A genetic association study of two genes linked to neurodegeneration in a Sardinian multiple sclerosis population: the *TARDBP* Ala382Thr mutation and *C9orf72* expansion

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Background. Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by inflammation and accompanied and followed by neurodegeneration.[1] Missense mutations of the TAR DNA Binding Protein gene (TARDBP) located in the chromosome 1p36.22 region, and the hexanucleotide repeat expansions in chromosome 9 open reading frame 72 (C9orf72) are pathogenic in other neurodegenerative diseases such as amyotrophic lateral sclerosis and frontotemporal lobar degeneration. [2,3]

Aim. Assuming that TARDBP Ala382Thr mutation and C9orf72 expansion may underlie MS, we evaluated their frequency in a large cohort of MS patients and controls from Sardinia, an island characterized by a very high frequency of MS and an unusual genetic background.

Methods. Genomic DNA was extracted from peripheral blood and analyzed for the presence of a TARDBP Ala382Thr mutation and C9orf72 expansion. Difference in the frequency of these mutations between MS patients and controls was calculated using the χ^2 test with a standard 2×2 table.

Table 1 Demographic feature of the overall subjects TDP-43 mutation analyzed in this study

TDP-43 sample	HCs	MS
3308	1475	1833
MEAN AGE, YEARS	54,1±15,2	41,1±11,8
TARDBPAla382Thr mutation	20 (1,3%)	27 (1,4%)

The *TARDBP* p.Ala382Thr mutation in the heterozygous state was detected in 27 of 1833 (1.4%) MS patients and 20 of 1475 (1.3%) HCs. No difference in its frequency between MS patients and HCs was observed (p=0.8)

Table 2. Demographic features of the overall subjects C9ORF72 expansion analyzed in this study.

TOTAL SAMPLE ANCHOR PCR	MS ALL	HC ALL
1347	1014	333
MEAN AGE, YEARS	49,7±32,0	63,1±36,5
SEX, FEMALE	67,30%	53,40%

MS SPORADIC 655

MS FAMILIAL 359
MS Parents 45
MS Offspring 312
MS sisters 2

Table 3. C9ORF72 expansion analysis: ANCHOR PCR size classification in MS groups and HCs

	ANCHOR PCR SIZE			
	≤ 20	21-25	26-30	> 30
MS SPORADIC (655)	651	0	2	2
MS FAMILIAL (359)				
Parents (49)	46	1	0	2
Offspring (310)	305	1	2	2
HEALTY (333)	327	1	3	2

Pathogenic repeat expansion (>30 repeats) was found in two sporadic MS patients, four familial MS patients, and two HCs (total MS patients vs HCs P=0.9; sporadic vs familial MS; P=0.1)

Individuals carrying the mutations did not present with other neurodegenerative conditions and any differences were reported between groups.

Conclusions. *TARDBP* Ala382Thr variant and *C9orf72* expansion do not play a major role in MS pathogenesis in the Sardinian population. Further analyses are needed to better define the possible role of these genetic variants in neurodegenerative process in MS.

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