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LETTER

Association of *MGMT* and *BIN1* genes with Alzheimer's disease risk across sex and *APOE ε4* status

Chung et al. reported a novel association of the Alzheimer's disease (AD) risk with genetic variants in the *MGMT* gene in women.[1] The genome-wide significant signals were found in women lacking the apolipoprotein E ε4 allele (*APOEε4*-) from 30 studies of the Alzheimer's Disease Genetics Consortium (ADGC) (3399 AD cases and 6905 controls), and in a Hutterite cohort (31 members of a consanguineous kindred with different *APOEε4* statuses, including 5 AD cases who were all women). The effect sizes reported were large: odds ratio [OR] = 1.44 [1.26–1.64], $P = 4.95 \times 10^{-8}$ in ADGC for rs12775171, and OR = 2.02 [1.80–2.26], $P = 1.9 \times 10^{-14}$ in the Hutterites for rs2803456 and rs12256016. The association found in the ADGC was consistent across studies and not significant in the three other subsets defined by sex and *APOEε4* status (women *APOEε4*+, men *APOEε4*-, and men *APOEε4*+) for which effect sizes were not reported.

We aimed at replicating the association of *MGMT* with AD risk in the meta-analysis of 6 case–control studies from the European Alzheimer & Dementia Biobank (EADB) consortium: EADB-core,[2] EADI (European Alzheimer's Disease Initiative),[3,4] GERAD (Genetic and Environmental Risk in AD),[5] DemGene,[6] GR@ACE-DEGESCO,[7] and Bonn.[2] We considered a total of 33,677 AD cases and 48,158 controls, all of European ancestry, including 10,354 AD cases and 19,910 controls who were female and *APOEε4*- (Figure 1, Tables S1, and S2 in supporting information). The samples were genotyped with different chips and then imputed using the TOPMed reference panel[2] (supporting information). In each study, we tested the association of *MGMT* variants with AD in the four subsets defined by sex and *APOEε4* status. Analyses were adjusted on principal components, and results were combined across studies in a fixed effect meta-analysis with an inverse-variance weighted approach (supporting information).

None of the *MGMT* variants identified by Chung et al. were found to be associated with AD risk ($P < 0.05$) in the different subsets (Figures S1–S6 in supporting information). The effect of rs12775171 was larger in *APOEε4*- women (OR = 1.06 [0.98–1.14], $P = 0.17$) than in the other subsets (OR = 1.03, 1.00, and 0.99 in *APOEε4*- men, *APOEε4*+ women, and *APOEε4*+ men, respectively), but those differences were not significant ($P = 0.69$, 0.37, and 0.39 for the comparison of the OR in *APOEε4*- women with the one in *APOEε4*- men, *APOEε4*+ women, and *APOEε4*+ men, respectively, Figure 1). Of note, our study in *APOEε4*- women had more than 99% power to detect the association with rs12775171 as described by Chung et al., at the nominal significance level of 0.05 (supporting information).

The authors also identified in ADGC *APOEε4*- women a genome-wide significant association with AD for a known AD gene, *BIN1* (rs11680911, OR = 1.21 [1.13–1.29], $P = 2.22 \times 10^{-8}$). We sought to assess whether this association differed across the four sex-*APOEε4* subsets. We detected a genome-wide significant association ($P < 5 \times 10^{-8}$) with AD risk for rs11680911 in *APOEε4*- women (OR = 1.12 [1.07–1.16], $P = 2.21 \times 10^{-8}$) and in *APOEε4*- men (OR = 1.16 [1.10–1.21], $P = 1.75 \times 10^{-9}$), but not in the 2 other

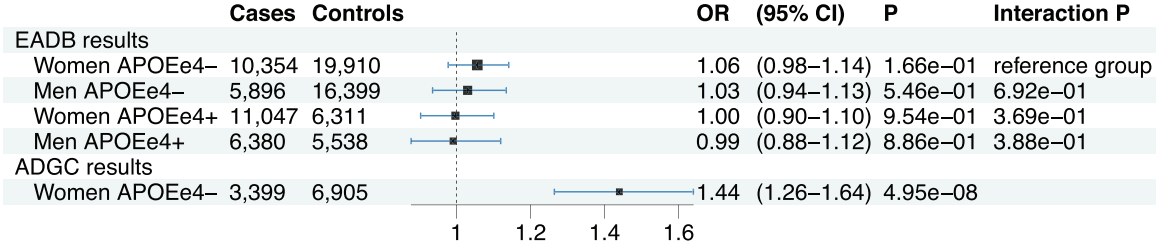

FIGURE 1 Results of rs12775171 association with Alzheimer's disease (AD) risk in apolipoprotein E (*APOE*) *ε4*- women and the other sex-*APOEε4* subsets compared with the effect reported in the Alzheimer's Disease Genetics Consortium (ADGC) *APOEε4*- women from Chung et al. 2022. The effect allele is G with a frequency of 0.06 in all models. The black square whose size is proportional to the sample size represents the odds ratio (OR) and the blue line the confidence interval (CI). Interaction *P* are *p*-values of the heterogeneity test between the different group pairs (1 degree of freedom test) using the *APOEε4*- women group as a reference for each test (supporting information). EA, Effect allele; *P*, *p*-value.

subsets (Figures S7–S8 in supporting information). However, the effects in all the subsets were similar (OR = 1.12, 1.16, 1.14, and 1.13 in *APOEε4*- women, *APOEε4*- men, *APOEε4*+ women, and *APOEε4*+ men, respectively), and effects were not significantly different between the subsets (Figures S7–S8 and Table S3 in supporting information).

We performed several sensitivity analyses in the EADB studies (supporting information, Tables S1–S4 and Figures S1–S12), but none of them identified a significant association of *MGMT* with AD risk in *APOEε4*- women or differences of association between subsets in *BIN1*.

In conclusion, we did not find a significant, nor suggestive association of the *MGMT* variants identified by Chung et al. with AD risk, in any of the subsets defined by sex and *APOEε4* status, where our sample size was up to three times larger than in the original publication. Additionally, we did not identify a significant effect difference of *BIN1* rs11680911 variant across sex and *APOEε4* status subsets.

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CONFLICT OF INTEREST STATEMENT

Martin Ingelsson is a paid consultant to BioArtic.

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REFERENCES

1. Chung J, Das A, Sun X, et al. Genome-wide association and multi-omics studies identify MGMT as a novel risk gene for Alzheimer's disease among women. *Alzheimer's Dement*. 2023; 19:896-908. doi:10.1002/alz.12719
2. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. 2022;54(4):412-436.
3. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22:316-325.
4. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009;41:1094-1099.
5. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009;41:1088-1093.
6. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet*. 2019;51(3):40ss4-413.
7. Moreno-Grau S, de Rojas I, Hernández I, et al. Genomeswide association analysis of dementia and its clinical endophenotypes reveal novel loci associated with Alzheimer's disease and three causality networks: the GR@ACE project. *Alzheimer's Dement*. 2009;15:1333-1347.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.