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DNA methyltransferase haplotype is associated with Alzheimer's disease

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HIGHLIGHTS

- Minor alleles of two SNPs (rs998382, rs2424913) in the *DNMT3B* gene were associated with Alzheimer's disease (AD) when compared to healthy controls.
- The *DNMT3B* TGG haplotype was associated with AD.
- This difference was not observed for *DNMT1* polymorphisms.

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ABSTRACT

Epigenetic mechanisms have been implicated in syndromes associated with neuropsychiatric disorders, but little is known about the role of epigenetics in Alzheimer's disease (AD). DNA methylation, one of the main epigenetic mechanisms, is a complex process carried out by specific enzymes, such as *DNMT1* and *DNMT3B*. This study aimed to investigate the association between *DNMT1* and *DNMT3B* polymorphisms and AD. Two hundred and ten elderly subjects (108 healthy controls and 102 with AD-NINCDS/ARDA, DSM-IV-TR criteria) were assessed. DNA was obtained from whole blood, and genotypes were detected by an allelic discrimination assay using TaqMan® MGB probes on a real-time PCR system. The polymorphisms studied were rs2162560, rs759920 (*DNMT1*) and rs998382, rs2424913, rs2424932 (*DNMT3B*). For both genes, the polymorphisms were in strong linkage disequilibrium. Carriers of the *DNMT3B* TGG haplotype were associated with AD (OR = 3.03, 95% CI 1.63 to 5.63, $P < 0.001$). No significant difference between AD and the control group were observed for *DNMT1* polymorphisms. This study is one of the first describing a significant association between *DNMT3B* polymorphisms and AD. This enzyme, which is responsible for methylation in a general way, may be involved in AD.

1. Introduction

Epigenetic mechanisms have been implicated in syndromes associated with neuropsychiatric disorders, but little is known about the role of epigenetics in sporadic Alzheimer's disease (AD), a complex multifactorial neurodegenerative disorder and the most common cause of dementia [3]. In this sense, epigenetic processes may have a role in the gene–environment interaction process, the most accepted model linked with neurodegeneration in sporadic AD. DNA methylation is the most stable epigenetic modification, modulating the transcriptional plasticity of mammalian genomes. It is linked to gene expression, with an inverse correlation between the degree of promoter DNA methylation and the level of expression [15,30]. This process is mediated by a family of conserved enzymes, DNA methyltransferases (DNMT), responsible for adding a methyl group to position 5 of the cytosine pyrimidine ring in the CpG dinucleotide [9]. The *DNMTs* (mainly *DNMT1* and *DNMT3B*) are enzymes responsible for establishing and maintaining DNA methylation patterns. *DNMT1* is a maintenance enzyme, which binds methyl groups to hemi-methylated DNA during DNA replication. *DNMT3B* are de novo methyltransferase, which establish methylation patterns during embryonic development [8,29].

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DNA methyltransferases were first investigated in some varieties of cancer [1,4], but interest in the neuropsychiatric field has been increasing [13,14,36], with most studies considering the *DNMT3B* enzyme. A study conducted with psychiatric patients with a history of suicide attempts showed significantly higher levels of global DNA methylation compared with controls, and this finding was associated with *DNMT3B* polymorphisms [29]. A post-mortem brain regions study revealed a marked reduction in DNA methylation in cortical neurons of AD subjects when compared to controls, and it was associated with increased *PSEN1* gene expression [32]. It is still not clear whether *DNMTs* polymorphisms imply hyper or hypo DNA methylation in Alzheimer's disease.

In addition, some genes that participate in amyloid-beta processing (*PSEN1, APOE*) and methylation homeostasis (*MTHFR, DNMT1*) show significant inter-individual epigenetic variability in AD brain samples, showing a notably age-specific epigenetic drift, which supports the potential role of epigenetic effects in developing the disease [35].

The complexity of AD degeneration, as well as the attractive hypothesis of epigenetic mechanisms contributing to AD pathogenesis and the influence of environmental factors on phenotypic constitution, justifies further studies on epigenetics. This study aims to evaluate the association of AD and five known *DNMT* gene polymorphisms (*DNMT1:* rs2162560, rs759920; *DNMT3B:* rs998382, rs2424932 and rs2424913).

2. Methods and materials

2.1. Study design

This is a case-control study comparing a group of Alzheimer's disease patients to healthy control subjects.

