

ALS cases Clinical Data (GSE124439)								
ALS molecular subtype (based on Tam et al 2019)	Gender	Age at onset (years)	Site of Motor Onset	Family History of ALS/FTD	Age at death (years)	Disease Duration (months)	Subject Group	Cause of Death
ALS-Ox: n=17	Female: 10 Male: 7	Range: 55-79 Average $\pm$ SD: 63.9 $\pm$ 7.6 (NA: n=2)	Limb: n= 10 Bulbar: n=4 Bulbar and Limb: n=1 NA: n= 2	Yes: n=2 No: n= 1 NA: n=14	Range: 53-80 Average $\pm$ SD: 67.9 $\pm$ 7.1	Range: 12-156 Average $\pm$ SD: 58.5 $\pm$ 43.8 (NA: n=2)	ALS Spectrum MND*: n= 15 ALS Spectrum MND, Other Neurological Disorders**: n= 2	ALS: n= 8 Respiratory [§] : n= 3 NA: n= 6
ALS cases available genetic data								
SOD1 mutation	C9orf72 expansions	ATXN2 expansions						
Negative: n= 17	Negative: n= 17	Negative: n= 16 Intermediate (30-33): n= 1						
Control data (GSE124439)								
Non-neurological	Gender	Age at death (years)	Cause of Death					
Control: n=6	Female: n= 5 Male: n=1	Range: 22 - 90 Average $\pm$ SD: 63 $\pm$ 23.8	Cardiovascular: n=1 Neoplastic: n=2 Respiratory: n=2 Gastrointestinal: n=1					

