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An *UNC5C* Allele Predicts Cognitive Decline and Hippocampal Atrophy in Clinically Normal Older Adults

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Abstract

Background: The *UNC5C* rs3846455[G] allele has been linked to poor cognitive resilience against age-related neuropathologies, but this association remains to be replicated, and the allele's effect on hippocampal neurodegeneration needs to be examined.

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Objective: To further validate the association between rs3846455^{G} and faster cognitive decline, especially among cognitively normal older adults, and to assess whether rs3846455^{G} predicts accelerated hippocampal volume loss in older adults.

Methods: We assessed participants in the Harvard Aging Brain Study (HABS), a longitudinal cohort study of older adults who were clinically normal at baseline. To avoid bias from population admixture, analyses were limited to participants of European descent with longitudinal neuroimaging data (n = 174). Linear mixed effect models were used to examine the effect of rs3846455^{G} on longitudinal change of the Preclinical Alzheimer Cognitive Composite (PACC) and MRI-measured bilateral hippocampal volume, adjusting for baseline amyloid-β (Aβ) measured by the cortical Pittsburgh Compound B PET distributed volume ratio. We also tested whether hippocampal atrophy mediates the association between rs3846455^{G} and greater PACC decline through a mediation analysis.

Results: rs3846455^{G} was associated with greater PACC decline (β = −0.087/year, 95% CI −0.169 to −0.005, p = 0.039) after controlling for baseline Aβ. Further, rs3846455^{G} predicted accelerated hippocampal atrophy after controlling for baseline Aβ (β = −57.3 mm^3/year, 95% CI −102.8 to −11.9, p = 0.014). The association between rs3846455^{G} and greater PACC decline was partially mediated by accelerated hippocampal atrophy (mediated effect (relative scale) = −0.014, 95% CI −0.032 to -6.0×10^{-4}, p = 0.039).

Conclusion: *UNC5C* rs3846455^{G} predicts greater cognitive decline and accelerated hippocampal atrophy in clinically normal older adults.

Keywords

Alzheimer’s disease; amyloid plaques; cognitive reserve; genetics; hippocampus; neuroimaging

INTRODUCTION

More than half of the heterogeneity in late-life cognitive decline remains unexplained even after accounting for common neuropathologies such as Alzheimer’s disease (AD), vascular brain injury, or Lewy body disease [1]. Understanding the genetic architecture of this variable resilience to neuropathologies could enable personalized prognostication and novel therapeutic target identification.

A recent genome-wide association study (GWAS) showed a relationship between two independent common alleles, *UNC5C* rs3846455^{G} and *ENC1* rs766629990^{A}, and worse cognition after accounting for known neuropathologies [2]. *UNC5C* rs3846455^{G} is of a particular interest, given other studies that implicated two other independent variants within the gene in cognitive aging: a rare *UNC5C* mutation (T835M) increases AD dementia risk by increasing hippocampal susceptibility to pathologic insults such as amyloid-β (Aβ) [3], and a common variant, rs28660566^{T}, is associated with a higher burden of cerebral amyloid angiopathy, an Aβ-related cerebrovascular pathology [4]. UNC5C is abundantly expressed in adult human hippocampus, suggesting the gene’s potential role in hippocampus [5].

However, the association of rs3846455^{G} with vulnerability to late-life cognitive decline should be further examined in an independent cohort, and the relationship between

rs3846455^{G} and longitudinal hippocampal neurodegeneration in older adults needs to be investigated. This knowledge gap should be addressed, especially in clinically normal older adults for whom neuroprotective treatments are most likely to prevent extensive neurodegeneration [6].

Therefore, we sought to do this in the current study, leveraging the structural and molecular neuroimaging data from the Harvard Aging Brain Study (HABS), a longitudinal cohort study that enrolls clinically normal older adults [7]. We aimed to replicate the previously reported association between rs3846455^{G} and greater cognitive decline [2], adjusting for baseline Aβ burden measured *in vivo*. In addition, we hypothesized that rs3846455^{G} would predict accelerated hippocampal atrophy, which could potentially account for the cognitive decline associated with rs3846455^{G}.

METHODS

Participants

HABS is a longitudinal observational cohort study of aging and preclinical AD that has enrolled over 300 clinically normal community-dwelling older adults. The inclusion criteria included Clinical Dementia Rating Scale global score of 0, Mini-Mental Status Exam (MMSE) score ≥27 (adjusted for age and education), and performance within the normal range on Logical Memory IIa Delayed Recall (adjusted for education; ≥9 for 16 or more years of education, ≥5 for 8 to 15 years of education, ≥3 for 0 to 7 years of education). Annual attrition rate was between 2% to 7%.Further details about HABS areavailable through previous publications [7].

Standard protocol approvals, registrations, and patient consents

Each participant has signed a written informed consent prior to undergoing any study procedure, and the Partners Healthcare Institutional Review Board has approved the protocols and procedures of HABS.

