A Genome-Wide Association Study highlights a possible involvement of mast cells and neutrophils in disease activity in multiple sclerosis

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1. Background

Recently, important data coming from genetic studies showed new biological pathways involved in the susceptibility to multiple sclerosis (MS) [International Multiple Sclerosis Genetics Consortium, Science 2019]. However, to date, no Genome-Wide Association Study (GWAS) has been published targeting disease activity (DA) in MS and the basis of the broad heterogeneity in the clinical spectrum of MS is still largely unknown.

2. Aim

To perform a GWAS in order to unravel possible genetic variants associated with DA in relapsing-remitting (RR) MS patients.

3. Methods

We studied a cohort of 790 patients with diagnosis of RR-MS at the beginning of a first-line disease-modifying treatment with available whole-genome genetic data [Table 1]. For each patient, we assessed DA during a 2-year follow-up according to the Non-Evidence/Evidence of Disease Activity-3 (NEDA/EDA) status. After per-marker and per-individual quality controls and principal component analysis, 778 patients and 607.864 Single-Nucleotide Polymorphisms (SNPs) underwent the GWAS.

Total no. of pts.	790
Gender	M: 240; F: 550. F/M ratio: 2.29
Age at onset	28.6±9.11 years
Disease duration	5.04±5.63 years
Previous treatments	No: 755 patients; Yes: 35 patients. IFN: 13; DMF: 1; AZA: 7; Clinical trials: 14
Median EDSS at baseline	1.5 (IQR: 1.0-2.0)
NEDA status at 2 years	NEDA: 157 (19.9%) EDA: 633 (80.1%)
Mean Time-To-First-Relapse	10.3±6.92 months

Table 1. Clinical features of the study cohort.

4. Results

We identified two SNPs in chromosome 14 (rs1956932 and rs17104242) which passed the threshold for genome-wide significance and exert a protective role toward EDA status at 2-years (rs1956932: OR=0.35 [95% CI: 0.24-0.50] and p=8.45E-09; rs17104242: OR=0.36 [95% CI: 0.25-0.52] and p=2.26E-08) [Figure 1 & Table 2]. For other SNPs in the same region of chromosome 14, we found a suggestive association for a protective effect toward DA. Functional annotation pointed out a possible involvement of the pathways of chymase-1 and cathepsin-G, which are known to modulate the activity and the degranulation of mast cells and neutrophils. Such cells are involved in mechanisms like the regulation of the permeability of the blood-brain barrier and the triggering of an immune reaction towards the central nervous systems at peripheral sites.

