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Putative association of *GPC5* polymorphism with the risk of inflammatory demyelinating diseases

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ABSTRACT

Inflammatory demyelinating diseases (IDDs) are severe inflammatory diseases of the central nervous system (CNS) that cause loss of myelin in the nerve sheaths and axonal degeneration. IDDs include multiple sclerosis (MS) and neuromyelitis optica (NMO). MS affects the axons of the brain and spinal cord, while NMO primarily affects the optic nerves and spinal cord. *Glypican 5* (*GPC5*) is known to be one of the susceptible genes for the risk of IDD, especially MS, based on genome-wide association studies (GWASs) and replication studies in Caucasians and African Americans. In the present study, in order to investigate the replicable genetic effects of *GPC5* polymorphisms on the risk of IDD in Korean subjects, nine genetic variants were selected and genotyped in 237 normal controls and 178 IDD patients (including 79 MS and 99 NMO). Statistical analysis revealed that *rs9523762* was associated with IDD and the association was retained even after correction for multiple testing (OR = 1.68, P^{corr} = 0.03). Marginal association was also observed in *rs1411751* (OR = 0.54, P = 0.02). In a subgroup analysis, *rs1411751* was found to be associated with NMO (OR = 0.36, P^{corr} = 0.03), and *rs9523762* was marginally associated with both NMO and MS. These results indicate that *GPC5* polymorphisms would be useful genetic indicators for IDDs, including NMO and MS.

1. Introduction

Inflammatory demyelinating diseases (IDDs) are a family that includes multiple sclerosis (MS) and neuromyelitis optica (NMO), inflammatory and neurodegenerative diseases that affect the central nervous system (CNS). CNS inflammation leads to demyelination and axonal degeneration [1] affecting the optic nerve and spinal cord. Loss of vision, weakness, stiffness, and painful spasms are known symptoms of inflammatory diseases, particularly MS [2–4]. Detection of a specific serum antibiotic marker (NMO-immunoglobulin G) in NMO is an important clinical characteristic that distinguishes NMO from MS [5–7]. Like most common diseases, MS is affected by multiple factors both genetic and environmental [8,9]. Twin studies from several populations provide evidence for a genetic etiology in MS in that a monozygotic twin is at higher risk for MS than is a dizygotic twin [10,11]. Several reports have shown that the classic susceptible loci for MS refined in a recent genome-wide association study (GWAS), such as *HLA-DRB1* and *HLA-A*, were also associated with the risk of NMO in Caucasians [12–15]. In addition, *IL2RA*, *IL7R*, *CD58*, *CLEC16A*, *DBC1*, and *GPC5* have been identified as factors influencing the pathogenesis of MS [8,16–21].

GPC5 is a member of the glypican family of genes encoding the glypican proteins, which regulate cell to cell signaling and maintain neural functions as neurotrophic factors. Each member of the glypican protein family has a different role in regulating the interaction between growth factors and their receptor, resulting in differential contributions to disease behaviors [18,22]. GPC1, GPC3, GPC5, and GPC6 among the glypican proteins are known to be overexpressed in several carcinomas. Recent GWASs have shown that genetic variations of *GPC5* were associated with a number of diseases such as nephrotic syndrome, sudden cardiac arrest, lung and breast cancer, and MS [23–27]. Interestingly, it has been recently demonstrated that the incidence of cancer was significantly decreased in individuals with MS [28]. Among the *GPC5* genetic variants, *rs9523762* was highly associated with the risk of MS in Caucasians [16], and its association has been replicated in several studies of Caucasians and African Americans [17,18,29–31].

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However, no association study connecting *GPC5* polymorphisms with the risk of MS or NMO has been reported in Asian populations, including Koreans. In the present study, we analyzed the association of *GPC5* polymorphisms with the risk of IDDs, specifically NMO and MS.

