Nicotinic acetylcholine receptors α 7 and α 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 α 7 and α 9 nicotinic acetylcholine receptors (nAChRs), respectively.

Objective. The determine if variation in the genes encoding α 7 and α 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.

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Birth year (SD) 1960 (10.8) 1961 (15.9) 0.66 1962 (11.1) (CHKWA) 153 52520507 C 0.53 (0.28, 0.98) 0.83 (0.69, 1.00) Age at interview (year; SD) 46.7 (11.0) 46.8 (15.7) 0.56 46.6 (10.9) rs12908877 15 32323454 A 0.52 (0.27, 0.95) 0.84 (0.69, 1.02) Female (%) 75.7 66.5 0.053 78.1 rs885073 15 32323919 A 0.53 (0.28, 0.97) 0.83 (0.69, 1.00) Years of education (%) 15.1 - - 5.1 rs885072 15 32323962 A 0.53 (0.28, 0.97) 0.83 (0.69, 1.00) Primary Progressive (%) 15.1 - - 5.1 rs868437 15 32324277 C 0.53 (0.28, 0.97) 0.83 (0.69, 1.00) Rever smoker (%) 55.3 40.3 0.0040 47.5 rs35114543 15 32350672 G 0.53 (0.28, 0.97) 0.85 (0.70, 1.03) Smoker before onset (%) 52.2 - - 44.5 rs8027814 15 32350672 G 0.53 (0.28, 0.97) 0.85 (0.70, 1.03) 0.85 (0.70, 1.03) <td>Ν</td> <td>206 1</td> <td>76</td> <td>1,0</td> <td>53</td> <td>CHDMA</td> <td>7</td> <td>087454</td> <td>15</td> <td>2222004</td> <td>Allele</td> <td>0.54 (0.20</td> <td>0.08)</td> <td>0 82 (0 4</td> <td>0 1 00)</td>	Ν	206 1	76	1,0	53	CHDMA	7	087454	15	2222004	Allele	0.54 (0.20	0.08)	0 82 (0 4	0 1 00)
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	Birth year (SD)	1960 (10.8) 1961	(15.9) 0.0	66 1962 ((11.1)	CIIMIA	/ 185	06/434	15	3232090		0.54 (0.28	, 0.98)	0.85 (0.0	9, 1.00)
Female (%)75.766.50.05378.1rs8850731532323919A0.53 (0.28, 0.97)0.83 (0.69, 1.00)Years of education (%)15.7 (2.7)15.9 (3.0)0.4115.9 (2.9)rs8850721532323962A0.53 (0.28, 0.97)0.83 (0.69, 1.00)Primary Progressive (%)15.15.1rs8684371532324277C0.53 (0.28, 0.97)0.83 (0.69, 1.00)Age of onset (year; SD)33.9 (9.9)33.4 (9.7)rs8684371532324277C0.53 (0.28, 0.97)0.83 (0.69, 1.00)Ever smoker (%)55.340.30.004047.5rs351145431532347464T0.53 (0.28, 0.97)0.85 (0.70, 1.03)Smoker before onset (%)52.244.5rs80278141532350672G0.53 (0.28, 0.97)0.85 (0.70, 1.03)HLA-DRB1*15:01 carriers (%)46.634.70.02246.21532350672G0.53 (0.28, 0.97)0.85 (0.70, 1.03)	Age at interview (year; SD)	46.7 (11.0) 46.8	(15.7) 0.:	56 46.6 (10.9)		rsl	2908877	15	3232345	64 A	0.52 (0.27	, 0.95) (0.84 (0.6	9, 1.02)
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 rs8027814 rs8027814 rs8027814 rs8027814 rs8027814 15 3232962 A 0.53 (0.28, 0.97) 0.83 (0.69, 1.00)	Female (%)	75.7 60	6.5 0.0	53 78	.1		rs	885073	15	3232391	9 A	0.53 (0.28	, 0.97)	0.83 (0.6	9, 1.00)
Primary Progressive (%) 15.1 - 5.1 5.1 6.1 5.1 6	Years of education (%)	15.7 (2.7) 15.9	(3.0) 0.4	41 15.9	(2.9)		rs	885072	15	3232396	52 A	0.53 (0.28	. 0.97)	0.83 (0.6	9, 1.00)
Age of onset (year; SD) 33.9 (9.9) - - 33.4 (9.7) 15000457 15 52324277 C 0.55 (0.28, 0.97) 0.85 (0.69, 1.00) Ever smoker (%) 55.3 40.3 0.0040 47.5 rs35114543 15 32347464 T 0.53 (0.28, 0.97) 0.85 (0.70, 1.03) Smoker before onset (%) 52.2 - - 44.5 rs8027814 15 32350672 G 0.53 (0.28, 0.97) 0.85 (0.70, 1.03) HLA-DRB1*15:01 carriers (%) 46.6 34.7 0.022 46.2 rs8027814 15 32350672 G 0.53 (0.28, 0.97) 0.85 (0.70, 1.03)	Primary Progressive (%)	15.1		- 5.	1			868/27	15	3737477		0.53 (0.20	007)	0 83 (0 4	0 1 00)
Ever smoker (%) 55.3 40.3 0.0040 47.5 rs35114543 15 32347464 T 0.53 (0.28, 0.97) 0.85 (0.70, 1.03) Smoker before onset (%) 52.2 - - 44.5 rs8027814 15 32350672 G 0.53 (0.28, 0.97) 0.85 (0.70, 1.03) HLA-DRB1*15:01 carriers (%) 46.6 34.7 0.022 46.2 rs8027814 15 32350672 G 0.53 (0.28, 0.97) 0.85 (0.70, 1.03)	Age of onset (year; SD)	33.9 (9.9)		- 33.4	(9.7)		18	500457	15	5252421		0.55 (0.28	, 0.97)	0.05 (0.0	9, 1.00)
Smoker before onset (%) 52.2 - - 44.5 HLA-DRB1*15:01 carriers (%) 46.6 34.7 0.022 46.2	Ever smoker (%)	55.3 40	0.3 0.0	040 47	.5		rs3	5114543	15	3234746	54 T	0.53 (0.28	, 0.97) (0.85 (0.7	0, 1.03)
HLA-DRB1*15:01 carriers (%) 46.6 34.7 0.022 46.2	Smoker before onset (%)	52.2		- 44	.5		rs8	027814	15	3235067	2 G	0.53 (0.28	. 0.97)	0.85 (0.7	0, 1.03)
	HLA-DRB1*15:01 carriers (%)	46.6 34	4.7 0.0	922 46	.2		- 50		-		-	(,,	(*/	,,

