DECODING THE NEUROGENETIC LANDSCAPE OF ONE-CARBON METABOLISM IN ALS RISK AND PROGRESSION

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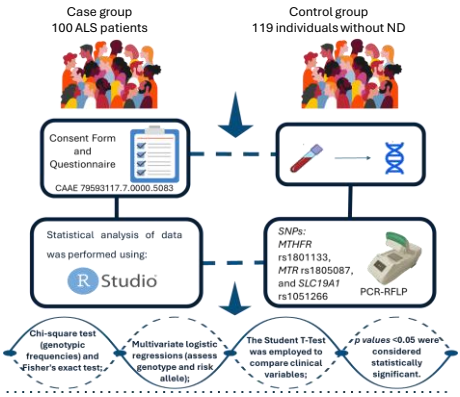
INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is an idiopathic neurodegenerative disease affecting both upper and lower motor neurons, leading to progressive muscle atrophy. Its pathogenesis involves complex interactions between environmental and genetic factors. Among the genes implicated are *MTHFR*, *MTR*, and *SLC19A1*, which participate in the folate cycle (one-carbon metabolism), a critical pathway for cellular metabolism. Reduced enzymatic activity in this pathway can disrupt intracellular concentrations and elevate homocysteine (Hcy) levels, a factor linked to neurotoxicity and ALS progression. This study aimed to evaluate the association of Single Nucleotide Polymorphisms (SNPs) *MTHFR* rs1801133, *MTR* rs1805087, and *SLC19A1* rs1051266 with susceptibility to ALS.

METHODOLOGY



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RESULTS

Table 1. Association between genotypes in *MTHFR* and ALS, using genetic inheritance models

Models	Genotype	Control, n (%)	Case, n (%)	Statistics OR (95% CI)	Statistics *p*
Codominant	C/C	76(51.701%)	41(40.594%)	Ref	Ref
	C/T	67(45.578%)	50(49.505%)	1.383(0.817-2.352)	0.228
	T/T	4(2.721%)	10(9.901%)	**4.634** (1.452-17.745)	**0.014**
Dominant	C/C	76(51.701%)	41(40.594%)	Ref	Ref
	C/T+T/T	71(48.299%)	60(59.406%)	1.566(0.941-2.625)	0.086
Recessive	C/C+C/T	143(97.279%)	91(90.099%)	Ref	Ref
	T/T	4(2.721%)	10(9.901%)	**3.929** (1.273-14.663)	**0.024**
Overdominant	C/C+T/T	80(54.422%)	51(50.495%)	Ref	Ref
	C/T	67(45.578%)	50(49.505%)	1.171(0.705-1.947)	0.543
Alleles	C	219	132	-	0.036
	T	75	70	-	-

n = absolute frequency; % = relative Frequency; C = cytosine; CI = confidence interval OR = Odds ratio; Ref = Reference; T = thymine

Table 2. Association between genotypes in *MTHFR* and ALS in women, using genetic inheritance models

Models	Genotype	Control, n (%)	Case, n (%)	Statistics OR (95% CI)	Statistics *p*
Codominant	C/C	54(56.25%)	19(42.222%)	Ref	Ref
	C/T	40(41.667%)	21(46.667%)	1.492(0.71-3.158)	0.291
	T/T	2(2.083%)	5(11.111%)	**7.105** (1.405-52.59)	**0.026**
Dominant	C/C	54(56.25%)	19(42.222%)	Ref	Ref
	C/T+T/T	42(43.75%)	26(57.778%)	1.759(0.864-3.636)	0.122
Recessive	C/C+C/T	94(97.917%)	40(88.889%)	Ref	Ref
	T/T	2(2.083%)	5(11.111%)	**5.875** (1.211-42.229)	**0.039**
Overdominant	C/C+T/T	56(58.333%)	24(53.333%)	Ref	Ref
	C/T	40(41.667%)	21(46.667%)	1.225(0.598-2.502)	0.577
Allele	C	148	59	-	0.058
	T	44	31	-	-

n = absolute frequency; % = relative Frequency; C = cytosine; CI = confidence interval OR = Odds ratio; Ref = Reference; T = thymine.