2. Materials and methods

2.1. Study subjects

For genotyping of *GPC5* polymorphisms, a total of 415 subjects were included in the study, with 99 NMO patients, 79 MS patients, and 237 controls (average age = 47.3 (38.0–60.0), female/male = 156/81). To have a biologically homogenous study population, we only included the patients with both optic neuritis and longitudinally extensive myelitis, according to the revised diagnostic criteria for NMO [32] or the limited form of NMO, who were seropositive for the aquaporin-4 antibody [4], and the patients who fulfill the revised 2005 McDonald criteria in the MS group [33]. Detailed demographics and clinical characteristics of the NMO patients were previously described elsewhere [6]. We measured the anti-AQP4 antibodies with an enzyme-linked immune sorbent assay (ELISA) and cell-based assay (CBA) with a commercial slide kit (Euroimmun, Luebeck, Germany) [7,34]. Patients were evaluated in the MS center at the National Cancer Center (NCC) of Korea. In addition, 237 healthy and old-age controls of Korean ethnicity were recruited who do not have IDD including NMO, classical MS, optic neuritis, and transverse myelitis. The study protocol was approved by the Institutional Review Board of the NCC of Korea. Written informed consent was obtained from each subject before the study. The clinical characteristics of the samples are shown in Table 1.

2.2. SNP selection and genotyping

Candidate single-nucleotide polymorphisms (SNPs) of *GPC5* were selected from the National Center for Biotechnology Information (NCBI; build 36; http://www.ncbi.nlm.nih.gov) and previous studies. The polymorphism *rs553717* was selected from NCBI SNP DB, and the rest of the SNPs were added from previous studies [17,18,30]. Nine polymorphisms were genotyped in 178 IDD patients and 237 normal controls using a TaqMan assay on the ABI prism 7900HT (Applied Biosystems, Foster City, CA, USA) [35]. Genotyping quality control was performed in 10% of the samples by duplicate checking as positive controls (rate of concordance in duplicates 100%) and distilled water was used for negative control. SNP call rates are 99.99% and sample call rates are 100%. Probe information on the polymorphisms is available in Supplementary Table 1.

2.3. Statistics

Linkage disequilibrium (LD) was obtained using Haploview v4.2 software from the Broad Institute (http://www.broadinstitute.org/mpg/haploview), with examination of Lewontin's D′ (|*D*′|) and the LD coefficient r^2 between all pairs of bi-allelic loci [36]. Haplotypes were estimated using PHASE software [37]. Comparison of genotype distributions between IDD patients and normal subjects was carried out with a logistic regression model adjusted for age (continuous value) and sex (male = 0, female = 1) as covariates using SAS, version 9.2 (SAS Inc., Cary, NC, USA). Significant associations are shown in boldface ($P \leq 0.05$). In subgroup analysis, association analyses between cases (NMO or MS) and normal subjects were also performed as described above. The effective number of independent marker loci was calculated for multiple testing corrections using SNPSpD (http://genepli.qimr.edu.au/general/daleN/SNPSpD/), a program that is based on the spectral decomposition (SpD) of matrices of pair-wise LD between SNPs. The sum total of independent marker loci in the gene was calculated as 8.8846, and this value was applied to correct for multiple testing ($P \times 8.88$).

Table 1
Clinical characteristics of study subjects.

	IDD (NMO + MS)	NMO	MS	Controls
N	178	98	80	237
Age (year, mean(range))	37.0(11–67)	39.9(11–67)	34.3(14–57)	47.3(38–60)
Sex (male/female)	39/139	10/88	29/51	81/156
Onset age (year, mean ± Std)	31.99 ± 11.50	33.4 ± 12.38	30.08 ± 10.23	–
Duration (year, mean ± Std)	5.86 ± 4.26	7.0 ± 4.40	4.45 ± 3.59	–

IDD, inflammatory demyelinating disease; NMO, neuromyelitis optica; MS, multiple sclerosis.

3. Results

Nine SNPs were selected from previous studies [16–18,29–31] and the NCBI SNP database (Fig. 1A). Detailed information about polymorphisms such as allele, position, minor allele frequency (MAF), heterozygosity, and Hardy–Weinberg equilibrium is presented in Table 2. LDs among SNPs were measured by calculating Lewontin's D′ and r^2 values. *GPC5* polymorphisms were parsed into two LD blocks. Each block (BL) was composed of three major haplotypes (ht) with over 5% of MAF (Fig. 1B and C). Among the haplotypes, three haplotypes, *BL1_ht1*, *BL2_ht2*, and *BL2_ht3*, were tagged with *rs39017789*, *rs9523762*, and *rs9523787*, respectively, and those haplotypes were excluded from further analysis (data not shown).

