Association analysis of *IL7R* polymorphisms with inflammatory demyelinating diseases

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Abstract. Multiple sclerosis (MS) and neuromyelitis optica (NMO), which are referred to as inflammatory demyelinating diseases (IDDs), are autoimmune diseases affecting the central nervous system. *Interleukin-7 receptor (IL7R)* encodes for a receptor protein that is important in the development of immune cells. Several studies have reported significant associations between *IL7R* polymorphisms and MS. The aim of the present study was to investigate a possible association between *IL7R* polymorphisms and IDDs such as MS and NMO. Thirteen single nucleotide polymorphisms (SNPs) were selected based on their linkage disequilibrium (LD), minor allele frequency (MAF) and location, and were genotyped in 178 IDD patients and 237 healthy controls. The association of SNPs with IDD risk was analyzed by logistic regression. A meta-analysis on the association between *rs6897932* and the risk of MS was also performed. Statistical analyses revealed that a common SNP, *rs6897932,* was marginally associated with IDD in a recessive model (P=0.003, $P^{cor.}$=0.03), which had shown significant associations with MS in previous studies. The results replicated the significant association found between *rs6897932* and IDD. In addition, the meta-analysis of *rs6897932* clearly demonstrates a higher magnitude of risk in Asian populations than in Caucasian populations. Although there are certain limitations to our study, the results indicate that the genetic variation of *IL7R* may be associated with IDDs such as MS and NMO in the population studied.

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease (IDD) caused by damage to the myelin sheaths of axons in the central nervous system, leading to demyelination and scarring (1). A patient with MS may suffer from a broad spectrum of signs or symptoms, including, but not limited to, changes in sensation, muscle weakness, ataxia, difficulties with speech, swallowing and vision, fatigue and chronic pain. Psychological symptoms such as depression and unstable mood are also commonly observed. The onset of MS usually occurs in young adults, and more often in females than in males. The cause of the disease is not fully understood, but researchers agree that a combination of genetic and environmental factors are responsible for the development of the disease (2). Advances in the field of genetics research have led to the identification of various genes related to MS. One of the most well-known genetic regions that affects MS is the *human leukocyte antigen* (*HLA*) region in chromosome 6. However, this region explains only a fraction of MS genetic etiology (2). In order to investigate the genetic factors of MS, a number of studies have searched for risk genes using the latest technology. As a result, several genes, such as *interleukin-7 receptor* (*IL7R*), *interleukin-2 receptor α* (*IL2RA*), *glypican-5* (*GPC5*), *cluster of differentiation 6* (*CD6)* and *tumor necrosis factor receptor superfamily member 1 α* (*TNFRSF1A*) have been found to be associated with MS risk (3-6).

Neuromyelitis optica (NMO) is another type of IDD that particularly affects the optic nerve and spinal cord, leading to optic neuritis and demyelination. Although its signs and symptoms overlap with MS in certain ways, evidence from neuroimaging and laboratory findings indicate that NMO etiology is different from that of MS (7,8). In addition, while MS is an uncommon disease in Asian populations, NMO is more prevalent in Asians when compared with MS (9-11). Although numerous studies have been conducted on the association between MS and genetic polymorphisms, studies on correlations between NMO and polymorphisms are less common. We previously conducted a genome-wide association study (GWAS) for NMO and MS, which showed that the risk polymorphisms for NMO were different from those of MS (12).

Table I. Clinical characteristics of subjects.

Characteristics	NMO	MS	IDD (NMO+MS)	NC
No. of subjects	98	80	178	237
Age [mean (min-max)]	39.9 (11-67)	34.3 (14-57)	37.0 (11-67)	47.3 (38-60)
Gender (male/female)	10/88	29/51	39/139	81/156
Onset age (age, mean ± SD)	33.4±12.38	30.08±10.23	31.99±11.50	-
Duration (year, mean ± SD)	7.0±4.40	4.45±3.59	5.86±4.26	-

NMO, neuromyelitis optica; MS, multiple sclerosis; IDD, inflammatory demyelinating diseases; NC, normal controls.

