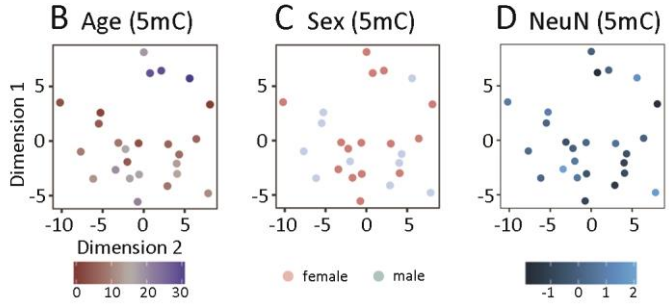
Supplement Figures

Supplement Fig S1

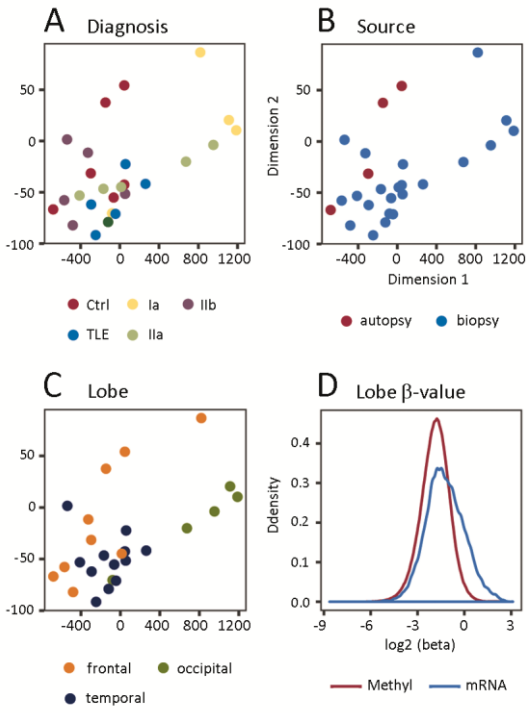
A External Model Validation

			p-value	
	Ranked Beta Value	Gene Set	Correlated	Anti-correlated
DNA Methylation	Sex(male)	X Genes	1.00E+00	0.00E+00
	Sex(male)	Y Genes	2.59E-106	1.00E+00
	Age	Horvath Up	3.25E-01	6.75E-01
	Age	Horvath Dn	9.98E-01	2.24E-03
	NeuN Methylation	Neuron Marker	1.20E-05	1.00E+00
RNA	Sex(male)	X Genes	1.00E+00	7.75E-12
	Sex(male)	Y Genes	1.00E-12	1.00E+00
	Age	Horvath Up	9.98E-01	1.52E-03
	Age	Horvath Down	6.89E-01	3.11E-01
	NeuN mRNA	Neuron Marker	2.19E-104	1.00E+00



