Supplementary Table 1 - SNP selection by known associations with inflammation, neurodegeneration and clinical outcomes in multiple sclerosis

SNP (alleles)	Minor Allele	CHR	Position	Variant Function	Call-rate	MAF	HWE p-value	Gene	Associations		
									Inflammation	Neurodegeneration	Clinical
rs3135388 (T/C)	T	6	32413051	Intergenic	1.000	0.24	0.75	*HLA-DRB1*1501*	Increased WM lesion measures.[1–3] Inflammation within both cortical NAGM and lesional GM, and more extensive cortical lesions in younger multiple sclerosis patients.[4] Greater frequency and number of cortical lesions.[5]	Whole brain atrophy and GM atrophy.[1,2]	Lower age of onset[1,6] and worse cognitive impairment.[1]
rs2743951 (A/G)	A	6	29709234	Intron	1.000	0.39	0.29	*HLA B*4402*	Reduced T2 WM lesion burden.[7]	Preserved brain parenchymal fraction[7] and protective on subcortical GM atrophy.[8]	Protective effect on cognition assessed by SDMT.[9] Protective for both conversion to multiple sclerosis and relapses.[10]
rs4713274 (G/C)	G	6	29937493	Intergenic	0.951	0.16	0.69	*HLA A*02:01*	Weak protective effect on new WM lesions.[11] Weak protective effect on T2 WM lesion volume in DRB1*1501-ve patients.[9]		Associated with weak protective effects on disability (EDSS and MSSS).[11] Decreased hazard ratio for SPMS.[12] Weak protective effect on SDMT in DRB1*1501 +ve patients.[9]
rs4315313 (T/C)	T	16	83086717	Intron	0.967	0.41	0.9	*CDH13*	WM T2 lesion load.[13]		
rs6917747 (A/G)	A	6	160402705	Intron	0.951	0.17	0.51	*IGF2R*	WM T2 Lesion Load.[13]		
rs2039485* (A/G)	G	14	32353250	Intergenic	0.918	0.24	3E-11	*NUBPL*	WM T2 Lesion Load.[13]		
rs17208888* (A/G)	A	6	32379506	Intergenic	0.984	0.13	0.015	*HLA-DRB1*11:04*	Thoracic cord WM lesions.[14]		
rs59655222 (T/C)	C	1	200875897	Intron	0.951	0.34	0.52	*C1orf106, KIF21B*	*KIF21B* associated with more extensive GM demyelination.[15]		Multiple sclerosis risk variant in IMSGC 2019.[16] Accelerated development of EDSS 6 in multiple sclerosis patients.[15]
rs2389963 (A/G)	G	7	18588445	Intron	0.967	0.37	0.5	*HDAC*		Histone deacetylase gene variants predict brain volume changes in multiple sclerosis.[17]	
rs2074633 (T/C)	C	7	19035920	3 prime untranslated region	0.951	0.28	0.7	*HDAC9*		Histone deacetylase gene variants predict brain volume changes in multiple sclerosis.[17]	
rs1927457* (T/C)	C	10	30008663	Intron	0.934	0.33	0.43	*SVIL*		Brain parenchymal volume atrophy.[13]	
rs11957313 (A/G)	A	5	169950394	Intron	0.967	0.24	0.81	*KCNIP1*		Brain parenchymal volume atrophy.[13]	

