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Genetic variants and magnetic resonance imaging measures in multiple sclerosis: a systematic review

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ABSTRACT

Introduction. Although environmental factors play the major role in the etiopathogenesis of multiple sclerosis (MS), genetic factors are implicated as well. We aimed to summarize the current knowledge on the relationship between genetic variants and magnetic resonance (MR) imaging measures in MS.
Material and Methods. A systematic review. In December 2016, Scopus (since the year 1980; including MEDLINE) was searched for studies meeting predefined criteria designed to identify articles regarding: multiple sclerosis, genetic variants, and MR imaging. These were then analyzed to identify publications linking polymorphisms and MR findings.
Results. The search yielded 290 items; 26 were included in the final analysis. Two genome-wide association studies (GWAS) and two projects employing panels of a few dozen of genes of interest provided most of the data. The other publications concerned no more than 5 genes at a time. Twenty studies reported positive findings. The relationship between *HLA-DRB1*15:01* or *BDNF* rs6265 (Val66Met) and the radiologic course of MS was not consistent across the studies. An intersection of the results of the two GWAS yielded: *OPCML* (rs11223055), *PTPRD* (rs1953594), and *WWOX* (rs11150140, rs1116525) (brain atrophy) as well as *CDH13* (rs692612) and *PLCB1* (rs6118257) (lesion load).
Conclusions. Genetic variants were shown to correlate with MS-related brain atrophy and lesion load. Further research in the field is required.

Keywords: brain, spinal cord, cortical, atrophy, lesion, polymorphism, snp, haplotype, imaging.

Introduction

Although environmental factors play the major role in the development of multiple sclerosis (MS; OMIM: 126200), genetic factors are implicated as well. Firstly, variants in human leukocyte antigen (HLA) complex genes are known to confer susceptibility to MS. The strongest evidence in this respect exists for the *HLA-DRB1*15:01* haplotype. Secondly, over a hundred single-nucleotide polymorphisms not related to HLA system are also known to influence the risk and/or course of this disease [1]. A number of studies specifically investigated the potential associations

between genetic variants and measures of central nervous system involvement in magnetic resonance (MR) imaging. We aimed to systematically review the literature on this topic and present the main data in a legible format.

Material and Methods

On December 8th, 2016, Scopus (Elsevier, Amsterdam, Netherlands; includes MEDLINE [2]) was queried with the following term: "TITLE (multiple sclerosis) AND TITLE-ABS-KEY (lesion OR lesions OR hyperintensity OR hyperintensities OR hyperintense OR hypointensity OR hypointensities OR hypointense OR enhancing OR enhanced OR enhance) AND TITLE-ABS-KEY (rs* OR variant OR variants OR polymorphism OR polymorphisms)." All types of documents were thus searched without a time limit. The 290 results were exported and further analyzed after excluding one item published before the year 1980, when magnetic resonance was first used in a clinical setting; although the first studies of genetic polymorphisms in MS were performed later, we did not filter our results further on the basis of the year published. All the entries were written in English. After screening titles and abstracts for information confirming that the studies investigated genetic variants, 91 of them were selected for further assessment. Among these, 26 reported investigating a possible link between genetic variation and radiological findings in the abstract; these were chosen for the final analysis (there were no duplicates). One of the articles was not included since the full text could not be obtained and imaging-related results in the abstract were unclear [3]. Another article was identified as relevant in references of the chosen studies [4]. We followed the approach proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5].

Results

Out of 26 studies, 20 found relationships between genetic variants and radiological findings in MR imaging of the central nervous system (**Table 1**).

The two genome-wide association studies (GWAS) provided a wealth of data [8, 19]. Of special interest are also the works by Sombekke et al., in which variants found in 44 MS-related genes were analyzed in the context of MR findings [14], and by Inkster et al., who focused on genes involved in epigenetic regulation [12]. The relationships between one or more HLA haplotypes and MR measures were searched for by seven non-GWAS studies. The remaining studies focused on particular genes of interest, of which most commonly researched were *BDNF* and *CCR5*. The methods of MR data acquisition and image method analysis varied between the studies, as did characteristics of patient groups.

None of the SNPs that were top-rated by the study of 44 genes by Sombekke et al. was found on the list of MR parameter covariates by Baranzini et al. *BTNL2* rs2076530 associated with MS susceptibility, but not MR measures. None of the findings from studies of individual genes (*GRIN1*, *BDNF*, *IRF5*, *PCK1, CCL5, CCR5, SIRT4, HDAC11, HDAC9*) was replicated by Baranzini et al. The above-listed genes were also missing from the list of 67 genes correlating with MR measures in all cerebral regions of interest in the two recruitment centers of GWAS by Matsushita et al. An intersection of the list by Matsushita et al. with the regression correlate list by Baranzini et al. yielded: *OPCML* (rs11223055), *PTPRD* (rs1953594), and *WWOX* (rs11150140, rs1116525) (Baranzini et al.: brain atrophy) as well as *CDH13* (rs692612) and *PLCB1* (rs6118257) (lesion load). The relationship between BDNF rs6265 (Val66Met) and the radiologic course of MS was not consistently replicated across the studies. While this was also true for *HLA-DRB1*15:01*, the recent evidence is convincing [6]. Overall, few positive findings of the reported studies were consistent.