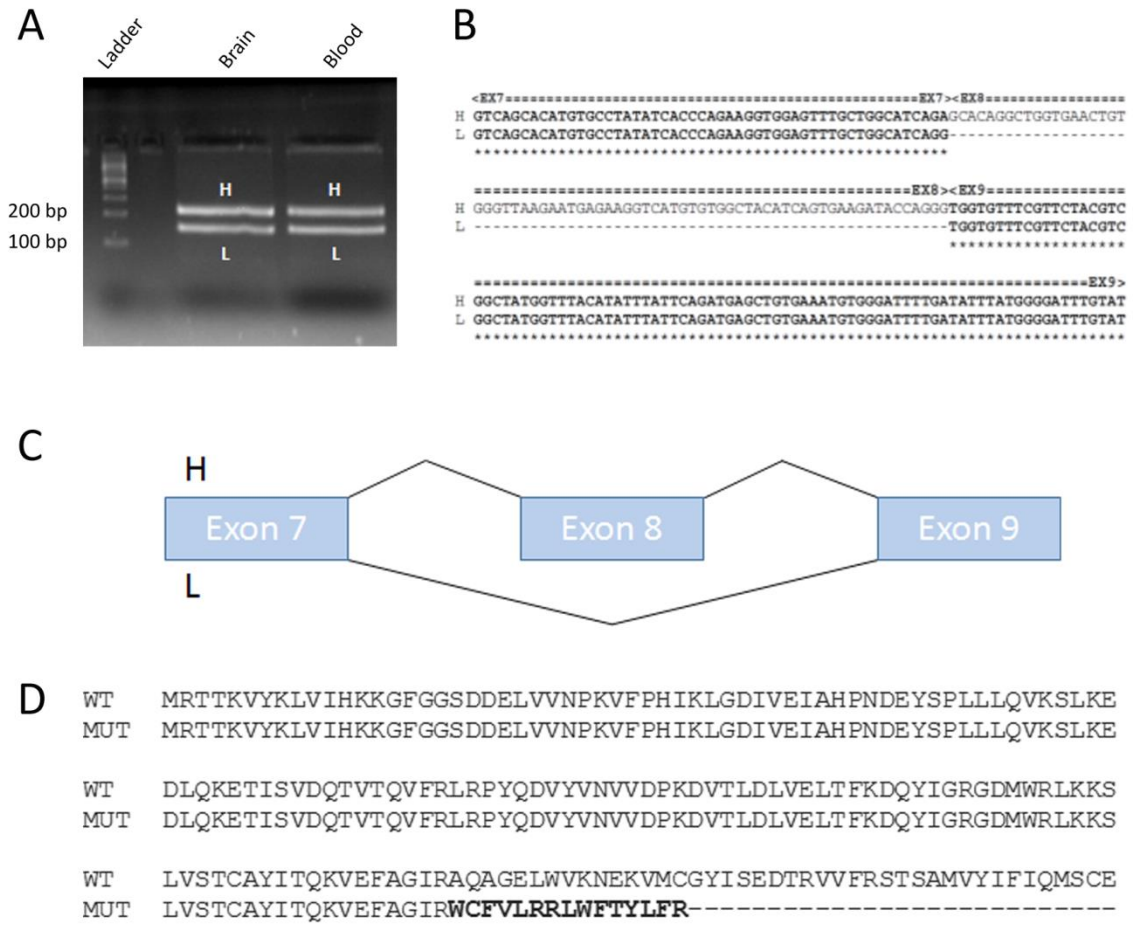
Legend to Supplement Fig S1: **A)** Identification of confounding factors for DNA methylation and mRNA profiling data according to the association between generalized linear model beta values and externally derived gene sets (see methods section for reference and details). Columns: Ranked beta value - the set of beta values which will be tested; Gene set - externally derived gene set; p-value - p-values derived from a Wilcox Mann-Whitney rank test measuring the association of the ranked beta value and the gene set. Next MDS plots were generated from significant DMRs (p<1e-4) with low confounding variable influence (beta<0.5). Samples were labelled with the covariates: **B)** Age, **C)** Sex, f – female, m – male, **D)** NeuN (RBFOX3) promoter methylation levels. Values were library size normalized, scaled and centered. The methylation signature of neurons does not drive group level clustering seen in **Fig 2D**. According to this evidence, DMRs should be considered to be robust to variations in cell mixture along with the other confounding variables.

