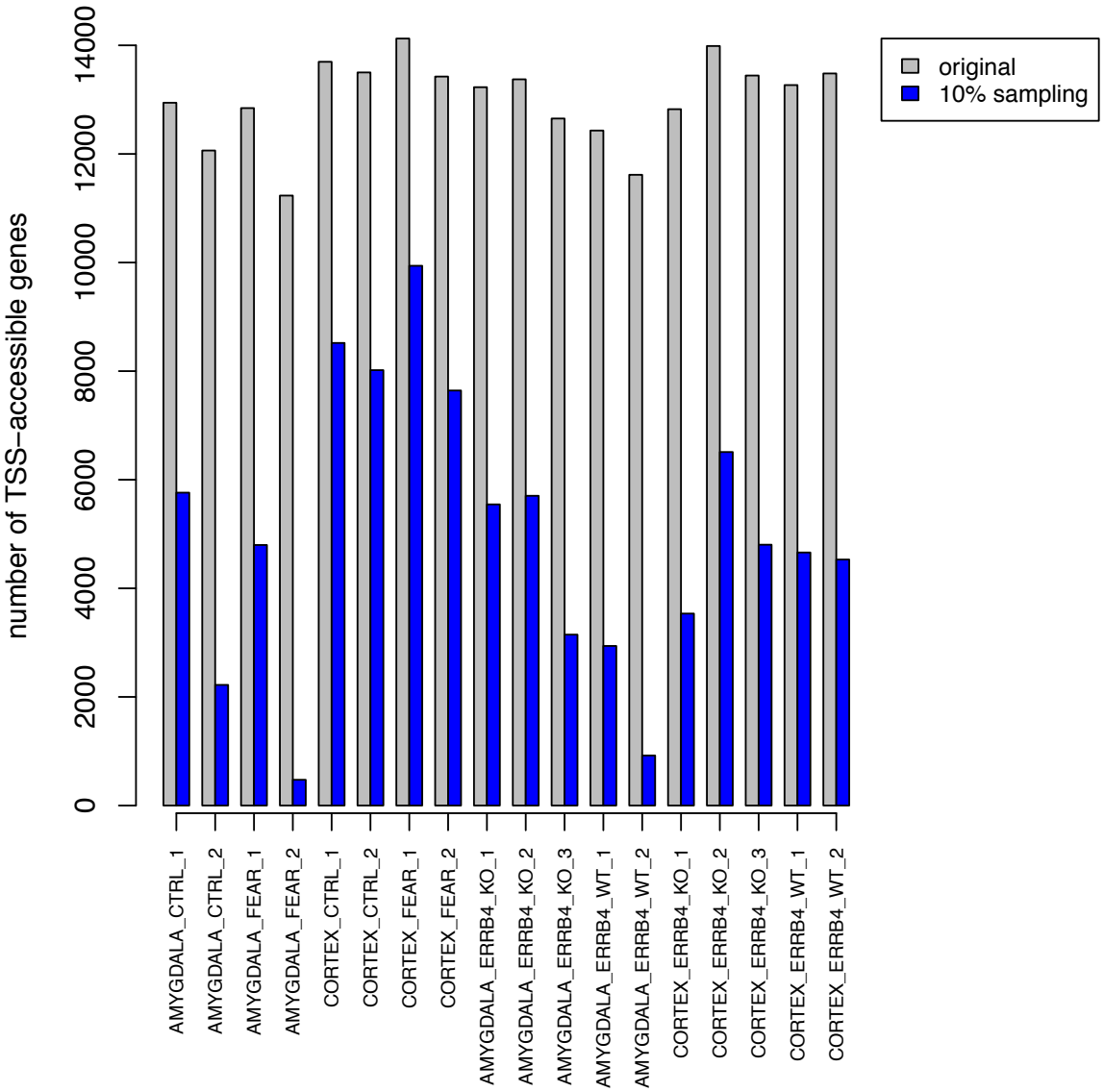
S3 Figure. Fraction of peaks with fold-change of read signals below 2. Left panel is from *narrow* peaks and right panel is from *broad* peaks.



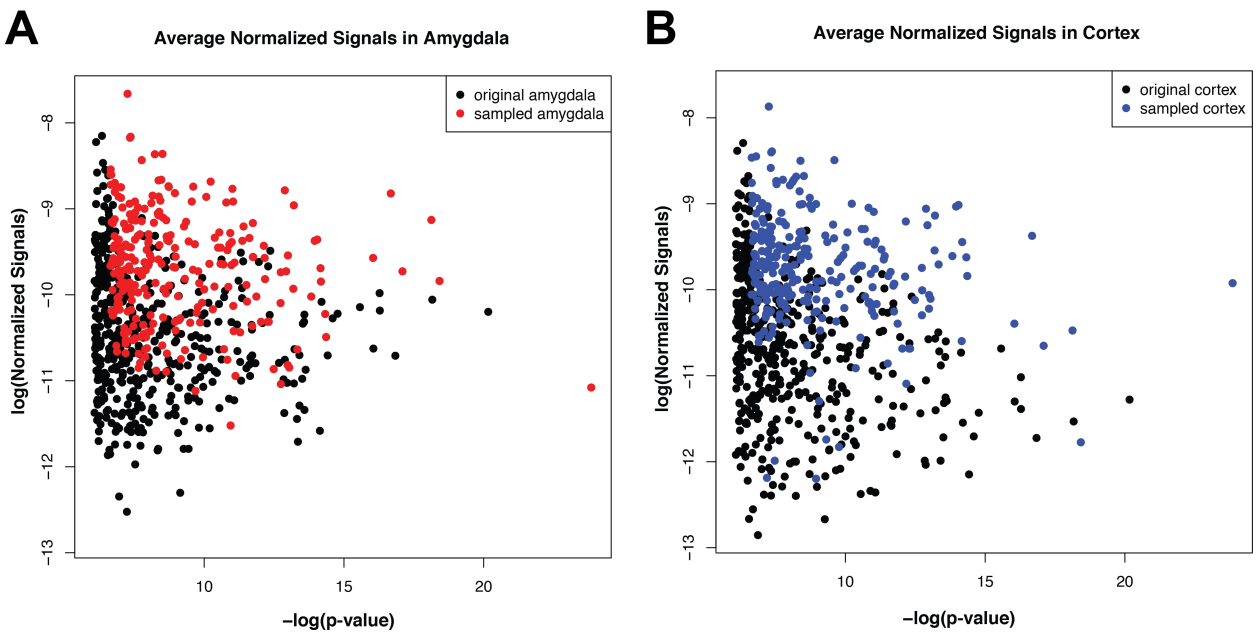
S4 Figure. Distribution of q-values of lost peaks at 90% sampling. Q-values are transformed to negative log scale. Y-axis is the relative frequency.



S5 Figure. Related to Figure 4, with broad peaks: (A) Probability of a gene exhibiting a TSS-accessible peak across 193 samples. Black line is for peaks overlapping with TSS, green line is for peaks overlapping in TSS regions, and blue line is for peaks overlapping with genic regions (+/- 1kb of gene body). 50% or more samples have peaks in roughly 55% of genic regions in RefSeq. (B) Ranked mean expression (y-axis) of genes across compared to their variation in expression (SD, x-axis). TSS-accessible genes are highlighted in blue. The histogram on the top shows the distribution of SDs for the subset of 438 TSS-accessible genes, and the histogram on the right shows the distribution of ranked expression.



S6 Figure. Number of TSS-accessible genes called after applying 10% downsampling strategy. A gene is called TSS-accessible if called in more than 9 replicates.



S7 Figure. Normalized signals vs. p-value of amygdala and cortex