IL7R, located on the surface of immune cells, is a heterodimer known to be important in the development of lymphocytes (13). This protein also controls the accessibility of the T-cell receptor γ gene (14). Thus, several studies have investigated a possible association between genetic polymorphisms of *IL7R* and MS. A GWAS revealed that polymorphisms of *IL7R* were associated with MS (6), and several follow-up studies have confirmed this association in different ethnic populations, including European, Australian, American and Japanese populations (6,15-17).

In this study, we examined the association analysis between *IL7R* polymorphisms and IDD, including MS and NMO, in a Korean population. Additionally, we conducted a meta-analysis of MS studies carried out in various populations to compare and contrast the effects of *IL7R* polymorphisms.

Materials and methods

Subjects. For the genotyping of *IL7R* polymorphisms, a total of 415 patients were recruited, including 98 NMO patients, 80 MS patients (178 IDD patients in total) and 237 normal control patients. Individuals with each disease were evaluated and invited to participate in the study at the MS centers of the Asian Medical Center, Ewha Woman's University Medical Center and National Cancer Center of Korea from July 2006 to September 2007. Thorough attention was given to age, gender, disease duration, age at disease onset and assessment of disease severity using the Expanded Disability Status Scale (18). In addition, 237 healthy and elderly controls of Korean ethnicity were included who had not suffered from IDDs, including NMO, classical MS or idiopathic recurrent transverse myelitis. The study protocol was approved by the Institutional Review Board of the National Cancer Center of Korea. Written informed consent was obtained from each subject prior to initiation of the study.

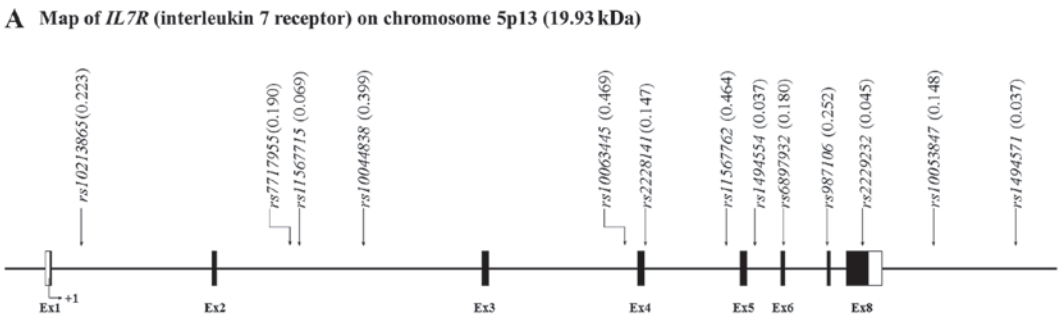
Single-nucleotide polymorphism (SNP) selection and genotyping. Thirteen SNPs of *IL7R* were selected based on linkage disequilibrium (LD), minor allele frequency (MAF) (>0.05), locations (SNPs in exons were preferred) and amino acid changes (non-synonymous SNPs were preferred) from the Asian (Chinese and Japanese) population database of the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/). The selected SNPs were then genotyped in 178 IDD cases and 237 normal control subjects using a TaqMan assay from the ABI prism 7900HT sequence detection system (Applied Biosystems, Foster City, CA, USA). Genotyping quality control was performed in 10% of the samples by duplicate checking (rate of concordance in duplicates >99.5%).

Statistical analysis. The LD was obtained using the 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 the pairs of bi-allelic loci (19). Haplotypes were first estimated using PHASE software (20), and then computed using a Statistical Analysis System (SAS). Associations for IDD, MS and NMO in a logistic model were adjusted for age (continuous value) and gender (male was 0, female was 1) as covariates, using SAS. In order to correct for the multiple testing error, the Single Nucleotide Polymorphism Spectral Decomposition program (http://gump.qimr.edu.au/general/daleN/SNPSpD/) was used, with the correction number of 9.4353. The meta-analysis was conducted with the R program package 'meta'. Comparisons between ethnic groups were conducted with an SAS using a Chi-square test, and an LD plot of the ethnic groups was obtained using the Haploview software. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Subjects and IL7R characteristics. A total of 415 subjects were enrolled in the present study: 178 IDD patients, which included 80 MS patients and 98 NMO patients, and 237 normal controls. Information about the subjects, including age, gender, age of disease onset and duration of disease is listed in Table I. A physical map of *IL7R* and the location of the SNPs are shown in Fig. 1A. In addition, information on five common haplotypes and the LD block of *IL7R* are shown in Fig. 1B and C, respectively. The LD block of *IL7R* showed that the SNPs formed one tight block. Detailed information on the 13 SNPs selected from *IL7R* is listed in Table II. All the SNPs had an MAF >0.05 and none of the SNPs broke the Hardy-Weinberg equilibrium in the case, control or total populations.