rs4866550 (T/C)	T	5	3308312 9.0807	Intergenic	0.984	0.31	0.43	*IRX1*		Brain parenchymal volume atrophy.[13]	
rs4473631 (T/G)	G	4	174501769	Intron	0.951	0.29	0.52	*MORF4*		Brain parenchymal volume atrophy.[13]	
rs1869410 (T/C)	C	2	525735 11.8860	Intergenic	0.967	0.3	0.26	*SOX11*		Brain parenchymal volume atrophy.[13]	
rs9486902 (T/C)	T	6	108878052	Intergenic	0.984	0.14	0.83	*FOXO3A*		Brain parenchymal volume atrophy.[13]	
rs7104613* (T/C)	T	11	14079931	Intron	1.000	0.13	0.028	*SPON1*		Reduced deep grey matter volume.[18]	
rs77970177 * (T/C)	T	1	72962190	Intergenic	1.000	0.05	<0.0001	*GRIN2B*		Reduced deep grey matter volume.[18]	
rs17157903 * (A/G)	A	7	103628036	Intron	0.967	0.14	0.0033	*RELN*			Age of multiple sclerosis onset.[13]
rs1386330* (A/G)	G	11	87819427	Intron	0.918	0.19	0.4	*RAB38*			Age of multiple sclerosis onset.[13]
rs1557351 (A/G)	G	18	54752314	TF binding site	0.951	0.15	0.79	*WDR7*			Age of multiple sclerosis onset.[13]
rs694739 (T/C)	C	11	64097233	Intergenic	0.967	0.35	0.94	*PRDX5, CCDC88B*			Increased risk of conversion to multiple sclerosis.[10]
rs802734* (A/G)	A	6	128278798	Intergenic	0.934	0.23	0.44	*PTPRK, THEMIS*			GG phenotype associated with increased risk of conversion to multiple sclerosis.[10]
rs1323292 (A/G)	A	1	192541021	Intergenic	0.984	0.23	0.44	*RGS1, RGS21*			AG+GG phenotype associated with increased risk of conversion to multiple sclerosis.[10]
rs12988804 * (T/C)	T	2	170117811	Intron	0.934	0.27	0.42	*LRP2*			First variant validated at genome wide significance as marker of multiple sclerosis severity (relapse rate) with hazard ratio (HR) 2.18.[19,20]
rs9277561 (A/G)	G	6	33056749	Intergenic	0.967	0.25	0.9	*HLA-DPB1*			Susceptibility variant,[16] also linked to increased relapse risk.[10]
rs1154801 (T/G)	T	6	135739355	Intron	0.951	0.40	0.3	*AHI1*			Known multiple sclerosis risk allele.[16] Also associated with increased relapse rate.[21]
rs11810217 (A/G)	A	1	93148377	Intron	0.984	0.33	0.7	*EVI5*			Multiple sclerosis risk variant in IMSGC 2019.[16] Associated with increased relapse risk.[22]
rs2300603 (T/C)	C	14	76005557	Intron	0.951	0.22	0.41	*BATF*			Multiple sclerosis risk variant in IMSGC 2019.[16] Associated with increased relapse risk.[22]

rs7775055* (A/G)	G	6	32657916	TF binding site	0.980	0.02	0.9	*HLA DRB1*08*			More prevalent among RRMS patients and was associated with the lower rate of relapse, degree of disability and IgG index.[23] 75% lower odds that RRMS will change to a progressive course multiple sclerosis.[24]
rs2283792* (T/G)	G	22	22131125	Intron	0.934	0.46	0.54	*MAPK1*			One of seven non-HLA SNPs predicting annualised ΔEDSS with dose-response when incorporated into a cumulative genetic risk score.[10]
rs2546890 (T/C)	C	5	158759900	Non coding transcript exon	1.000	0.43	0.25	*LOC285626*			One of seven non-HLA SNPs predicting annualised ΔEDSS with dose-response when incorporated into a cumulative genetic risk score.[10]
rs10516537 (T/G)	T	4	107628071	Regulatory region	0.967	0.17	0.78	*DKK2*			Disability (MSSS).[13]
rs4803766 (A/G)	A	19	45371168	Intron	0.967	0.44	0.81	*PVRL2*			Disability (MSSS).[25]
rs752092 (A/G)	G	15	101781934	Intron	0.951	0.37	0.59	*CHSY1*			Disability (MSSS).[13]
rs12638253 (A/G)	A	3	156626091	Intron	1.000	0.47	0.87	*FLJ16641*			Disability (MSSS).[13]
rs10518025 (A/G)	G	4	68064440	Regulatory region	0.967	0.15	0.17	*CENPC1*			Disability (MSSS).[13]
rs12142240 (A/G)	G	1	46747301	Intron	0.951	0.26	0.26	*LRRC41*			Disability (MSSS).[13]

