# GENE-ENVIRONMENT INTERACTION STUDY IN MULTIPLE SCLEROSIS

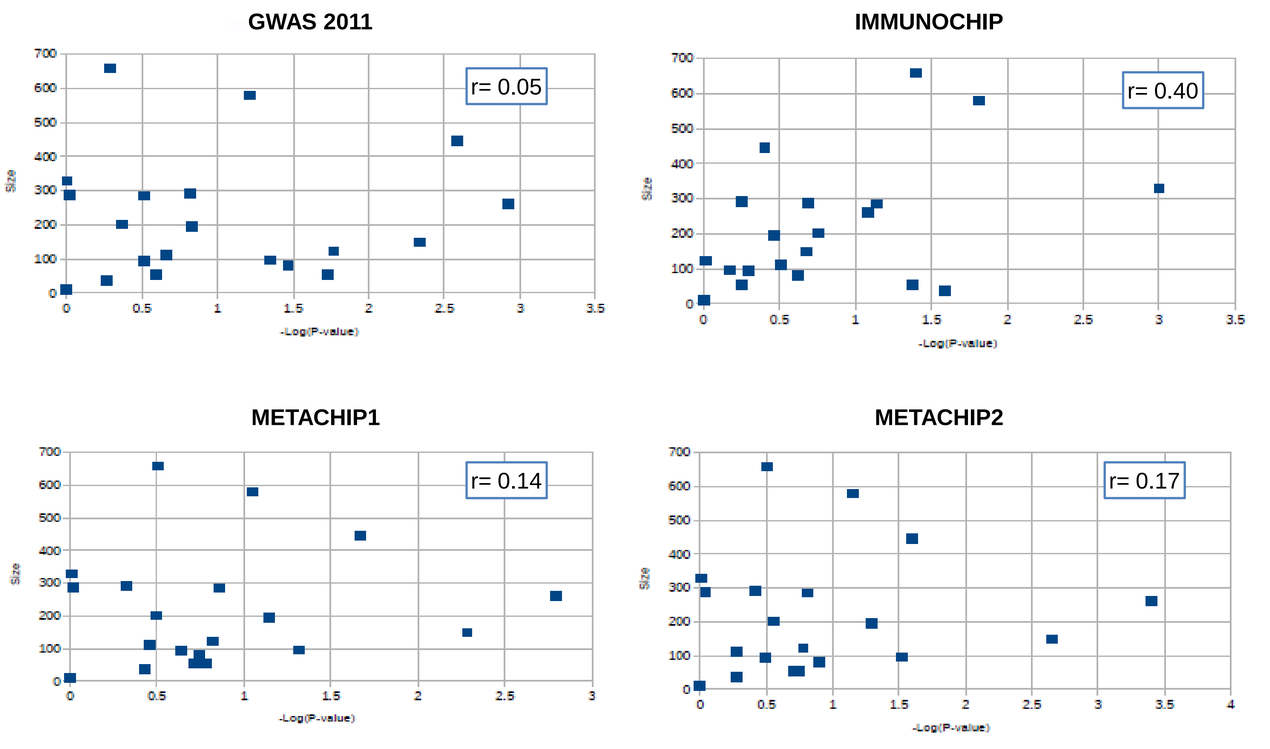
**R. Mechelli[1], R. Umeton[1], IMSGC WTCCC2[2], G. Ristori[1], M. Salvetti[1]**

**[1]Centre for Experimental Neurological Therapies (CENTERS), Department of Neurosciences, Mental Health and Sensory Organs, Sapienza University, Rome [2]The International Multiple Sclerosis Consortium & the Wellcome Trust Case Control Consortium 2, Oxford, United Kingdom**

XLVII CONGRESSO NAZIONALE
22-25 OTTOBRE 2016 – VENEZIA

We proposed a "candidate interactome" (i.e. a group of genes whose products are known to physically interact with environmental factors that may be relevant for disease pathogenesis) analysis of genome-wide association data in multiple sclerosis (MS) to highlight possible factors that may participate to disease etiology interacting with predisposing genetic variants. The choice of interactomes is based on biological plausibility and physical interactions experimentally verified between proteins and/or nucleic acids. We obtained 20 candidate interactomes from the literature: 9 viruses, 1 bacterium, 10 cellular factors (9 proteins and 1 noncoding RNAs target repository) (Table).

**Figure: Spearman Correlation coefficients**




The results did not show correlation between size and statistical relevance of interactomes when GWAS 2011 and METACHIP1-2 were used. A moderate correlation was observed in IMMUNOCHIP analysis, suggesting that some effect-size artifacts are possible (Figure). Despite this observation we found that some factors (VIRORF, Polyomavirus, AHR, SIRT7, Chlamydia) may be associated with MS through their genetic autoimmune component (IMMUNOCHIP), especially AHR and Polyomavirus, that show high statistical significance respect to MS in spite of the small size of the interactomes (Table). Overall the viruses are the interactomes more associated with MS (Table), specifically herpes viruses showed statistical significance in all the analysis except for IMMUNOCHIP and among others Epstein-Barr virus is confirmed as the most associated virus to MS.

