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# A "Candidate-Interactome" Aggregate Analysis of Genome-Wide Association Data in Multiple Sclerosis

**Rosella Mechelli[9], Renato Umeton[9], Claudia Policano, Viviana Annibali, Giulia Coarelli, Vito A. G. Ricigliano, Danila Vittori, Arianna Fornasiero, Maria Chiara Buscarinu, International Multiple Sclerosis Genetics Consortium[¶], Wellcome Trust Case Control Consortium,2[¶], Silvia Romano, Marco Salvetti*, Giovanni Ristori**

Centre for Experimental Neurological Therapies, S. Andrea Hospital-site, Department of Neuroscience, Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University, Rome, Italy

## Abstract

Though difficult, the study of gene-environment interactions in multifactorial diseases is crucial for interpreting the relevance of non-heritable factors and prevents from overlooking genetic associations with small but measurable effects. We propose 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. We looked for statistical enrichment of associations among interactomes that, at the current state of knowledge, may be representative of gene-environment interactions of potential, uncertain or unlikely relevance for multiple sclerosis pathogenesis: Epstein-Barr virus, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, HHV8-Kaposi sarcoma, H1N1-influenza, JC virus, human innate immunity interactome for type I interferon, autoimmune regulator, vitamin D receptor, aryl hydrocarbon receptor and a panel of proteins targeted by 70 innate immune-modulating viral open reading frames from 30 viral species. Interactomes were either obtained from the literature or were manually curated. The P values of all single nucleotide polymorphism mapping to a given interactome were obtained from the last genome-wide association study of the International Multiple Sclerosis Genetics Consortium & the Wellcome Trust Case Control Consortium, 2. The interaction between genotype and Epstein Barr virus emerges as relevant for multiple sclerosis etiology. However, in line with recent data on the coexistence of common and unique strategies used by viruses to perturb the human molecular system, also other viruses have a similar potential, though probably less relevant in epidemiological terms.

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* E-mail: marco.salvetti@uniroma1.it

[9] These authors contributed equally to this work.

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## Introduction

As in other multifactorial diseases, genome-wide association studies (GWAS) are providing important data about disease-associated loci in multiple sclerosis (MS) [1]. In parallel, sero-epidemiological studies are reinforcing the evidence that nonheritable factors such as Epstein-Barr virus (EBV) and vitamin D are associated with disease pathogenesis [2].

However, the effect size of the gene variants identified so far in MS appears small. It is therefore important (but difficult: Sawcer and Wason, 2012) [3] to establish if and in which cases (including those gene variants with small but measurable effect size that do not reach the significance threshold of GWAS) the interaction with nonheritable factors may help understand their true impact on disease pathogenesis [4]. Furthermore, as far as the sero-epidemiological associations are concerned, their causal relevance and underlying pathogenetic mechanisms become clearer if interpreted in the light of genetic data.

As an attempt to consider, beyond the statistical paradigms of GWAS analysis, which gene-environment interactions may associate with the development of MS, we performed an interrogation of GWAS data [1] through a "candidate interactome" approach, investigating statistical enrichment of associations in genes whose products "interact" with putative environmental risk factors in MS.

We elected to center the analysis on viral interactomes, based on the classical hypothesis of a viral etiology of MS. Importantly, we examined only direct interactions between viral and human proteins as it has recently been shown that these are the interactions that are more likely to be of primary importance for the phenotypic impact of a virus in "virally implicated diseases" [5]. The chosen interactomes reflect the compromise between

informative size and potential relevance for MS. In detail, EBV was chosen as main association to be verified against phylogenetically related or unrelated viruses. Given the profound influence of EBV on the immune response, and the preponderance of (auto)immune-mediated mechanisms in the pathogenesis of the disease, we added two interactomes of immunological relevance, human innate immunity interactome for type I interferon (hu-IFN) and autoimmune regulator (AIRE). Finally, we included the vitamin D receptor (VDR) and the aryl hydrocarbon receptor (AHR) interactomes to evaluate, on the same grounds, also part of the molecular interactions that compose other established or emerging "environmental" associations.

## Methods

Seven interactomes were obtained from the literature: EBV [6], Human Immunodeficiency virus (HIV) [7], Hepatitis C virus (HCV) [8], AIRE [9], hu-IFN [10], Influenza A virus (H1N1) [11], Virus Open Reading Frame (VIRORF) [12]. Four interactomes were manually curated: Human Herpesvirus 8 (HHV8), Cytomegalovirus (CMV), JC virus (JCV), Hepatitis B virus (HBV). VDR and AHR interactomes were extracted from BIOGRID (http: //thebiogrid.org) [13].

As reference to gather gene and single nucleotide polymorphism (SNP) details from their HUGO Gene Nomenclature Committee (HGNC) Ids and rsids, we employed a local copy of the Ensembl Human databases (version 66, databases *core* and *variation*, including SNPs coming from the 1000 Genome project); the annotation adopted for the whole analysis was GRCh37-p6, that includes the release 6 patches (Genome Reference Consortium: human assembly data - GRCh37.p6 - Genome Assembly. http: // www.ncbi.nlm.nih.gov/genome/assembly/304538/).

The genotypic p-values of association for each tested SNP were obtained from the International Multiple Sclerosis Genetics Consortium & Wellcome Trust Case Control Consortium,2 study. All SNPs which did not pass quality checks in the International Multiple Sclerosis Genetics Consortium & the Wellcome Trust Case Control Consortium,2 study were filtered out from the original data. We used ALIGATOR [14,15] to evaluate how single genes get summed to provide total contribution of candidate interactomes (Table S1). The idea behind ALIGATOR's strategy is to evaluate gene category significance by means of an empirical approach, comparing each interactome with the null hypothesis, built using random permutations of the data. Such method begins its analyses by evaluating the Gene Ontology (GO) category association in each interactome provided: (i) each SNP with a p-value stronger than the P-CUT parameter is associated to the gene within 20 kb; then the most representative SNP for each gene is selected; (ii) LD filter of SNPs that have an $r2 \leq 0.2$ and those that are farther than 1000 kb; (iii) count the number of genes significant in each GO category. This is the real observed data.

