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Identification of *ABCA7* SNP-by-CpG interactions associated with cognition in older African Americans

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Abstract

Background: The *ABCA7* gene confers the largest genetic risk for Alzheimer's Disease (AD) in African Americans (AA) after *APOE* ε4. However, the relationship between *ABCA7* and cognitive function has not been thoroughly examined in AA without dementia. We investigated the effect of genetic variants and epigenetic markers in *ABCA7*, as well as their interaction, on cognition in older AA without dementia.

Method: The sample included 629 cognitively normal AA from the Genetic Epidemiology Network of Arteriopathy (GENOA). Methylation at 72 CpG sites located within 5kb of *ABCA7* were measured using the Illumina EPIC array. General cognitive function (cognition) was measured by taking the first principal component of five cognitive tests. The association between SNPs and cognition was assessed using linear mixed models controlling for age, sex, education, population structure and relatedness. The association between CpGs and cognition was assessed using the same model with further adjustment for white blood cell proportions, batch effects and smoking. We also evaluated SNP-by-CpG interactions.

Result: No SNPs were associated with cognition at $p<0.05$. A 1% change in methylation at three CpGs (cg22271697, cg11714200, cg12082025) was associated with a 0.02-0.10 standard deviation (SD) increase in cognition ($p<0.05$; no associations significant at FDR $q<0.1$). Four SNP-by-CpG interactions were associated with cognition (FDR $q<0.1$). Contrast tests show that methylation is associated with cognition in some genotype groups ($p<0.05$): a 1% methylation increase at cg22271697 is associated with a 0.13 SD increase in cognition for those with the AA rs3764647 genotype, a 1% increase at cg06169110 is associated with a 0.35 SD decrease in cognition for those with the rs115550680 GG or AG genotype, and a 1% increase at cg00135882 is associated with a 1.19 SD decrease in cognition for those with a rs3764650 GG genotype.

Conclusion: While AD risk SNPs in *ABCA7* are not associated with cognition in the full sample of older African Americans, some do interact with proximal methylation to influence cognition. This suggests that a complicated interplay between genetic and epigenetic factors in *ABCA7* may influence cognition in cognitively normal AA. A similar mechanism may play a role in cognitive aging and decline.