**References**

[1] International Multiple Sclerosis Genetics Consortium (IMSGC), Nature, 2011;476(7359):214-9
[2]International Multiple Sclerosis Genetics Consortium (IMSGC), Nat. Genet. 2013;45(11):1353-60
[3] Stark C. et al. Nucleic Acids Res. 2011;39:D698-704
[4] Mirrashidi KM. et al. Cell Host Microbe. 2015;18(1):109-21
[5] Mechelli R. et al. PLoS One. 2013;8(5):e63300
[6] Joshi P. et al. Mol Syst Biol. 2013;9:672
[7] Xiao F. et al. Nucleic Acids Res. 2009 37(Database issue):D105-10
[8] Calderone A. et al. Nucleic Acids Res.2015;43(Database issue):D588-92

***Acknoledgment:*** This study is supported by Fondazione Italiana Sclerosi Multipla (2014/R/12)

The genome wide association data were obtained from the latest published GWAS in MS: a) the first data set published in 2011 [1]; b) Immunochip data, published in 2013 [2], in which were studied SNPs selected from autoimmune associated loci. To evaluate globally the contribution of all the SNPs analysed in both the datasets, we constructed METACHIP1: a combination of the former two where GWAS 2011 data was given preference in case of overlap (eg, if both chips had a SNP in the same position, the GWAS-2011 p-value was preferred) and METACHIP2 where Immunochip data was given preference.

We used ALIGATOR (Association LIst Go AnnoTatOR) program to search for statistical enrichment of associations between interactomes genes and genome-wide association data (considering SNPs with a p-value<0.05 of association with MS). A Spearman's correlation coefficient (r) was calculated to evaluate a possible dependence between the size of interactomes and their cumulative p-value of association with the disease (Figure).

**Table: List of interactomes and related P-values of association with MS**

| INTERACTOME | SIZE | SOURCE | P-VALUE GWAS 2011 | P-VALUE IMMUNOCHIP | P-VALUE METACHIP1 | P-VALUE METACHIP2 |
|---|---|---|---|---|---|---|
| AHR | 38 | BioGRID [3] | 0.5428 | 0.0260 | 0.3744 | 0.5332 |
| AIRE | 80 | BIOGRID [3] | 0.0342 | 0.2412 | 0.181 | 0.1276 |
| Chlamydia | 329 | Experimental data [4] | 0.9910 | 0.0010 | 0.9864 | 0.982 |
| CMV | 96 | manually curated | 0.0444 | 0.6720 | 0.0482 | 0.0298 |
| EBV | 261 | manually curated | 0.0012 | 0.0828 | 0.0016 | 0.0004 |
| H1N1 | 87 | Experimental data [5] | 0.9572 | 0.4228 | 0.9738 | 0.9516 |
| HBV | 123 | manually curated | 0.0170 | 0.9636 | 0.1504 | 0.1668 |
| HCV | 202 | Experimental data [5] | 0.4244 | 0.1758 | 0.3216 | 0.2818 |
| HDACs | 287 | Experimental data [6] | 0.9610 | 0.2060 | 0.9562 | 0.9126 |
| HHV8 | 149 | manually curated | 0.0046 | 0.2094 | 0.0052 | 0.0022 |
| HIV | 446 | Experimental data [5] | 0.0026 | 0.3970 | 0.0216 | 0.0256 |
| hu-IFN | 113 | Experimental data [5] | 0.2176 | 0.3104 | 0.3452 | 0.5364 |
| Human-miRNA targets | 294 | miRecord [7] | 0.1514 | 0.5590 | 0.4754 | 0.3818 |
| Inflammasome | 194 | manually curated | 0.1470 | 0.3410 | 0.0722 | 0.051 |
| JCV | 10 | manually curated | 1.0000 | 1.0000 | 1.0000 | 1.0000 |
| Polyomavirus | 56 | VirusMentha [8] | 0.2536 | 0.0418 | 0.1912 | 0.1996 |
| SIRT1 | 285 | BioGRID [3] | 0.3032 | 0.0724 | 0.1374 | 0.1542 |
| SIRT7 | 658 | BioGRID [3] | 0.5146 | 0.0400 | 0.3138 | 0.3144 |
| VDR | 92 | BioGRID [3] | 0.3020 | 0.5102 | 0.2302 | 0.3212 |
| VIRORF | 579 | Experimental data [5] | 0.0610 | 0.0152 | 0.089 | 0.0704 |

Abbreviations: AHR= Aryl hydrocarbon receptor; AIRE= autoimmune regulator; BioGRID= Biological General Repository for Interaction Datasets; CMV= Cytomegalovirus; EBV= Epstein-Barr virus; HBV= Hepatitis B virus; HCV= Hepatitis C virus; HDACs=Histone deacetylases; HHV8= Human Herpesvirus 8; HIV= Human Immunodeficiency virus; H1N1= Influenza A virus; hu-IFN= human innate immunity interactome for type I interferon; Human-miRNA targets= gene targets for human miRNA; Inflammasome= multiprotien complex responsible for activation of inflammatory processes and pyroptosis; JCV= JC virus; SIRT1= Sirtuin 1; SIRT7= Sirtuin 7; VIRORF= Virus Open Reading Frame; VDR= vitamin D receptor;