Association between rs6897932 and IDD. We analyzed the 13 selected SNPs for the risk of IDD, MS and NMO (Table III).



B Haplotypes of *IL7R*

Hap.	rs10213865	rs7717955	rs11567715	rs10044838	rs10063445	rs2228141	rs11567762	rs1494554	rs6897932	rs987106	rs2229232	rs10053847	rs1494571	Freq.
ht1	A	C	C	C	A	C	A	A	C	T	C	G	C	0.524
ht2	C	T	C	T	C	C	G	A	T	A	C	G	C	0.175
ht3	A	C	C	T	C	T	G	A	C	T	C	A	C	0.149
ht4	A	C	A	C	C	C	G	A	C	T	T	G	C	0.045
ht5	C	C	C	T	C	C	G	A	C	A	C	G	C	0.035
Others	.	.	.	.	.	.	.	.	.	.	.	.	.	0.071

C LD Block of *IL7R*

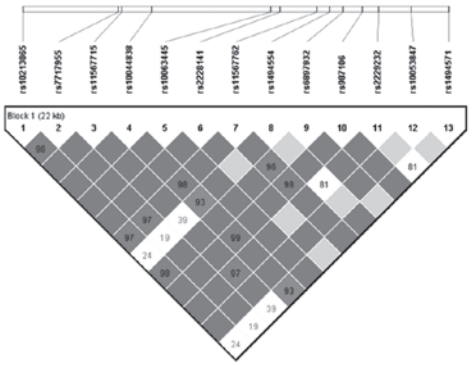


Figure 1. (A) A gene map of *interleukin-7 receptor* (*IL7R*). Exons are marked with black boxes while 5' and 3' untranslated regions are marked with white boxes. Single-nucleotide polymorphisms (SNPs) are marked along with their minor allele frequencies. (B) Haplotypes (ht) of *IL7R*. A total of five haplotypes with frequencies >0.05 were used for statistical analysis. (C) Linkage disequilibrium plot among *IL7R* SNPs.