A non parametric bootstrap approach was used to generate a null hypothesis as follows: (i) build 5000 random interactomes (of the same size of the one under analysis, this procedure is repeated for each interactome); (ii) obtain category-specific p-values by comparing each random interactome with the remaining 4999 built; (iii) elect one of the interactomes in (i) as simulated observed data; (iv) randomly sample interactomes in (i) to generate category-specific p-values; (v) repeat (iv) to simulate 1000 simulated studies. The GO category association distribution in the real observed data is then compared with the null hypothesis: (i) generate an expected number of significant genes in each category, using the simulated studies; (ii) compare the number of significant categories in the real observed data with (i). ALIGATOR parameters that we used are those of its reference paper [14]. p-value cut-off was taken at 0.05, only the SNPs with marginal p-value less than this cut-off were employed (p-value cut-offs were also taken at 0.005 and 0.03 for the re-analysis of interactomes that resulted associated at 0.05, see results). Furthermore, to limit the uncertainties introduced by combined SNP effects in the MHC extended region (that is the haplotype set with the strongest signal in our analysis), we computed two different statistical evaluations for each interactome, one including and the other one excluding SNPs coming from such region (we considered as belonging to the extended MHC region all those SNPs that participate in at least one of the following haplotypes: HSCHR6_MHC_APD, HSCHR6_MHC_COX, HSCHR6_MHC_DBB, HSCHR6_MHC_MANN, HSCHR6_MHC_MCF, HSCHR6_MHC_QBL, HSCHR6_MHC_SSTO according to GRC data). In both cases we used Ensembl API [16] and BioPerl [17] (version 1.2.3) to gather all SNP information, haplotype participation, genes position and size [18]; such annotated information was then fed into ALIGATOR together with the interactomes.

Ingenuity Pathway Analysis (IPA) was employed twice: (i) before the ALIGATOR statistics, to characterize the composition of our interactomes (Table S2), and (ii) on the genes with nominally significant evidence of association [1] that ALIGATOR took as representative of each interactome-SNP relation (Table S3). In both cases we performed the IPA-"core analysis", and we restricted the settings to show only molecular and functional associations. Afterwards, we used IPA-"comparative analysis" to produce the p-value of association between each functional class and all our interactomes. IPA knowledge base (ie, the input data used by IPA) was set to the following criteria in every analyses: consider only molecules and/or relationships where the species in object was human (or it was a chemical), and the datum was experimentally observed. Since IPA-"comparative analysis" provides p-value ranges associated to functional classes, we took as reference the value used by IPA to fill its reports, namely the best p-value for that class.

## Results

We performed 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.

We obtained 13 interactomes, 7 from the literature (as such) and 6 by manually selecting those interactions that were reported by two independent sources or were confirmed by the same source with distinct experimental approaches. In all cases we considered only physical-direct interactions (Table S2,Table 1).

Preliminarily to the enrichment of association analysis, we used IPA to obtain a sense of the cellular signaling pathways that are targeted by each interactome. A classification for molecular and cellular functions showed a comparable distribution of components in most interactomes except for VDR, HBV, VIRORF and hu-IFN where a relative enrichment of some functional pathways (cell signaling, cellular growth and proliferation, cellular development, cell cycle, cell death and survival, protein synthesis, RNA post-transcriptional modification, gene expression) was present (Figure 1).

We investigated statistical enrichment of associations within each one of the above interactomes (Table 1). The analyses were performed with and without considering SNPs falling in the MHC extended region. In both cases the interactomes of EBV, HIV and HBV reached significance. To verify the sensitivity of our results

**Table 1.** Statistical enrichment of MS-associated genes within each interactome.

| Interactome | Size | Source | p-value with MHC | p-value without MHC |
|---|---|---|---|---|
| VIRORF | 579 | Experimental data [12] | 0.0610 | 0.0632 |
| HIV | 446 | Experimental data [7] | 0.0026 | 0.0034 |
| HCV | 202 | Experimental data [8] | 0.4244 | 0.4424 |
| hu-IFN | 113 | Experimental data [10] | 0.2176 | 0.1838 |
| EBV | 110 | Experimental data [6] | 0.0140 | 0.0446 |
| H1N1 | 87 | Experimental data [11] | 0.9572 | 0.9648 |
| AIRE | 45 | Experimental data [9] | 0.4322 | 0.4012 |
| HBV | 85 | manually curated | 0.0124 | 0.0236 |
| CMV | 41 | manually curated | 0.1156 | 0.3322 |
| HHV8 | 40 | manually curated | 0.1132 | 0.0920 |
| JCV | 10 | manually curated | 1.0000 | 1.0000 |
| VDR | 78 | BioGRID | 0.1848 | 0.1802 |
| AHR | 30 | BioGRID | 0.8752 | 0.8522 |

ALIGATOR-obtained interactome p-values (overall contribution given by SNP p-values to each interactome, with and without SNPs falling in the MHC region). The SNPs with marginal p-value less than 0.05 were employed.
MS = multiple sclerosis; ALIGATOR = Association LIst Go AnnoTatOR; SNP = single nucleotide polymorphism; MHC = Major histocompatibility complex;
BioGRID = Biological General Repository for Interaction Datasets; VIRORF = Virus Open Reading Frame; HIV = Human Immunodeficiency virus; HCV = Hepatitis C virus; hu-IFN = human innate immunity interactome for type I interferon; EBV = Epstein Barr virus; H1N1 = Influenza A virus; HBV = Hepatitis B virus; VDR = vitamin D receptor; AIRE = autoimmune regulator; CMV = Cytomegalovirus; HHV8 = Human Herpesvirus 8; JCV = JC virus; AHR = Aryl hydrocarbon receptor.
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with respect to a choice (SNPs p-value cut-off at 0.05) that is not obvious based on the literature published so far, we evaluated different cut-offs ($p<0.005$ and $p<0.03$) on the three interactomes that were MS-associated at $p<0.05$. These analyses supported the consistency of the results (Table S4).