The case–control analysis of the association of *GPC5* polymorphisms with the risk of IDD revealed that two polymorphisms, *rs1411751* and *rs9523762*, and two haplotypes, *BL1_ht3* and *BL2_ht1*, showed marginal associations (OR = 0.54–1.68, P = 0.004–0.02; Table 3), though only *rs1411751* retained its association after correction for multiple testing (P^{corr} = 0.03). In the subgroup analysis of MS and NMO, *rs1411751* and *rs9523762* showed genetic effects on the risk of NMO (OR = 0.36 and 1.60, P = 0.005 and 0.02, P^{corr} = 0.03 and 0.17, respectively), and two haplotypes, *BL1_ht3* and *BL2_ht1*, were associated with the risk of NMO (P = 0.004 and 0.048, P^{corr} = 0.03 and 0.33, respectively). Moreover, *rs9523762* and *rs1287985* were marginally associated with the risk of MS (OR = 1.68 and 0.39, P = 0.05 and 0.04, P^{corr} = 0.34 and 0.27, respectively).

In comparison to previous studies, several SNPs had been reported as having association with the risk of MS. Among them, the associations of two polymorphisms, *rs9523762* and *rs1287985*, were replicated in the current study (Table 4). In order to investigate whether our results were due to ethnic differences, we calculated the differences in allelic distribution among three ethnic groups from the International HapMap database, including Africans, Asians, and Caucasians, using a chi-square test (Supplementary Table 2). Polymorphisms that failed to replicate their associations in the current study showed significant differences in allele distribution between Asian and other ethnic groups. LDs of the selected *GPC5* polymorphisms were also analyzed among three different races. The structure of LDs was nearly same across the populations, although *rs9523762* showed a relatively lower LD with other SNPs, as its |D′| values were lower than those of other SNPs', *rs17233850*, *rs9523793*, and *rs9516129*. This SNP was found to be highly associated with the risk of disease in previous studies as well as in the current study (Supplementary Fig. 1).

4. Discussion

The current study examined the association of *GPC5* polymorphisms that were known to be susceptible loci for inflammatory diseases, including MS and NMO. [16,29–31,38]. Recently, GWASs and replication studies have suggested a possible genetic role of *GPC5* in the development

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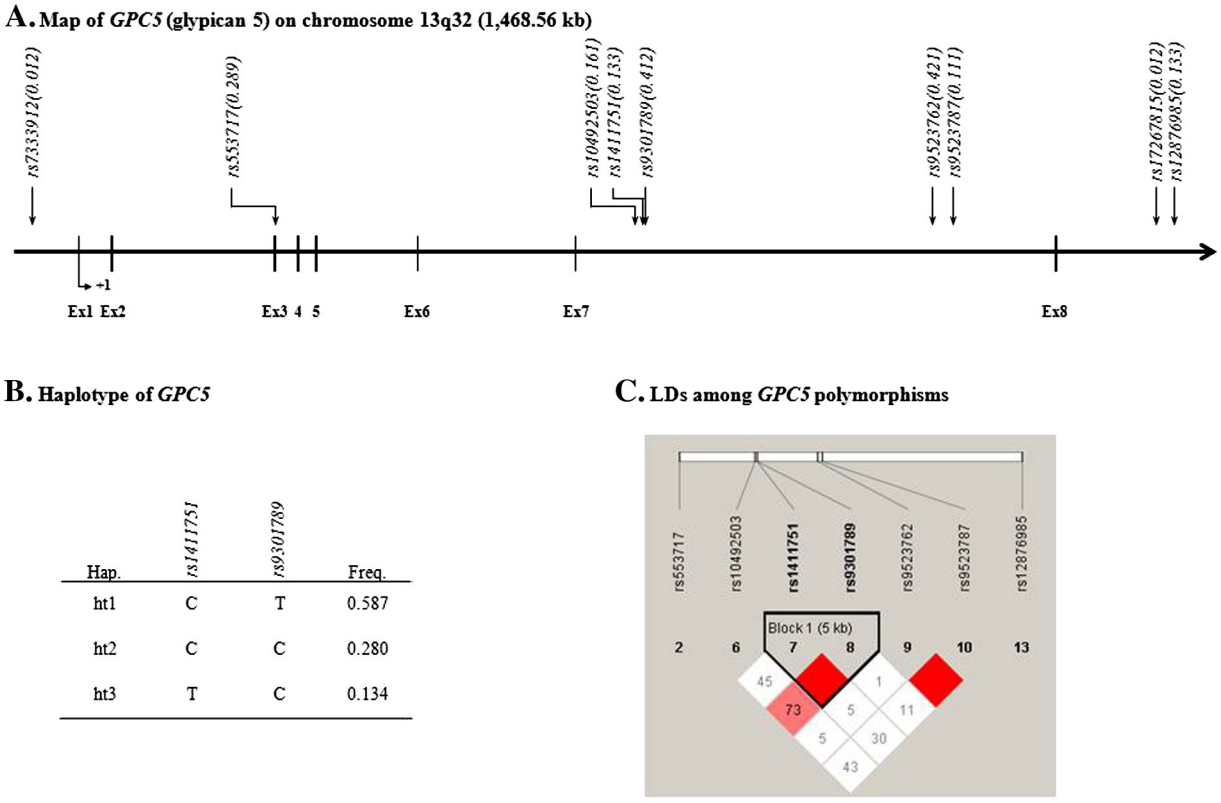