Genotyping

APOE genotyping was done through a targeted Taqman assay for rs7412 and rs429358, and people with at least one *APOE ε*4 haplotype was grouped as *APOE ε*4 carriers.

Genome-wide genotyping was available for 285 HABS participants. The genotyping was performed in two batches, using the same genotyping platform (Axiom™ Biobank Genotyping Array): the first batch (n = 189) was genotyped in 2013, while the second batch (n = 96) was completed in 2016. For quality control, we selected single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) >0.01 in both batches, and subsequently merged the two batches. We performed additional quality control with the following parameters: sex concordance, genotype missing rate (variant) <0.1, genotype missing rate (sample) <0.05, Hardy-Weinberg equilibrium $p > 10^{-50}$, non-extreme heterogyzosity (inbreeding coefficient estimate (F) between −0.1 and 0.1), and identity by descent (IBD) pi-hat < 0.5. All these steps were conducted with PLINK v1.90b3.32. A total of 262 participants and 326,033 SNPs passed quality control.

To assess the population structure, we combined our data with the HapMap 3 samples [8] and used EIGENSTRAT [9] to derive principal components of genotype covariance matrix. We calculated means and standard deviations for each of the first three principal components from the genotype covariance matrix (EV1–3) in HABS participants who reported their race as White. We classified the participants as of European descent only if each of their EV1–3 values were within three standard deviations from these mean values. We confirmed that the EV1–3 values of the HABS participants we classified as of European descent overlapped with the values from the HapMap 3 participants of European descent. *UNC5C* rs3846455 genotype was available for a total of 259 participants, and 219 participants among them were of European descent. We limited our analyses to participants of European descent to avoid confounding from population admixture. We used rs3846455^{G} carrier status instead of minor allele count in all analyses, as there was only one participant who was a homozygote for the minor allele rs3846455^{G} (i.e., genotype GG).

Neuropsychological testing

Cognitive performance was measured annually with a modified version of the Preclinical Alzheimer Cognitive Composite (PACC) [10-12], a cognitive composite averaging z-scores of (1) MMSE total score, (2) the Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale-Revised, (3) the Logical Memory Delayed Recall, and (4) the combined sum of the Free and Cued Selective Reminding Test Free Recall and Total Recall. The z-score for each test was derived using the baseline mean and standard deviation of the entire HABS cohort [10]. Higher scores indicate better cognitive performance. Our study included only participants with baseline and at least one follow-up on the PACC.

Positron emission tomography

To estimate Aβ burden, ^{11}C Pittsburgh Compound B-positron emission tomography (PiB-PET) scans were obtained at the MGH PET facility at baseline. An 8.5–15 mCi bolus of PiB was injected, and the PiB-PET images were acquired through 60 min dynamic acquisitions. PiB-PET data were processed as previously detailed [12]. Baseline PiB distribution volume ratio (DVR) was calculated from a cortical aggregate region including frontal, lateral parietal, lateral temporal, and retrosplenial cortices using a cerebellar gray matter reference [12]. Baseline PiB DVR was used in our study as a measure of Aβ. PiB-PET data were not partial-volume corrected.

Magnetic resonance imaging

Our study included participants with baseline and at least one follow-up structural brain MRI. There were total 174 participants of European descent with *UNC5C* rs3846455 genotypes, baseline Aβ, and two or more measurements for both PACC and HV. At baseline (for all (n = 174) subjects included in this study), 18 months from the baseline (for n = 32 subjects included in this study), 3 years from the baseline (for n = 168 subjects included in this study), and 5 years from the baseline (for n = 85 subjects included in this study), structural brain MRIs were obtained on one of two matched Siemens Tim Trio 3T scanners at the Massachusetts General Hospital (MGH) – Athinoula A. Martinos Center for Biomedical Imaging, with a 12-channel phasedarray head coil. Hippocampal volume (HV) was calculated from structural T1-weighted, volumetric magnetization-prepared, rapid

acquisition gradientecho scans (repetition time 6400 ms, echo time 2.8 ms, inversion time 900 ms, flip angle 8°, and resolution 1×1×1.2 mm) using FreeSurfer v5.1. Summed bilateral HV was used in our analyses, and we included the total intracranial volume (ICV) as a covariate in all HV analyses.

Statistical analysis

All statistical analyses were done with R version 3.3.3, and the threshold for significance was twosided $p < 0.05$. This study is a hypothesis-driven study that builds on the previous findings related to a SNP, so genome-wide correction for multiple testing was not necessary. We indicated the number of participants included in each analysis in the table legends, if different from $n = 174$ due to missing values.

