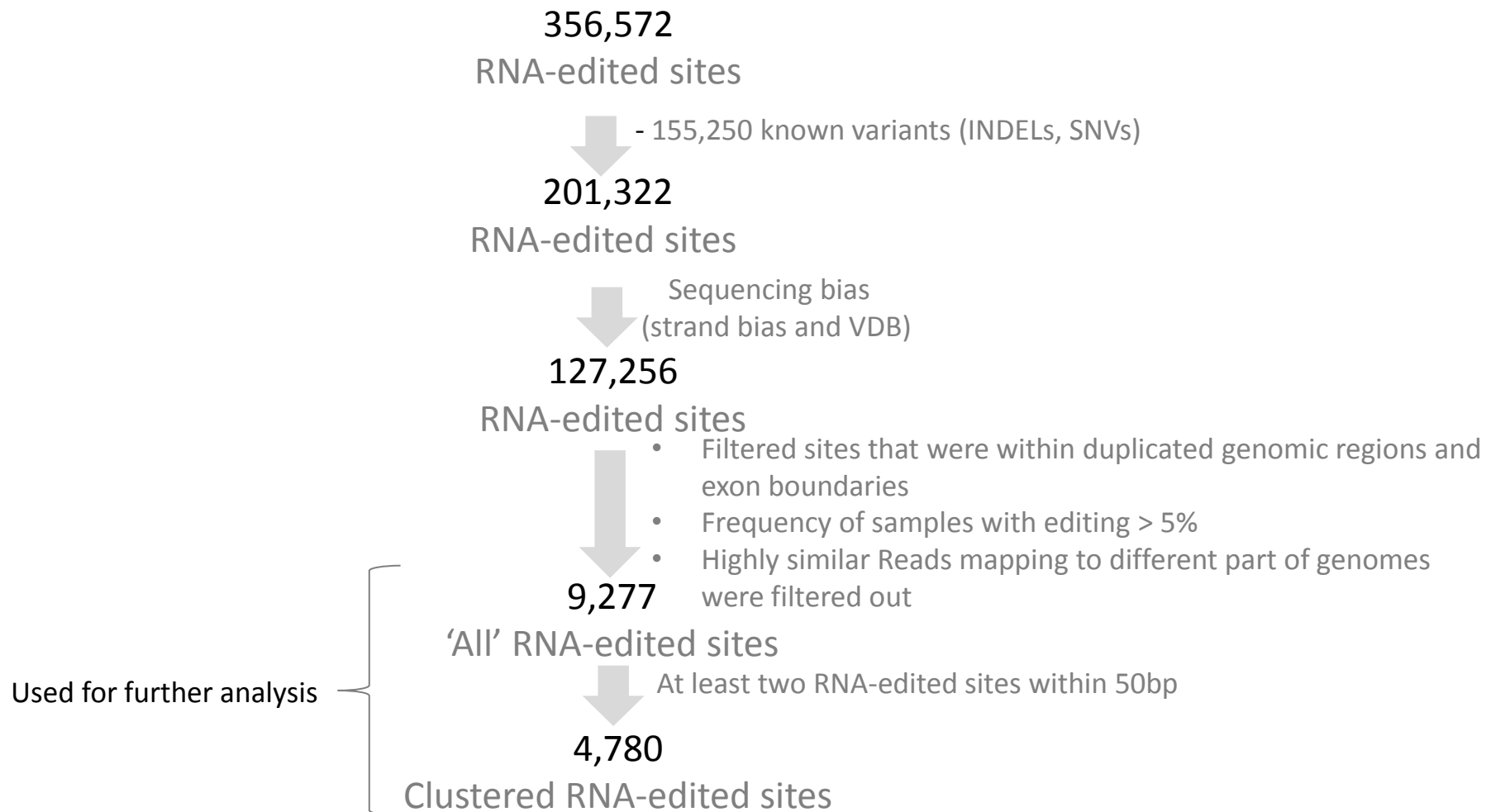
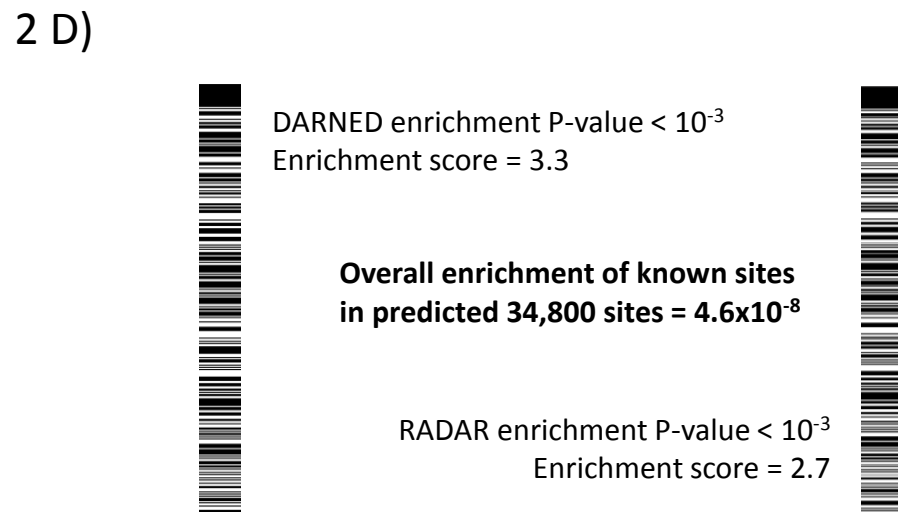
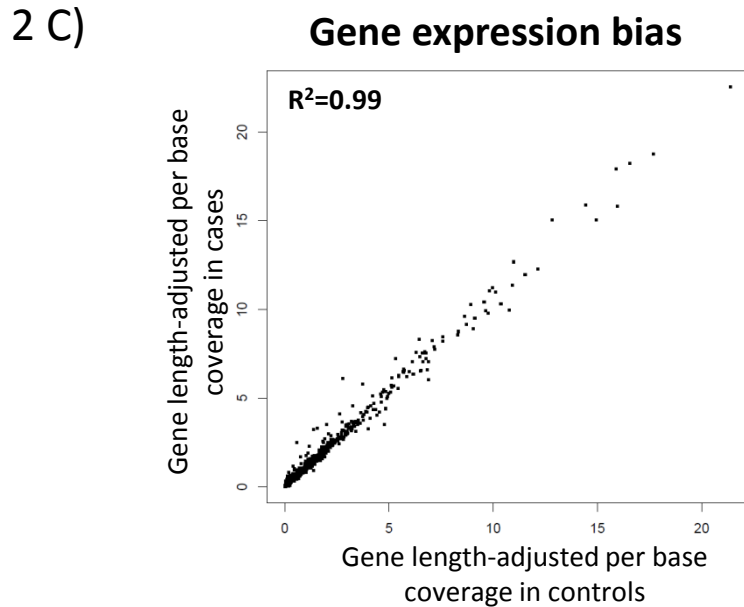