The study was approved by the bioethics committees of the participating institutions and was performed in compliance with the Declaration of Helsinki. All participants or their proxies in AD cases provided written informed consent.

2.2. Participants

All participants (AD patients and healthy controls) were Caucasian and were from a similar geographic region, matched for the same low-income economic status.

One hundred and two sporadic AD patients were recruited by convenience from two academic outpatient neuropsychiatric services located in a southern Brazilian city. All of them fulfilled probable NINCDS-ADRDA [25] and DSM-IV-TR [2] AD criteria. This diagnosis was ascertained by a psychiatrist or neurologist from the research team with expertise in the dementia field. Brain tomography or magnetic resonance imaging and complete medical and laboratory evaluations were performed to exclude other causes of dementia. Other exclusion criteria were history of cancer, family history of dementia and any other neurological or psychiatric disorders.

A control group of 108 age and sex-matched cognitively healthy and independent community-dwelling elderly individuals were recruited from the catchment areas of the same academic services. The inclusion criteria were age greater than 65 years, clinical dementia rating (CDR) of 0 [27], mini mental state examination (MMSE) score higher than 26 [12] and independence for activities of daily living (ADL) [17,20]. Controls were excluded if they presented chronic renal disease, history of significant head injury or stroke, history of cancer, family history of dementia, other psychiatric conditions such as major affective disorder or evidence of current depression, uncorrectable vision or hearing loss or other conditions such as substance abuse or use of medications that could impair cognitive function.

2.3. Genotyping

The DNA was extracted from 500 μL of EDTA-treated whole blood using the salting out method [19]. After extraction, the DNA was quantified on a UV visible spectrophotometer (Biospec® Nano). The final concentration of DNA used was from 10 ng/mL. The single nucleotide polymorphism (SNP) selection investigated in this study was performed using the HapMap (HapMap Genome Browser release #24) (Phases 1 and 2—full dataset) using the following settings for the tool "annotate TagSNP Picker": European population (CEU), minimum frequency of the rarer allele of 20% and a coefficient of determination (R2) of 80%. The five polymorphisms were genotyped with the use of TaqMan Genotyping Master Mix and TaqMan SNP Genotyping assays (Applied Biosystems®).

For each reaction plate, genomic control DNA samples and non-template controls (water) were included. A control on the TaqMan SNP genotyping assay was also performed (25% of randomly chosen samples from both groups) to check for genotyping accuracy, and identical genotypes were identified in all repeated samples. The researchers who performed the genotyping were blinded to the patients' diagnostic status.

2.4. Statistical analysis

The results were entered into a database, and statistical package SPSS® version 18.0 was used to perform the analyses.

A non-parametric Mann–Whitney test was used to calculate the differences in age and education between cases and controls. For sex comparisons, a chi-squared test of association was used. The Student *t* test was used to compare economic income between the AD group and the control group.

Frequencies were described as proportions for categorical variables and as mean plus standard deviations for quantitative variables. Allelic frequencies were obtained by direct counting throughout the genotype frequency.

Chi-square testing was carried out to verify whether the genotypic frequencies were in agreement with Hardy-Weinberger equilibrium. The linkage disequilibrium between the polymorphisms in each genomic region was estimated with MLocus 3.0 [22], and haplotypes were imputed with PHASE 2.1 [33,34]. Haplotypes with frequencies less than 3% were pooled.

Univariate analyses to verify the associations between the polymorphisms in the genes encoding the enzymes *DNMT1* and *DNMT3B* and Alzheimer's disease were carried out by chi-square association tests with a dominant model. The Bonferroni test was performed for multiple testing corrections.

Multivariate logistic regression analysis was performed for the outcome AD, with polymorphisms or haplotypes as independent variables. The confounders entered in the model were age and education, based on the literature review [3,7].

A two-tailed $P < 0.05$ was considered significant for all analyses.

3. Results

The sample is depicted in Table 1. The AD and control groups were comparable by age and sex. Education and MMSE scores were significantly lower in the AD group than in the control group. Family income (US$/mouth) was not significantly different between the AD group (M = 587.32; SD = 491.21) and healthy controls (M = 640.13; SD = 501.12) ($t = 0.96$, $P = 0.31$).