SNP – single nucleotide polymorphism, CHR – Chromosome, MAF – minor allele frequency, HWE – Hardy-Weinberg equilibrium, WM – white matter, GM – grey matter, NAGM – normal appearing grey matter, MS – multiple sclerosis, SDMT – Symbol digit Modalities Test, EDSS – expanded disability status scale, MSSS – multiple sclerosis severity score, NF – neurofibrillary, RRMS – relapsing-remitting MS. TF – Transcription Factor. Variant function of SNPs as provided in ENSEMBL using Genome Reference Consortium Human Build 37 patch release 13 (GRCh37.p13).

SNP Selection and genotyping

Potential variants were identified from GWAS catalog (https://www.ebi.ac.uk/gwas), and dbSNP (https://www.ncbi.nlm.nih.gov/snp) through searches for "multiple sclerosis" with either "lesion", "inflammation", "neurodegeneration", volume", "atrophy", "relapse", "onset", "severity", "phenotype", or "disability" using an "AND" Boolean operator. A Pubmed search was undertaken with the same search targets: ("multiple sclerosis"[Title]) AND ("gene"[Title] OR "SNP"[Title] OR "genetic"[Title] OR "genome"[Title] OR "HLA"[Title]) AND ("lesion"[Title] OR "inflammation"[Title] OR "neurodegeneration"[Title] OR "volume"[Title] OR "atrophy"[Title] OR "severity"[Title] OR "phenotype"[Title] OR "disability" [Title] OR "onset"[Title])).

Where tagging SNPs for potential genetic variants were not provided within the study article or supplementary material, these were identified, if available, through cross-referencing with GWAS catalog and dbSNP databases. Thirty-eight genetic variants, including *HLA-DRB1*1501*, were identified with tagging SNPs identifiable using the Infinium Global Screening Array-24 v3.0 Beadchip from Illumina (San Diego, CA, USA). This included variants from several GWAS studies, with suggestive genetic associations that did not reach genome wide significance, and longitudinal cohort studies, of shorter follow-up than our cohort, where phenotypic associations were identified either with SNPs individually or within cumulative genetic risk scores. Eleven SNPs were excluded (*) from analysis if minor allele frequency (MAF) was <0.05, call rate <95%, if there was significant deviation from Hardy-Weinberg equilibrium ($p<0.05$) or individual heterozygosity rate >3 standard deviations from mean.[28] MAF threshold was set at <0.05 to cautiously limit rare genetic variants, given the relatively small cohort size.

Supplementary Table 2 – All significant (p<0.05) SNP associations at 30-year follow-up in all participants (MS and CIS)