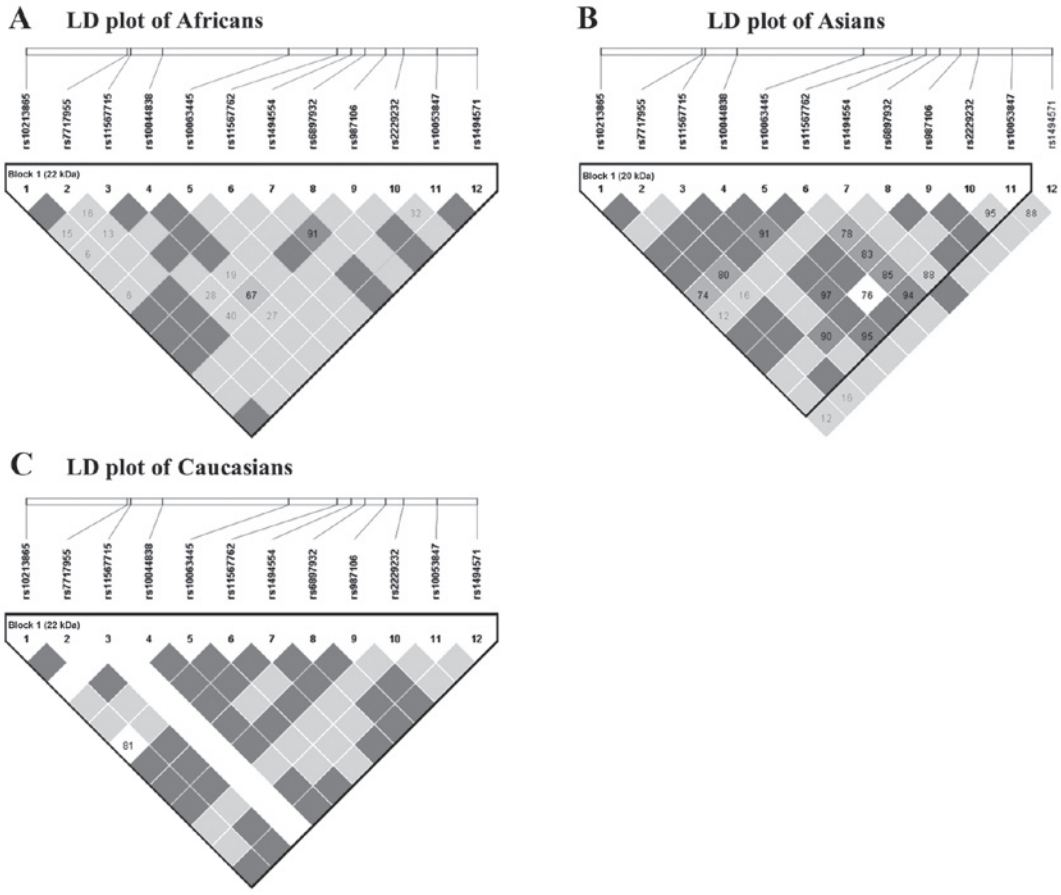


Figure 2. Linkage disequilibrium (LD) plots for *IL7R* single nucleotide polymorphisms in different ethnic groups. LD plots were based on data from the International HapMap Project. LD plot of (A) Africans; (B) Asians, including Koreans from the present study; and (C) Caucasians.

Table II. Genotype distributions and allele frequencies of *IL7R* SNPs.

SNP	Position	Genotypes (n=415)			MAF	Heterozygosity	HWE
rs10213865	Intron 1	AA (247)	AC (142)	CC (20)	0.222	0.346	0.944
rs7717955	Intron 2	CC (273)	CT (125)	TT (16)	0.19	0.307	0.721
rs11567715	Intron 2	CC (359)	AC (53)	AA (3)	0.071	0.132	0.502
rs10044838	Intron 2	CC (158)	CT (183)	TT (72)	0.396	0.478	0.135
rs10063445	Intron 3	AA (118)	AC (205)	CC (92)	0.469	0.498	0.868
rs2228141	Exon 4	CC (302)	CT (99)	TT (12)	0.149	0.253	0.270
rs11567762	Intron 4	AA (119)	AG (199)	GG (90)	0.464	0.497	0.693
rs1494554	Intron 5	AA (387)	AC (25)	CC (1)	0.033	0.063	0.385
rs6897932	Exon 6	CC (279)	CT (121)	TT (14)	0.180	0.295	0.843
rs987106	Intron 6	TT (238)	AT (150)	AA (27)	0.246	0.371	0.609
rs2229232	Exon 8	CC (375)	CT (36)	TT (2)	0.048	0.092	0.271
rs10053847	3'-UTR	GG (301)	AG (100)	AA (12)	0.150	0.255	0.299
rs1494571	3'-UTR	CC (389)	CG (25)	GG (1)	0.033	0.063	0.382

IL7R, interleukin-7 receptor; SNPs, single-nucleotide polymorphisms; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; UTR, untranslated region.

The analyses showed *rs6897932* and *haplotype 2* (*ht2*) to be significantly associated with IDD, even after multiple-testing correction ($P^{cor.}$=0.03 and 0.04, respectively). In order to compare the role of *rs6897932* in different populations, we listed studies carried out with *rs6897932* and conducted a meta-analysis (Table IV). There were certain exceptions in European and Australian populations (21-23); however, the majority of studies reported a significant correlation between *rs6897932* and MS (6,15-17,24-28). This association was also detected in Asian populations, in which the magnitude of risk was greater than in Caucasian populations [odds ratio (OR)=0.47 and 0.54 in the two studies with Asian populations and 0.82 in Caucasian populations]. We also investigated the genetic makeup of three different ethnic groups: Africans, Asians and Caucasians (Table V and Fig. 2). As expected, there were notable differences between the three populations.

