Multiple Sclerosis and HLA genotypes: a possible influence on brain atrophy

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Background. Notoriously, the strongest Multiple Sclerosis (MS) genetic determinant is located at the human leukocyte antigen (HLA) class II DRB1 and DQB1 loci (Hauser SL, 2006). Previously, our group stated a rank of genotypes conferring a variable degree of risk to the disease in Sardinian population (Cocco et al. 2013). The present study was aimed to explore the possible role of predisposing/protective HLA genotypes in determining the brain atrophy in MS patients.

Methods. DRB1-DQB1 HLA genotyping was performed for enrolled MS patients, classifying haplotypes as predisposing or protective, according to our previous study (Cocco et al.2013). HLA genotypes were categorized as high risk (presence of two predisposing haplotype) or medium/low risk (presence of one or none of predisposing haplotype). Patients underwent a brain MRI study and volumes of white matter (WM), grey matter (GM), and whole brain (WB) were estimated with SIENAX (Smith et al., 2002). In addition, longitudinal atrophy was assessed with SIENA (Smith et al., 2002).

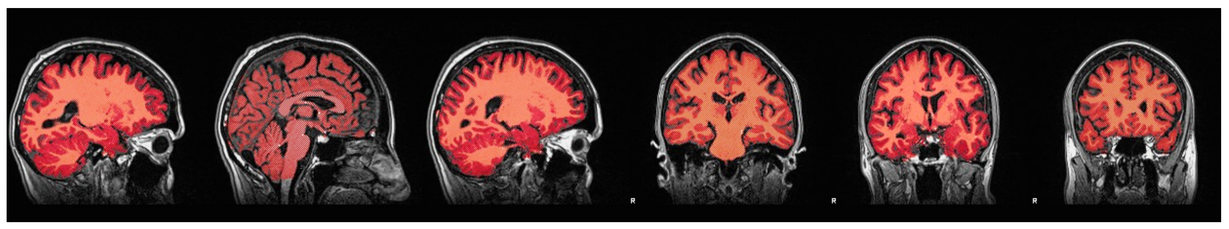
Results. The study included 240 MS patients (67/240, 28% male; 22/240 (9%) progressive) with mean age 43.1 (SD ±10.7) years, disease duration 14,1 (SD ±4,2) years and mean EDSS 4.2 (SD ±3.1).

In 51/240 (21%) subjects was observed the high-risk HLA genotype, while in 109/240 (45%) and 80/240 (34%) the medium and low risk HLA genotype, respectively.

Multiple regression analysis indicated that the high-risk HLA genotype is associated to significant diminishing in WB (p 0.02) and GM (p 0.03) volumes compared to the medium/low risk HLA genotype, resulting in an average decrease of 31 ml and 21 ml, respectively, independently from MS clinical features.

The longitudinal study included 60 patients and showed a brain volume loss of - 0.79 % in high-risk HLA genotype group vs. – 0,56% in low-risk HLA genotype.

Table 1. Demographic and clinical features of MS patients included in the study



	Total sample (240 patients)	High Risk HLA (51; 21%)	Medium Risk HLA (109;45%)	LowRisk HLA (80;34%)	p value
Male Gender	67 (28%)	20 (39.2%)	24 (22%)	23 (28.7%)	ns*
Age (years) at examination	43.1±10.7	43.2±8.8	43±11.2	41.9±11	ns§
Progressive course	22 (9%)	4 (7.8%)	9 (8.2%)	9 (11.2%)	ns*
EDSS score	4.2±3.1	3±2.2	2.8±2	2.7±2	ns§
Disease Duration (years)	14,1±4.2	14.5±3.5	14.3±8.1	13.1±7	ns§

HLA haplotype groups were classified as high-risk (presence of two predisposing haplotypes), medium-risk (presence of one predisposing haplotype) and low-risk (none predisposing haplotypes)
Demographic and clinical variables were compared among the 3 HLA genotype risk-groups by using Chi squared test* and ANOVA test§

Table 2. Mean values of WB, WM and GM with cortical GM in the high-risk, medium and low-risk HLA genotype groups and association with the risk-class.