Discussion

This brief systematic review gathered the data relating genetic variants to MR correlates of neurological lesions in MS. Any comparison of the included studies should consider the fact that MS diagnostic criteria constantly evolve [32]. MR imaging was featured in the clinical criteria in the year 2001, then reviewed in 2005 and 2010. For instance, the latest revision of McDonald criteria permit for an earlier MS diagnosis, but at the cost of the specificity. The work to further improve the guidelines is ongoing [33].

The association of MR measures in MS patients and *CDH13*, *PLCB1*, *PTPRD*, *OPCML*, and *WWOX* polymorphisms listed above warrants additional study. In conclusion, genetic variants were shown to correlate with MS-related brain atrophy and lesion load.

Table 1. Summary of the evidence regarding the relationship between genetic variants and magnetic resonance (MR) measures in multiple sclerosis (MS) patients

Study	n_{MS}	Gene	Variant	Evidence
Isobe et al. 2016 [6]	586	HLA-A, HLA-B, HLA-DRB1, HLA-DQB1	HLA-DRB1*15:01	In women, higher HLA genetic burden associated with lower volume of subcortical grey matter. *HLA-DRB1*15:01* was the haplotype most strongly linked to the finding and HLA-B*4402 had a protective role. No relationship between *HLA-A*02:01* and MR findings.
Yaldizli et al. 2016 [7]	85	HLA-DRB1	rs3135388 (*HLA-DRB1*15:01*)	No association of *HLA-DRB1*15:01* haplotype with cortical grey matter volume or magnetization transfer ratios in lesion or healthy grey matter.
Matsushita et al. 2015 [8]	464 211	Genome-wide association study	550,067 SNPs	*RYR2* and *CDH13* consistently associated with cortical thickness in 9 predefined regions in both MS cohorts. Additionally, 194 genes associated with one or more regions in both MS populations. No single SNP reached the significance threshold.
Huang et al. 2013 [9]	123	HLA-DRB1 HLA-DPB1 NOTCH4 IL7R	genotyping genotyping rs422951 rs6897932	In MS not meeting the Barkhof criteria *HLA-DRB1*04:05* was more frequent. In MS meeting the Barkhof criteria: *HLA-DPB1*03:01* and rs6897932-CC were more frequent; *HLA-DRB1*09:01* and *HLA-DPB1*04:01* less frequent.
Rossi et al. 2013 [10]	691	GRIN1	rs4880213	No association with lesion load. (Association of rs4880213-TT with thinning of the retinal nerve fiber thickness on optical coherence tomography in PPMS.)
Fera et al. 2013 [11]	26	BDNF	rs6265 (Val66Met)	Brain response greater than in HS while encoding and retrieving information in Val66 homozygous MS. Lower connectivity between the hippocampus and the posterior cingulate cortex on retrieval in Val66 homozygous MS. Other specific findings.
Inkster et al. 2013 [12]	326	Epigenetic regulatory genes	467 SNPs rs3135388 (HLA-DRB1*15:01) 3997 supplementary SNPs	Associations of *SIRT4* rs2522129; *HDAC11* rs2675231; *HDAC9* rs2389963 with various of 7 performed MR brain measurements, which included normalized brain volume and brain volume change in a year. No association between HLA-DRB1*15:01 and the volume of T2 lesions.
Vosslamber et al. 2011 [13]	75	IRF5	rs2004640 rs47281420	More new T2 lesions on MR during interferon-beta therapy in patients with *IRF5* rs2004640-TT. Association with MR non-responder status.
Sombekke et al. 2011 [14]	208	A selection of SNPs associated with MS	69 SNPs in 44 genes	An increased probability of lesions: *CCL5* rs2107538-CC, *IFNGR2* rs9808753-AA, *BTNL2* rs2076530-AG, *PNMT* rs876493-AG, MHC class II (*HLA-DRA*) region rs2227139-CT (most consistently associating); the major alleles of *CCL5* rs2107538 and *IFNGR2* rs9808753. A decreased probability of lesions: *FAS* rs3781202-CT, rs2234978-TT, *BTNL2* rs2076530-GG, *CRYAB* rs762550-AA, *NDUFS7* rs2074897-GG, *UCP2* rs659366-CC. Association with total T2 lesion volume: *UCP2* rs659366-CC, *BTNL2* rs2076530-GG and AG.
Ramasamy et al. 2011 [15]	188	BDNF	rs6265 (Val66Met)	Higher cingulate grey matter volume patients carrying at least one copy of Met66.
Weinstock-Guttman et al. 2011 [16]	209	BDNF	rs2030324	TT genotype associated with lower left thalamic volume, but not with total lesion measures or brain volume.
Xia et al. 2010 [17]	641	PICALM CR1 CLU PCK1 ZNF224	rs3851179 rs6656401 rs11136000 rs8192708 rs3746319	*PCK1* rs8192708-G associated with a smaller brain volume (brain parenchymal fraction) and a higher hyperintense T2 lesion load.
Sombekke et al. 2009 [18]	150	A selection of SNPs associated with MS	68 SNPs in 44 genes	Correlation with the count of lesions in the spinal cord: *MHC2* rs3135388, rs2395182, rs2239802, rs2227139, rs2213584. *CCL5* rs2107538 associated with T2 lesion load (false discovery rate-corrected p = 0.07).

