A GENOME WIDE APPROACH TO EXPLORE ETIOLOGY OF CLINICAL FEATURES IN PATIENTS WITH MULTIPLE SCLEROSIS

Alessandro Pizzino[1], Muralidharan Thavamani [1], Valentina Ciampana[1], Martina Tosi[1], PROGEMUS[2], Domizia Vecchio[3], Eleonora Virgilio[3], Roberto Cantello[3], Maurizio Leone[2], Nadia Barizzone[1], Sandra D'Alfonso[1]

1 Department of Health Sciences, University of Eastern Piedmont, Novara, and CAAD (Research Center of Autoimmune and Allergic Diseases).

2 SC Neurologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo.

3 MS Centre, SCDU Neurology, AOU Maggiore della Carità, Novara, Italy.

email: **alessandro.pizzino@uniupo.it**

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BACKGROUND

Multiple Sclerosis (MS) is a complex autoimmune disease of the central nervous system caused by an interaction of multiple genetic and environmental factors[(1)]. Recently, international efforts (IMSGC 2011, 2013, 2019)[(2,3,4)] conducted through genome wide association studies (GWAS) have identified 30 HLA markers independent from the HLA-DRB1*15:01 and 201 non-HLA MS risk loci, one of these located on the X-chromosome[(4)]. Conversely, these studies have poorly contributed to understand how genetics may influence the disease phenotype.

AIM OF THE STUDY

General AIM: Evaluate the possible association of genetic factors with clinical features of MS and their predictive role on disease course

Specific AIMS:

1. To determine whether genetic variants are associated with a worsening in terms of the number of relapses
2. To determine whether genetic variants are associated with risk of developing sequelae

MATERIALS AND METHODS AIM-1

For the first purpose, we replicated a recent study (Fig. 1) (Vandebergh 2021)[(5)] with our own case series with information regarding the relapse rate in the first two years of the disease. To study the relapse rate, we examined 10 SNPs recently reported as significantly associated with a shorter time to relapse.

RESULTS AIM-1

To replicate the associations reported by Vandeberg et al., in our Italian cohort, we analysed two MS cohorts of 220 and 578 samples MS patients, respectively comparing the patients who had 0-1 relapses vs those that had 2 or more relapses, respectively. For each SNP were compared patients homozygous or heterozygous for A1 (minor allele) and patients homozygous for A2 (major allele). No genotype showed a statistically significant association with relapse rate (Tab. 1). However, the hazard ratio (HR) conferred by 2 variants showed the same effect direction as reported by Vandebergh, et al., in both our cohorts.

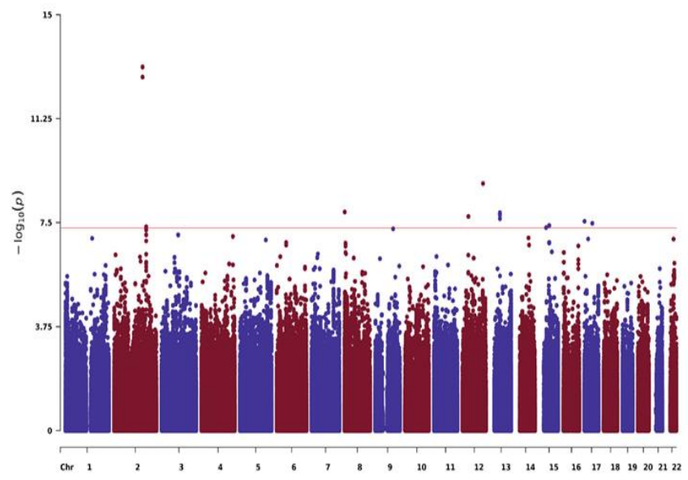

Fig.1: Manhattan plot showing genomewide association results of the survival analysis for time to relapse in the discovery phase (Vandebergh 2021)[(5)]

LITERATURE COHORT							REPLICATION COHORT				
506 SAMPLES							220 SAMPLES			578 SAMPLES	
SNP	CHR	A1	A2	HR	P-value	MAF	HR	95 % CI	P-value	HR	P-value
rs139075191	2	G	A	1.85	4.44 × 10−8	0.03	0,63	0.16 - 2.41	0,5007	0.8135	0.6914
rs36084110	2	T	C	2.58	7.72 × 10−14	0.02	1,21	0.19 - 7.38	0,8363	0.9271	0.8962
rs79434188	12	A	T	**0.49**	1.90 × 10−8	0.03	**0,88**	0.34 - 2.26	0,7957	**0.8286**	**0.5688**
rs77836326	13	G	A	0.52	1.42 × 10−8	0.03	1,21	0.19 - 7.38	0,8363	0.4966	0.1309
rs17817182	15	C	A	2.00	4.85 × 10−8	0.03	0,8	0.11 - 5.78	0,825	0.5962	0.182
rs79719335	15	A	G	**2.13**	4.04 × 10−8	0.02	**2,05**	0.34 - 2,26	0,3968	**1.184**	**0.6499**
rs76915261	17	T	C	2.00	2.85 × 10−8	0.03	0,26	0.026 - 2.55	0,249	1.9	0.114
rs11871306	17	C	T	2.08	3.37 × 10−8	0.02	0,79	0.24 - 2.54	0,6964	0.9347	0.8933