		Gene, *SNP (allele)*														
Outcome at 30-year Follow Up		***HLA-DRB1*1501 rs3135388 (T)***	***HDAC rs2389963 (G)***	***LOC285626 rs2546890 (C)***	***BATF rs2300603 (C)***	***PVRL2 rs4803766 (A)***	***IRX1 rs4866550 (T)***	***KCNIP1 rs11957313 (A)***	***HDAC9 rs2074633 (C)***	***CHSY1 rs752092 (G)***	***WDR7 rs1557351 (G)***	***FLJ16641 rs12638253 (A)***	***EVI5 rs11810217 (A)***	***CDH13 rs4315313 (T)***	***RGS1, RGS21 rs1323292 (G)***	***DKK2 rs10516537 (T)***	***IGF2R rs6917747 (A)***
Inflammation																	
White Matter																	
WMLs *(n)*	Estimate	54.99															
	95% CI	3.60 to 104.79[b]															
	R^2	0.15															
	p-value	0.021															
WMLV *(ml)*	Estimate	11.60															
	95% CI	5.49 to 18.29[b]															
	R^2	0.28															
	p-value	**0.001****															
WML MTR *(pu)*	Estimate	-1.17															
	95% CI	-0.24 to -2.26[b]															
	R^2	0.18															
	p-value	0.013															
NAWM MTR *(pu)*	Estimate	-0.85															
	95% CI	-0.14 to -1.66[b]															
	R^2	0.20															
	p-value	0.021															
Grey Matter																	
GM lesions (*n*)	Estimate				-0.81	0.83											
	95% CI				-0.20 to -1.41[b]	0.08 to 1.66[b]											
	R^2				0.14	0.16											
	p-value				0.029	0.042											
GM lesions *(Y/N?)*	OR				0.09 0.01	7.23	0.22										
	95% CI				to 0.81	1.13 to 46.21	0.05 to 0.99										
	R^2				0.37	0.38	0.34										
	p-value				0.032	0.037	0.049										
cGM MTR gradient (pu/band)	Estimate						0.15										
	95% CI						0.02 to 0.29[b]										
	R^2						0.23										
	p-value						0.019										
Brain Volume																	
GMF (%)	Estimate	-0.62					0.76	-0.72	-0.72								
	95% CI	0.00 to -1.36[b]					0.28 to 1.29[b]	-0.12 to -1.55[b]	-0.10 to -1.37[b]								

	R^2	0.41					0.42	0.44	0.41							
	p-value	0.03					**0.008***	0.016	0.014							
MEDW *(mm)*	Estimate						0.28	-0.25								
	95% CI						0.03 to 0.46[b]	-0.02 to -0.49								
	R^2						0.14	0.14								
	p-value						0.042	0.035								
TVW *(mm)*	Estimate						-1.82			-1.71						
	95% CI						-0.52 to -3.22[b]			-0.18 to -3.06[b]						
	R^2						0.22			0.23						
	p-value						0.014			0.027						
Clinical Neuropsychology																
BVMTR-z	Estimate										1.10	-0.81	-0.85	-0.83	-0.79	
	95% CI										0.35 to 1.85	-0.00 to -1.63	-0.16 to -1.54[b]	-0.50 to -1.60[b]	-0.12 to -1.45	
	R^2										0.27	0.18	0.23	0.19	0.21	
	p-value										**0.005***	0.050	0.017	0.032	0.021	
CVLT-z	Estimate		0.634													
	95% CI		0.03 to 1.24													
	R^2		0.43													
	p-value		0.041													
SDMT-z	Estimate					0.715			0.736					-0.70		
	95% CI					0.02 to 1.42			0.05 to 1.42					-0.04 to -1.37		
	R^2					0.23			0.24					0.24		
	p-value					0.046			0.035					0.038		
BICAMS Total	Estimate					15.23										
	95% CI					4.94 to 26.31[b]										
	R^2					0.23										
	p-value					0.016										
FSS	Estimate						-7.98		12.92						-9.62	
	95% CI						-0.10 to -15.87[b]		3.05 to 18.81						-0.37 to -18.86	
	R^2						0.26		0.23						0.18	
	p-value						0.047		**0.008***						0.042	
PASAT-3	Estimate															7.41
	95% CI															0.20 to 14.62
	R^2															0.20
	p-value															0.044
Disability																
9HPT-ND *(s)*	Estimate			6.17			-6.38									
	95% CI			2.17 to 10.39[b]			-2.32 to -11.14									
	R^2			0.32			0.32									
	p-value			0.013			**0.009***									
EDSS	Estimate					1.72	-1.35									
	95% CI					0.49 to 2.93[b]	-0.29 to -2.48[b]									
	R^2					0.25	0.22									
	p-value					0.013	0.026									

Phenotype Progression to SPMS *(Y/N?)*	OR 95% CI R^2 p-value					12.25 1.15 to 23.10[b] 0.31 0.031											

