EXPLORING THE IMPACT OF LXRA AND LXRB GENETIC VARIANTS ON AMYOTROPHIC LATERAL SCLEROSIS SUSCEPTIBILITY

Jacqueline Soares Barros Bittar[1]; Nayane Soares de Lima[1]; Caroline Christine Pincela da Costa[1]; Leandro do Prado Assunção[1]; Angela Adamski da Silva Reis[1,2]; Rodrigo da Silva Santos[1,2]

[1]Neurogenetics Research Center, Institute of Biological Sciences (ICB II), Federal University of Goiás (UFG), Goiânia, Goiás, Brazil.
[2]Department of Biochemistry and Molecular Biology, Institute of Biological Sciences (ICB II), Federal University of Goiás (UFG), Goiânia, Goiás, Brazil.

Correspondence: jacqueline_bittar@discente.ufg.br; rdssantos@ufg.br

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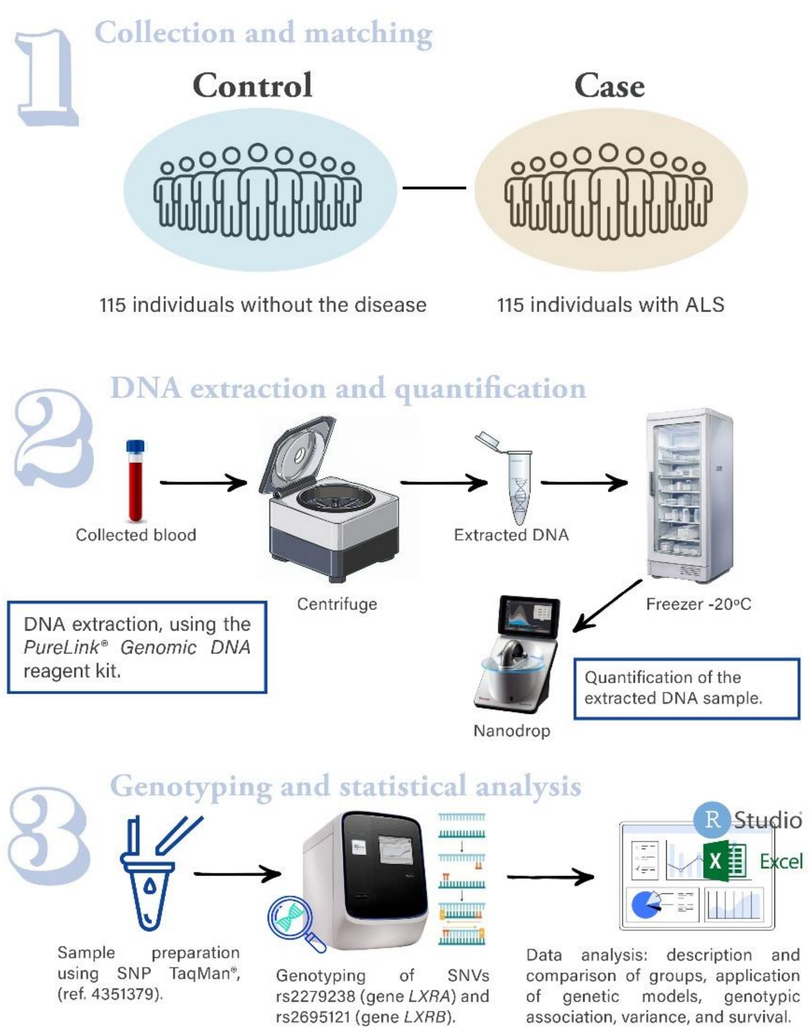
INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a chronic, fatal neurodegenerative disease that affects motor neurons. An important characteristic refers muscle weakness because to motor neurons death, in the brain, brainstem, and spinal cord[1,2]. Dysfunctions maybe occur in a combined form between upper and lower motor neurons, causing phenotypic heterogeneity[3], but two forms are most common: Classical ALS and Bulbar ALS[1,2,3]. Another classification considers its genetic architecture, which can be Familial or Sporadic ALS[4-6]. In most cases, its etiology remains unknown and has been described as a complex syndrome involving genetic predisposition, endogenous biological factors, and exogenous environmental influences[7-9]. The *LXRA* and *LXRB* genes encode the LXR-alpha and LXR-beta proteins, respectively[10]. These nuclear receptors function as key transcription factors involved in lipid metabolism and exert neuroprotective and anti-inflammatory effects in the central nervous system[11,12]. ALS phenotypes are variable and can be influenced by energy metabolism modulators, affecting the cholesterol regulation at he muscle level[10].

OBJECTIVE

Investigate a possible association between rs2279238 (*LXRA*) and rs2695121 (*LXRB*) genetic variants and ALS phenotypes.

METHODOLOGY



A case-control study was carried out in the ALS population of the Brazilian Midwest, between 2017 and 2024.

SUPPORT

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RESULTS AND DISCUSSION

Table 1. Genetic models of ALS, for the variants rs2279238 *LXRA*, rs2695121*LXRB* and the interaction between the two variants of the *LXRA/LXRB* genes.