Tab.1: Association of genetic variants with relapse hazard

We also investigated the association of the time to second relapse with the same 10 SNPs. We found that one variant (**rs79719335**) shows a significant association (Fig. 2) mapping in the intron of DMXL2 gene, encoding a protein involved in the regulation of NOTCH signaling pathway. Indeed the survival analysis showed that 80% of carriers of the rare allele show a shorter time to second relapse compared to those who are non carriers (p=0.003 log rank test).

MATERIALS AND METHODS AIM-2

For the second aim, no literature data are reported regarding the association of genetic variants with the presence of sequelae, therefore we performed the first GWAS (Fig. 3) (215 patients).

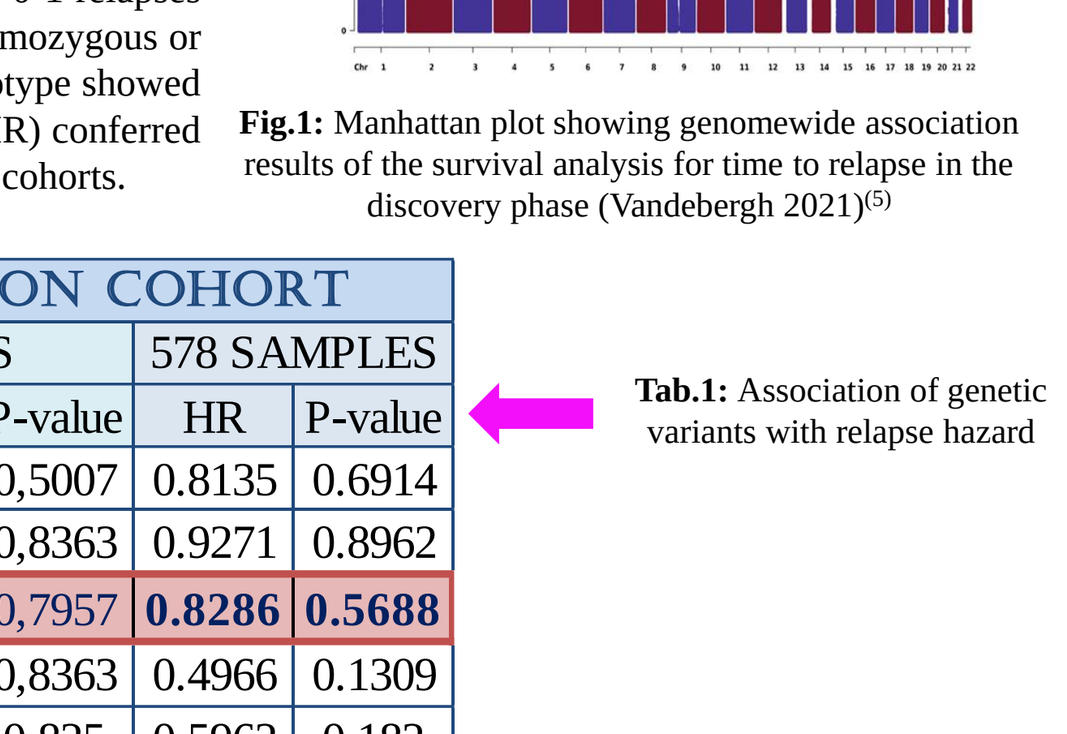

Fig.2: Time to second relapse by genotype

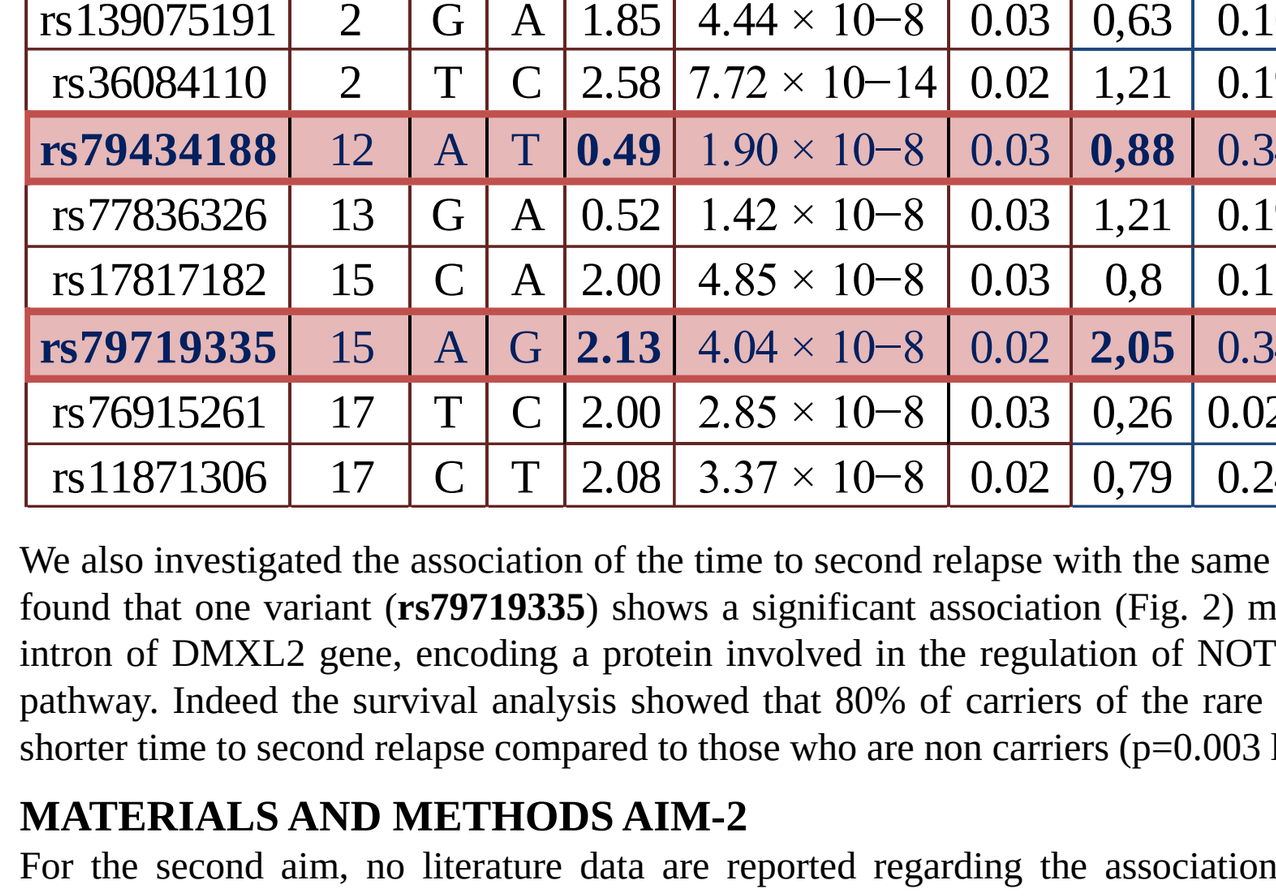

Fig. 3: Manhattan plot showing the association of genetic variants with the presence of sequelae

RESULTS AIM-2

Four SNPs presented suggestive association ($p<1*10^{-5}$) with the sequela event (Tab. 2). Interestingly, two of these SNPs (**rs4689846** and **rs12507674**, in high linkage disequilibrium, r2>0.92) map in the intron of SORCS2 gene, encoding a receptor for the precursor forms of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Considering that the sequelae can be the consequence of an impaired regenerative process of myelin damaging during the relapse, our variant seems to fall into an interesting biological path for sequelae events.

Tab. 2: SNPs that present suggestive association (10-6) results with the sequela event.

SNP	Position (hg18)	CHR	Gene	HR	CI 95%	P
rs4689846	**7788241**	**4**	**SORCS2**	**2.781**	**1.817 - 4.257**	**2,49 e-06**
rs12507674	**7788447**	**4**	**SORCS2**	**2.827**	**1.849 - 4.323**	**1,62 e-06**
rs7658972	114577981	4	LOC105377374	2.904	1.825 - 4.62	6,77 e-06
rs4841108	9082416	8	LOC101929198	2.418	1.688 - 3.462	1,43 e-06

CONCLUSIONS AND FUTURE PROSPECTIVES

In conclusion the results of this study, if replicated in a larger cohort, could have an important translational consequence toward a precision medicine approach: indeed, clinicians could tailor a specific and more efficient pharmacological therapy taking into account also genetic markers.

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