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

Jan K. Nowak¹, Izabela Guzikowska-Ruszkowska², Jadwiga Łopaciuch³, Wiesława Jankowska³, Ewa Piotrowska⁴, Ewa Dziedzic-Szeszuła⁵, Kinga Kapecka⁶, Jarosław Walkowiak¹

Introduction

Although environmental factors play the major role in the etiopathogenesis of multiple sclerosis (MS; OMIM: 126200), 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 hypointense 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 MR imaging; 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 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.
| Study                        | n<sub>MS</sub> | Gene and Variants                          | 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            | 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 genotype   | 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 rs6897392-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            | 467 SNPs (rs3135388, HLA-DRB1*15:01, rs422951, rs6897392) | 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 year. No association between HLA-DRB1*15:01 and the volume of T2 lesions. |
| Sombekke 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.                                                                    |
| Vosslamber et al. 2011 [14]  | 208            | A selection of SNPs associated with MS      | Correlation with the count of lesions in the spinal cord: MHC2 rs3135388, rs2395182, rs2239802, rs2227139, rs223584. CCL5 rs2107538 associated with T2 lesion load (false discovery rate-corrected p = 0.07). |
| Sombeke et al. 2009 [15]     | 150            | A selection of SNPs associated with MS      | TT genotype associated with lower left thalamic volume, but not with total lesion measures or brain volume. PCK1 rs8192708-G associated with a smaller brain volume (brain parenchymal fraction) and a higher hyperintense T2 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\_\text{obs} | 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, C2orf133 (MACROD2) rs368380, MORF4 rs4473631, SOX11 rs1869410, BIDCI rs261902, CAST71 rs1171946, CHORDC1 rs1334913, NLGN1 rs18067869, PPP3CA rs9307252, FOXO3A rs9408685 and rs9486902, SVIL rs1927457, MXI1 rs16595, KONIP1 rs11957313, SLITRK6 rs9319189, CDCA1 rs10917727. Associated with the load of T2 lesions: PLD5 rs12097657, KIAA1706 rs1806468, GPR126 rs146250, HIVEP2 rs263153, NPH1 rs5794496, CHRDN rs2602397, JFT9 rs6899560, NUBPL rs2039485, HIP2 rs305124, IGF2R rs6917747, CPAMD8 rs11665377 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-Г. 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)       | 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 if rs429358-C, rs7412-C, rs429358-Т, 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 between 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 (CCR5A32) 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 CCR5A32 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-DRB1 | 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

[Table 1. (continued)](334)
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References

1. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol. 2016. doi:10.1038/nrneurol.2016.187.

2. Scopus Content Coverage Guide. 2016. https://www.elsevier.com/__data/assets/pdf_file/0007/69451/scopus_content_coverage_guide.pdf [accessed on December 16th, 2016]

3. Allam M, Helmy H, Soliman R, Ali N, El-Shafy S. Association of Interleukin-1 Gene Polymorphism and Multiple Sclerosis. Egypt J Neurol Psychiatry Neurosurg. 2014;51:45–51.

4. Okuda DT, Srinivasan R, Oksenberg JR, Goodin DS, Baranzini SE, Beheshti A et al. Genotype-Phenotype correlations in multiple sclerosis: HLA genes influence disease severity inferred by TH1MR spectroscopy and MRI measures. Brain J Neurol. 2009;132:250–9.

5. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6:e1000097.

6. Isobe N, Keshavan A, Gourraud P-A, Zhu AH, Datta E, Schlaeger R et al. Association of HLA Genetic Risk Burden With Disease Phenotypes in Multiple Sclerosis. JAMA Neurol. 2016;73:795.

7. Yaldizli Ö, Sethi V, Pardini M, Tur C, Mok KY, Muhlert N et al. HLA-DRB1-1501 associations with magnetic resonance imaging measures of grey matter pathology in multiple sclerosis. Mult Scler Relat Disord. 2016;7:47–52.

8. Matsushita T, Madireddy L, Sprenger T, Khankhanian P, Magon S, Naegelin Y et al. Genetic associations with brain cortical thickness in multiple sclerosis: DNA variation affects cortical thickness in MS. Genes Brain Behav. 2015;14:217–27.

9. Huang J, Isobe N, Matsushita T, Yoshimura S, Sato S, Yonekawa T et al. Distinct genetic profiles between Japanese multiple sclerosis patients with and without Barkhof brain lesions. Clin Exp Neuroimmunol. 2013;1:473–80.

10. Rossi S, Studer V, Moscatelli A, Motta C, Coghe G, Fenu G et al. Opposite Roles of NMDA Receptors in Relapsing and Primary Progressive Multiple Sclerosis. PLoS ONE 2013;8:e67357.

11. Fera F, Passamonti L, Cerasa A, Gioia MC, Ligouri M, Manna I et al. The BDNF Val66Met Polymorphism Has Opposite Effects on Memory Circuits of Multiple Sclerosis Patients and Controls. PLoS ONE 2013;8:e61063.

12. Inkster B, Strijbis EMM, Younou M, Kappos L, Radue E-W, Matthews PM et al. Histone deacetylase gene variants predict brain volume changes in multiple sclerosis. Neurobiol Aging. 2013;34:238–47.

13. Vosslander S, van der Voort LF, van den Elskamp IJ, Heijmans R, Aubin C, Uttelhag BMJ et al. Interferon regulatory factor 5 gene variants and pharmacological and clinical outcome of Interferon therapy in multiple sclerosis. Genes Immun. 2011;12:466–72.

