

**Supplementary table 1.** Flow chart.

Study		Included in the study	Data on smoking, birth year, and gender. No overlap EIMS/GEMS.	Past smokers excluded	HLA genotype available. Dataset for analysis.
EIMS	Cases	2488	2488	2230	1626
	Controls	6122	6122	4945	2295
GEMS	Cases	6156	6085	4983	4212
	Controls	5408	5357	4405	3117
Total	Cases	9036	8965	7210	5838
	Controls	11530	11479	9349	5412

**Supplementary table 2.** OR with 95% CI of developing MS for subjects categorized by smoking and each of the HLA alleles associated with MS risk with a frequency exceeding 5% among controls. Attributable proportion due to interaction between smoking and each of the HLA alleles.

Interaction between smoking and DRB1*15:01				
Smoking	DRB1*15:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	-	1324/2571	1.0 (reference)	
-	+	1888/1010	3.9 (3.2-4.3)	
+	-	1138/1325	1.6 (1.4-1.8)	
+	+	1488/506	6.5 (5.7-7.5)	0.3 (0.2-0.4)
Interaction between smoking and absence of A*02:01				
Smoking	A*02:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	+	1336/1959	1.0 (reference)	
-	-	1876/1622	1.7 (1.5-1.9)	
+	+	1146/1035	1.6 (1.4-1.8)	
+	-	1480/796	2.8 (2.3-2.9)	0.2 (0.05-0.3)
Interaction between smoking and absence of B*44:02				
Smoking	B*44:02	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	+	392/687	1.0 (reference)	
-	-	2820/2894	1.5 (1.3-1.7)	
+	+	362/341	1.9 (1.6-2.4)	

+	-	2264/1490	2.3 (2.0-2.6)	-0.06 (-0.2-0.1)
Interaction between smoking and DRB1*03:01				
Smoking	DRB1*03:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	-	2576/2735	1.0 (reference)	
-	+	636/846	0.9 (0.8-1.0)	
+	-	2085/1409	1.6 (1.4-1.7)	
+	+	541/422	1.5 (1.3-1.7)	0.007 (-0.2-0.2)
Interaction between smoking and DQB1*03:02				
Smoking	DQB1*03:02	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	-	2445/2614	1.0 (reference)	
-	+	767/967	1.3 (1.2-1.5)	
+	-	2054/1374	1.7 (1.5-1.8)	
+	+	572/457	2.0 (1.7-2.5)	0.02 (-0.1-0.2)

<sup>1</sup>number of exposed cases and controls; <sup>2</sup>adjusted for age, gender, residential area, study, ancestry, rs9277565, rs2229092, DRB1\*13:03, DRB1\*08:01, B\*38:01,

B\*55:01, DQA1\*01:01, DQB1\*03:01, and when appropriate for DRB1\*15:01. A\*02:01, B\*44:02, DRB1\*03:01, DQB1\*03:02, homozygote correction for

DRB1\*15:01, DRB1\*03:01, and A\*02:01.



**Supplementary table 3.** OR with 95% CI of developing MS for subjects categorized by DRB1\*15:01 and each of the other HLA alleles associated with MS risk with a frequency exceeding 5% among controls. Attributable proportion due to interaction between DRB1\*15:01 and each of the HLA alleles.

Interaction between DRB1*15:01 and absence of A*02:01				
DRB1*15:01	A*02:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	+	973/2133	1.0 (reference)	
-	-	1489/1763	1.7 (1.5-1.9)	
+	+	1509/861	4.2 (3.7-4.8)	
+	-	1867/655	7.0 (6.0-8.0)	0.3 (0.2-0.4)
Interaction between DRB1*15:01 and absence of B*44:02				
DRB1*15:01	B*44:02	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	+	309/756	1.0 (reference)	
-	-	2153/3140	1.3 (1.1-1.6)	
+	+	445/272	4.1 (3.3-5.0)	
+	-	2931/1244	5.5 (4.7-6.6)	0.2 (0.07-0.3)
Interaction between DRB1*15:01 and DRB1*03:01				
DRB1*15:01	DRB1*03:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
-	-	1746/2843	1.0 (reference)	
-	+	716/1053	0.9 (0.8-1.0)	
+	-	2915/1301	3.5 (3.2-3.9)	

+	+	461/215	3.5 (2.9-4.2)	0.02 (-0.2-0.2)
Interaction between DRB1*15:01 and DQB1*03:02				
DRB1*15:01	DQB1*03:02	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
+	+	1660/2705	1.0 (reference)	
+	-	802/1191	1.3 (1.1-1.5)	
-	+	2839/1283	3.6 (3.2-4.0)	
-	-	537/233	4.6 (3.8-5.5)	0.2 (-0.03-0.3)

<sup>1</sup>number of exposed cases and controls; <sup>2</sup>adjusted for age, gender, residential area, study, ancestry, smoking, rs9277565, rs2229092, DRB1\*13:03, DRB1\*08:01,

B\*38:01, B\*55:01, DQA1\*01:01, DQB1\*03:01, homozygote correction for DRB1\*15:01, and when appropriate for A\*02:01, B\*44:02, DRB1\*03:01, and

DQB1\*03:02, homozygote correction for DRB1\*03:01 and A\*02:01.