Fig. 1. Schematic physical map of *GPC5*. (A) Polymorphisms of *GPC5*. Black blocks indicate coding exons; white blocks, 5′- and 3′-untranslated regions. First base of translation site is denoted as nucleotide +1. (B) Haplotypes of *GPC5* in a Korean population. (C) LDs among *GPC5* polymorphisms. Values in LD box showed |D′| value. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of MS in Caucasians [16,17,29,31,39]. In MS, the auto-immune system attacks the myelin sheath, which leads to demyelination of brain axons, while NMO selectively affects the optic nerves and spinal cord [3,4,40–43]. Immunopathology of MS and NMO is mainly regulated by CD4 positive T cells and NMO-immunoglobulin-G (NMO-IgG), respectively. By interacting with NMO-IgG, AQP4 acts as a pathogen and is a factor that distinguishes NMO from MS [3,5,34,41,44]. In the current study, although the number of study subjects was smaller than previous studies, we only enrolled patients who had been definitively diagnosed using NMO-IgG to avoid the potential for case ascertainment error. All patients with NMO were seropositive for the AQP4 antibody based on highly specific assays, and their symptoms were typical for NMO patients. In addition, the diagnosis of all patients with MS was made by a qualified MS specialist. As a result, we believe that the possibility of ascertainment error was reduced.

Based on the functional characteristics of *GPC5* and its plausible genetic contributions to the auto-immune diseases under study, nine SNPs were analyzed in 178 IDD patients and 237 normal controls. Among the analyzed SNPs, two polymorphisms, *rs1411751* and *rs9523762*, were found to be significantly associated with the risk of IDD, and *rs9523762* was marginally associated with the risk of NMO and MS. Interestingly, the genetic effects of *rs9523762* differ across populations. In the current study, *rs9523762* G allele was found to be a minor allele and showed an increased risk of MS development (OR = 1.68). In contrast, *rs9523762* G allele was found to be a common allele in Caucasians and African Americans and its effects varied depending on the population (Table 4) [16,18,29,30]. Moreover, studies in Northern European and Spanish populations have demonstrated that genetic effects can be different among similar ethnic groups [16,18]. These differences might be clues suggesting

Table 2
Allele frequency of *GPC5* polymorphisms in Korean subjects (n = 415).

SNP	Allele	Amino acid change	Position	Genotype distribution			MAF	Heterozygosity	HWE		
				C/C	C/R	R/R			IDD	NC	Total
rs7333912	C > G	–	5′ UTR	403	10	0	0.012	0.024	0.879	0.843	0.803
rs553717	G > A	A155V	Exon3	211	167	36	0.289	0.411	0.382	0.763	0.718
rs10492503	A > T	–	Intron7	294	107	13	0.161	0.270	0.576	0.136	0.398
rs1411751	C > T	–	Intron7	307	90	9	0.133	0.231	0.872	0.563	0.434
rs9301789	T > C	–	Intron7	138	207	66	0.412	0.485	0.215	0.942	0.427
rs9523762	A > G	–	Intron7	129	221	64	0.421	0.488	0.049	0.245	0.054
rs9523787	G > T	–	Intron7	332	74	9	0.111	0.197	0.054	0.334	0.052
rs17267815	G > A	–	3′ flanking	403	8	1	0.012	0.024	0.970	0.002	0.000
rs12876985	G > A	–	3′ flanking	309	102	4	0.133	0.230	0.111	0.459	0.160

C/C, C/R, and R/R refer to the common homozygote, heterozygote, and minor homozygote, respectively.
MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

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Table 3
Logistic analysis of *GPC5* polymorphisms with inflammatory demyelinating diseases, neuromyelitis optica and multiple sclerosis in Korean subjects.