We then performed the same IPA classification as in Figure 1 (Figure 2) on the MS-associated genes within the EBV, HIV and HBV interactomes (Table S3). The aim was to verify whether the associations emerging from the three interactomes implied new and MS-specific perturbations and whether these perturbations are virus-specific or shared by the three pathogens. The comparison between pre- and post-match distribution of the functional classes (Figure 3) showed that the MS-associated interactomes did not reflect a clear cut involvement of specific pathways though, in the case of EBV, an enrichment of some biological functions (cellular function and maintenance, cell morphology, cellular assembly and organization, energy production) was present. On the other hand the most frequent changes for HBV and HIV could be in accord with the post-match reduction of the interactome sizes.

## Discussion

Of the 13 interactomes, 3 show a statistical enrichment of associations. In line with the epidemiological and immunological literature, the EBV interactome is among these. The lack of significant associations with the hu-IFN and AIRE interactomes suggests, though does not exclude, that the result is not an effect of the immunological connotation of the EBV interactome. The absence of associations with the interactomes of phylogenetically related viruses (CMV and HHV8, both herpesviruses with the latter that shares the same site of latency as EBV and belongs to the same subfamily of gamma-herpesviridae) reinforces the specificity of the EBV result. The fact that a portion of the genetic predisposition to MS may be attributable to variants in genes that interact with EBV may be complementary to another our finding showing that EBV genomic variants significantly associate with MS (unpublished data): the two results suggest a model of genetic jigsaw puzzle, whereby both host and virus polymorphisms affect MS susceptibility and, through complex epistatic interactions, eventually lead to disease development.

The associations with the HBV and HIV interactomes were unexpected. Overall, epidemiological data do not support a role of these viruses in the pathogenesis of MS though some controversy still holds concerning the safety of HBV vaccination [19–23]. Interestingly, Gregory et al. (2012) [24] demonstrated that in the TNFRSF1A gene, which is part of the HBV interactome, the MS-associated variant directs increased expression of a soluble tumor necrosis factor receptor 1.

Concerning HIV, the lack of epidemiological association seems more established. However, demyelination is a feature of HIV encephalomyelopathy [25] and cases of difficult differential diagnoses or association between the two conditions are described in the literature [26,27]. All this considered, it might not be surprising that some molecular interactions that take place between HIV and host may predispose to demyelination. Other viruses, sharing homology with HIV may possess better paraphernalia and be more prone to cause MS. The HERV-W family has long been associated with MS [28] and HERV-W/Env, whose expression is associated with MS [29], is able to complement an env-defective HIV strain [30] suggesting a certain degree of functional kinship.

Apart from any conjectures about the data on HBV and HIV interactomes, it remains true, as recently demonstrated by Pichlmair and colleagues (2012) [12], that viruses use unique but also common strategies to perturb the human molecular network. Our pathway analyses do not suggest, in fact, any specific cellular signaling target for the three viruses in MS, perhaps with some exceptions as far as the EBV interactome is concerned. Though preliminary, this acquisition may be in accord with the largely accepted view that, alongside the risk associated with EBV infection, there can be a more general risk of developing MS linked to a variety of other infections [31,32].