SNV	Model	Genotype	ALS Control	ALS Case	Odds (CI 95%)	p-value	AIC	BIC
LXRA rs2279238	Codominant	Wild	26(22.6%)	20(17.4%)	Ref	Ref		
	Codominant	Heterozigous	61(53.0%)	64(55.6%)	1.364(0.693-2.716)	0.371	323.838	334.152
	Codominant	Mutant	28(24.3%)	31(26.9%)	1.439(0.665-3.149)	0.357		
	Dominant	Wild	26(22.6%)	20(17.4%)	Ref	Ref	321.867	328.743
	Dominant	Heterozigous + Mutant	89(77.3%)	95(82.6%)	1.388(0.726-2.685)	0.324		
	Recessive	Wild + Heterozigous	87(75.6%)	84(73.0%)	Ref	Ref	322.642	329.519
	Recessive	Mutant	28(24.3%)	31(26.9%)	1.147(0.634-2.081)	0.651		
	Overdominant	Wild + Mutant	54(46.9%)	51(44.3%)	Ref	Ref	322.69	329.566
	Overdominant	Heterozigous	61(53.0%)	64(55.6%)	1.111(0.661-1.869)	0.691		
	Allele	C	113	104	-	0.455	-	-
	Allele	T	117	126	-	-	-	-
LXRB rs2695121	Codominant	Wild	56(48.7%)	30(26.09%)	Ref	Ref		
	Codominant	Heterozigous	50(43.5%)	67(58.3%)	2.501(1.416-4.484)	0.002	311.326	321.64
	Codominant	Mutant	9(7.8%)	18(15.7%)	3.733(1.529-9.682)	0.005		
	Dominant	Wild	56(48.7%)	30(26.1%)	Ref	Ref	310.143	317.019
	Dominant	Heterozigous + Mutant	59(51.3%)	85(73.9%)	2.689(1.555-4.721)	0.000		
	Recessive	Wild + Heterozigous	106(92.2%)	97(84.3%)	Ref	Ref	319.39	326.267
	Recessive	Mutant	9(7.8%)	18(15.6%)	2.186(0.959-5.314)	0.07		
	Overdominant	Wild + Mutant	65(56.5%)	48(41.7%)	Ref	Ref	317.802	324.678
	Overdominant	Heterozigous	50(43.5%)	67(58.3%)	1.815(1.079-3.073)	0.025		
	Allele	C	162	127	-	0.001	-	-
	Allele	T	68	103	-	-	-	-
LXRA/LXRB		Wild/Wild	7	9	Ref	Ref	309.619	340.561
		Wild/Heterozigous	16	10	0.486 (0.133-1.706)	0.264		
		Wild/Mutant	3	1	0.259 (0.011-2.539)	0.284		
		Heterozigous/Wild	33	13	0.306 (0.091-0.985)	0.049		
		Heterozigous/Heterozigous	23	41	1.386 (0.443-4.218)	0.565		
		Heterozigous/Mutant	5	10	1.556 (0.364-7.005)	0.553		
		Mutant/Wild	16	8	0.389 (0.101-1.407)	0.155		
		Mutant/Heterozigous	11	16	1.131 (0.318-3.978)	0.847		
		Mutant/Mutant	1	7	5.444 (0.716-114.515)	0.152		

Legend: Binomial Logistic Regression. AIC: Akaike Information Criterion. BIC: Bayesian Information Criterion; OR: Odds Ratio. Reference (Ref.). Wild type (C/C); Mutant (T/T); Heterozygous (C/T). Source: Own authorship.

The *LXRA* variant rs2279238 showed similar genotypic frequencies in both the case and control groups, indicating no significant association with ALS risk. However, the *LXRB* variant rs2695121 showed a strong association with ALS phenotypes. In the codominant inheritance model, individuals with the C/T genotype had a 2.5-fold increased risk (p = 0.002), and those with the T/T genotype had a 3.7-fold increased risk (p = 0.005), compared to the C/C wild type. The dominant model (C/T + T/T vs. C/C) indicated a 2.7-fold higher risk (p < 0.001). In the overdominant model (C/T vs. C/C + T/T), heterozygotes had an odds ratio of 1.81 (p = 0.025), suggesting an independent association with disease risk. When analyzing gene-gene interactions, individuals with the heterozygous rs2279238 (*LXRA*) variant combined with the wild-type rs2695121 (*LXRB*) genotype exhibited a reduced risk of ALS, with a statistically significant association (OR = 0.31; p = 0.049). These findings suggest an association between the *LXRB* gene and ALS susceptibility and highlight the potential modulatory role of *LXRA* in reducing in the heterozygote genotype.

CONCLUSION

The rs2695121 variant in the *LXRB* gene is associated with ALS phenotypes. While the rs2279238 variant in *LXRA* was not directly associated with the disease, its presence in heterozygous form may confer a protective effect when combined with the wild-type *LXRB* genotype. Therefore, exploring potential gene-environment interactions and the functional impact of these genetic variants will be critical for understanding their relevance as biomarkers. This work is the first study involving LXRs gene and ALS in Brazil.

REFERENCES

References