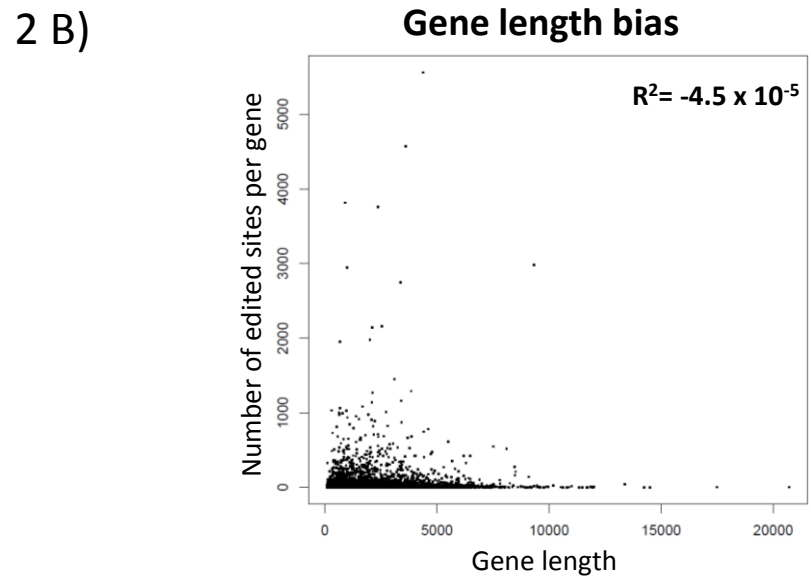
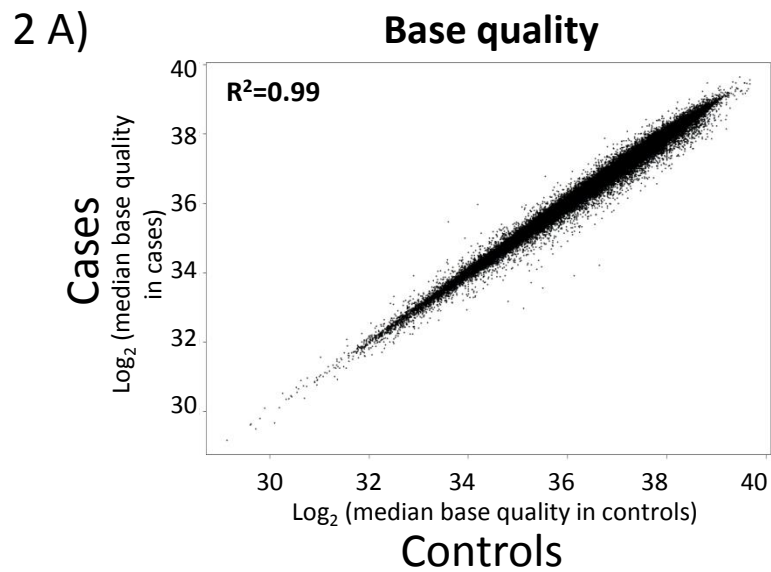


