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BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

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GENETICS

Genome-wide DNA methylation in early-onset dementias brain tissue and lymphoblastoid cell lines

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Abstract

Background: Epigenetic mechanisms as a potential underlying pathogenic mechanism of neurodegenerative diseases have been the scope of several studies performed so far. However, there is a gap in analyzing different forms of early-onset dementia to minimize the effect of aging and the use of Lymphoblastoid cell lines (LCLs) as a possible disease model for earlier clinical phases.

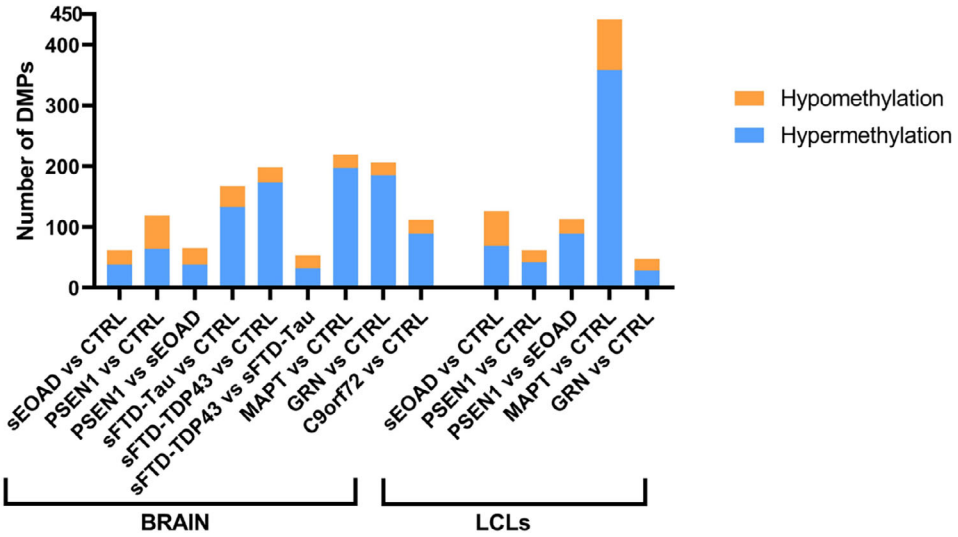
Method: We performed a genome-wide DNA methylation analysis in 64 samples (from prefrontal cortex and lymphoblastoid cell lines) from Alzheimer's Disease (AD) and Frontotemporal dementia (FTD) using the Illumina Infinium MethylationEPIC V2.0 array. The studied cohort included sporadic early-onset (sEOAD, sFTD-TP43, sFTD-Tau) and genetic subgroups of AD (*PSEN1*) and FTD (*MAPT*, *GRN*, *C9orf72*), with n = 5 subjects/group. We analyzed the differentially methylated positions (DMPs) using the Beta regression model, with age and sex as covariates, and all p-values adjusted by False Discovery Rate (FDR). Venn diagrams to visualize common genes between pairwise comparisons and heatmaps were performed to further explore the most important DMPs. Elastic Net logistic regression was used to obtain epigenetic diagnostic signatures. We also performed a correlation analysis of DNA methylation levels with Clariom D array gene expression data for the same cohort.

Result: Results showed hypermethylation in patients' groups as the most frequent finding in both tissues studied (Fig. 1). We identified common DMPs when comparing patients with healthy controls (CTRL) for each respective disease (Fig. 2, 3). Biological significance analysis revealed common pathways altered in AD and FTD affecting neuron development, metabolism, signal transduction and immune system pathways. These alterations were also found in LCLs, even some related to neuron development.

We obtained diagnostic signatures to differentiate patients from CTRL. In the brain, CpG methylation presented an inverse correlation with gene expression, while in LCLs we observed mainly a positive correlation.

Conclusion: This study enhances our understanding about the biological pathways that are associated with neurodegeneration, describes differential methylation patterns, and suggests LCLs are a potential cell model for studying neurodegenerative diseases in early clinical phases.