The genotypic frequencies of *DNMT1* and *DNMT3B* polymorphisms were consistent with Hardy-Weinberg equilibrium

Table 1
Sample description.

Variable	Total sample	Control group	AD group	P[a]
N	210	108	102	
Age (years)	75.83 (7.60)	74.91 (7.75)	76.80 (7.34)	0.072*
Sex (female)	67.6	72.2	62.7	0.184**
Education (years)	6.55 (3.97)	7.98 (4.18)	5.03 (3.09)	<0.001*
MMSE	20.36 (8.50)	27.55 (2.02)	12.74 (5.60)	<0.001*

Note: AD: Alzheimer's disease. MMSE: mini mental state examination score. Variables are described as % or mean (standard deviation).
[a] Comparison between the control group and AD Group.
* Mann–Whitney test.
** Chi-square test.

Table 3
Haplotype distribution.

Gene	Haplotype*	Frequency
DNMT3B	TGG	0.35
	CAA	0.31
	CAG	0.25
	TAG	0.05
	TAA	0.03
	Others	0.01

* *DNMT3B*: rs2424913/rs998382/rs2424932.

($P > 0.05$). For both genes, the polymorphisms were in strong linkage disequilibrium ($D' > 0.8$ and $P < 0.001$ in all comparisons).

The genotypic and allelic frequencies related to each gene polymorphism are described in Table 2 for both groups.

Univariate analyses showed that the G allele of *DNMT3B* polymorphism rs998382 and the T allele of *DNMT3B* polymorphism rs2424913 were associated with AD ($P = 0.005$ and $P = 0.046$, respectively). The frequency of *DNMT3B* haplotypes in the whole sample is shown in Table 3.

In order to verify whether the effect of the haplotype was independent of age and education, a multivariate logistic regression analysis was performed. The AD group was associated with the presence of the TGG haplotype (OR = 3.03, 95% CI 1.63 to 5.63, $P < 0.001$). These results are shown in Table 4.

4. Discussion

This study evaluated the association between Alzheimer's disease and polymorphisms in genes encoding the enzymes DNA methyltransferase *1* and *3B*. The TGG haplotype in the *DNMT3B* gene showed significant association with Alzheimer's disease. Individuals carrying the TGG haplotype have an increased risk of Alzheimer's disease (OR = 3.03, 95% CI 1.63 to 5.63, $P < 0.001$). The same was not observed in the SNPs investigated for gene *DNMT1*. To the best of our knowledge, this is the first study describing a significant association.

We have studied *DNMT3B* rs998382, rs2424932 and rs2424913, while a previous study conducted on an Italian sample focused on *DNMT3B* rs2424932 and rs1569686 [10]. In contrast to our results, no difference in allelic or genotypic frequencies was found for either polymorphism between AD subjects and the healthy control group in this previous investigation [10]. Despite these conflicting results, it should be noted that AD has a complex inheritance pattern, which means that the individual is the product of the interaction between genetic inheritances and the environment they live in, so the analyzed populations may differ in their genetic background and exposure to environmental factors. Accordingly, it should be noted that, for example, the onset of AD in identical twins can differ by more than 20 years [21], and it is also known that young pairs of identical twins are essentially indistinguishable in their epigenetic profiles, while twin pairs show substantial differences in their epigenetic marks with advancing age [24]. These variations can be precisely explained by epigenetic drift mediated by *DNMTs*, caused, for example, by environmental exposure, lifestyle, diet, drug use or simply stochastic fluctuations.

Moreover, according to the epigenetic perspective, some genes may not predispose to disease *per se*, but rather act through interaction with specific environmental triggers. This interaction between genes and environmental risk may explain why putative association studies of complex diseases sometimes cannot be replicated in different geographic areas [31].

Furthermore, it is known that *DNMT3B* functions as a *de novo* methylations, which occur during embryonic development [11]. However, another important role of *DNMT3B* is to maintain DNA methylation patterns, correcting errors left by *DNMT1* [16]. According to this theory, many studies have shown that epigenetic changes occur more frequently than gene mutations and could thus be particularly important in age-related phenotypes [5]. The high frequency of epimutations catalyzed by *DNMT3B* suggests that epigenetic alterations accumulate during aging. Small epimutations in essential genes could be tolerated to a certain extent and reflect only the range of inter-individual variation. However, once a critical threshold of epigenetic deregulation is reached, the

Table 2
Genotype and Allelic Frequencies of *DNMT3B* gene polymorphisms rs998382, rs2424913, rs2424932 and *DNMT1* rs2162560, rs759920 in AD and control groups: descriptive and univariate analyses.