Loci	Diagnosis														
	Inflammatory demyelinating diseases(IDD)					Neuromyelitis optica(NMO)					Multiple sclerosis(MS)				
	MAF		OR(95% CI)	*P*	P^{corr}	MAF		OR(95% CI)	*P*	P^{corr}	MAF		OR(95% CI)	*P*	P^{corr}
	Case	Control				Case	Control				Case	Control			
	IDD (n = 178)	NC (n = 237)				NMO (n = 99)	NC (n = 237)				MS (n = 79)	NC (n = 237)			
rs7333912	0.011	0.013	1.37(0.32–5.78)	0.67	1	0.010	0.013	1.31(0.24–7.11)	0.75	1	0.013	0.013	2.02(0.2–20.84)	0.55	1
rs553717	0.297	0.283	1.22(0.85–1.73)	0.28	1	0.278	0.283	1.12(0.73–1.70)	0.60	1	0.321	0.283	1.23(0.75–2.04)	0.41	1
rs10492503	0.149	0.169	0.74(0.48–1.15)	0.18	1	0.162	0.169	0.78(0.47–1.29)	0.33	1	0.133	0.169	0.61(0.31–1.20)	0.15	1
rs1411751	0.083	0.169	0.54(0.32–0.91)	**0.02**	0.15	0.063	0.169	0.36(0.18–0.73)	**0.005**	**0.03**	0.108	0.169	0.91(0.44–1.87)	0.80	1
rs9301789	0.384	0.434	0.87(0.62–1.22)	0.41	1	0.387	0.434	0.78(0.53–1.15)	0.22	1	0.380	0.434	0.97(0.59–1.60)	0.91	1
rs9523762	0.483	0.375	1.68(1.18–2.40)	**0.004**	**0.03**	0.490	0.375	1.60(1.06–2.42)	**0.02**	0.17	0.475	0.375	1.68(1.00–2.84)	**0.05**	0.34
rs9523787	0.098	0.120	0.89(0.53–1.50)	0.67	1	0.096	0.120	0.92(0.51–1.67)	0.78	1	0.101	0.120	0.78(0.35–1.74)	0.54	1
rs17267815	0.003	0.019	0.30(0.04–2.29)	0.24	1	0.005	0.019	0.43(0.06–3.17)	0.41	1	0.000	0.019	–	–	–
rs12876985	0.107	0.152	0.60(0.36–1.02)	0.058	0.40	0.126	0.152	0.76(0.43–1.35)	0.35	1	0.082	0.152	0.39(0.16–0.95)	**0.04**	0.27
BL1_ht2	0.298	0.266	1.16(0.81–1.66)	0.43	1	0.323	0.266	1.21(0.81–1.82)	0.36	1	0.266	0.266	0.94(0.54–1.61)	0.81	1
BL1_ht3	0.087	0.169	0.59(0.36–0.97)	**0.04**	0.24	0.066	0.169	0.37(0.19–0.74)	**0.004**	**0.03**	0.114	0.169	1.05(0.53–2.08)	0.89	1
BL2_ht1	0.419	0.504	0.65(0.46–0.91)	**0.013**	0.09	0.414	0.504	0.67(0.45–1.00)	**0.048**	0.33	0.424	0.504	0.68(0.41–1.13)	0.14	1

IDD, inflammatory demyelinating disease; NC, normal control; NMO, neuromyelitis optica; MS, multiple sclerosis.
MAF, minor allele frequency; OR, odds ratio; CI, confidence interval.
The *P*-values and odds ratios with 95% CI were calculated using the co-dominant model.
GPC5-BL1_ht1, *BL2_ht2*, and *BL2_ht3* were excluded in the current analysis because they were equivalent to *rs9301789*, *rs9523762*, and *rs9523787*, respectively.
The effective number of independent marker loci in *GPC5* was calculated to correct for multiple testing using SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/). The number of independent marker loci in *GPC5* was calculated as 8.8846.

