

Nicotinic acetylcholine receptors $\alpha 7$ and $\alpha 9$ modifies tobacco smoke risk for multiple sclerosis.

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Introduction. Tobacco smoke exposure is an established risk factor for multiple sclerosis (MS), yet how it confers risk is not known. Evidence from observational studies suggests nicotine may be a protective component. Animal studies further support this hypothesis, demonstrating nicotine's protective effect in MS is mediated by the presence and absence of $\alpha 7$ and $\alpha 9$ nicotinic acetylcholine receptors (nAChRs), respectively.

Objective. The determine if variation in the genes encoding $\alpha 7$ and $\alpha 9$ nAChRs (cholinergic receptor nicotinic alpha 7 [CHRNA7] and alpha 9 [CHRNA9]) will modify MS risk conferred by tobacco smoking in non-Hispanic white adults.

Methods. A multi-stage gene-environment (G×E) framework was utilized, including a case-control analysis (286 cases, 176 controls) with haplotype- and gene-based analyses, followed by an extension case-only (1,053 cases) analysis for overlapping variants (Figure 1; Table 1).

Results. The results for SNP, haplotype and gene-based tests suggested that CHRNA7 and CHRNA9 modifies MS risk conferred by tobacco smoke, where risk amongst smokers was increased in carriers of the minor CHRNA9 haplotype and in non-carriers the minor CHRNA7 haplotype (Tables 2 & 3). Similar associations for CHRNA7 were observed for overlapping SNPs in the case-only analysis (Table 4). The findings are consistent with the pharmacology of these receptors and animal studies of MS.

Conclusions. This study implicates novel processes in MS initiation and demonstrate the need for further G×E studies to advancing our understanding of the missing heritability of MS.

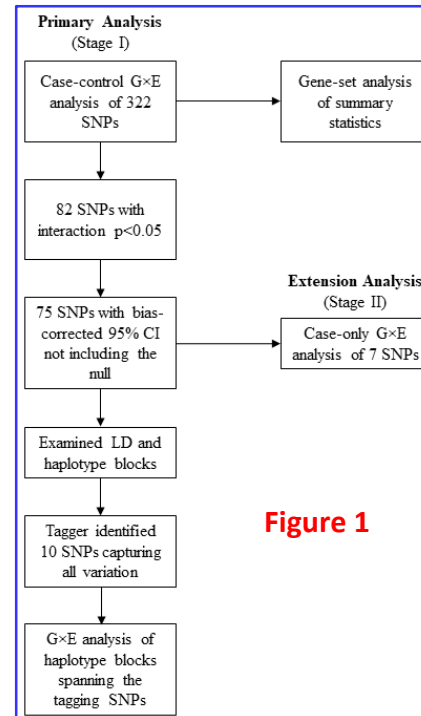


Figure 1

Table 2. Stage I Results for 10 SNPs That Captured all Variation Amongst the 75 SNPs With Significant G×E Interactions.