Discussion

In the present study, a significant association was found between *rs6897932* and IDD (P=0.0003; OR [95% confidence interval (CI)]=0.10 [0.01-0.75]). However, this association may have come from MS and not from NMO, as case MAFs were lower than control MAFs in both IDD and MS (Table III), while NMO case and control MAFs were almost the same. The significant association detected for *ht2* is most likely due to *rs68797932*, as the haplotype is almost tagged by *rs68797932*. In the subgroup analyses for MS and NMO, none of the genetic variants showed a significant association, including *rs6897932* and *ht2*.

Numerous studies on the association between MS and risk genes have led to the identification of how gene variants may increase the risk of MS. A group of investigators found a significant association between an *IL7R* genetic variant and MS in a Caucasian population, and explained its possible mechanism via sequence analysis (28). Their analysis showed that *rs6897932* affected the function of the receptor by inducing the transcripts to skip exon 6 while encoding. The investigators suspected that the SNP either weakened an exonic splicing enhancer or strengthened an exonic splicing silencer, stating that the latter was more likely. The exclusion of exon 6 changed the number of soluble and membrane-bound isoforms of IL7R, which in turn led to the increased susceptibility for MS.

As shown in Table IV, significant associations between the risk allele of *rs6897932* and MS were identified in various studies. Notably, the magnitude of risk (OR) was higher in Asian populations (Japanese and Korean) than that in Caucasian samples. Thus, *rs6897932* is a potentially stronger risk factor in Asian populations than in Caucasian populations. This hypothesis was strengthened by the results of the present study (OR=0.82 in Caucasian and 0.49 in Asian; Table IV). Table V and Fig. 2 show that the frequencies and LD structures of Africans, Asians and Caucasians are different from each other, which partly explains the different influence of *rs6897932* on MS in Asians compared with that in Caucasians.

One limitation of our study was the small number of study samples. However, we only recruited patients whose diagnoses were clear in order to avoid the possibility of ascertainment error. In the present study, patients who were enrolled in the NMO group were seropositive for the AQP4 antibody, as determined by highly specific assays, and their clinical features were otherwise typical for NMO. Furthermore, for patients enrolled in the MS group, a diagnosis was made by expert MS specialists. Therefore, the possibility of ascertainment error in our study was reduced as much as possible.

In conclusion, in the present study, we conducted association studies of 13 *IL7R* SNPs for MS, NMO and IDD. We found

Table III. Logistic analyses of *IL7R* polymorphisms with the risk of inflammatory demyelinating diseases in a Korean population (n=415).