Table 4
Comparison of genetic effects of *GPC5* SNPs on multiple sclerosis in previous studies.

Loci	Reference															
	Baranzini et al. (2009)		Cenit et al. (2009)		Lorentzen AR et al. (2010)		Johnson et al. (2010)		Cavanillas et al. (2011)		This study					
	European		Spanish		Norwegian		African American		Spanish		Korean					
	MS[a]		MS		MS		MS		MS		MS		NMO		IDD	
	(978 vs. 883)[b]		(199 vs.493)		(1355 vs.1446)		(918 vs. 656)		(2863 vs. 2930)		(79 vs. 237)		(99 vs. 237)		(178 vs. 237)	
	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*
rs7333912	–	–	–	–	**0.53**	**0.02**	–	–	–	–	2.02	0.55	1.31	0.75	1.37	0.67
rs553717	–	–	–	–	1.06	0.55	**1.28**	**0.007**	–	–	1.23	0.41	1.12	0.6	1.22	0.28
rs10492503	–	–	**0.38**	**0.0005**	–	–	–	–	–	–	0.61	0.15	0.78	0.33	0.74	0.18
rs1411751	–	–	**0.28**	**0.0007**	–	–	–	–	–	–	0.91	0.8	0.36	**0.005**	0.54	**0.02**
rs9523554	–	–	0.67	0.6	–	–	–	–	–	–	–	–	–	–	–	–
rs9301789	–	–	–	–	–	–	–	–	–	–	0.97	0.91	0.78	0.22	0.87	0.41
rs9523762	**1.23**	**1×10^{-6}**	–	–	1.03	0.6	1.15	0.154	**0.81**	**1.6×10^{-5}**	1.68	**0.05**	1.6	**0.02**	1.68	**0.004**
rs9523787	–	–	–	–	**1.32**	**0.0002**	–	–	–	–	0.78	0.54	0.92	0.78	0.89	0.67
rs17233850	–	–	–	–	1.02	0.75	–	–	–	–	–	–	–	–	–	–
rs9523793	–	–	–	–	0.97	0.67	–	–	–	–	–	–	–	–	–	–
rs9516129	–	–	–	–	1.04	0.57	–	–	–	–	–	–	–	–	–	–
rs9516133	–	–	–	–	1.05	0.41	–	–	–	–	–	–	–	–	–	–
rs17267815	–	–	–	–	0.89	0.03	–	–	–	–	N	N	0.43	0.41	0.3	0.24
rs12876985	–	–	–	–	0.89	0.04	–	–	–	–	0.39	**0.04**	0.76	0.35	0.6	0.058

MS, multiple sclerosis; NMO, neuromyelitis optica; IDD, inflammatory demyelinating disease.
OR, odds ratio; –, not done; N, not analyzed.
The SNPs *rs9523554*, *rs17233850*, *rs9523793*, *rs9516129*, and *rs9516133* were excluded from the current study because they were not polymorphic in Asian subjects from the International HapMap Database (presented in Supplementary Table 2).
[a] Disease categorization.
[b] (number of cases vs. number of controls).

the presence of additional factors such as environmental or geographical. This hypothesis might be supported by the fact that the incidence of clinical MS in Northern Europeans is significantly higher than that of Southern Europeans [45]. A different prevalence based on geographic location could be caused by vitamin D levels. Ultraviolet light increases production of vitamin D in the skin [46]. The mechanism of interaction between vitamin D and MS is not fully understood, but several studies indicate that sufficient levels of vitamin D show a protective effect against MS [9,47].

The SNP *rs1411751*, another significantly associated locus with IDD in this study, showed a same direction of genetic effect to MS from previous study in a Spanish population (OR = 0.91 in the current study and 0.28 in Spanish) [31]. The polymorphism *rs553717*, which is located in the coding region and causes an amino acid change (Ala155Val) showed an effect on the risk of MS in African Americans [29]. However, association with the risk of inflammatory diseases was not found and noticeable functional change was not predicted using in silico analysis in the current study (data not shown).

To determine whether the effects of polymorphisms came from the ethnic difference, allele distributions of *GPC5* polymorphisms were compared among Asians, Caucasians, and Africans. Significant differences were observed between Asians and other populations in several SNPs. These differences could cause difference in genetic effects and might be a plausible reason for the apparent lack of association (Supplementary Table 2).