Gene	SNP	CHR	Base position	Minor Allele	MAF	OR _{IDN} (95% CI)	Carriers of the minor allele		Non-carriers of the minor allele	
							OR _{SMK} (95% CI)	P	OR _{SMK} (95% CI)	P
CHRNA9	rs6812832	4	40338720	G	0.450	2.16 (1.2, 3.77)	2.41 (1.44, 4.04)	0.00082	0.99 (0.48, 2.03)	0.97
	rs7681304	4	40342059	A	0.292	1.97 (1.01, 3.71)	2.31 (1.24, 4.30)	0.0084	1.39 (0.79, 2.45)	0.26
	rs4861307	4	40345239	G	0.487	1.79 (1.01, 3.12)	2.15 (1.31, 3.52)	0.0024	1.10 (0.50, 2.39)	0.82
CHRNA7	rs11635209	15	32333997	T	0.058	0.17 (0.04, 0.69)	0.26 (0.04, 1.67)	0.157	2.27 (1.46, 3.55)	0.00030
	rs35114543	15	32347464	T	0.275	0.53 (0.28, 0.97)	1.25 (0.66, 2.35)	0.495	2.26 (1.28, 4.01)	0.005
	rs2175886	15	32355947	C	0.440	0.53 (0.28, 0.96)	1.44 (0.86, 2.42)	0.161	2.29 (1.08, 4.86)	0.030
	rs1604265	15	32374369	G	0.106	0.32 (0.13, 0.88)	0.55 (0.17, 1.76)	0.312	2.30 (1.44, 3.67)	0.00046
	rs8033518	15	32381609	A	0.060	0.15 (0.04, 0.61)	0.24 (0.04, 1.48)	0.123	2.31 (1.48, 3.61)	0.00024
	rs2133965	15	32384554	A	0.078	0.24 (0.08, 0.78)	0.34 (0.08, 1.50)	0.153	2.24 (1.43, 3.53)	0.00047
rs6494212	15	32385119	T	0.324	1.95 (1.01, 3.80)	2.40 (1.33, 4.33)	0.0036	1.39 (0.76, 2.57)	0.29	

Table 3. The Association Between Ever Smoking and MS Status by Haplotype Combinations.

Haplotype combination	CHRNA9-AG copies		
	0	1	2
0	1.65 (95% CI: 0.90, 3.01)	2.08 (95% CI: 1.04, 4.16)	36.40 (95% CI: 3.74, 354.41)
CHRNA7-TTCGAA copies	0.49 (95% CI: 0.09, 2.53)	0.90 (95% CI: 0.091, 8.90)	NA
1	NA	NA	NA
2	NA	NA	NA

CHRNA7 haplotype: rs11635209T-rs35114543T-rs2175886C-rs1604265G-rs8033518A-rs2133965A
CHRNA9 haplotype: rs7681304A-rs4861307G

Table 1. Study Population Characteristics.

Characteristic	Stage I : Case-control analysis			Stage II : Case-only analysis
	MS	Control	P	MS
N	206	176		1,053
Birth year (SD)	1960 (10.8)	1961 (15.9)	0.66	1962 (11.1)
Age at interview (year; SD)	46.7 (11.0)	46.8 (15.7)	0.56	46.6 (10.9)
Female (%)	75.7	66.5	0.053	78.1
Years of education (%)	15.7 (2.7)	15.9 (3.0)	0.41	15.9 (2.9)
Primary Progressive (%)	15.1	-	-	5.1
Age of onset (year; SD)	33.9 (9.9)	-	-	33.4 (9.7)
Ever smoker (%)	55.3	40.3	0.0040	47.5
Smoker before onset (%)	52.2	-	-	44.5
HLA-DRB1*15:01 carriers (%)	46.6	34.7	0.022	46.2

Table 4. Coefficients for the Multiplicative Interaction term in Stage I and Stage II, assuming an additive genetic model and ever smoker as the operational definition of the exposure.

Gene	SNP	CHR	Base position	Minor Allele	Stage I	Stage II
					OR (95% CI)	OR (95% CI)
CHRNA7	rs3087454	15	32320967	C	0.54 (0.28, 0.98)	0.83 (0.69, 1.00)
	rs12908877	15	32323454	A	0.52 (0.27, 0.95)	0.84 (0.69, 1.02)
	rs885073	15	32323919	A	0.53 (0.28, 0.97)	0.83 (0.69, 1.00)
	rs885072	15	32323962	A	0.53 (0.28, 0.97)	0.83 (0.69, 1.00)
	rs868437	15	32324277	C	0.53 (0.28, 0.97)	0.83 (0.69, 1.00)
	rs35114543	15	32347464	T	0.53 (0.28, 0.97)	0.85 (0.70, 1.03)
rs8027814	15	32350672	G	0.53 (0.28, 0.97)	0.85 (0.70, 1.03)	

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