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APOE Genotype and White Matter Hyperintensities in Sporadic Alzheimer Disease

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1 **Letter to the Editor: Etiology of White Matter Hyperintensities in Autosomal Dominant**
2 **and Sporadic Alzheimer Disease**

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16 **To The Editor:**

17 We read with interest the paper entitled, "**Etiology of White Matter Hyperintensities (WMH) in**
18 **Autosomal Dominant and Sporadic Alzheimer Disease (AD)**".¹ Using multimodal imaging
19 data from three complimentary cohorts (DIAN, ADNI, and HABS), the authors concluded that
20 the results strongly suggest cerebral amyloid angiopathy (CAA) as the likely etiology for WMH in
21 AD.

22 We previously examined cross-sectional T1/T2-weighted MRI and neuropsychological data from
23 patients with AD and dementia with Lewy bodies (DLB) from the Sunnybrook Dementia Study
24 (SDS) and in an AD sample from ADNI.² Using a robust imaging pipeline to quantify WMH
25 volume in SDS, we demonstrated that greater WMH burden was strongly associated with worse
26 performance on multiple cognitive domains, including attention/executive functions, learning/
27 memory, and language, in *APOE-ε4* carriers. We did not observe such associations in non-
28 carriers. Meta-analyses of results from SDS and ADNI (n=487) showed that the association
29 between greater WMH burden and worse cognition was indeed only present in *APOE-ε4*
30 carriers.² We hypothesized that since *APOE-ε4* is a genetic risk factor for CAA, AD and DLB,
31 WMH in *APOE-ε4* carriers with AD, DLB or mixed AD with DLB may be more likely to be due to
32 CAA and might be more 'toxic' to cognition than WMH caused by ischemia secondary to
33 cardiovascular risk factors alone. This hypothesis was partially supported by examining a small
34 autopsy subset of SDS (n=34): all patients (7/7) homozygous for *APOE-ε4* had CAA, compared
35 to 39-50% of patients with other genotypes.

36 First, based on our findings, and the fact that *APOE-ε4* increases the risk of CAA,³ we wonder if
37 the authors looked at the effects of *APOE* genotype in their large imaging cohort, particularly in
38 those with sporadic AD/mild cognitive impairment. Given the increased risk of both parenchymal
39 and intravascular amyloid deposition posed by *APOE-ε4*, if *APOE-ε4* status is associated with
40 WMH increase even in amyloid PET-negative individuals, this would support the idea that the
41 relationship between brain amyloid and WMH is through the presence of CAA. Second, it would
42 be helpful to know why the authors used only a measure of global atrophy, i.e., a non-specific
43 marker of neurodegeneration, as opposed to more specific markers of AD-related
44 neurodegeneration, such as hippocampal atrophy, focal medial temporal lobe loss or cortical
45 thinning.^{4,5} We believe that inclusion of *APOE* genotype and more specific AD-regional atrophy
46 patterns might account for additional variance in their study.

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