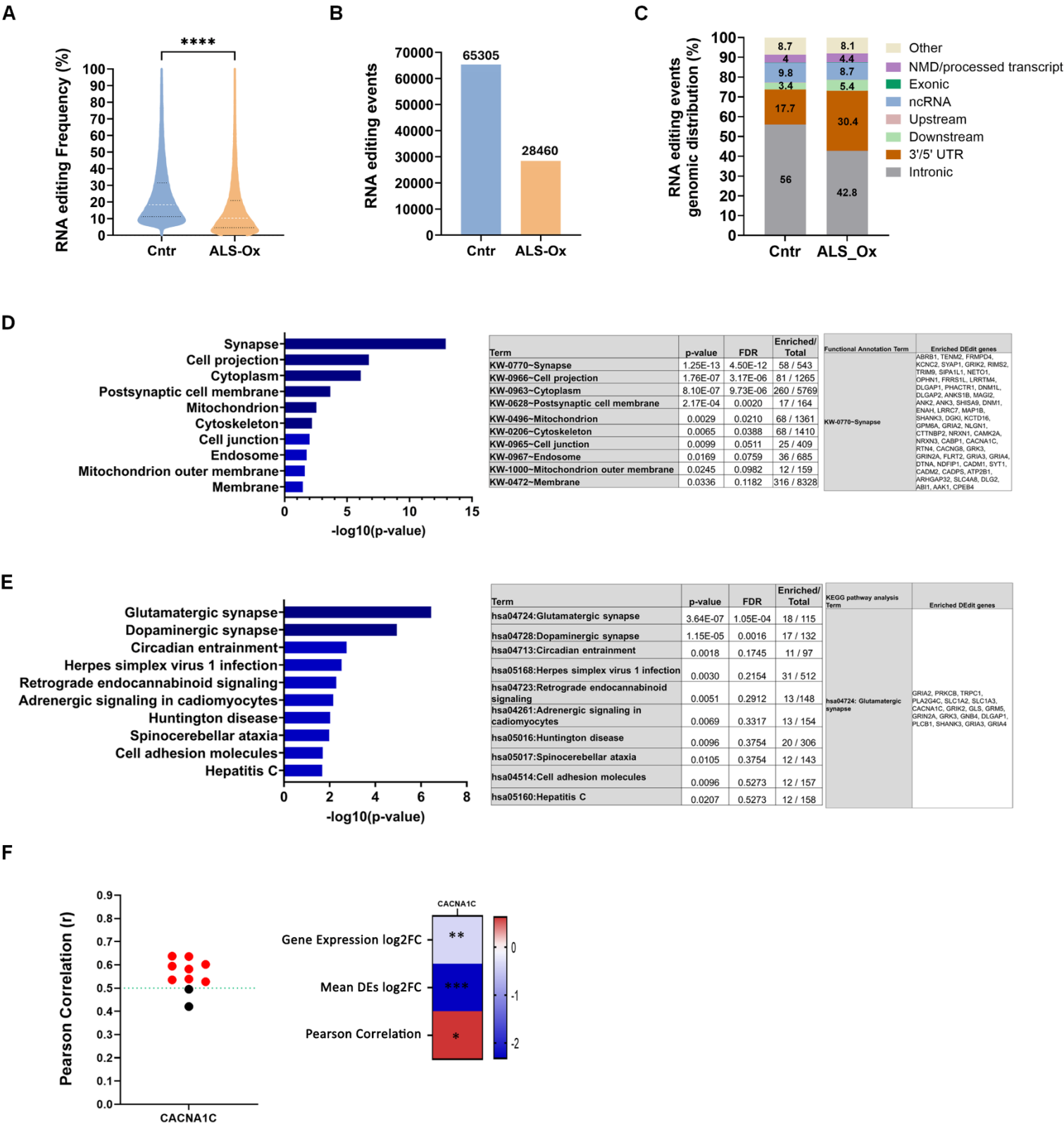
MND: Motor Neuron Disease

NA: not available/unknown

* Classical/Typical ALS

** Classical/Typical ALS, Dementia with Lewy Bodies (DLB) (n=1) & Classical/Typical ALS, Alzheimer's Disease (AD) (n=1)

[§] Respiratory Failure (n=2), Pneumonia (n=1)



RNA editomes in the frontal cortex of control and ALS-Ox cases (cohort GSE124439). **A.** Reduced global RNA editing frequency in ALS-Ox cases compared to controls. Violin plots present the distribution of global RNA editing events levels (% mean editing frequency per editing site) in the control and ALS-Ox groups. The white dotted line indicates the median. Statistical significance was determined by Wilcoxon's signed-rank test. **** $p < 0.001$. **B-C.** Reduced number of RNA editing events (**B**) and altered genomic distribution of RNA editing (**C**) in ALS-Ox cases compared to controls. The bar graph depicts the number of RNA editing events detected per phenotype group. The graphs in **C** present the percent (%) distribution of RNA editing events per genomic region (intronic, 3'/5' UTR, downstream, upstream, ncRNA, exonic, NMD/processed transcript, other) following the colour code legend on the right. Reduced representation of editing in intronic regions and increased representation in 3'UTRs is observed in ALS-Ox compared

to control cases. **D-E.** Functional annotation (**D**) and pathway analysis (**E**) on differentially edited transcripts highlights enrichment in the synapse compartment and in pathways associated with synaptic function. The graphs show enrichment, as determined by $-\log_{10}(\text{p-value})$, for functional annotation terms (**D**) and KEGG pathways (**E**). The tables list enriched terms along with corresponding p-values and FDR values, as well as the number of enriched genes (Enriched) against the total number of genes per term (Total). For the terms of interest (synapse in **D**, glutamatergic synapse in **E**) the enriched gene names are also listed. **F.** Correlation between RNA editing in CACNA1C and corresponding expression levels. The plot depicts Pearson correlation (r) values determined for each DEdit site in CACNA1C transcript. Sites presenting Pearson correlation (r) values > 0.5 are marked in red. The heatmap presents changes in ALS-Ox cases relative to controls referring to gene expression ($\log_2\text{FC}$ expression change) and editing ($\log_2\text{FC}$ mean differential editing changes) following the colour code on the right. Statistical significance (Mann-Whitney or Unpaired two-tailed t-test) is denoted by star symbols (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$). The Pearson correlation between gene expression and mean DEdit is also shown.