IS THE ANGIOTENSIN-CONVERTING ENZYME (*ACE*1) I/D POLYMORPHISM INVOLVED IN ALS RISK? A PRELIMINARY ANALYSIS

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease marked by the progressive loss of upper and lower motor neurons, leading to muscle weakness, atrophy, and paralysis. Its causes are not fully understood, but genetic factors may be associated. Angiotensin-Converting Enzyme (ACE), part of the Renin-Angiotensin-Aldosterone System (RAAS) is present in brain tissue. ACE produces Angiotensin II activates inflammatory pathways through the ATR1 receptor. A specific genetic variant in the *ACE* gene (insertion/deletion) influences genic expression, where the D allele is linked to higher enzyme levels and increased neuroinflammation, potentially contributing to ALS development. This case-control study aimed to evaluate the impact of the insertion/deletion (I/D) polymorphism in the *ACE* gene on the risk of developing ALS.

METHODOLOGY

1 Collection and pairing

CASE GROUP
115 individuals with ALS

CONTROL GROUP
123 healthy controls

Obtaining clinical data approved by the ethics committee.

2 DNA extraction

DNA was extracted from peripheral blood samples and subsequently quantified in the Nanodrop®.

3 Genotyping and statistical analysis

Genotyping was performed using **Real-Time PCR** (QuantStudio 6 Pro) by **SYBR Green®**.

Logistic regression analysis was used to **predict disease risk**, with a significance threshold of **p < 0.05**.

Application of dominant, recessive, codominant, and overdominant inheritance models.

SUPPORT

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RESULTS AND DISCUSSION

Table 1. Genotypic and allele frequencies of the investigated polymorphisms and the association between ALS and control group, using models of inheritance.

Model	Genotype	DR	DMT2	OR	95% CI	p
Codominant	II	56	34		Reference	
	ID	54	67	0.48	(0,280 to 0,854)	0.011*
	DD	5	22	0.13	(0,047 to 0,398)	0.0003*
	II	56	34		Reference	
Dominant	ID + DD	59	89	0.40	(0,234 to 0,068)	0.0009*
Recessive	II+ID	110	101		Reference	
	DD	5	22	0.20	(0,076 to 0,571)	0.002*
Overdominant	II+DD	61	56		Reference	
	ID	54	22	2.25	(1,211 to 4,164)	0.009*

Allelic Frequencies

Alleles	Case	Control	X^2	DF	p
I	0,73	0.54	0.0778	1	0. 78
D	0,27	0,46			

Analysis by multiple logistic regression to obtain adjustedoddsratio values (OR) and confidence intervals (95% CI). *Significant difference between groups (p,0.05).

Our findings support the possibility of a genetic influence of the *ACE* I/D polymorphism on ALS susceptibility, particularly under the overdominant model. Although the observed association did not reach conventional statistical significance, the 2.25-fold increased risk in heterozygous individuals may indicate a biological trend worth exploring. This aligns with the notion that intermediate expression levels of ACE, potentially found in heterozygotes, could exacerbate inflammatory pathways implicated in ALS pathogenesis. Due to the complexity of ALS, findings should be interpreted cautiously. The lack of strong genetic associations highlights the need for further research with larger samples and functional analyses to better understand ACE's potential role in the disease.

CONCLUSION

Although no significant associations were observed in the codominant, dominant, and recessive models, the overdominant model revealed a borderline association between the *ACE* I/D polymorphism and ALS risk. These preliminary findings suggest that heterozygous individuals may have increased susceptibility to ALS, supporting the need for further investigation. Functional studies are essential to clarify ACE's potential role in ALS pathogenesis and to explore its relevance as a biomarker or therapeutic target.

REFERENCES

References

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