In summary, an association analysis between *GPC5* polymorphisms and the risk of IDD, including MS and NMO as subgroups, showed that a single SNP, *rs9523762*, was significantly associated with the development of IDD, and this association was evident in both NMO and MS patients. The current study demonstrates that *GPC5* polymorphisms could be useful genetic markers for inflammatory diseases. Although further studies should be conducted to confirm these findings in other ethnic groups, the current study is likely the first to report the importance of *GPC5* as a genetic factor in inflammatory diseases, which may prove useful for identifying the etiology of IDD among Asians.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2013.08.031.

Conflict of interest

The authors declare that they have no conflicts of interest.

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References

[1] Hauser SL, Oksenberg JR. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron 2006;52:61–76.
[2] McElroy JP, Oksenberg JR. Multiple sclerosis genetics. Curr Top Microbiol Immunol 2008;318:45–72.
[3] Kenealy SJ, Pericak-Vance MA, Haines JL. The genetic epidemiology of multiple sclerosis. J Neuroimmunol 2003;143:7–12.
[4] Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805–15.
[5] Chihara N, Aranami T, Sato W, Miyazaki Y, Miyake S, Okamoto T, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc Natl Acad Sci U S A 2011;108:3701–6.
[6] Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Clinical spectrum of CNS aquaporin-4 autoimmunity. Neurology 2012;78:1179–85.
[7] Kim W, Lee JE, Li XF, Kim SH, Han BG, Lee BI, et al. Quantitative measurement of anti-aquaporin-4 antibodies by enzyme-linked immunosorbent assay using purified recombinant human aquaporin-4. Mult Scler 2011;18:578–86.
[8] Hoffjan S, Akkad DA. The genetics of multiple sclerosis: an update 2010. Mol Cell Probes 2010;24:237–43.
[9] Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol 2004;3:709–18.
[10] Hansen T, Skytthe A, Stenager E, Petersen HC, Bronnum-Hansen H, Kyvik KO. Concordance for multiple sclerosis in Danish twins: an update of a nationwide study. Mult Scler 2005;11:504–10.
[11] Islam T, Gauderman WJ, Cozen W, Hamilton AS, Burnett ME, Mack TM. Differential twin concordance for multiple sclerosis by latitude of birthplace. Ann Neurol 2006;60:56–64.
[12] Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, Moutsianas L, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 2011;476:214–9.
[13] Asgari N, Nielsen C, Stenager E, Kyvik KO, Lillevang ST. HLA, PTPN22 and PD-1 associations as markers of autoimmunity in neuromyelitis optica. Mult Scler 2012;18:23–30.
[14] Field J, Browning SR, Johnson LJ, Danoy P, Varney MD, Tait BD, et al. A polymorphism in the HLA-DPB1 gene is associated with susceptibility to multiple sclerosis. PLoS One 2010;5:e13454.
[15] Martinelli-Boneschi F, Esposito F, Brambilla P, Lindstrom E, Lavorgna G, Stankovich J, et al. A genome-wide association study in progressive multiple sclerosis. Mult Scler 2012;18:1384–94.
[16] 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.
[17] Byun E, Caillier SJ, Montalban X, Villoslada P, Fernandez O, Brassat D, et al. Genome-wide pharmacogenomic analysis of the response to interferon beta therapy in multiple sclerosis. Arch Neurol 2008;65:337–44.
[18] Cavanillas ML, Fernandez O, Comabella M, Alcina A, Fedetz M, Izquierdo G, et al. Replication of top markers of a genome-wide association study in multiple sclerosis in Spain. Genes Immun 2011;12:110–5.
[19] Goldstein BA, Hubbard AE, Cutler A, Barcellos LF. An application of Random Forests to a genome-wide association dataset: methodological considerations & new findings. BMC Genet 2010;11:49.
[20] Oksenberg JR, Baranzini SE, Sawcer S, Hauser SL. The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. Nat Rev Genet 2008;9:516–26.