# Supplementary Figure 1

## Workflow for predicting RNA-editing event

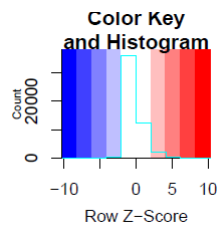


**Supplementary Figure 1:** Summary of the steps involved for the removal of technical artifacts from the predicted RNA-editing events: (i) removal of know variants such as SNPs and INDELs, (ii) Strand and variant distance biases (VDB), (iii) filtering for sites that lacked biological reproducibility and were near exonic boundaries and (iv) for clustered RNA-editing events we filtered sites that were not within 50 bp vicinity of another RNA editing event.



**Supplementary Figure 2:** To test for potential systematic biases we checked for (A) read base quality showing no differences between cases and controls, (B) low correlation between number of RNA edited sites per gene and gene length, (C) for the RNA edited sites we show equal per base read coverage for epileptic and control hippocampi, (D) GSEA analysis demonstrating enrichment of previously reported RE sites from DARNED and RADAR databases among sites DRE between epileptic cases and control.

# Supplementary Figure 3

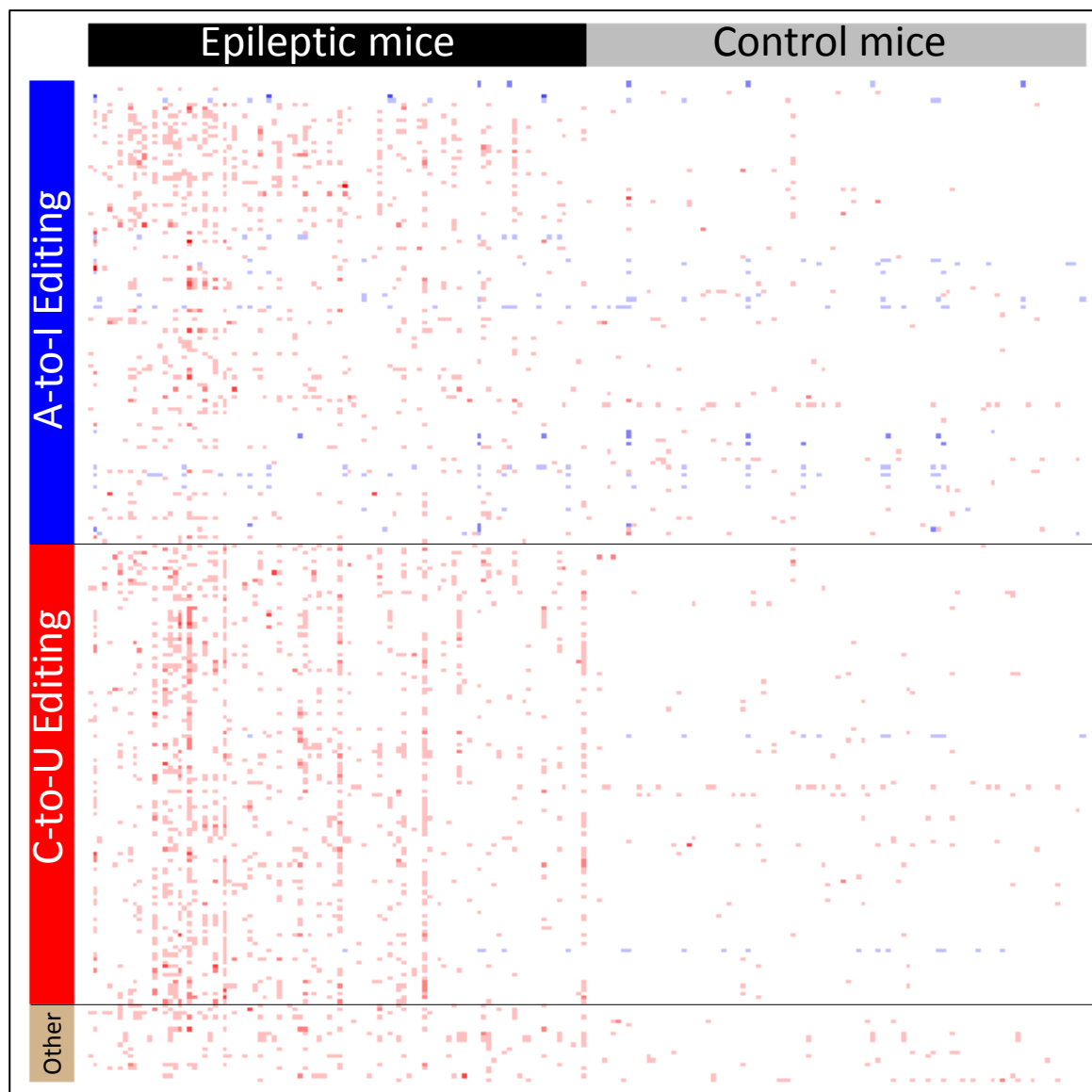


## Fold Change

73% high editing levels  
27% low editing levels

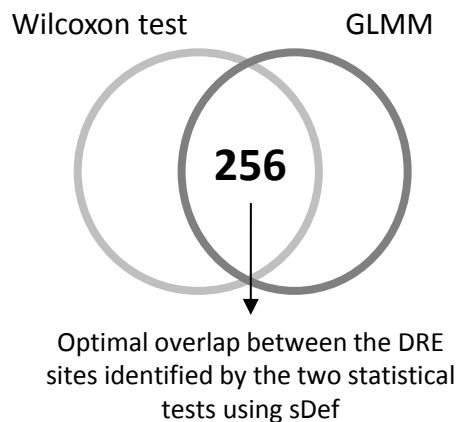
95% high editing levels  
5% low editing levels