		Genotype frequency			*P*	Allelic frequency (%)		*P*
		%	%	%		%	%	
DNMT3B	**rs2424913**	CC	CT	TT	0.036*	C	T	0.046*
	Control	38.9	48.1	13.0		62.95	37.05	
	Alzheimer	24.5	48.0	27.5		48.50	51.50	
	rs998382	AA	AG	GG	0.015*	A	G	0.005*
	Control	50.9	36.1	13.0		68.95	31.05	
	Alzheimer	25.5	47.0	27.5		49.0	51.0	
	rs2424932	AA	AG	GG	*NS*	A	G	*NS*
	Control	17.6	44.4	38.0		39.8	60.2	
	Alzheimer	15.7	37.2	47.1		34.25	65.75	
DNMT1	**rs2162560**	AA	AG	GG	*NS*	A	G	*NS*
	Control	17.6	46.3	36.1		40.75	59.25	
	Alzheimer	15.7	48.0	36.3		39.7	60.3	
	rs759920	AA	AG	GG	*NS*	A	G	*NS*
	Control	20.5	53.6	25.9		47.3	52.7	
	Alzheimer	22.5	53.9	23.6		49.45	50.55	

Note: Control: Control Group. Alzheimer: Alzheimer's disease Group.
* Bonferroni adjusted *P*-values. *NS:* not significant.

Table 4
Multiple logistic regression analysis for outcome AD.

Variables in the model	B	OR	95% CI	*P*
***DNMT3B* TGG haplotype**	1.11	3.03	1.63–5.63	<0.001
Education (years)	0.22	1.25	1.14–1.36	<0.001
Age (years)	−0.029	0.97	0.93–1.01	0.166

Note: *DNMT3B* TGG haplotype: rs2424913/rs998382/rs2424932; OR: odds ratio; B: estimated coefficient; 95% CI: confidence interval 95%.

cerebral apparatus goes into deregulation, justifying the relevance of this enzyme in neurodegenerative diseases [5]. In addition, it was found that, in aging cells, changes in the gene expression of *DNMTs* were observed, with the mRNA of *DNMT1* and *DNMTa* becoming reduced, while the production of *DNMT3B* increased progressively [6]. Other issue to be discussed is that *DNMT3B* SNPs (rs998382 and rs2424913) are located in noncoding regions. Although, they do not translate protein, these regions are receiving attention due their predictive role in transcription regulation, DNA replication, chromosome pairing, and chromosome condensation [23,26]. Also, polymorphisms in the 3′UTR region may have effects on gene expression regulation. For example, analyzing the prediction of its functionality through bioinformatics tools, the rs2424932 (*DNMT3B*) seems to create a binding site for transcription factors [29].

Our study didn't find an association between the AD and control groups for the rs759920 and rs2162560 gene polymorphisms in *DNMT1*. This enzyme is a key maintenance methyltransferase enzyme responsible for copying pre-existing methylation patterns onto newly replicated DNA strands during cell divisions [18]. Aberrant expression of the *DNMT1* gene has previously been associated with schizophrenia [37]. Moreover, polymorphisms in *DNMT1* have been investigated to assess their influence on conditions such as deafness, dementia and other neuropathies. Some studies have been conducted to analyze the polymorphisms described above, but so far there are no data that associate them with a particular condition [13,28].

Some limitations should be pointed out. (a) The difference in education between the control and AD groups was expected, taking into account the well-known role of cognitive reserve as a protective factor in the development of Alzheimer's disease—a concept that encompasses education, occupation and mental activities [7]. However, in the multiple logistic regression model adjusted for age and education, the risk variant TGG haplotype maintained its significance, suggesting that the mutation has an independent effect. (b) Considering the exploratory nature of this study, our results should be replicated in larger and separate samples in order to confirm our findings.

In conclusion, our findings highlight the hypotheses of epigenetic mechanisms related to AD, stressing the role of DNA methyltransferase SNPs as risk factors for this complex neurodegenerative disease. Further studies investigating the effects of these polymorphisms in the DNA methylation should the addressed.

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