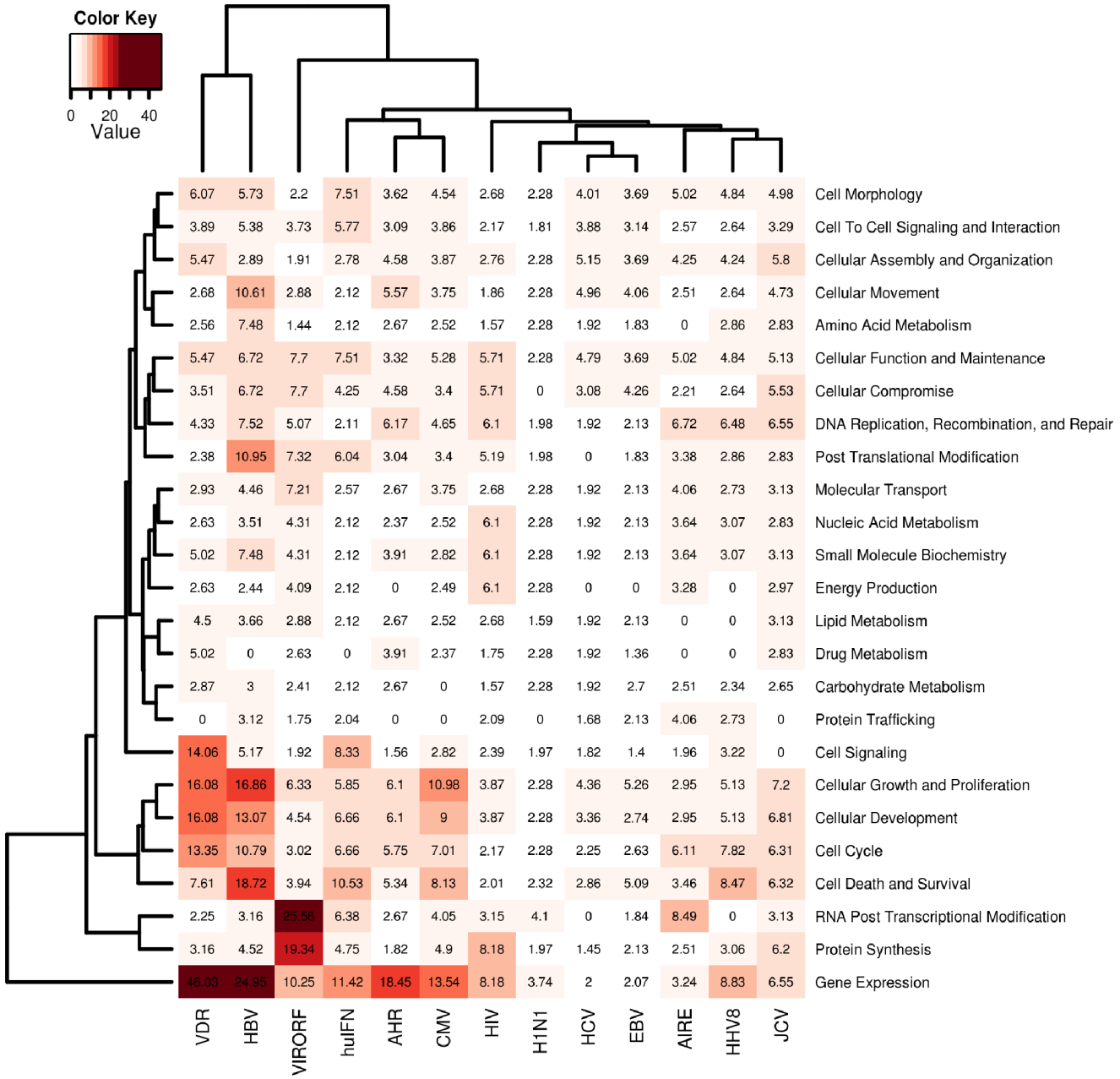


**Figure 1. Heatmap from Ingenuity Pathway Analysis of each interactome.** Statistical significance (in –log[p-value] notation, where $p<0.05$ corresponds to a –log[p]>1.3) of the functional components in each interactome, as obtained through a Comparative Core-Analysis in IPA (Ingenuity Pathway Analysis). The functional components identified at the molecular and cellular level are presented row-wise (right); the interactomes are presented column-wise (bottom). Each cell in position (*i,j*) contains a number that represents in $-\log$ notation the strength of the association between the functional class *i* and the interactome *j*; this information is also color-matched with a color gradient that moves from white ($-\log[p]=0.0$, $p=1$) to crimson ($-\log[p]=50$, $p<10^{-50}$). Two hierarchical cluster analyses were employed to group functional classes that share similar patterns of associations across all interactomes (left-side clustering), and to group interactomes that share similar functional compositions (top-chart clustering).
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The VDR interactome does not show significant enrichment of associations. The result does by no means diminishes the importance of the epidemiological association between vitamin D and MS: its causal relevance is already supported by data that are starting to explain the molecular basis of this association, upstream [33–35,1] and downstream the interactions between the VDR and its protein cofactors [36,37].

Current approaches for gene set analysis are in their early stage of development and there are still potential sources of bias or discrepancy among different methods, including those used in our study. As the reproducibility of the techniques increases, and new facilities [38] and methods become available to identify interactions that still escape detection, new lists will become available for matching with GWAS data. In parallel, also the assessment of human genetic variation will become more comprehensive [39].