85% high editing levels  
15% low editing levels

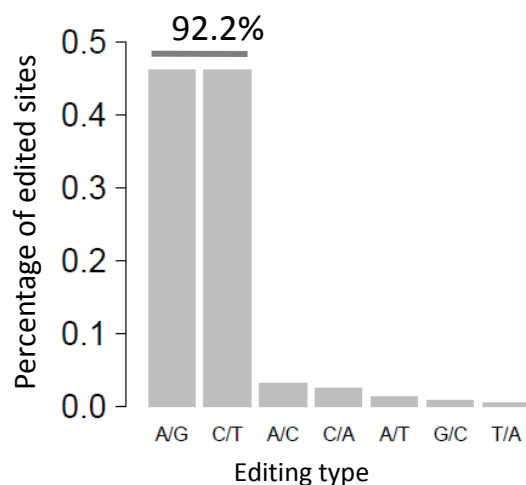


**Supplementary Figure 3:** Heatmap for RE editing levels for the DRE sites by type of editing. While the C-to-U sites are consistently highly edited in epileptic hippocampus (95%), the A-to-I editing represents a mixture of high (73%) and low (27%) edited sites with respect to control hippocampus.

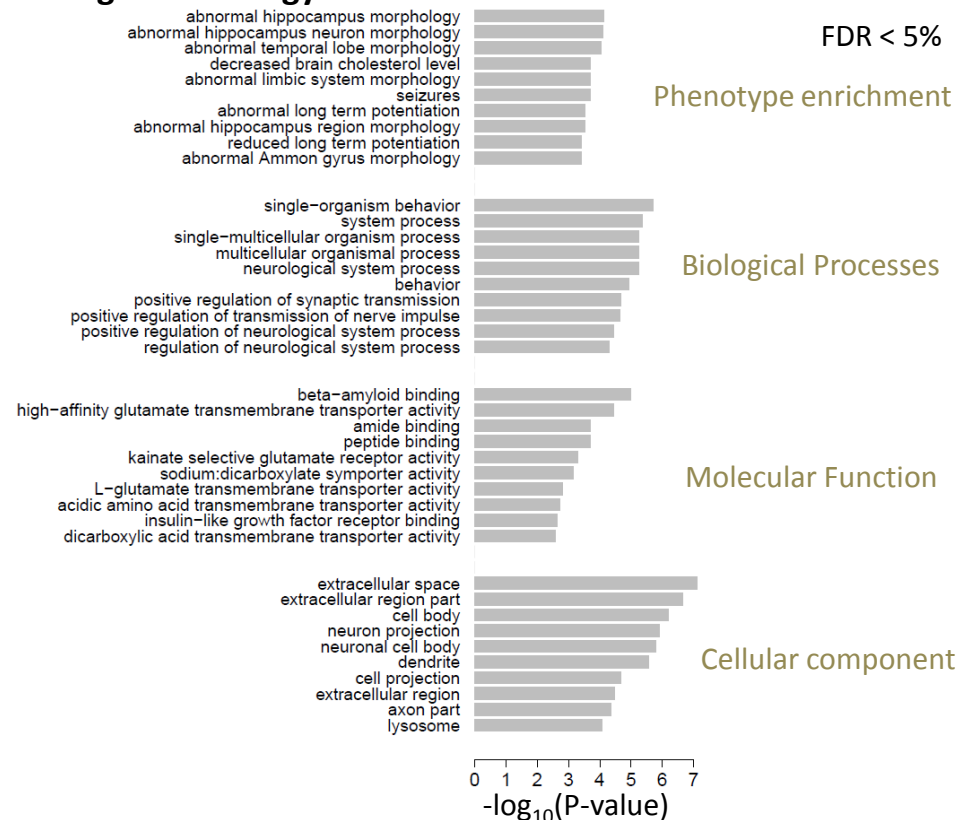
#### 4 A) Differential RNA-editing sites