SNP and haplotypes	Allele change	IDD vs. NC								MS vs. NC								NMO vs. NC							
		MAF		Co-dominant		Dominant		Recessive		MAF		Co-dominant		Dominant		Recessive		MAF		Co-dominant		Dominant		Recessive	
		Case	Control	P	$P^{cor.}$	P	$P^{cor.}$	P	$P^{cor.}$	Case	Control	P	$P^{cor.}$	P	$P^{cor.}$	P	$P^{cor.}$	Case	Control	P	$P^{cor.}$	P	$P^{cor.}$	P	$P^{cor.}$
rs10213865	A>C	0.220	0.225	0.90	NS	0.57	NS	0.34	NS	0.191	0.225	0.29	NS	0.35	NS	0.43	NS	0.242	0.225	0.41	NS	0.19	NS	0.46	NS
rs7717955	C>T	0.183	0.195	0.75	NS	0.82	NS	0.12	NS	0.158	0.195	0.15	NS	0.18	NS	0.36	NS	0.202	0.195	0.67	NS	0.30	NS	0.13	NS
rs11567715	C>A	0.079	0.065	0.78	NS	0.96	NS	0.25	NS	0.089	0.065	1.00	NS	0.99	NS	NA	NA	0.071	0.065	0.76	NS	0.98	NS	0.20	NS
rs10044838	C>T	0.381	0.407	0.51	NS	0.96	NS	0.23	NS	0.380	0.407	0.68	NS	0.75	NS	0.70	NS	0.383	0.407	0.71	NS	0.85	NS	0.34	NS
rs10063445	A>C	0.466	0.470	0.70	NS	0.97	NS	0.48	NS	0.475	0.470	0.78	NS	0.99	NS	0.64	NS	0.460	0.470	0.88	NS	1.00	NS	0.80	NS
rs2228141	C>T	0.138	0.157	0.41	NS	0.25	NS	0.60	NS	0.171	0.157	0.57	NS	0.79	NS	0.27	NS	0.112	0.157	0.17	NS	0.11	NS	0.91	NS
rs11567762	A>G	0.466	0.463	0.83	NS	0.83	NS	0.55	NS	0.475	0.463	0.85	NS	0.93	NS	0.66	NS	0.459	0.463	1.00	NS	0.91	NS	0.90	NS
rs1494554	A>C	0.028	0.036	0.68	NS	0.63	NS	NA	NA	0.013	0.036	0.77	NS	0.77	NS	NA	NA	0.041	0.036	0.92	NS	0.99	NS	NA	NA
rs6897932	C>T	0.171	0.186	0.50	NS	0.84	NS	**0.003**	**0.03**	0.152	0.186	0.10	NS	0.20	NS	0.06	NS	0.187	0.186	0.93	NS	0.36	NS	NA	NA
rs987106	T>A	0.242	0.249	0.97	NS	0.71	NS	0.41	NS	0.209	0.249	0.36	NS	0.44	NS	0.46	NS	0.268	0.249	0.50	NS	0.30	NS	0.74	NS
rs2229232	C>T	0.059	0.040	0.27	NS	0.25	NS	0.99	NS	0.071	0.040	0.31	NS	0.30	NS	NA	NA	0.051	0.040	0.40	NS	0.38	NS	0.88	NS
rs10053847	G>A	0.138	0.159	0.36	NS	0.22	NS	0.60	NS	0.171	0.159	0.60	NS	0.82	NS	0.27	NS	0.112	0.159	0.15	NS	0.09	NS	0.91	NS
rs1494571	C>G	0.028	0.036	0.68	NS	0.64	NS	NA	NA	0.013	0.036	0.77	NS	0.77	NS	NA	NA	0.040	0.036	0.91	NS	0.99	NS	NA	NA
IL7R_ht1	NA	0.466	0.470	0.70	NS	0.97	NS	0.48	NS	0.475	0.470	0.78	NS	0.99	NS	0.64	NS	0.46	0.470	0.88	NS	1.00	NS	0.80	NS
IL7R_ht2	NA	0.169	0.181	0.59	NS	0.76	NS	**0.005**	**0.04**	0.146	0.181	0.12	NS	0.24	NS	0.07	NS	0.187	0.181	0.84	NS	0.32	NS	NA	NA
IL7R_ht3	NA	0.143	0.158	0.38	NS	0.22	NS	0.58	NS	0.171	0.158	0.59	NS	0.82	NS	0.27	NS	0.121	0.158	0.17	NS	0.10	NS	0.86	NS
IL7R_ht4	NA	0.059	0.040	0.33	NS	0.30	NS	0.99	NS	0.070	0.040	0.37	NS	0.36	NS	NA	NA	0.051	0.040	0.40	NS	0.38	NS	0.88	NS
IL7R_ht5	NA	0.042	0.027	0.11	NS	0.11	NS	NA	NA	0.044	0.027	0.11	NS	0.11	NS	NA	NA	0.040	0.027	0.21	NS	0.21	NS	NA	NA

Logistic regression models were used for calculating odds ratios (95% confidence interval) and corresponding P-values with age and gender as covariates. Bold values indicate significant associations (P<0.05). IDD, inflammatory demyelinating disease; NC, normal control; MS, multiple sclerosis; NMO, neuromyelitis optica; SNP, single-nucleotide polymorphism; MAF, minor allele frequency; NS, not significant; NA, not applicable.

Table IV. Comparison and meta-analysis of the genetic effect of *IL7R* SNP *rs6897932* on MS in previous studies.