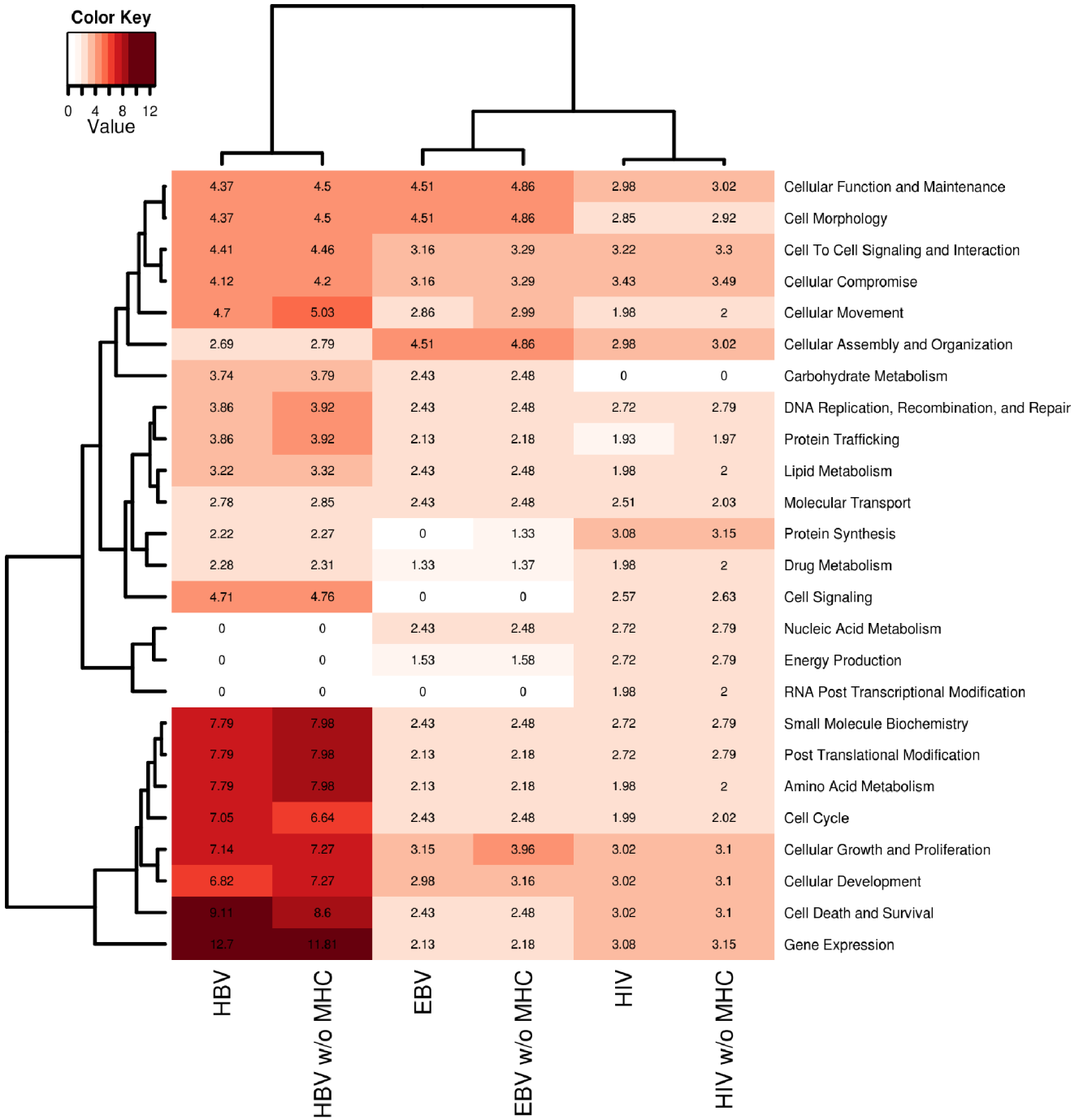


**Figure 2. Heatmap from Ingenuity Pathway Analysis of MS-associated interactomes.** Statistical significance (in –log[p-value] notation, where $p<0.05$ corresponds to a –log[p]>1.3) of the functional components in each one of the three MS-associated interactomes (Table S3) computed by ALIGATOR (Association LIst Go AnnoTatOR) first flow process. These p-values were obtained through a Comparative Core-Analysis in IPA (Ingenuity Pathway Analysis). The functional components identified at the molecular and cellular level are presented row-wise; the interactome sub-sets are presented column-wise. Each cell in position (*i,j*) contains a number that represents in $-\log$ notation the strength of the association between the functional class *i* and the interactome; this information is also color-matched with a color gradient that moves from white ($-\log[p]=0.0$, $p=1$) to crimson ($-\log[p]=14$, $p<10^{-14}$). Two hierarchical cluster analyses were employed to group functional classes that share similar patterns of associations across all interactome sub-sets (left-side clustering), and to group interactome sub-sets that share similar functional compositions (top-chart clustering).
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Hence, the "candidate interactome" approach may become an increasingly meaningful strategy to interpret genetic data in the light of acquisitions from epidemiology and pathophysiology. Notably, this approach appears to be complementary to other studies, which look for statistical enrichment of associations in an unbiased way, and may disclose unexpected pathways in MS susceptibility [40].

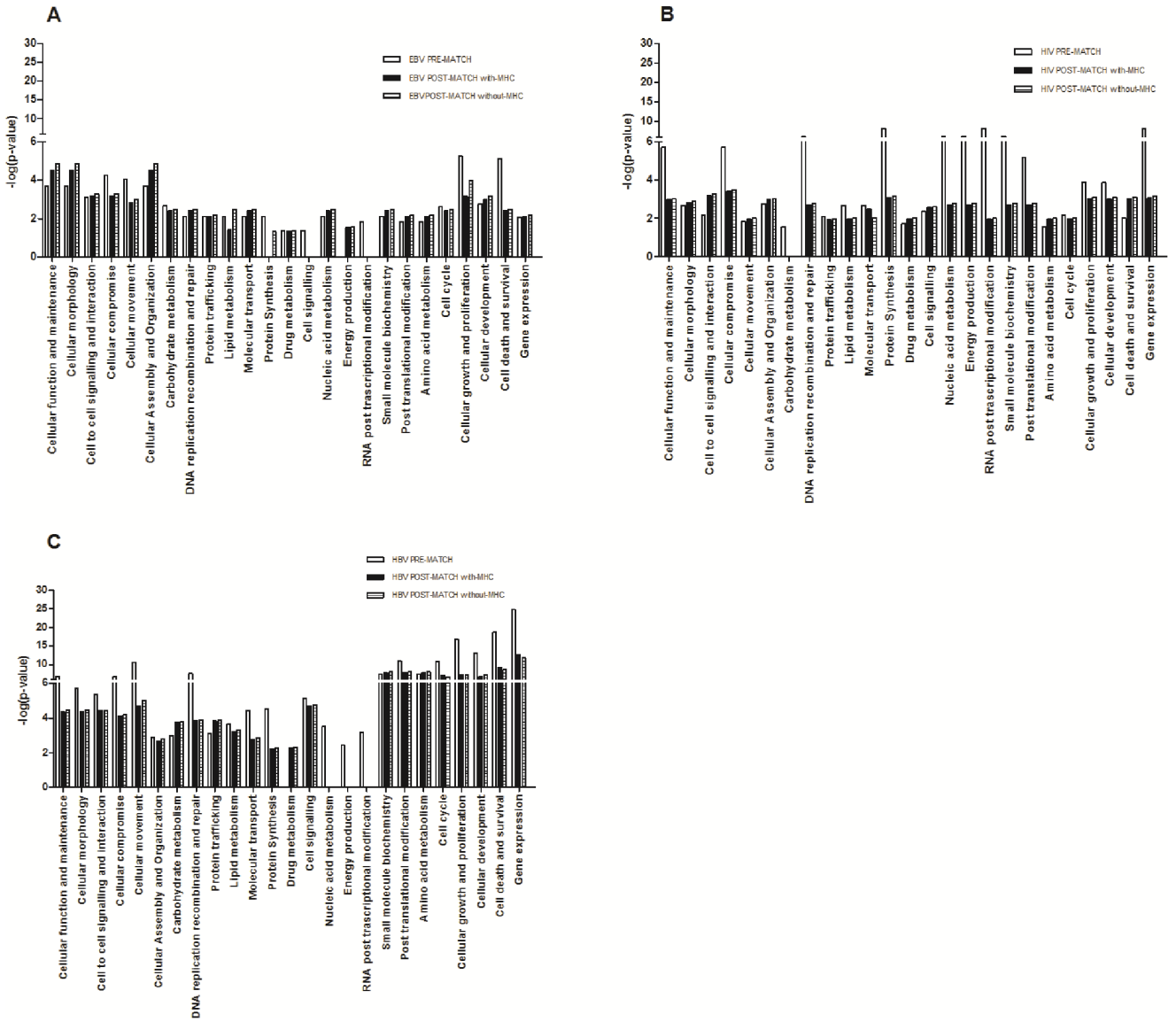


**Figure 3. Histograms of functional class distribution of MS-associated interactomes.** The histograms show the strength of the association between each IPA functional class and the 3 MS-associated interactomes (EBV [A], HIV [B] and HBV [C]). For each functional class 3 values were derived according to its distribution before (Figure 1) and after (Figure 2, with and without MHC [Major histocompatibility complex]) the ALIGATOR (Association LIst Go AnnoTatOR) statistical analysis of association.
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At present, our results support a causal role of the interaction between EBV and the products of MS-associated gene variants. Other viruses may be involved, through common and unique mechanisms of molecular perturbation.