Figure 1. Number of differentially methylated positions (DMPs) filtered for Beta difference.



Barplot showing the amount of hyper 125 and hypomethylated CpGs found in each comparison performed per tissue. Filters applied: in 126 brain adjusted-p value <0.05, absolute value of Beta difference >0.25; in LCLs adjusted-p value 127 <0.01, absolute value of Beta difference >0.35. Abbreviations: CTRL, healthy controls; sEOAD, 128 sporadic early-onset Alzheimer's disease; PSEN1, autosomal dominant Alzheimer's disease caused 129 by mutation in PSEN1 gene; MAPT, GRN, C9orf72, familial frontotemporal dementia caused by 130 mutation in MAPT, GRN or C9orf72 genes; sFTD-Tau, sporadic frontotemporal dementia with tau 131 deposits; sFTD-TDP43, sporadic frontotemporal dementia with TDP43 deposits; LCLs, 132 lymphoblastoid cell lines.

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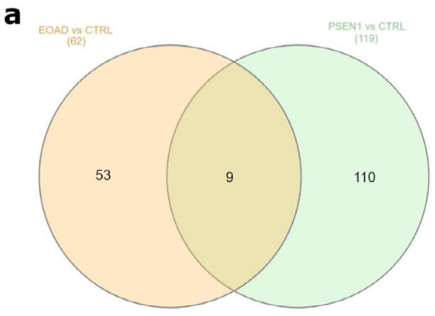
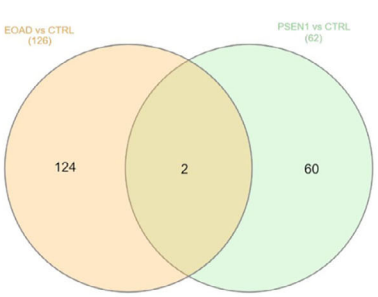
Figure 2. Common differentially methylated positions (DMPs) found between different AD comparisons.



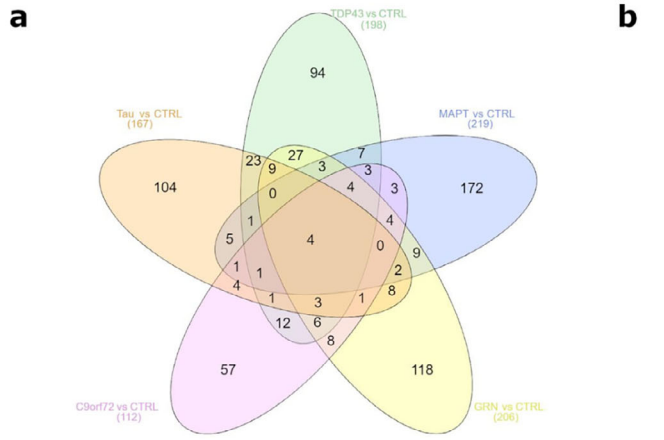
		EOAD vs CTRL		PSEN1 vs CTRL	
CpG	Gene	Beta dif.	Adj.pval	Beta dif.	Adj.pval
cg17925226	*BMPR1B*	0.3946	0.0135	0.4042	0.0000
cg08522473	*TAGLN3*	-0.3732	0.0184	-0.3100	0.0093
cg05232042	*GCH1*	0.2793	0.0000	0.2514	0.0003
cg06354054	*DHX37*	0.3957	0.0000	0.3786	0.0001
cg14866535	*FAM65C*	0.4218	0.0021	0.4206	0.0115
cg02945674	*ABCA1*	0.3327	0.0119	0.3794	0.0013
cg14827740	*ACCN1*	0.2524	0.0022	0.2505	0.0000
cg05966078	*EPHB3*	0.3001	0.0000	0.3039	0.0009
cg01059116	*GLIS1*	0.3842	0.0000	0.3169	0.0007
cg05966078	*EPHB3*	0.3001	0.0000	0.3039	0.0009
cg01059116	*GLIS1*	0.3842	0.0000	0.3169	0.0007