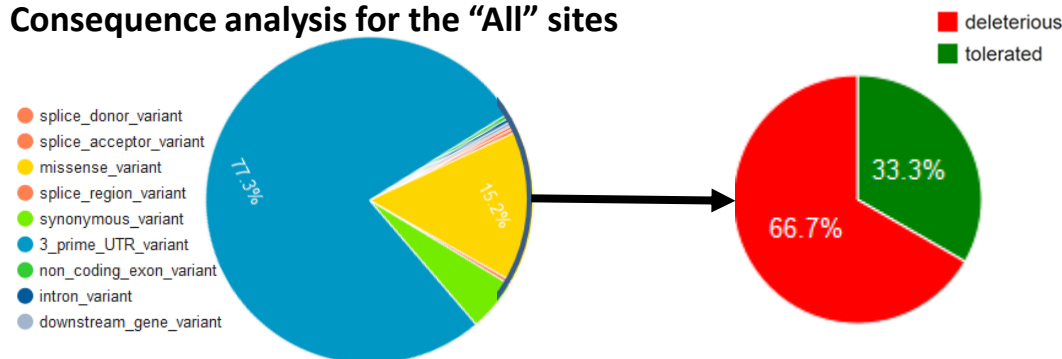
#### 4 B) Distribution of substitutions in DRE sites



#### 4 B) Overrepresented gene ontology terms



#### 4 D) Consequence analysis for the "All" sites



**Supplementary Figure 4:** Characterization of All predicted RNA-edited sites **A)** Differential RNA edited sites estimated from the two methods, **B)** Functional enrichment of the genes with differential RNA editing events by considering expressed genes as background showing enrichment for pathways highly relevant to epilepsy, **C)** Distribution of base-substitutions due to RNA editing events, and **D)** Consequence analysis for the "All" sites

## 5A) Differential RNA-editing for known sites

8,891 known RNA edited sites (RE)  
(Combined DARNED and RADAR databases)

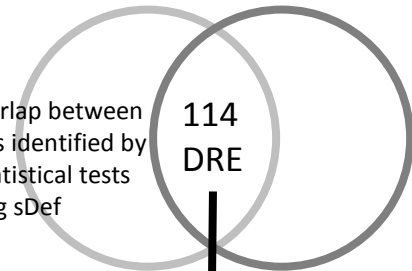


1,652 Known RNA edited sites present in at least 5% of the samples (n=10)



Test for differential RNA editing between cases and control

Wilcoxon test      GLMM



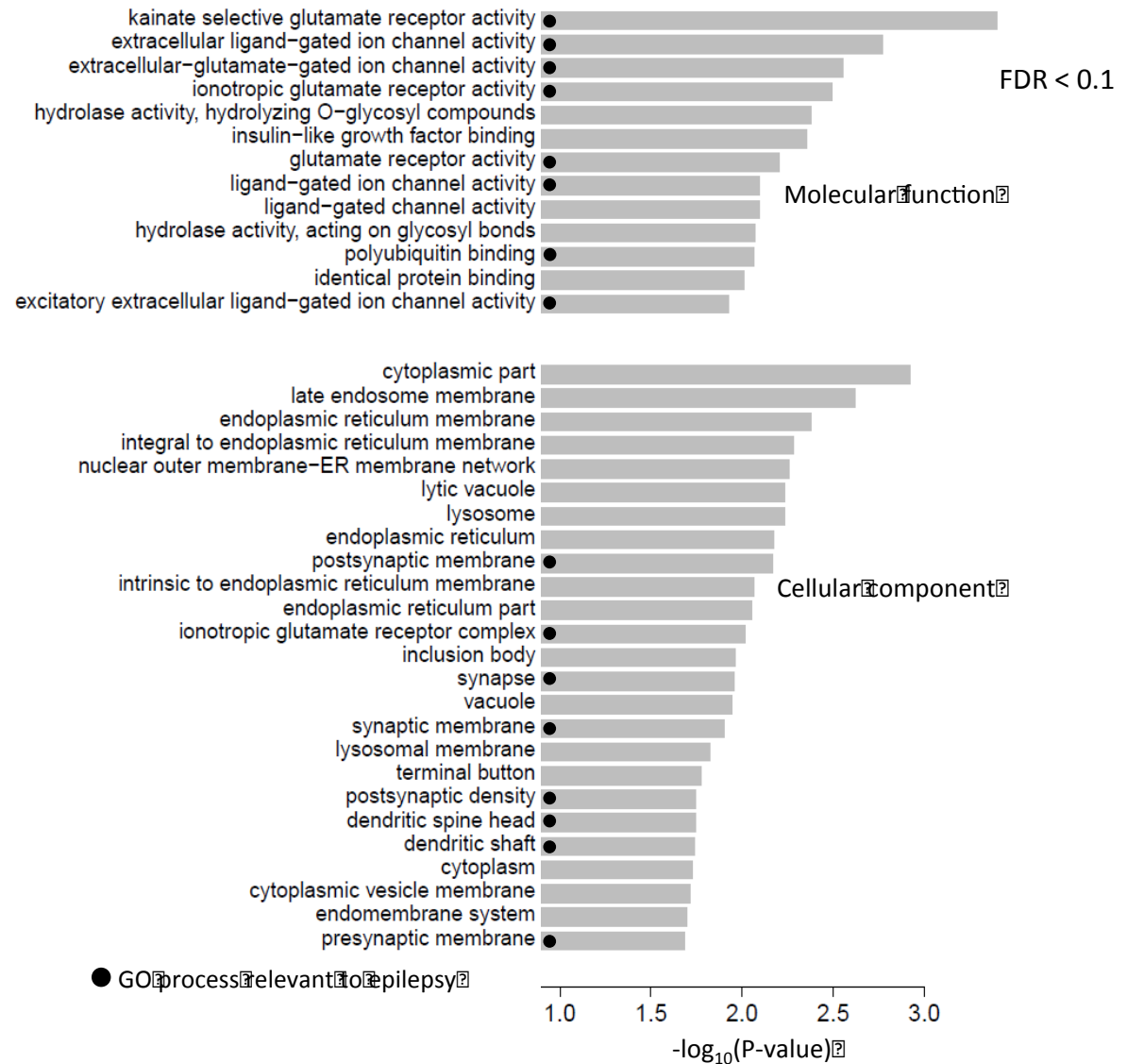
Optimal overlap between the DRE sites identified by the two statistical tests using sDef