	HLA genotype Risk	Mean Value (ml)	Lower limit of CI % 95	Upper limit of CI % 95	SD
WB	Low	1459.98*	1442.0	1478.0	80.9
	Medium	1448.07	1432.8	1463.4	80.6
	High	1426.59*	1401.6	1451.6	89.0
WM	Low	685.84	677.0	694.7	40.0
	Medium	683.11	676.5	689.7	35.0
	High	676.25	664.7	687.8	41.1
GM	Low	774.02*	759.8	788.2	63.7
	Medium	764.97	752.7	777.2	64.6
	High	750.35*	734.2	766.5	57.4
Cortical GM	Low	603.7*	593.3	611.3	47.5
	Medium	587.72	578.7	598.2	45.4
	High	580.20*	568.2	592.5	46.0

*P value < 0.05

T-test was used to compare brain volumes between groups with different genetic risk (high risk group vs low risk, high risk group vs medium risk, medium risk group vs low risk).

Table 3. Multiple regression analyses. Relationship of brain volumes (WB, WM, GM and cortical GM) with demographic, MS clinical features, DMDs (use of second-line therapy) and high risk HLA genotype.

		WB				WM				GM				cortical GM			
			95% C.I. for EXP (B)				95% C.I. for EXP (B)				95% C.I. for EXP (B)				95% C.I. for EXP (B)		
		B	Lower	Upper	p	B	Lower	Upper	p	B	Lower	Upper	p	B	Lower	Upper	p
Variables	Female	-38.5	-59.9	-17.1	**0,001**	-17.0	-27.8	-6.1	**0,002**	-21.6	-36.9	-6.3	**0.006**	-14,6	-27,1	-2,2	**0,022**
	Age	-1.2	-2.3	-0.2	**0,013**	-0.5	-0.1	1.0	**0,052**	-1.8	-2.5	-1.0	**0.001**	-1,4	-2,0	-0,7	**0,001**
	Progressive Course	27.9	-14.9	70.7	0,222	12.3	18.3	42.9	0,431	12.3	18.3	42.9	0.433	8,6	-16,9	34,1	0,511
	Disease Duration	-1.8	-3.3	-0.3	**0,012**	-0.5	-1.2	0.3	0,233	-1.4	-2.4	-0.3	**0.007**	-0,8	-1,7	0,0	**0,054**
	EDSS score	-12.9	-18.9	-6.9	**0,001**	-3.9	-7.0	-0.8	**0,015**	-9.0	-13.3	-4.7	**0.001**	-6,6	-10,4	-2,9	**0,001**
	2th line Theraphy	1	-9.7	11.9	0.844	-10.4	-31	10.9	0.334	-11.4	-26.6	3.7	0.140	-5,1	-17,5	7,3	0,421
	High risk HLA	-30.9	-56.9	-4.9	**0,022**	-9.5	22.8	3.7	0,164	-21.2	-39.8	-2.6	**0.030**	-16,2	-29,7	-2,7	**0,020**

Abbreviation: WB: whole brain; WM: white matter; GM: grey matter.
CI: confidence interval; SD: standard deviation.
*P value < 0.05

Multiple linear regression analysis was used to examine the relationship between brain volumes (whole brain (WB), white matter (WM), grey matter (GM) and cortical GM), which were included in the model as dependent variables, and the high-risk HLA genotype (presence of two predisposing haplotypes), while controlling for demographic (sex, age) and clinical variables (disease course, disease duration, EDSS score and concomitant use of second line therapies).

Conclusions. Our results suggested an influence of HLA genotypes on B and GM atrophy. Further investigations in larger cohorts are necessary to confirm these data and to understand the underlying disease mechanisms.

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