## Supporting Information

**Table S1 ALIGATOR settings.**
(XLS)

**Table S2 Composition of all the interactomes.** Lists of genes of each interactome as obtained from the literature. VIRORF = Virus Open Reading Frame; HIV = Human Immunodeficiency virus; HCV = Hepatitis C virus; hu-IFN = human innate immunity interactome for type I interferon; EBV = Epstein Barr virus; H1N1 = Influenza A virus; HBV = Hepatitis B virus; VDR = vitamin D receptor; AIRE = autoimmune regulator; CMV = Cytomegalovirus; HHV8 = Human Herpesvirus 8; JCV = JC virus; AHR = Aryl hydrocarbon receptor.
(DOC)

**Table S3 List of genes within molecular and functional classes in the three MS-associated interactomes (p-value cut-off<0.05).** MS = multiple sclerosis; HIV = Human Immunodeficiency virus; EBV = Epstein Barr virus; HBV = Hepatitis B virus; MHC = Major histocompatibility complex
(XLS)

**Table S4 Statistical enrichment of MS-associated interactomes (p-value cut-off<0.005; 0.03).** ALIGATOR-obtained interactome p-values (overall contribution given by SNP p-values to each interactome, with and without SNPs falling in the MHC region). MS = multiple sclerosis; ALIGATOR = Associa-

tion LIst Go AnnoTatOR; SNP = single nucleotide polymorphism; MHC = Major histocompatibility complex; HIV = Human Immunodeficiency virus; EBV = Epstein Barr virus; HBV = Hepatitis B virus.
(DOC)

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Mycko,[24] Michelle Ricketts,[7] Manuel Comabella,[25] Naomi Hammond,[7]Ingrid Kockum,[26] Owen T. McCann,[7] Maria Ban,[1] Pamela Whittaker,[7] Anu Kemppinen,[1] Paul Weston,[7] Clive Hawkins,[27]Sara Widaa,[7] John Zajicek,[28] Serge Dronov,[7] Neil Robertson,[29] Suzannah J. Bumpstead,[7] Lisa F. Barcellos,[30,31] Rathi Ravindrarajah,[7] Roby Abraham,[27] Lars Alfredsson,[32] Kristin Ardlie,[4] Cristin Aubin,[4] Amie Baker,[1] Katharine Baker,[29]Sergio E. Baranzini,[33] Laura Bergamaschi,[19] Roberto Bergamaschi,[34] Allan Bernstein,[31] Achim Berthele,[13] Mike Boggild,[35] Jonathan P. Bradfield,[36] David Brassat,[37] Simon A. Broadley,[38] Dorothea Buck,[13] Helmut Butzkueven,[39,42]Ruggero Capra,[43] William M. Carroll,[44] Paola Cavalla,[45] Elisabeth G. Celius,[21] Sabine Cepok,[13] Rosetta Chiavacci,[36]Françoise Clerget-Darpoux,[46] Katleen Clysters,[9] Giancarlo Comi,[20] Mark Cossburn,[29] Isabelle Cournu-Rebeix,[12] Mathew B. Cox,[47] Wendy Cozen,[48] Bruce A.C. Cree,[33] Anne H. Cross,[49] Daniele Cusi,[50] Mark J. Daly,[4,51,52] Emma Davis,[53]Paul I.W. de Bakker,[3,4,54,55] Marc Debouverie,[56] Marie Beatrice D'hooghe,[57] Katherine Dixon,[53] Rita Dobosi,[9] Bénédicte Dubois,[9] David Ellinghaus,[58] Irina Elovaara,[59,60] Federica Esposito,[20] Claire Fontenille,[12] Simon Foote,[61] Andre Franke,[58] Daniela Galimberti,[62] Angelo Ghezzi,[63] Joseph Glessner,[36] Refujia Gomez,[33] Olivier Gout,[64] Colin Graham,[65]Struan F.A. Grant,[36,66,67] Franca Rosa Guerini,[68] Hakon Hakonarson,[36,66,67] Per Hall,[69] Anders Hamsten,[70] Hans-Peter Hartung,[71] Rob N. Heard,[8] Simon Heath,[72] Jeremy Hobart,[28] Muna Hoshi,[13] Carmen Infante-Duarte,[73] Gillian Ingram,[29]Wendy Ingram,[28] Talat Islam,[48] Maja Jagodic,[26] Michael Kabesch,[74] Allan G. Kermode,[44] Trevor J. Kilpatrick,[39,40,75]Cecilia Kim,[36] Norman Klopp,[76] Keijo Koivisto,[77] Malin Larsson,[70] Mark Lathrop,[72] Jeannette S. Lechner-Scott,[47,78]Maurizio A. Leone,[79] Virpi Leppä,[11,80] Ulrika Liljedahl,[81] Izaura Lima Bomfim,[26] Robin R. Lincoln,[33] Jenny Link,[26]Jianjun Liu,[82] Åslaug R. Lorentzen,[22,83] Sara Lupoli,[50,84] Fabio Macciardi,[50,85] Thomas Mack,[48] Mark Marriott,[39,40]Vittorio Martinelli,[20] Deborah Mason,[86] Jacob L. McCauley,[87] Frank Mentch,[36] Inger-Lise Mero,[21,83] Tania Mihalova,[27]Xavier Montalban,[25] John Mottershead,[88,89] Kjell-Morten Myhr,[90,91] Paola Naldi,[79] William Ollier,[53] Alison Page,[92] Aarno Palotie,[7,11,93,94] Jean Pelletier,[95] Laura Piccio,[49] Trevor Pickersgill,[29] Fredrik Piehl,[26] Susan Pobywajlo,[5] Hong L. Quach,[30] Patricia P. Ramsay,[30] Mauri Reunanen,[96] Richard Reynolds,[97] John D. Rioux,[98] Mariaemma Rodegher,[20]Sabine Roesner,[16] Justin P. Rubio,[39] Ina-Maria Rückert,[76] Erika Salvi,[50,100] Adam Santaniello,[33]Catherine A. Schaefer,[31] Stefan Schreiber,[58,101] Christian Schulze,[102] Rodney J. Scott,[47] Finn Sellebjerg,[10] Krzysztof W. Selmaj,[24]David Sexton,[103]Ling Shen,[31] Brigid Simms-Acuna,[31] Sheila Skidmore,[1] Patrick M.A. Sleiman,[36,66] Cathrine Smestad,[21] Per Soelberg Sørensen,[10] Helle Bach Søndergaard,[10] Jim Stankovich,[61] Richard C. Strange,[27] Anna-Maija Sulonen,[11,80] Emilie Sundqvist,[26] Ann-Christine Syvänen,[81] Francesca Taddeo,[100] Bruce Taylor,[61]Jenefer M. Blackwell,[104,105] Pentti Tienari,[106] Elvira Bramon,[107] Ayman Tourbah,[108] Matthew A. Brown,[109]Ewa Tronczynska,[24]Juan P. Casas,[110] Niall Tubridy,[40,111] Aiden Corvin,[112] Jane Vickery,[28] Janusz Jankowski,[113] Pablo Villoslada,[114] Hugh S. Markus,[115] Kai Wang,[36,66] Christopher G. Mathew,[116] James Wason,[117] Colin N.A. Palmer,[118] H-Erich Wichmann,[76,119,120] Robert Plomin,[121] Ernest Willoughby,[122]Anna Rautanen,[2] Juliane Winkelmann,[13,123,124] Michael Wittig,[58,125] Richard C. Trembath,[116] Jacqueline Yaouanq,[126] Ananth C. Viswanathan,[127] Haitao Zhang,[36,66] Nicholas W. Wood,[128] Rebecca Zuvich,[103] Panos Deloukas,[7] Cordelia Langford,[7] Audrey Duncanson,[129] Jorge R. Oksenberg,[33] Margaret A. Pericak-Vance,[87] Jonathan L. Haines,[103] Tomas Olsson,[26] Jan Hillert,[26] Adrian J. Ivinson,[51,130] Philip L. De Jager,[4,5,51] Leena Peltonen,[7,11,80,93,94] Graeme J. Stewart,[8] David A. Hafler,[4,131] Stephen L. Hauser,[33] Gil McVean,[2] Peter Donnelly,[2,6] and Alastair Compston[1]