OR – Odds Ratio, CI – confidence interval, SNP – single nucleotide polymorphism, WML – white matter lesion, WMLV – white matter lesion volume, NAWM – normal appearing white matter, MTR – magnetisation transfer ratio, pu – percentage units, GM – grey matter, cGM – cortical grey matter, GMF – grey matter fraction, BVMTR-z - Brief Visuospatial Memory Test–Revised z-score adjusted for age, sex and education, BICAMS – brief international cognitive assessment for MS, CVLT-z – California verbal learning test z-score, FSS – fatigue severity scale, PASAT-3 – paced serial auditory test-3, SDMT-z – Symbol digit Modalities Test z-score, 9HPT-D – 9 hole peg test dominant hand, 9HPT-ND – 9 hole peg test non-dominant hand, EDSS -expanded disability status scale, MS – multiple sclerosis, SPMS – Secondary progressive MS,

[b] – Bootstrapped confidence intervals using 1000 replicates

*** p-value < 0.01**

**** p < 1.85 x 10-3** (Bonferroni correction for number of variants = 0.05/27 variants)

Supplementary Table 3 – All significant (p<0.05) SNP associations at 30-year follow-up in participants with MS only (excluding CIS)

Outcome at 30-year Follow Up		Gene, *SNP (allele)*													
		*HLA-DRB1*1501* rs3135388 *(T)*	*HLA B*4402* rs2743951 *(A)*	*BATF* rs2300603 *(C)*	*PVRL2* rs4803766 *(A)*	*IRX1* rs4866550 *(T)*	*HDAC9* rs2074633 *(C)*	*WDR7* rs1557351 *(G)*	*CHSY1* rs752092 *(G)*	*EVI5* rs11810217 *(A)*	*LRRC41* rs12142240 *(G)*	*CENPC1* rs10518025 *(G)*	*FLJ16641* rs12638253 *(A)*	DKK2 rs10516537 *(T)*	*IGF2R* rs6917747 *(A)*
Inflammation															
White Matter															
WMLs *(n)*	Estimate	57.94													
	95% CI	1.03 to 114.84													
	R^2	0.13													
	p-value	0.046													
WMLV *(ml)*	Estimate	11.05													
	95% CI	3.18 to 18.87[b]													
	R^2	0.22													
	p-value	0.011													
WML MTR *(pu)*	Estimate	-1.37													
	95% CI	-0.41 to -2.46[b]													
	R^2	0.26													
	p-value	0.014													
NAWM MTR *(pu)*	Estimate	-0.816											-1.087		
	95% CI	-0.03 to -1.63[b]											-0.08 to -2.07[b]		
	R^2	0.22											0.25		
	p-value	0.045											0.022		
Grey Matter															
cGM MTR *(pu)*	Estimate		0.584										-0.712		
	95% CI		0.06 to 1.17[b]										-0.01 to -1.69[b]		
	R^2		0.29										0.29		
	p-value		0.049										0.034		
Cortical lesions (*n*)	Estimate			-1.11	1.13										
	95% CI			-0.18 to -2.05[b]	0.15 to 2.12[b]										
	R^2			0.19	0.16										
	p-value			0.021	0.047										
Cortical lesions *(Y/N?)*	OR			0.07	9.85	0.14				5.70					
	95% CI			0.01 to 0.65	1.20 to 81.04	0.03 to 0.73				1.07 to 30.30					
	R^2			0.43	0.38	0.39				0.34					
	p-value			0.020	0.033	0.020				0.041					
cGM MTR gradient (pu/band)	Estimate						-0.19								
	95% CI						-0.03 to -0.37[b]								
	R^2						0.26								
	p-value						0.031								

