

Distinct Cerebral Microbleed Topographies And Cognitive Profiles In Non-demented *APOE* ε4 Homozygous And *NOTCH3* R544C Carriers

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1. *NOTCH3* R544C carriers have more deep cerebral microbleeds (CMBs), while *APOE* ε4 homozygous carriers show a widespread distribution.
2. Deep CMBs associate with executive dysfunction in *NOTCH3*, while widespread CMBs associate with memory impairment in *APOE*.
3. CMBs topography serves as a genotype-specific marker for predicting early, pre-dementia cognitive decline.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS																												
● Cerebral small vessel disease, commonly manifested as cerebral microbleeds (CMBs), is a key contributor to cognitive impairment. ● <i>APOE</i> ε4 homozygosity links to lobar CMBs and amyloid pathology, whereas the East Asian-prevalent <i>NOTCH3</i> R544C mutation associates with subcortical vascular damage. ● How these genotype-specific CMB distributions relate to domain-specific cognitive performance in non-demented individuals remains poorly understood.	● We recruited non-demented <i>APOE</i> ε4 homozygous and <i>NOTCH3</i> R544C carriers. ● Demographic data, CMBs counts by anatomical location (cortical, subcortical, and deep), and neuropsychological performance were analyzed. ● Group differences were assessed, and age-adjusted partial correlation analyses were conducted to examine associations between CMBs burden and cognitive domains, with false discovery rate correction for multiple comparisons.	● The total CMBs counts did not differ significantly between groups; however, <i>NOTCH3</i> R544C carriers exhibited a significantly higher number of deep CMBs. ● In <i>APOE</i> ε4 homozygous carriers, widespread CMBs burden is more closely related to memory impairment (cortical, subcortical, and deep CMBs: partial r = -0.29, -0.31, -0.22, respectively; all p < 0.05). ● In <i>NOTCH3</i> R544C carriers, deep CMBs counts were specifically associated with worse executive function, as measured by the Color Trails Test-2 (Deep CMBs: partial r = 0.28, p < 0.05) <table><tr><th></th><th><i>APOE</i> 4/4 (n=95)</th><th><i>NOTCH3</i> R544C (n=66)</th><th>P value</th></tr><tr><td>Age</td><td>61.4 (7.2)</td><td>56.2 (10.6)</td><td>0.004</td></tr><tr><td>Female</td><td>49 (51.6%)</td><td>33 (50%)</td><td>0.97</td></tr><tr><td>CMBs total number</td><td>3.6 (30.8)</td><td>2.2 (7.3)</td><td>0.07</td></tr><tr><td>Cortical CMBs number</td><td>3.2 (28.4)</td><td>0.8 (4.3)</td><td>0.83</td></tr><tr><td>Subcortical CMBs number</td><td>0.3 (1.8)</td><td>0.4 (1.1)</td><td>0.73</td></tr><tr><td>Deep CMBs number</td><td>0.1 (0.7)</td><td>1.0 (3.7)</td><td><0.001</td></tr></table>		<i>APOE</i> 4/4 (n=95)	<i>NOTCH3</i> R544C (n=66)	P value	Age	61.4 (7.2)	56.2 (10.6)	0.004	Female	49 (51.6%)	33 (50%)	0.97	CMBs total number	3.6 (30.8)	2.2 (7.3)	0.07	Cortical CMBs number	3.2 (28.4)	0.8 (4.3)	0.83	Subcortical CMBs number	0.3 (1.8)	0.4 (1.1)	0.73	Deep CMBs number	0.1 (0.7)	1.0 (3.7)	<0.001	● CMBs topography serves as a genotype-specific marker for predicting early, pre-dementia cognitive decline. CONTACTS Dr. Wei-Ju Lee E-mail: winster.lee@msa.hinet.net  ALZHEIMER'S ASSOCIATION AAIC 26
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