[21] Pravica V, Popadic D, Savic E, Markovic M, Drulovic J, Mostarica-Stojkovic M. Single nucleotide polymorphisms in multiple sclerosis: disease susceptibility and treatment response biomarkers. Immunol Res 2012;52:42–52.
[22] Veugelers M, Vermeesch J, Reekmans G, Steinfeld R, Marynen P, David G. Characterization of glypican-5 and chromosomal localization of human GPC5, a new member of the glypican gene family. Genomics 1997;40:24–30.
[23] Handel AE, Ramagopalan SV. GPC5 and lung cancer in multiple sclerosis. Lancet Oncol 2010;11:714.
[24] Li Y, Yang P. GPC5 gene and its related pathways in lung cancer. J Thorac Oncol 2011;6:2–5.
[25] Zhang C, Zhang S, Zhang D, Zhang Z, Xu Y, Liu S. A lung cancer gene GPC5 could also be crucial in breast cancer. Mol Genet Metab 2011;103:104–5.
[26] Arking DE, Reinier K, Post W, Jui J, Hilton G, O'Connor A, et al. Genome-wide association study identifies GPC5 as a novel genetic locus protective against sudden cardiac arrest. PLoS One 2010;5:e9879.
[27] Okamoto K, Tokunaga K, Doi K, Fujita T, Suzuki H, Katoh T, et al. Common variation in GPC5 is associated with acquired nephrotic syndrome. Nat Genet 2011;43:459–63.
[28] Handel AE, Ramagopalan SV. Multiple sclerosis and risk of cancer: a meta-analysis. J Neurol Neurosurg Psychiatry 2010;81:1413–4.
[29] Johnson BA, Wang J, Taylor EM, Caillier SJ, Herbert J, Khan OA, et al. Multiple sclerosis susceptibility alleles in African Americans. Genes Immun 2010;11:343–50.
[30] Lorentzen AR, Melum E, Ellinghaus E, Smestad C, Mero IL, Aarseth JH, et al. Association to the Glypican-5 gene in multiple sclerosis. J Neuroimmunol 2010;226:194–7.
[31] Cenit MDC, Blanco-Kelly F, Heras VDL, Bartolome M, de la Concha EG, Urcelay E, et al. Glypican 5 is an interferon-beta response gene: a replication study. Mult Scler 2009;15:913–7.
[32] Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485–9.
[33] Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840–6.
[34] Jarius S, Probst C, Borowski K, Franciotta D, Wildemann B, Stoecker W, et al. Standardized method for the detection of antibodies to aquaporin-4 based on a highly sensitive immunofluorescence assay employing recombinant target antigen. J Neurol Sci 2010;291:52–6.
[35] Livak KJ. Allelic discrimination using fluorogenic probes and the 5′ nuclease assay. Genet Anal 1999;14:143–9.
[36] Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263–5.
[37] Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet 2001;68:978–89.
[38] De Jager PL, Jia X, Wang J, de Bakker PI, Ottoboni L, Aggarwal NT, et al. Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci. Nat Genet 2009;41:776–82.
[39] Habek M, Brinar VV, Borovecki F. Genes associated with multiple sclerosis: 15 and counting. Expert Rev Mol Diagn 2010;10:857–61.
[40] Compston A, Coles A. Multiple sclerosis. Lancet 2002;359:1221–31.

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[41] Niino M, Uesugi H, Takahashi T, Fukazawa T, Minami N, Tashiro J, et al. Recurrent brainstem lesions mimicking infarctions in an elderly patient with neuromyelitis optica spectrum disorder. Intern Med 2012;51:809–12.
[42] Racke MK, Ratts RB, Arredondo L, Perrin PJ, Lovett-Racke A. The role of costimulation in autoimmune demyelination. J Neuroimmunol 2000;107:205–15.
[43] Stinissen P, Raus J, Zhang J. Autoimmune pathogenesis of multiple sclerosis: role of autoreactive T lymphocytes and new immunotherapeutic strategies. Crit Rev Immunol 1997;17:33–75.
[44] Sato D, Fujihara K. Atypical presentations of neuromyelitis optica. Arq Neuropsiquiatr 2011;69:824–8.
[45] Rosati G. The prevalence of multiple sclerosis in the world: an update. Neurol Sci 2001;22:117–39.
[46] Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. Lancet Neurol 2010;9:599–612.
[47] Simon KC, Munger KL, Ascherio A. Vitamin D and multiple sclerosis: epidemiology, immunology, and genetics. Curr Opin Neurol 2012;25:246–51.

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