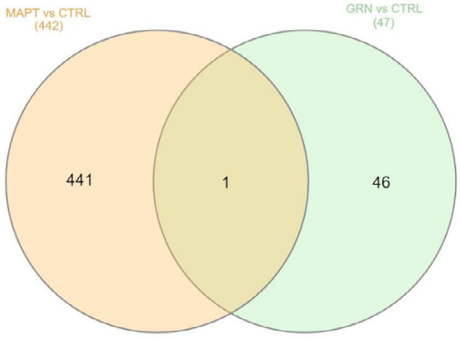
		EOAD vs CTRL		PSEN1 vs CTRL	
CpG	Gene	Beta dif.	Adj.pval	Beta dif.	Adj.pval
cg25004725	*ANXA6*	0.4396	0.0007	0.4028	0.0003
cg05665811	*CATSPER2*	0.3814	0.0039	0.3836	0.0000

Venn diagrams showing common DMPs among brain (a) and LCLs comparisons (b). Underneath each Venn diagram, a table shows the common DMPs found and their corresponding gene, Beta difference (Beta dif.) and adjusted-p value (Adj.pval). Filters applied: in brain adjusted-p value <0.05 and absolute value of Beta difference >0.25; in LCLs adjusted-p value <0.01 and absolute value of Beta difference >0.35. Abbreviations: CTRL, healthy controls; sEOAD, sporadic early-onset Alzheimer's disease; PSEN1, autosomal dominant Alzheimer's disease caused by mutation in PSEN1 gene; LCLs, lymphoblastoid cell lines.

Figure 3. Common differentially methylated positions (DMPs) found between different FTD comparisons.



		sFTD-Tau vs CTRL		sFTD-TDP43 vs CTRL		MAPT vs CTRL		GRN vs CTRL		C9orf72 vs CTRL	
CpG	Gene	Beta dif.	Adj.pval	Beta dif.	Adj.pval	Beta dif.	Adj.pval	Beta dif.	Adj.pval	Beta dif.	Adj.pval
cg17925226	*BMPR1B*	0.3718	0.0007	0.4702	0.0000	0.4267	0.0000	0.4659	0.0000	0.3109	0.0396
cg00571519	*SRPK2*	0.3691	0.0198	0.3841	0.0030	0.3204	0.0483	0.4430	0.0020	0.3718	0.0391
cg15829774	*BTBD8*	0.2576	0.0039	0.2643	0.0023	0.2624	0.0015	0.2631	0.0106	0.2514	0.0318
cg07902519	*MYBPC1*	0.2503	0.0048	0.3108	0.0025	0.3346	0.0108	0.3151	0.0164	0.3598	0.0048



		MAPT vs CTRL		GRN vs CTRL	
CpG	Gene	Beta dif.	Adj.pval	Beta dif.	Adj.pval
cg07497120	*FOCAD*	0.4107	0.0000	0.3733	0.0036

Venn diagrams showing common DMPs among brain (a) and LCLs comparisons (b). The table underneath Venn (a) shows the common DMPs found and their correspondent gene, Beta difference (Beta dif.) and adjusted-p value (Adj.pval). Filters applied: in brain adjusted-p value <0.05 and absolute value of Beta difference >0.25; in LCLs adjusted-p value <0.01 and absolute value of Beta difference >0.35. Abbreviations: CTRL, healthy controls; MAPT, GRN, C9orf72, familial frontotemporal dementia caused by mutation in MAPT, GRN or C9orf72 genes; sFTD-Tau, sporadic frontotemporal dementia with tau deposits; sFTD-TDP43, sporadic frontotemporal dementia with TDP43 deposits; LCLs, lymphoblastoid cell lines.