14. Sombekke MH, Vellinga MM, Uttelhag BMJ, Barkhof F, Polman CH, Artesa T et al. Genetic Correlations of Brain Lesion Distribution in Multiple Sclerosis: An Exploratory Study. Am J Neuroradiol. 2011;32:695–703.

15. Ramasamy DP, Ramanathan M, Cox J, Antulov R, Weinstock-Guttman B, Berglund N et al. Effect of Met66 allele of the BDNF rs6265 SNP on regional grey matter volumes in patients with multiple sclerosis: A voxel-based morphometry study. Pathophysiology. 2011;18:53–60.

16. Weinstock-Guttman B, Benedict RHB, Tamaño-Blanco M, Ramasamy DP, Stosis M, Polito J et al. The rs2030324 SNP of brain-derived neurotrophic factor (BDNF) is associated with visual cognitive processing in multiple sclerosis. Pathophysiology. 2011;18:43–52.

17. Xia Z, Chibnik LB, Blazek BI, Ligouri M, Shulman JM, Tran D et al. A Putative Alzheimer’s Disease Risk Allele in PCK1 Influences Brain Atrophy in Multiple Sclerosis. PLoS ONE 2010;5:e14169.

18. Sombekke MH, Lukas C, Crusius JBA, Tejedor D, Kill-estein J, Artesa T et al. HLA-DRB1*1501 and Spinal Cord Magnetic Resonance Imaging Lesions in Multiple Sclerosis. Arch Neurol. 2009:66.

19. Baranzini SE, Wang J, Gibson RA, Galwey N, Naegelin Y, Barkhof F et al. Genome-wide association analysis of susceptibility and clinical phenotype in multiple sclerosis. Hum Mol Genet. 2009;18:767–78.

20. Zivadinov R, Weinstock-Guttman B, Benedict R, Tama-no-Blanco M, Hussein S, Abdelrahman N et al. Preservation of grey matter volume in multiple sclerosis patients with the Met allele of the rs6265 (Val66Met) SNP of brain-derived neurotrophic factor. Hum Mol Genet. 2007;16:2659–68.

21. van Veen T, Nielsen J, Barkhof J, Barkhof F, Kamphorst W, Bó I et al. CCL5 and CCR5 genotypes modify clinical, radiological and pathological features of multiple sclerosis. Neuroimmunol. 2007;190:157–64.

22. Kaimen-Maciej DR, Reiche EMV, Brum Souza DG, Fro-ta Comini ER, Bobroff F, Morimoto HK et al. CCR5-Del-ta32 genetic polymorphism associated with benign clinical course and magnetic resonance imaging findings in Brazilian patients with multiple sclerosis. Int J Mol Med. 2007;20:337–44.

23. Liguori M, Fera F, Gioia MC, Valentino P, Manna I, Condi-no F et al. Investigating the role of brain-derived neurotrophic factor in relapsing-remitting multiple sclerosis. Genes Brain Behav. 2007;6:171–5.

24. Wergeland S, Beiske A, Nyland H, Hovdal H, Jensen D, Larsen JP et al. IL-10 promoter haplotype influence on interferon treatment response in multiple sclerosis. Eur J Neurol. 2005;12:171–5.

25. Schrijver HM, Crusius JBA, Garcia-González MA, Pol-man CH, Peña AS, Barkhof F et al. Gender-Related Association Between the &t; TGFBI &t; 669 Poly-morphism and Multiple Sclerosis. J Interferon Cytokine Res. 2004;24:536–42.

26. Zwemmer JNP, Van Veen T, Van Wijden L, Van Kamp GJ, Barkhof F, Polman CH et al. No major association
of ApoE genotype with disease characteristics and MRI findings in multiple sclerosis. Mult Scler. 2004;10:272–7.

27. Vanveen T, Crusius J, Vanwinsen L, Xia B, Barkhof F, Salvadorpena A et al. CTLA-4 and CD28 gene polymorphisms in susceptibility, clinical course and progression of multiple sclerosis. J Neuroimmunol. 2003;140:188–93.

28. van Veen T, Kalkers N, Crusius JB, van Winsen L, Barkhof F, Jongen PJ, et al. The FAS-670 polymorphism influences susceptibility to multiple sclerosis. J Neuroimmunol. 2002;128:95–100.

29. Schreiber K, Oturai A, Ryder L, Madsen H, Jørgensen O, Svejgaard A et al. Disease severity in Danish multiple sclerosis patients evaluated by MRI and three genetic markers (HLA-DRB1*1501, CCR5 deletion mutation, apolipoprotein E). Mult Scler. 2002;8:295–8.

30. Weatherby SJ, Mann CL, Davies MB, Fryer AA, Haq N, Strange RC et al. A pilot study of the relationship between gadolinium-enhancing lesions, gender effect and polymorphisms of antioxidant enzymes in multiple sclerosis. J Neurol. 2000;247:467–70.

31. Kondo K. Abstracts of the 41st annual meeting of the Japan society of human genetics October 23–25, 1996, Sapporo, Japan. Jpn J Hum Genet. 1997;42:23–167.

32. Przybek J, Gniatkowska I, Mirowska-Guzel D, Członkowska A. Evolution of diagnostic criteria for multiple sclerosis. Neurol Neurochir Pol. 2015;49:313–21.

33. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evange-lou N, Kappos L et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016;15:292–303.