Supplement Fig S2



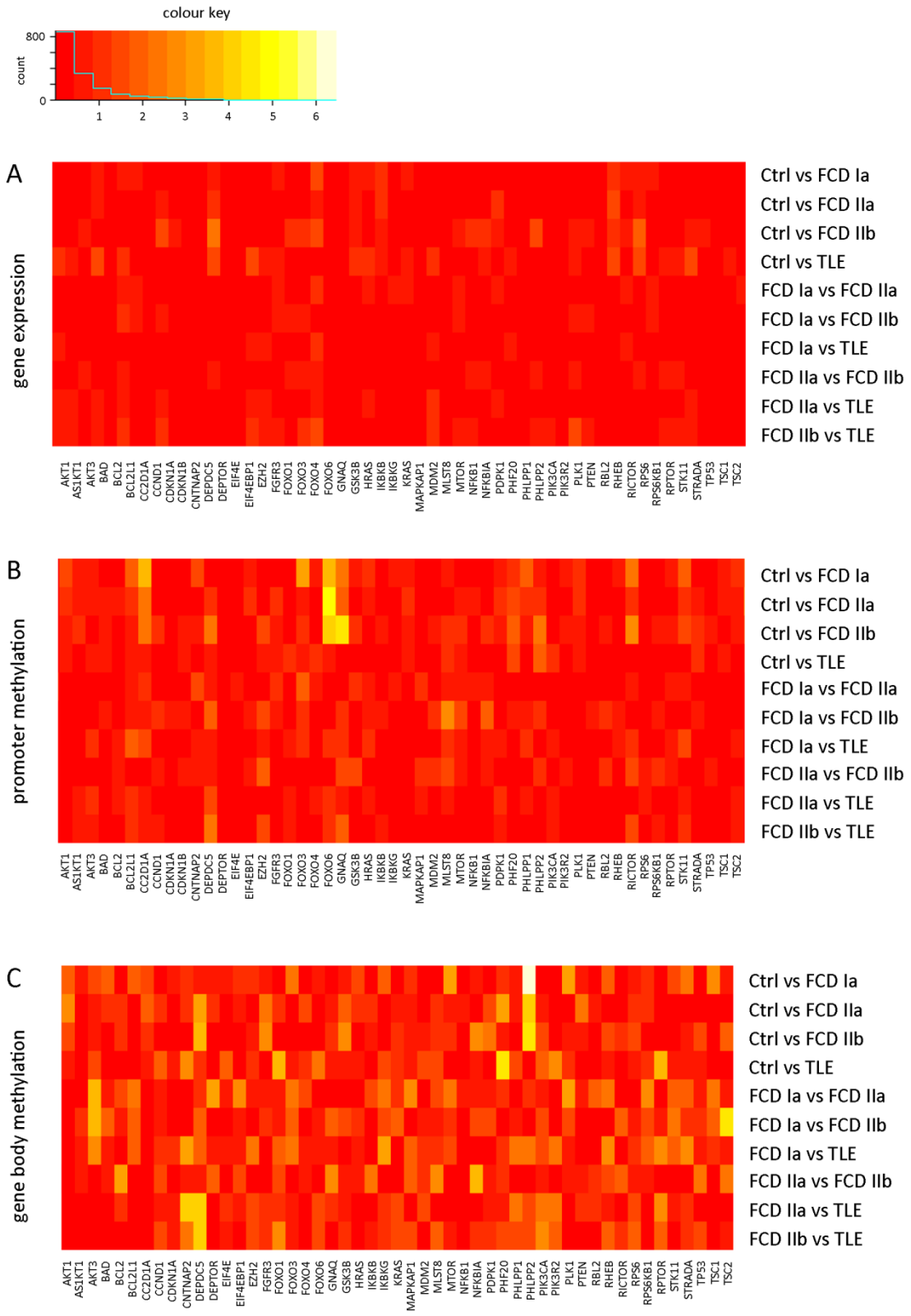
Legend to Supplement Fig S2: **A)** An MDS plot was generated from significant DEGs (p<1-e4) with low confounding variable influence (beta <0.5). Samples were labelled with epilepsy subtypes and non-epilepsy control groups. Differentially expressed genes (DEGs) were not strongly associated with epilepsy subtype and also not associated with **B)** sample source. However, DEGs showed clustering by **C)** Lobe. **D)** The distribution of log2(beta) for anatomic lobe showed a stronger effect in mRNA expression than DNA methylation. Ctrl – no seizure control; Ia – FCD Ia; IIa – FCD IIa; IIb – FCD IIb; TLE – temporal lobe epilepsy; f – female; m – male; Methyl – genome-wide DNA methylation.

Supplement Fig S3



Legend to Supplement Fig S3: RNA analysis demonstrating that the c.483+1G>A variant causes DEPDC5 exon 8 skipping. **A)** Agarose gel electrophoresis showing the presence of two bands in RT-PCR products obtained amplifying cDNA synthetized from mRNA extracted from dysplastic brain tissue and blood. **B)** Sanger sequencing results showing that the bigger RT-PCR product (H) retains DEPDC5 exon 8, while in the smaller RT-PCR product (L) exon 8 is missed. **C)** Graphic representation of the splicing occurring in the bigger and the smaller RT-PCR products. **D)** ClustalW alignment between the first 180 amino acids of the wild-type DEPDC5 protein (WT) and the predicted mutant protein produced by the DEPDC5 mRNA missing exon 8 (MUT). If translated, the mutant protein is predicted to contain only 153 amino acids instead of 1603 and the last 15 amino acids, indicated in bold, would be completely different from those of the wild-type form.

Supplement Fig S4



Legend to Supplement Fig S4: Heatmap summarizing differential mRNA expression **(A)**, promoter methylation **(B),** and gene body methylation **(C)** of mTOR pathway associated and

developmental genes. No significant gene expression changes were detectable. PHLPP1 gene body and FOXO6 promoter hypermethylation distinguished FCDs from TLE and non-epilepsy controls, but no mTOR pathway related gene was differentially methylated between FCD subtypes.