Table 1. (continued)

Study	n_{MS}	Gene	Variant	Evidence
Okuda et al. 2009 [4]	505	HLA-DRB1	HLA-DRB1*15:01	Association of *HLA-DRB1*15:01* with increased white matter lesion volume and decreased normalized brain parenchymal volume.
Baranzini et al. 2009 [19]	794	Genome-wide association study	551,642 SNPs	Associated with brain parenchymal volume: *IRX1* rs4866550, *CDH10* rs10078091, *C20orf133* (*MACROD2*) rs368380, *MORF4* rs4473631, *SOX11* rs1869410, *BICD1* rs261902, *CAST1* rs11719646, *CHORDC1* rs1354913, *NLGN1* rs13067869, *PPP3CA* rs9307252, *FOXO3A* rs9480865 and rs9486902, *SVIL* rs1927457, *MXI1* rs716595, *KCNIP1* rs11957313, *SLITRK6* rs9319189, *CDCA1* rs10917727. Associated with the load of T2 lesions: *PLD5* rs12097667, *KIAA1706* rs1806468, *GPR126* rs146250, *HIVEP2* rs263153, *NPHP3* rs6794496, *CHRND* rs2602397, *FUT9* rs6899560, *NUBPL* rs2039485, *HIP2* rs305124, *IGF2R* rs6917747, *CPAMD8* rs11666377 and rs6512158, *IGF2R* rs12202350.
Zivadinov et al. 2007 [20]	209	BDNF	rs6265 (Val66Met)	The presence of Met66 associated with larger normalized grey matter volume and smaller T2 lesion volume. No link to whole brain or white matter volume.
van Veen et al. 2007 [21]	192	CCL5 CCR5	rs2107538 rs1799987 rs333 (CCR5Δ32)	A smaller risk of severe axonal loss with *CCL5* rs2107538-G. Lower T1 and T2 lesion volumes in MS with CCR5 rs1799987-G. Lower T2 lesion volume and black hole ratio when CCR5Δ32 present.
Kaimen-Maciel 2007 [22]	124	CCR5	rs333 (CCR5Δ32)	Associated with a lower frequency of at least one gadolinium-enhancing lesions.
Liguori et al. 2007 [23]	50	BDNF	rs6265 (Val66Met)	Lower cerebral grey matter volume in RRMS carriers of Met66.
Wergeland et al. 2005 [24]	63	IL10	rs1800896 rs3021097 rs1800872	More T1 contrast-enhancing lesions in patients with GCC phenotype during first 6 months of treatment with interferon.
Schrijver et al. 2004 [25]	96	TGFB1	rs1800470 (rs1800473) rs1800471	MS homozygous for *TGFB1* rs1800470-C (Leu10Pro) had greater annual increases in ventricular fraction and hypointense T1 lesions.
Zwemmer et al. 2004 [26]	408	APOE	ε4 (rs429358-C; rs7412-C) ε2 (rs429358-T; rs7412-T)	No link between ε2 or ε4 genotype and lesion volume or brain atrophy.
van Veen et al. 2004 [27]	514	CTLA4 CD28	rs5742909 rs231775 rs3116496	No link to lesion volume or brain atrophy.
van Veen et al. 2002 [28]	382	FAS	rs1800682	No link to lesion volume or brain atrophy.
Schreiber et al. 2002 [29]	70	DRB1 CCR5 APOE	*HLA-DRB1*15:01* rs333 (CCR5Δ32) ε4	No association of *HLA-DRB1*15:01* and *APOE* ε4 to total lesion area divided by MS duration. A non-significant trend for a lower value of this measure in CCR5Δ32 carriers.
Weatherby et al. 2000 [30]	50	GSTM1, GSTM3, GSTP1, GSTT1	genotyping	*GSTT1* null genotype associated with more gadolinium-enhancing lesions and more frequent occurrence of ≥ 3 lesions.
Nishimura et al. 1997 [31]	57	HLA-DRB1, HLA-DRB3, HLA-DRB5	genotyping	*HLA-DRB1*15:01* associated with the Western (more brain lesions, less enhancing spinal cord lesions), as opposed to the Asian type of MS.

PPMS – primary progressive MS; RRMS – relapsing-remitting MS; SNP – single-nucleotide polymorphism

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Conflict of interest statement
The authors declare no conflict of interest.

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