114  
DRE



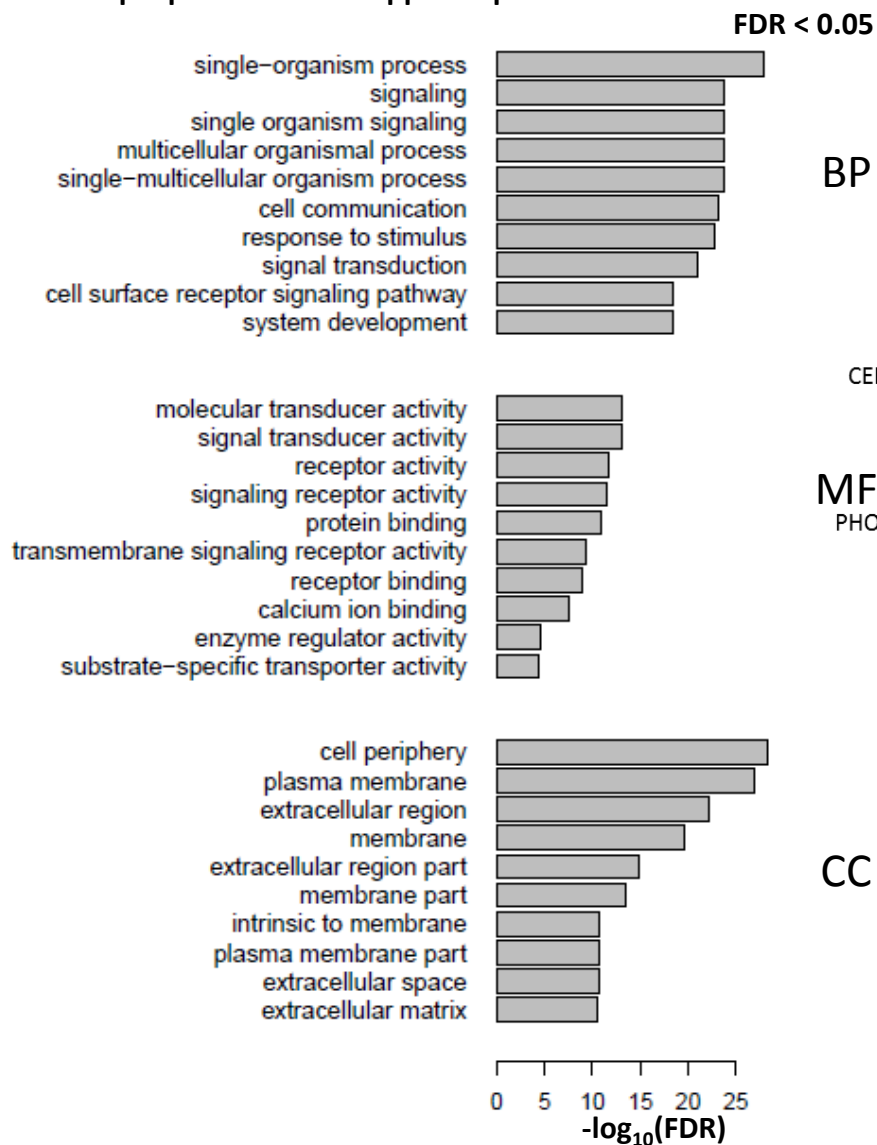
Residing in 70 genes

## 5B) Gene ontology enrichment for RE genes



**Supplementary Figure 5: Characterization of previously reported RNA-edited sites** A) Differential RNA edited sites estimated from the two methods, B) Functional enrichment of the genes with differential RNA editing events by considering expressed genes as background