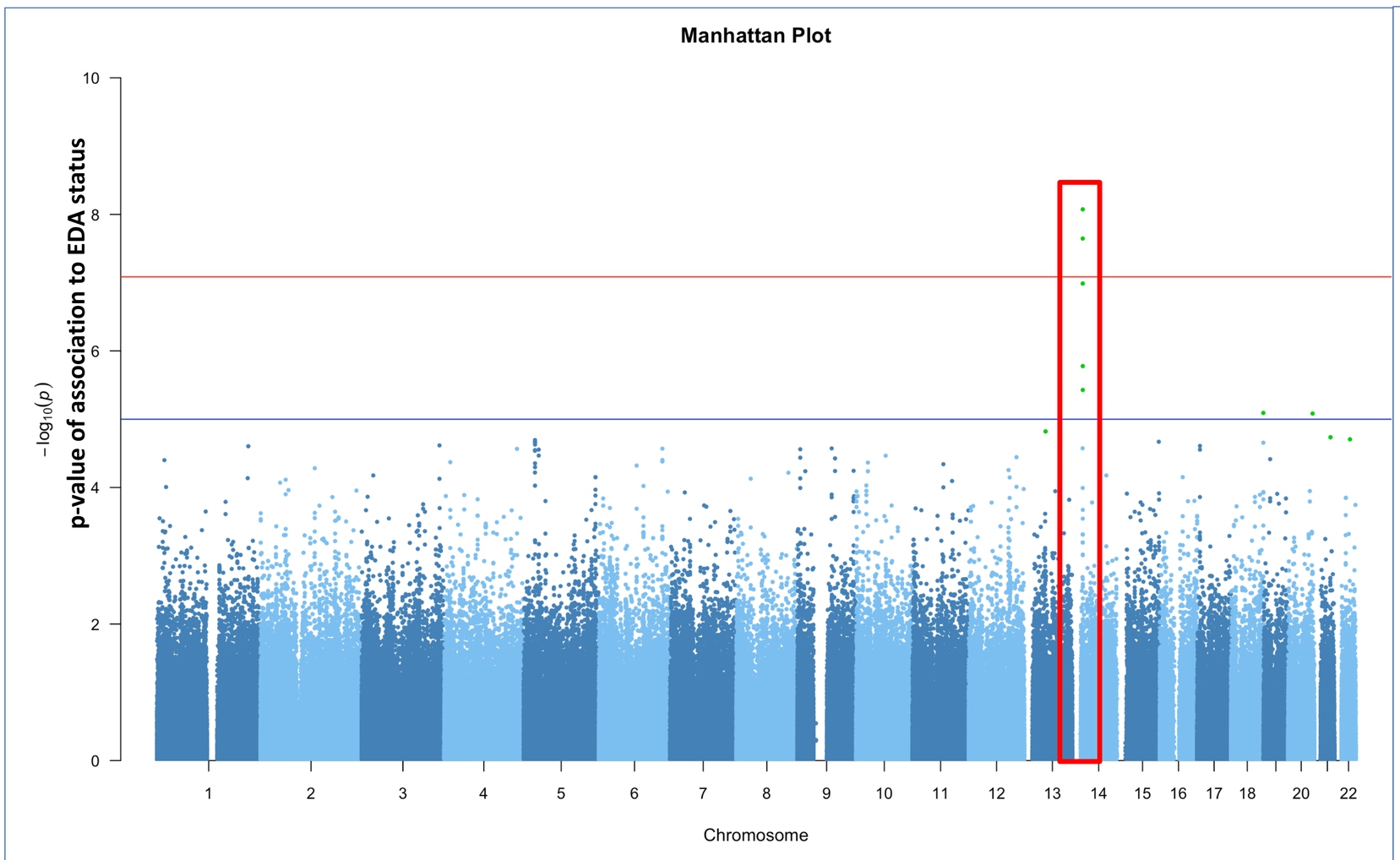

Figure 1. Manhattan plot showing the results of the GWAS. Blue line: threshold for suggestive association; red line: threshold for genome-wide significant association.

	CHR	SNP	A1	AF (%)	OR	L95	U95	p-value	Nearest gene(s)
1	**14**	**rs1956932**	**G**	**11.7**	**0.35**	**0.24**	**0.50**	**8.45E-09**	**LOC101927045, CMA1**
2	**14**	**rs17104242**	**A**	**11.8**	**0.36**	**0.25**	**0.52**	**2.26E-08**	**LOC101927045, CMA1**
3	14	rs5250	A	11.9	0.38	0.27	0.55	1.03E-07	CMA1
4	14	rs11623400	A	29.9	0.52	0.38	0.67	1.67E-06	CTSG
5	14	rs3759639	T	9.4	0.42	0.29	0.61	3.73E-06	CTSG
6	18	rs11665111	T	40.1	0.56	0.43	0.72	8.09E-06	KCNG2
7	20	rs17791789	A	7.8	0.41	0.28	0.61	8.26E-06	MIR646HG
8	13	rs806301	T	9.9	0.36	0.23	0.57	1.51E-05	DLEU1
9	21	rs2298330	A	11.8	0.45	0.31	0.64	1.84E-05	DYRK1A
10	22	rs229526	C	22.1	0.56	0.43	0.73	1.97E-05	C1QTNF6

Table 2. List of top 10 SNPs from the GWAS and nearest genes.

5. Discussion

In this preliminary GWAS, interesting signals have emerged regarding the function of mast cells and neutrophils which, if confirmed in further studies, may provide important knowledge on mechanisms underlying DA in RR-MS patients.