Study population	Study size (case vs. control)	MAF		P-value (OR)	Author (year) (ref.)
		Case	Control		
Dutch Caucasian	697 vs. 174	ND	ND	**0.0004 (0.61)**	Sombekke *et al* (2011) (24)
Australian and New Zealander[a]	3,874 vs. 5,723	0.240	0.264	**0.0013 (0.91)**	Australia and New Zealand Multiple Sclerosis Genetics Consortium (2009) (16)
Nordic	1,210 vs. 1,234	0.256	0.302	**0.02 (0.76)**	Lundmark *et al* (2007) (26)
USA	438 vs. 479	0.217	0.265	**0.05 (0.75)**	Gregory *et al* (2007) (28)
European	1,077 vs. 2,725	0.238	0.283	**0.0006 (0.81)**	
German	206 vs. 605	0.748	0.746	0.17 (0.88)	Weber *et al* (2008) (21)
Australian	1,134 vs. 1,265	0.252	0.254	0.58 (0.96)	Rubio *et al* (2008) (22)
Canadian	1,193 vs. 1,553	0.290[b]		**0.0002 (0.78)**	Ramagopalan *et al* (2007) (29)
[c]					
USA[a]	207 vs. 413	0.227	0.303	**0.0005**	O'Doherty *et al* (2008) (25)
UK[a]	463 vs. 530	0.255	0.264	0.638	
UK and US	2,322 vs. 2,987	0.250[b]		**0.00003 (0.85)**	Hafler *et al* (2007) (6)
German[a]	1,267 vs. 868	0.249	0.275	0.054	Akkad *et al* (2009) (23)
Finnish	922 vs. 1,392	0.310	0.350	**0.0002 (0.81)**	Kallio *et al* (2009) (27)
Spanish	599 vs. 594	0.225	0.274	**0.003 (0.75)**	Alcina *et al* (2008) (15)
Japanese	187 vs. 158	0.107	0.203	**0.002 (0.47)**	Fang *et al* (2011) (17)
Korean	82 vs. 298	0.146	0.187	0.06 (0.54)	Present study
Meta-analysis					
Caucasian	11,056 vs. 13,876	-	-	**4.60×10^{-18} (0.82)**	-
Asian	269 vs. 456	-	-	**0.0001 (0.49)**	-
All	11,325 vs. 14,332	-	-	**1.15×10^{-19} (0.81)**	-

IL7R, interleukin-7 receptor; SNP, single nucleotide polymorphism; MS, multiple sclerosis; MAF, minor allele frequency; OR, odds ratio; ND, not defined. Bold values indicate P-value <0.05. All study data were modified to show P-value and OR of T (minor) allele. [a]Not included in the meta-analysis because not enough data was present in the studies. [b]Only the allele frequencies of overall samples were present in the studies. [c]A letter to the editor of New England Journal of Medicine.

Table V. Minor allele frequencies and Chi-square distribution of *rs6897932* in different ethnic groups.

Race	N	MAF	P-value
African	510	0.073	-
Asian	733	0.182	-
Caucasian	253	0.241	-
AF vs. AS	-	-	**<0.0001**
AF vs. CA	-	-	**<0.0001**
AS vs. CA	-	-	**0.02**

MAF and P-values were calculated based on information from the International HapMap Project. Africans include ASW (African ancestry in Southwest USA), LWK (Luhya in Webuye, Kenya), MKK (Maasai in Kinyawa, Kenya) and YRI (Yoruban in Ibadan, Nigeria). Asians include CHB (Han Chinese in Beijing, China), CHD (Chinese in Metropolitan Denver, Colorado), JPT (Japanese in Tokyo, Japan) and Korean from the present manuscript. Caucasians include CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) and TSI (Tuscan in Italy). MAF, minor allele frequency; AF, African; AS, Asian; CA, Caucasian.

a significant association between *rs6897932* and IDD, which was likely due to the putative association between the SNP and MS. Furthermore, the results of the present study were similar to those from a previous study which identified *rs6897932* as a stronger risk factor in Asian populations than in Caucasian populations. This finding was also consistent with the results obtained from the meta-analysis. Therefore, the results from the present study support the hypothesis that *rs6897932* is a stronger risk factor for IDDs in Asians as compared to Caucasians.

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