**6A) Gene ontology terms enriched in genes differentially expressed between epileptic and naïve hippocampi**

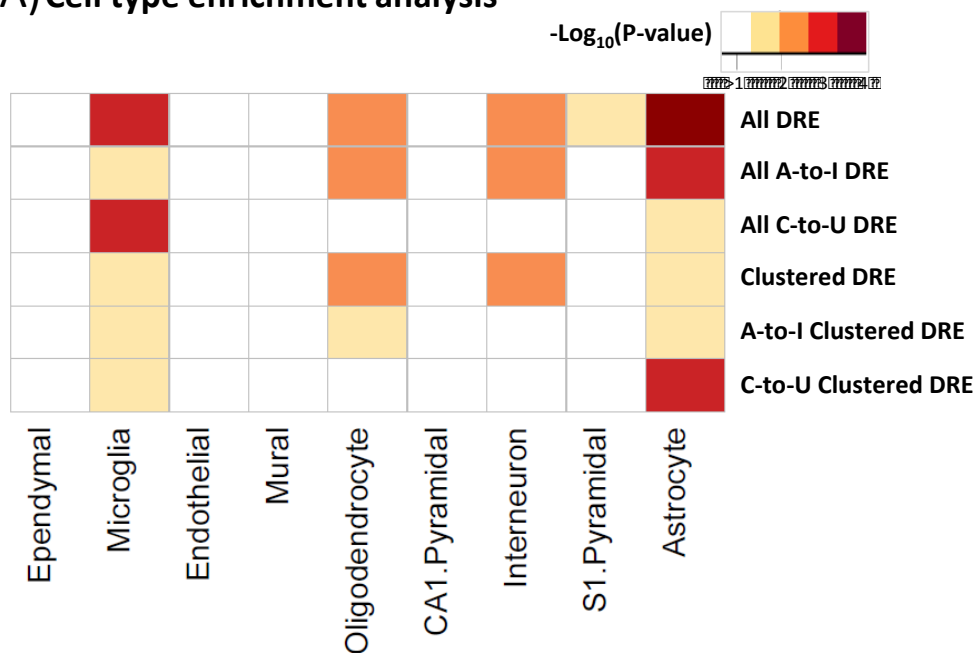


**6B) Gene ontology terms enriched in highly expressed genes in epileptic hippocampi**

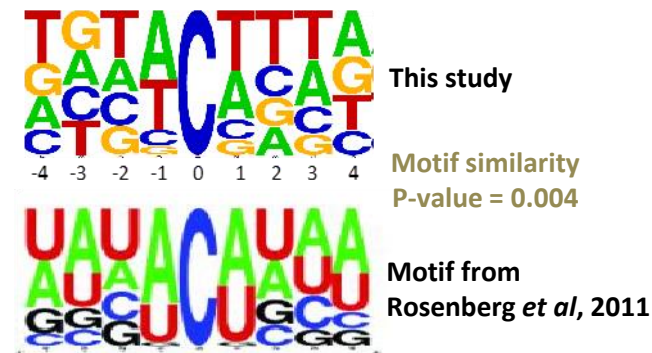


**Supplementary Figure 6:A)** Top 10 functional enrichment of the differentially expressed genes by considering expressed genes as background. **B)** Top 10 functional enrichment of the genes that were highly expressed in epileptic (grey bar) and control mice (black bar). The GO enrichment analysis was performed using GSEA approach with 10,000 permutations so the P-value cannot be less than  $10^{-5}$ . Therefore, on the X-axis, the maximum value for  $-\log_{10}(\text{P-value})$  is represented as  $>5$ . The results are summarized for the following gene ontology categories: Biological Processes (BP), Molecular Function (MF), and Cellular Components (CC).