Table 3. Association between genotypes of the *MTHFR* rs1801133 variant and the sociodemographic and clinical profile of ALS patients

	MTHFR, n (%) Wild (C/C)	Heterozygous (C/T)	Mutant (T/T)	*p**
Gender				
Female	19 (46.3)	21 (42.0)	5 (50.0)	0.85
Male	22 (53.7)	29 (58.0)	5 (50.0)	
Ethnicity				
White	20 (48.8)	28 (56.0)	1 (10.0)†	**0.005**
Black	6 (14.6)	1 (2.0)	0 (0.0)	0.23
Brown	15 (36.6)	21 (42.0)	9 (90.0)†	**0.001**
Physical Activity				
No	23 (56.1)	24 (48.0)	0 (0.0)	**0.006**
Yes	18 (43.9)	26 (52.0)	10 (100.0)†	
Alcohol Intake				
No	27 (65.9)	23 (46.0)	5 (50.0)	0.16
Yes	14 (34.1)	27 (54.0)	5 (50.0)	
Smoking				
No	29 (70.7)	29 (58.0)	7 (70.0)	0.42
Yes	12 (29.3)	21 (42.0)	3 (30.0)	
Classification				
Sporadic	39 (95.1)	46 (92.0)	10 (100.0)	0.57
Familial	2 (4.9)	4 (8.0)	0 (0.0)	
Neurological disease in the Family				
No	24 (58.5)	30 (60.0)	6 (60.0)	0.99
Yes	17 (41.5)	20 (40.0)	4 (40.0)	
Previous pathologies				
No	23 (56.1)	26 (52.0)	5 (50.0)	0.90
Yes	18 (43.9)	24 (48.0)	5 (50.0)	

*Post hoc Chi-square; † p < 0,05; n = absolute frequency; % = relative frequency. C = cytosine; T = thymine.

Table 4. *MTHFR* gene, comparison of sociodemographic variables and lifestyle habits between the groups

Variables	Control, n (%)	Case, n (%)	Total	*p*
Age (Mean ± SD)	57.92 (9.99)	57.34 (12.89)	57.68 (11.24)	0.700*
Gender				
Female	96 (65.31%)	45 (44.55%)	141 (56.85%)	**0.001****
Male	51 (34.69%)	56 (55.45%)	107 (43.15%)	
Alcohol Intake				
No	104 (70.75%)	55 (54.46%)	159 (64.11%)	**0.012****
Yes	43 (29.25%)	46 (45.54%)	89 (35.89%0	
Smoking				
No	90 (61.22%)	65 (64.36%)	155 (62.50%)	0.713**
Yes	57 (38.78%)	36 (35.64%)	93 (37.50%)	

*Student t-test; **Pearson's Chi-square test. n = absolute frequency; % = relative frequency; SD = standard deviation.

Table 5. Analysis of association of alcohol intake between groups with and without ALS diagnosis, *MTR* and *SLC19A1* genes

	ALS					
Alcohol intake	Yes	No	OR (95% CI)	*p*[a]	AIC	BIC
No	54	83	1.00	**0.013**	301.33	308.12
Yes	47	36	**2.00** (1.15–3.51)			

Note: Bold values are statistically significant data among the results presented.
Abbreviations: AIC, akaike information criterion; ALS, amyotrophic lateral sclerosis; BIC, schwarz bayesian information criterion; CI, confidence interval; OR, odds ratio.
[a] Logistic regression.

DISCUSSION

These findings suggest that the *MTHFR* rs1801133 polymorphism may contribute to ALS susceptibility through mechanisms related to Hcy-induced neurotoxicity and its interaction with lifestyle and genetic factors, such as ethnicity. In contrast, rs1805087 and rs1051266 do not appear to have a direct role. Notably, *SLC19A1* encodes the primary reduced folate carrier, but other transporters can compensate if its function is impaired. Methionine synthase (MTR) relies on methionine synthase reductase (MTRR) for proper activity; disruptions here may also affect folate metabolism.

CONCLUSION

In conclusion, further research is warranted to explore the combined effects of these genes and clarify their impact on ALS pathogenesis and progression. This study represents the first combined analysis of these SNPs in the context of ALS, highlighting the importance of continued investigation into the molecular mechanisms involved. These insights may contribute to the development of precision medicine strategies aimed at improving diagnosis, prognosis, and personalized therapeutic approaches for individuals with ALS.

REFERENCES AND SUPPLEMENTARY FILES

TABLE SUPLEMENTARY

LATTES

REFERENCES

SUPPORT

CAPES