[1]University of Cambridge, Department of Clinical Neurosciences, Addenbrooke's Hospital, Cambridge, UK
[2]Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford, UK
[3]Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[4]Broad Institute of Harvard University and Massachusetts Institute of Technology, Cambridge, MA, USA
[5]Center for Neurologic Diseases, Department of Neurology, Brigham & Women's Hospital, Boston, MA, USA
[6]Dept Statistics, University of Oxford, Oxford, UK
[7]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
[8]Westmead Millennium Institute, University of Sydney, Australia
[9]Laboratory for Neuroimmunology, Section of Experimental Neurology, Katholieke Universiteit Leuven, Leuven, Belgium
[10]Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[11]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland
[12]INSERM UMR S 975 CRICM, UPMC, Département de neurologie Pitié-Salpêtrière, AP-HP, Paris, France
[13]Department of Neurology, Klinikum Rechts der Isar der Technischen Universität, Munich, Germany
[14]Department of Neurology, University Medicine Mainz, Johannes Gutenberg University Mainz, Mainz, Germany
[15]Max Delbrueck Center for Molecular Medicine, Berlin, Germany
[16]Institute for Neuroimmunology and Clinical MS Research (inims), Centre for Molecular Neurobiology, Hamburg, Germany
[17]Department of Clinical Pharmacology, University of Oxford, Old Road Campus Research Building, Oxford, UK
[18]Queen's University Belfast, University Road, Belfast, Northern Ireland, UK
[19]Department of Medical Sciences and Interdisciplinary Research Center of Autoimmune Diseases (IRCAD), University of Eastern Piedmont, Novara, Italy
[20]Department of Neurology, Institute of Experimental Neurology (INSPE), Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy
[21]Department of Neurology, Oslo University Hospital, Oslo, Norway
[22]Department of Neurology, University of Oslo, Oslo, Norway
[23]Institute of Basal Medical Sciences, University of Oslo, Oslo, Norway
[24]Department of Neurology, Laboratory of Neuroimmunology, Medical University of Lodz, Lodz, Poland
[25]Clinical Neuroinmunology Unit, Multiple Sclerosis Center of Catalonia (CEM-Cat), Vall d'Hebron University Hospital, Barcelona, Spain
[26]Department of Clinical Neurosciences, Centre for Molecular Medicine CMM, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden
[27]Keele University Medical School, Stoke-on-Trent, UK
[28]Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth, Clinical Neurology Research Group, Tamar Science Park, Plymouth, UK
[29]Department of Neurology, University Hospital of Wales, Heath Park, Cardiff, UK
[30]Genetic Epidemiology and Genomics Laboratory, Division of Epidemiology, School of Public Health, University of California, Berkeley, USA
[31]Kaiser Permanente Northern California Division of Research, CA, USA
[32]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[33]Department of Neurology, University of California San Francisco, San Francisco, CA, USA
[34]Neurological Institute C. Mondino, IRCCS, Pavia, Italy
[35]The Walton Centre for Neurology and Neurosurgery, Liverpool, UK
[36]Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[37]INSERM U 563 et Pôle Neurosciences, Hopital Purpan, Toulouse, France
[38]School of Medicine, Griffith University, Australia
[39]Florey Neuroscience Institutes, University of Melbourne, Victoria, Australia
[40]Royal Melbourne Hospital, Parkville, Victoria, Australia,
[41]Box Hill Hospital, Box Hill, Australia
[42]Department of Medicine, RMH Cluster, University of Melbourne, Victoria, Australia
[43]Multiple Sclerosis Centre, Department of Neurology, Ospedali Civili di Brescia, Brescia, Italy
[44]Centre for Neuromuscular and Neurological Disorders, University of Western Australia, Perth, Australia
[45]Department of Neurosciences, University of Turin, A.O.U. San Giovanni Battista,Turin, Italy
[46]INSERM U535, Univ Paris-Sud, Villejuif, France
[47]University of Newcastle, University Drive, Callaghan NSW, Australia
[48]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[49]Department of Neurology, Washington University, St Louis MO, USA
[50]University of Milan, Department of Medicine, Surgery and Dentistry, AO San Paolo, University of Milan, c/o Filarete Foundation - Milano, Italy
[51]Harvard Medical School, Boston, MA, USA
[52]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA
[53]The UK DNA Banking Network, Centre for Integrated Genomic Medical Research, University of Manchester, UK
[54]Department of Medical Genetics, Division of Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands
[55]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[56]Service de Neurologie, Hôpital Central, Nancy, France
[57]National Multiple Sclerosis Center, Melsbroek, Belgium
[58]Institute for Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany
[59]Department of Neurology, Tampere University Hospital, Tampere, Finland
[60]University of Tampere, Medical School, Tampere, Finland
[61]Menzies Research Institute, Hobart, Tasmania, Australia [62]Department of Neurological Sciences, Centro Dino Ferrari, University of Milan, Fondazione Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy
[63]Centro Studi Sclerosi Multipla, Ospedale di Gallarate, Gallarate (VA), Italy
[64]Service de Neurologie, Fondation Ophtalmologique Adolphe de Rothschild, Paris, France
[65]Belfast Health and Social Care Trust, City Hospital, Belfast, Northern Ireland,UK
[66]Division of Genetics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[67]Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
[68]Laboratory of Molecular Medicine and Biotechnology, Don C. Gnocchi Foundation IRCCS, S. Maria Nascente, Milan, Italy
[69]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[70]Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Center for Molecular Medicine, Karolinska University Hospital Solna, Stockholm, Sweden
[71]Department of Neurology, Heinrich-Heine-University, Düsseldorf, Germany
[72]Centre National de Genotypage, Evry Cedex, France
[73]Experimental and Clinical Research Center, Charité – Universitätsmedizin Berlin and Max Delbrueck Center for Molecular Medicine, Berlin, Germany
[74]Clinic for Paediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Germany
[75]Centre for Neuroscience, University of Melbourne, Victoria, Australia
[76]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Munich, Germany
[77]Seinäjoki Central Hospital, Seinäjoki, Finland
[78]Hunter Medical Research Institute, John Hunter Hospital, Lookout Road, New Lambton NSW, Australia
[79]SCDU Neurology, Maggiore della Carità Hospital, Novara, Italy
[80]Unit of Public Health Genomics, National Institute for Health and Welfare, Helsinki, Finland
[81]Molecular Medicine, Department of Medical Sciences, Uppsala University, Entrance 70, 3rd Floor, Res Dept 2, Univeristy Hospital, Uppsala, Sweden
[82]Human Genetics and Cancer Biology, Genome Institute of Singapore, Singapore [83]Institute of Immunology, Oslo University Hospital, Oslo, Norway
[84]Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milan, Italy
[85]Dept of Psychiatry and Human Behavior, University of California, Irvine (UCI), Irvine CA, USA
[86]Christchurch School of Medicine, University of Otago, Christchurch, New Zealand
[87]John P. Hussman Institute for Human Genomics and The Dr. John T Macdonald Foundation Department of Human Genetics, University of Miami, Miller School of Medicine, Miami, USA
[88]Greater Manchester Centre for Clinical Neurosciences, Hope Hospital, Salford, UK
[89]The Department of Neurology, Dunedin Public Hospital, Otago, NZ
[90]The Multiple Sclerosis National Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway
[91]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[92]Plymouth Hospitals NHS Trust, Department of Neurology, Derriford Hospital, Plymouth, UK
[93]Department of Medical Genetics, University of Helsinki and University Central Hospital, Helsinki, Finland
[94]Program in Medical and Population Genetics and Genetic Analysis Platform, The Broad Institute of MIT and Harvard, Cambridge, MA, USA
[95]Pôle Neurosciences Cliniques,Service de Neurologie, Hôpital de la Timone, Marseille, France
[96]Department Neurology, Oulu University Hospital, Oulu, Finland
[97]UK MS Tissue Bank, Wolfson Neuroscience Laboratories, Imperial College London, Hammersmith Hospital, London, UK
[98]Université de Montréal & Montreal Heart Institute, Research Center, Montreal, Quebec, Canada
[100]KOS Genetic Srl, Milan - Italy
[101]Department of General Internal Medicine, University Hospital, Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany
[102]Systems Biology and Protein-Protein Interaction, Center for Molecular Neurobiology, Hamburg, Germany
[103]Center for Human Genetics Research, Vanderbilt University Medical Center, Nashville, USA
[104]Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Australia
[105]Cambridge Institute for Medical Research, University of Cambridge School of Clinical Medicine, Cambridge, UK
[106]Department of Neurology, Helsinki University Central Hospital and Molecular Neurology Programme, Biomedicum, University of Helsinki, Helsinki, Finland
[107]Division of Psychological Medicine and Psychiatry, Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London and The South London and Maudsley NHS Foundation Trust, Denmark Hill, London, UK
[108]Service de Neurologie et Faculté de Médecine de Reims, Université de Reims Champagne-Ardenne, Reims, France
[109]University of Queensland Diamantina Institute, Princess Alexandra Hospital, Brisbane, Australia
[110]Dept Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
[111]St. Vincent's University Hospital, Dublin, Ireland
[112]Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland