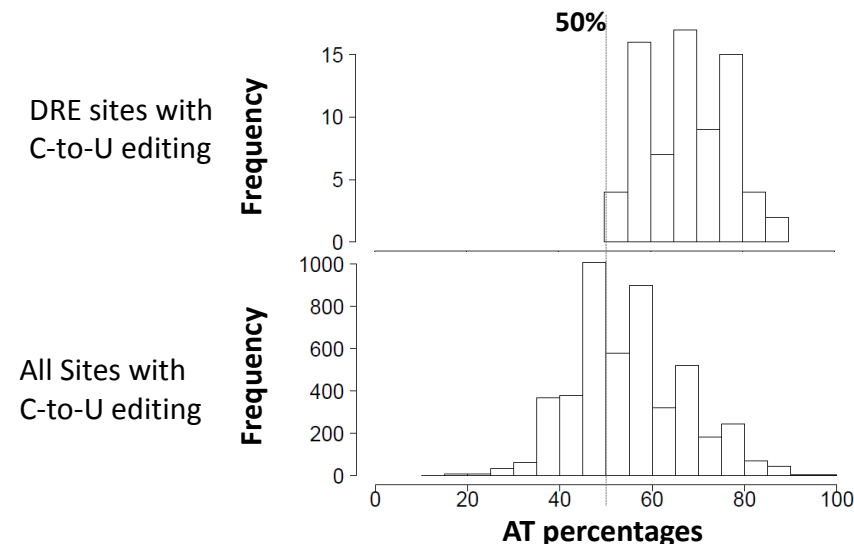
### 7A) Cell type enrichment analysis



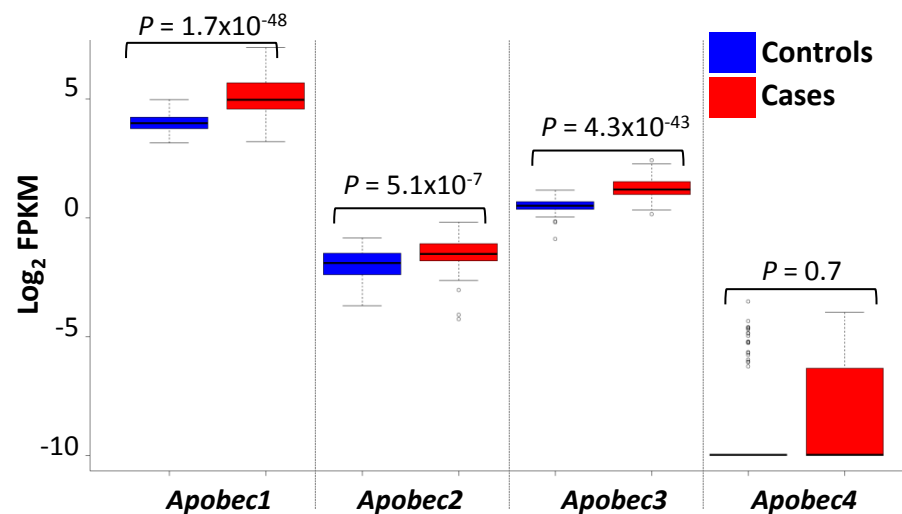
### 7B) Motif around C-to-U edited sites



### 7C) AT content $\pm$ 30bp of C-to-U edited sites



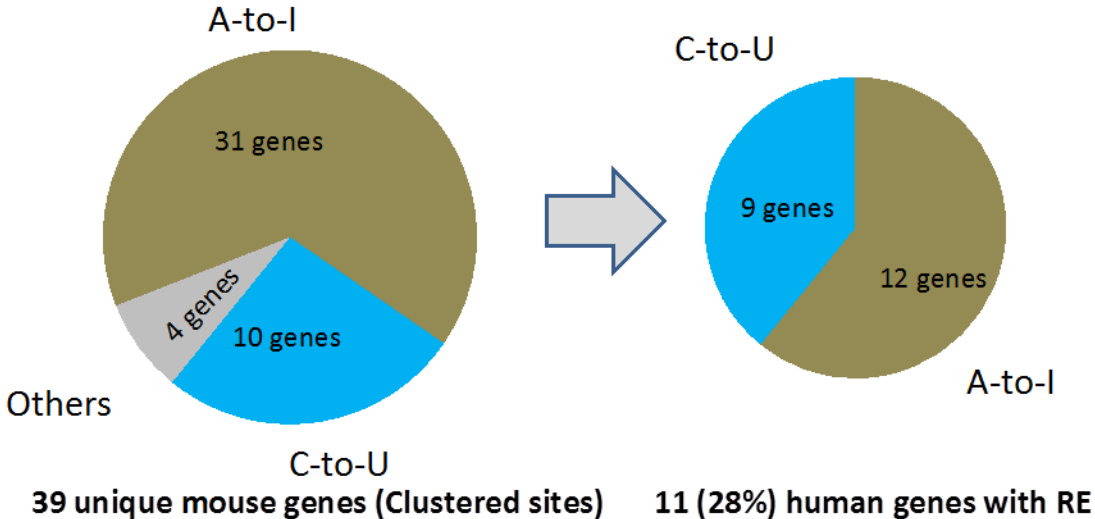
### 7D) mRNA expression levels of C-to-U RNA-editing enzymes



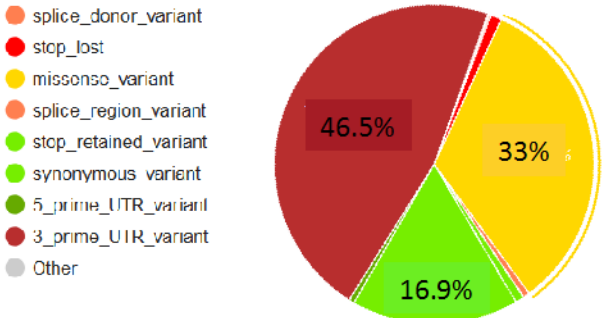
**Supplementary Figure 7: A)** Cell type enrichment analysis for the genes containing DRE sites **B)** Characterization of motif associated with non-clustered differential RNA edited sites, Top shows AT content around C-to-T edited site, **C)** Characterization of AT content associated with C-to-T RNA edited Top shows AT content around differential C-to-T edited site Bottom shows AT content around all predicted C-to-T edited sites. **D)** Gene expression differences for the key gene coding C-to-T RNA editing enzyme i.e. Apobec family

# Supplementary Figure 8:

## A) Conservation of RE in human epileptic hippocampi



## B) Consequence analysis of genes with RE sites



**Supplementary Figure 8: Conservation of RE in genes with differential RNA editing events in human epileptic hippocampi. A)** A figure showing degree of conservation between differential RNA-edited sites in human epileptic hippocampi. **B)** Consequence analysis of conserved RNA-edited sites in human epileptic hippocampi.