Brain Volume														
GMF (%)	Estimate					0.88	-1.18	-1.03						
	95% CI					0.28 to 1.64[b]	-0.48 to -2.08[b]	-0.18 to -2.20[b]						
	R^2					0.36	0.45	0.38						
	p-value					0.024	**0.002***	0.026						
MEDW *(mm)*	Estimate					0.31								
	95% CI					0.06 to 0.57								
	R^2					0.19								
	p-value					0.019								
TVW *(mm)*	Estimate					-2.03			-2.42					
	95% CI					-0.32 to -3.87[b]			-0.50 to -4.22[b]					
	R^2					0.19			0.23					
	p-value					0.035			0.023					
Clinical Neuropsychology														
BVMTR-z	Estimate				-1.09			1.21		-1.08	0.97			
	95% CI				-0.10 to -2.08			0.37 to 2.06[b]		-0.21 to -2.06[b]	0.06 to 1.93[b]			
	R^2				0.15			0.28		0.30	0.26			
	p-value				0.033			0.023		0.021	0.031			
CVLT-z	Estimate											-0.94		
	95% CI											-0.20 to -1.68		
	R^2											0.59		
	p-value											0.015		
SDMT-z	Estimate											-1.23	-1.12	
	95% CI											-0.12 to -2.00[b]	-0.26 to -1.98[b]	
	R^2											0.38	0.33	
	p-value											**0.006***	0.013	
BICAMS Total	Estimate									-15.63		-24.97		
	95% CI									-1.23 to -32.13 [b]		-7.70 to -42.24		
	R^2									0.33		0.39		
	p-value									0.046		**0.006***		
FSS	Estimate				13.77	-14.12	13.69						12.52	-11.49
	95% CI				2.52 to 25.03	-4.62 to -23.61	3.91 to 23.48						0.90 to 24.15	-1.05 to -22.61[b]
	R^2				0.24	0.28	0.26						0.20	0.19
	p-value				0.018	**0.008***	**0.008***						0.036	0.047
PASAT-3	Estimate													11.84
	95% CI													3.67 to 18.81[b]
	R^2													0.25
	p-value													0.013
Disability														
9HPT-ND *(s)*	Estimate			-7.10		-8.78								7.45
	95% CI			-0.70 to -13.97[b]		-3.70 to -14.16								-0.15 to 16.05[b]
	R^2			0.36		0.40								0.36
	p-value			0.031		**0.006***								0.044

9HPT-D *(s)*	Estimate												11.93		
	95% CI												3.07 to 24.18[b]		
	R^2												0.32		
	p-value												0.036		
EDSS	Estimate				2.60	-2.12									
	95% CI				1.30 to 3.87[b]	-0.87 to -3.44[b]									
	R^2				0.33	0.29									
	p-value				**0.002***	**0.005***									
Phenotype															
Progression to SPMS	OR				15.16	0.19									
(Y/N?)	95% CI				1.16 to 26.67[b]	0.04 to 0.92									
	R^2				0.31	0.24									
	p-value				0.029	0.042									

OR – Odds Ratio, CI – confidence interval, SNP – single nucleotide polymorphism, WML – white matter lesion, WMLV – white matter lesion volume, NAWM – normal appearing white matter, MTR – magnetisation transfer ratio, pu – percentage units, GM – grey matter, cGM – cortical grey matter, GMF – grey matter fraction, BVMTR-z - Brief Visuospatial Memory Test–Revised z-score adjusted for age, sex and education, BICAMS – brief international cognitive assessment for MS, CVLT-z – California verbal learning test z-score, FSS – fatigue severity scale, PASAT-3 – paced serial auditory test-3, SDMT-z – Symbol digit Modalities Test z-score, 9HPT-D – 9 hole peg test dominant hand, 9HPT-ND – 9 hole peg test non-dominant hand, EDSS -expanded disability status scale, MS – multiple sclerosis, SPMS – Secondary progressive MS,

[b] – Bootstrapped confidence intervals using 1000 replicates

*** p-value < 0.01**

NB: Bonferroni correction for number of variants = 0.05/27 variants = $p < 1.85 \times 10^{-3}$

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