**Supplementary table 4.** OR with 95% CI of developing MS for subjects categorized by A\*02:01 and each of the other HLA alleles associated with MS risk with a frequency exceeding 5% among controls. Attributable proportion due to interaction between A\*02:01 and each of the HLA alleles.

Interaction between absence of A*02:01 and DRB1*15:01				
A*02:01	DRB1*15:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
+	-	973/2133	1.0 (reference)	
+	+	1509/861	4.2 (3.7-4.8)	
-	-	1489/1763	1.7 (1.5-1.9)	
-	+	1867/655	7.0 (6.0-8.0)	0.3 (0.2-0.4)
Interaction between absence of A*02:01 and absence of B*44:02				
A*02:01	B*44:02	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
+	+	426/723	1.0 (reference)	
+	-	2056/2271	1.4 (1.2-1.7)	
-	+	328/305	1.9 (1.5-2.3)	
-	-	3028/2113	2.4 (2.1-2.8)	0.04 (-0.1-0.2)
Interaction between absence of A*02:01 and DRB1*03:01				
A*02:01	DRB1*03:01	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
+	-	2149/2423	1.0 (reference)	
+	+	333/571	0.9 (0.8-1.0)	

-	-	2512/1721	1.7 (1.5-1.8)	
-	+	844/697	1.6 (1.4-1.9)	0.07 (-0.08-0.2)
Interaction between absence of A*02:01 and DQB1*03:02				
A*02:01	DQB1*03:02	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	AP
+	-	1877/2146	1.0 (reference)	
+	+	605/848	1.2 (1.1-1.4)	
-	-	2622/1842	1.7 (1.5-1.9)	
-	+	734/576	2.2 (1.9-2.6)	0.1 (-0.003-0.3)

<sup>1</sup>number of exposed cases and controls; <sup>2</sup>adjusted for age, gender, residential area, study, ancestry, smoking, rs9277565, rs2229092, DRB1\*15:01, DRB1\*13:03,

DRB1\*08:01, B\*38:01, B\*55:01, DQA1\*01:01, DQB1\*03:01, homozygote correction for DRB1\*15:01, and A\*02:01, and when appropriate for B\*44:02,

DRB1\*03:01, DQB1\*03:02, homozygote correction for DRB1\*03:01.



Supplementary table 5. OR with 95% CI among subjects with different combinations of DQA1\*01:01 and DRB1\*15:01, in total and stratified by smoking. Attributable proportion due to interaction between absence of DQA1\*01:01 and DRB1\*15:01.

DQA1*01:01	DRB1*15:01	ca/co <sup>1</sup>	Total		Smokers		Never smokers	
			OR (95% CI) <sup>2</sup>	OR (95% CI) <sup>3</sup>	ca/co <sup>1</sup>	OR (95% CI) <sup>3</sup>	ca/co <sup>1</sup>	OR (95% CI) <sup>3</sup>
+	-	752/1198	1.0 (reference)	1.0 (reference)	369/447	1.0 (reference)	383/751	1.0 (reference)
-	-	1710/2698	0.9 (0.8-1.1)	0.9 (0.8-1.0)	769/878	1.0 (0.8-1.2)	941/1820	0.9 (0.8-1.1)
+	+	314/239	2.5 (1.7-3.5)	2.2 (1.8-2.8)	122/77	2.1 (1.5-3.0)	192/162	2.5 (1.9-3.2)
-	+	3062/1277	3.5 (3.0-4.2)	3.6 (3.2-4.1)	1366/429	3.9 (3.2-4.7)	1696/848	3.6 (3.1-4.2)
				0.4 (0.3-0.5)		0.5 (0.3-0.6)		0.3 (0.2-0.5)

<sup>1</sup>exposed number of cases and controls; <sup>2</sup>adjusted for age, gender, residential area, ancestry, and study; <sup>3</sup>adjusted for age, gender, residential area, ancestry, study, A\*0201, DRB1\*0301, DRB1\*1303, DRB1\*0801, B\*4402, B\*3801, B\*5501, DQA1\*0101, DQB1\*0301, DQB1\*0302, homozygote correction for DRB1\*15, DRB1\*0301 and A\*0201; AP=attributable proportion due to interaction.