DNA METHYLATION OF RE-1SILENCING TRANSCRIPTION FACTOR IN LATE-ONSET ALZHEIMER'S DISEASE PATIENTS.

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Introduction

Late-Onset Alzheimer's disease is the most frequent cause of dementia in elderly adults, however, the determining factors for its beginning are still unclear. The RE-1 silencing transcription factor (REST) has been described as a gene whose activation and expression in elderly could be determinant for neuroprotection process and good management of the amyloidogenic pathway.

Objectives

To analyze the methylation patterns of a minimal promoter region of REST gene and its expression in a group of 21 subjects diagnosed with late-onset Alzheimer's disease (LOAD) and a control group conformed by 20 elderly people cognitively healthy (EPCH).

Methods

From peripheral venous blood, genomic DNA was isolated and modified by Bisulfite treatment to preserve the methylated cytosines. Through pyrosequencing the differences in DNA-methylation patterns were determinated. The differences in gene expression of REST in peripheral blood mononuclear cells were stablished by real-time PCR.

Results

Characteristics of the 41 participants in the study sample are presented in **Table 1**.

	LOAD n=21		EPCH n=20		P value
	Average	**(SD)**	**Average**	**(SD)**	
Age	74,79	0,59	70,48	0,59	< 0,004
Sex %	**Female**	**Male**	**Female**	**Male**	
	75,6	82,5	24,1	17,5	< 0,01
Education %					
Low	89,6		75		< 0,01
High	10,34		25		< 0,05
DT2	24,14		20		0,44
Hypertension	41,38		40,0		0,49
Dyslipidemia	17,24		32,5		0,36

Table.1 Sociodemographic and health status characteristics between groups.

The group of patients with LOAD presented a general pattern of hypermethylation of the studied sequence in coordination with hypomethylation of a specific CpG dinucleotide (3-CpG), while the EPCH group showed global hypomethylation with hypermethylation of the 3-CpG dinucleotide **(Fig. 1)**.

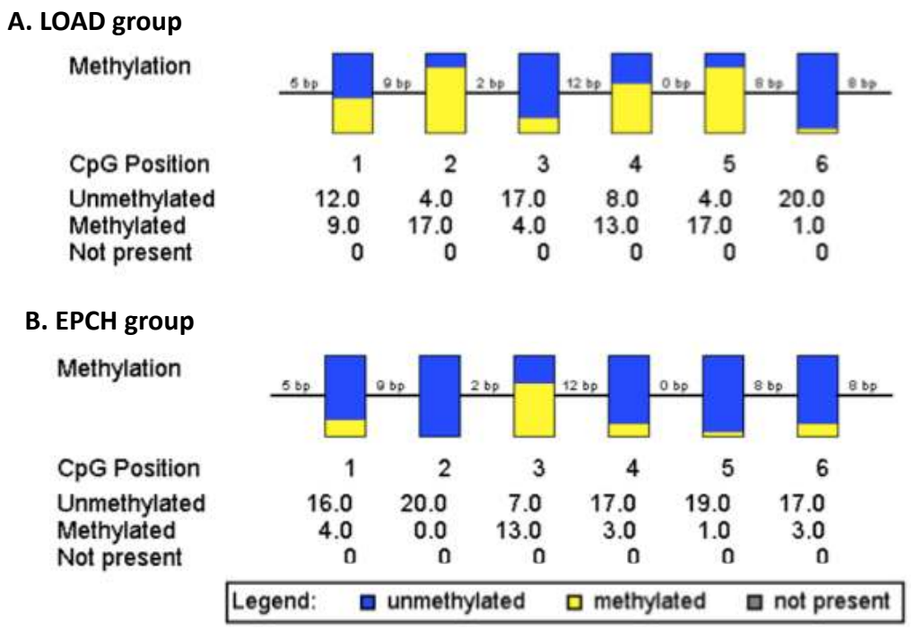

Fig.1 Aggregated Representation of Methylation Data. Each box corresponds to one CpG position in the genomic sequence. The colored bars summarize the methylation states of all sequences at that position. **A**. Late-onset Alzheimer's Disease patients**. B.** Elderly people cognitively healthy.

Relative gene expression was significantly lower in patients with Alzheimer's disease than in those who were cognitively healthy (p<0.001) **(Fig.2)**.

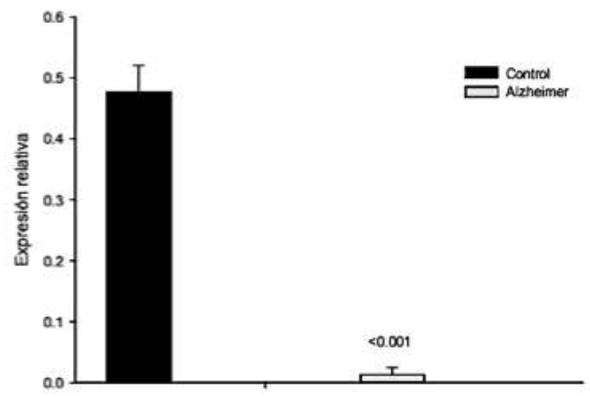

Fig.2 Peripheral Blood Mononuclear Cells mRNA gene-REST expression from late-onset Alzheimer's disease patients (gray) and elderly people cognitively healthy group (black).

Conclusions

The epigenetic regulation of REST transcription is coordinated by methylation and demethylation of specific sites in the sequence, causing the lack of expression of this factor in patients with LOAD. In cognitively healthy patients, specific regulation of the promoter REST region methylation, promotes its expression and neuroprotective effect.

In the future, determination of different methylation patterns could derive in early diagnosis and promisingly advances in editing gene could offer a deliberate turn-on REST expression in order to improve its neuroprotective effects so be a therapeutic target.

References

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