[113]Centre for Gastroenterology, Bart's and the London School of Medicine and Dentistry, London, UK
[114]Department of Neurosciences, Institute of Biomedical Research August Pi Sunyer (IDIBAPS), Hospital Clinic of Barcelona, Barcelona, Spain
[115]Clinical Neurosciences, St George's University of London, London, UK
[116]Dept Medical and Molecular Genetics, King's College London School of Medicine, Guy's Hospital, London, UK
[117]Medical Research Council Biostatistics Unit, Robinson Way, Cambridge, UK
[118]Biomedical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK
[119]Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany
[120]Klinikum Grosshadern, Munich, Germany
[121]King's College London, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Denmark Hill, London, UK
[122]Department of Neurology, Auckland City Hospital, Grafton Road, Auckland, New Zealand
[123]Institut für Humangenetik, Technische Universität München, Germany
[124]Institut für Humangenetik, Helmholtz Zentrum München, Germany
[125]Popgen Biobank, Christian-Albrechts University Kiel, Kiel, Germany
[126]Pôle Recherche et Santé Publique, CHU Pontchaillou, Rennes, France
[127]NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK
[128]Dept Molecular Neuroscience, Institute of Neurology, Queen Square, London, UK
[129]Molecular and Physiological Sciences, The Wellcome Trust, London, UK
[130]Harvard NeuroDiscovery Center, Harvard Medical School, Boston, MA, USA
[131]Department of Neurology & Immunology, Yale University Medical School, New Haven, CT, USA

## Author Contributions

Conceived and designed the experiments: RM RU GR MS. Performed the experiments: RM RU IMSGC WTCCC CP GC. Analyzed the data: RM RU CP GC VA. Contributed reagents/materials/analysis tools: VAGR AF SR DV MCB. Wrote the paper: RM RU GR MS.

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