Baseline demographic characteristics were compared across rs3846455^{G} non-carriers and carriers with two sample *t*-tests (for continuous variables; assuming equal variance) or chi-squared tests (for dichotomous variables). Association of rs3846455^{G} with baseline PACC or HV was tested with linear regression, controlling for covariates that are known predictors of each outcome variable [1, 13]: baseline age, sex, and years of education were adjusted for when PACC was the dependent variable, and baseline age, sex, and ICV were controlled when HV was the dependent variable. In addition, EV1–3 were controlled to further account for a potential confounding due to population stratification. Longitudinal relationships were assessed with the following linear mixed effect models (R "nlme" package), assuming random intercepts and slopes, and using the same set of covariates as the baseline linear models:

$$\text{Model 1: PACC or HV} \sim \text{rs3846455}^{G} \times \text{time} + \text{covariates} (+ \text{years of education in PACC models}) \times \text{time} (+ \text{ICV in HV models})$$

$$\text{Model 2: HV or PACC} \sim \text{rs3846455}^{G} \times \text{time} + \text{Baseline A}\beta \times \text{time} + \text{covariates} (+ \text{years of education in PACC models}) \times \text{time} (+ \text{ICV in HV models})$$

All main terms for product terms were also include in the regression analysis. We also performed analyses without covariates to rule out induced correlation from inclusion of covariates.

To evaluate whether the association between rs3846455^{G} and longitudinal HV change explains the link between rs3846455^{G} and longitudinal PACC change, we performed a *post-hoc* mediation analyses. First, we extracted adjusted random slopes of HV and PACC changes from the following linear mixed effect models:

$$\text{HV} \sim (\text{baseline age, sex}) \times \text{time} + \text{ICV (time-varying covariate)}$$
$$\text{PACC} \sim (\text{baseline age, sex, years of education}) \times \text{time}$$

Then, we defined a mediator model and an outcome model, based on results from our main analyses (Table 2 model 2 and model 4).

$$\text{Mediator model: HV slope} \sim (\text{rs3846455})^{G} + \text{baseline A}\beta + \text{EV1-3}$$
$$\text{Outcome model: PACC slope} \sim \text{HV slope} + \text{rs3846455}^{G} + \text{baseline A}\beta + \text{EV1-3}$$

Here, rs3846455^{G} is the binary causal (independent) variable, HV slope is a continuous mediator variable, and PACC slope is the continuous outcome variable. The indirect effect (average causal mediation effect = ACME), direct effect (average direct effect = ADE), and total effect, were estimated with the default quasi-Bayesian Monte Carlo method (10,000 simulations) from the R "mediation" package [14, 15].

RESULTS

The characteristics of the study participants (n = 174) are summarized in Table 1. Our participants had average 5.7 PACC measurements (range 4 to 7), and average 2.6 HV measurements (n = 87 with two measures, n = 63 with three measures, and n = 24 with four measures). Among these participants, there were 15 rs3846455^{G} minor allele carriers (14 heterozygotes and one homozygote), and the MAF was 0.05, similar to the European reference population MAF of 0.06 from the 1000 Genomes project [15, 16]. Baseline characteristics were not significantly different between rs3846455^{G} carriers and non-carriers (Table 1).

The rs3846455^{G} carrier status was not associated with baseline PACC (p = 0.17; adjusted for age, sex, years of education, and EV1–3), but the SNP was weakly associated with longitudinal decline in PACC, after controlling for the time interaction terms of baseline Aβ, baseline age, sex, years of education, and EV1–3 (β = −0.087/year, 95% CI −0.169 to −0.005, p = 0.039; Table 2 model 2; Fig. 1B). The standardized effect size (estimated effect ("β-value") divided by standard error) of rs3846455^{G} carrier status was −2.07, which is about 40% of the standardized effect size of baseline Aβ (−5.42) from the same model. Excluding a participant with rs3846455^{GG} genotype from Table 2 model 2 did not significantly change the result (β = −0.106/year, 95% CI −0.191 to −0.021, p = 0.015). Unadjusted association between rs3846455^{G} carrier status and longitudinal PACC also reached statistical significance (β = −0.090/year, 95% CI −0.179 to −0.001, p = 0.048), supporting that statistical over-fitting did not drive our result.

The rs3846455^{G} carrier status was not associated with baseline HV (p = 0.33; adjusted for age, sex, intracranial volume, and EV1–3). However, rs3846455^{G} was associated with longitudinal decline in HV (β = −57.1 mm^3/year, 95% confidence interval (CI) −103.0 to −11.2, p = 0.015; Table 2 model 3), even after additionally adjusting for baseline Aβ (β = −57.3 mm^3/year, 95% CI −102.8 to −11.9, p = 0.014; Table 2 model 4, Fig. 1A). The standardized effect size of rs3846455^{G} carrier status on longitudinal HV change was −2.49, slightly greater than the standardized effect size of baseline Aβ (−2.01) from the same model. The association between rs3846455^{G} and longitudinal HV was consistently observed

in an unadjusted model without covariates (β = −48.1 mm^3/year, 95% CI −95.3 to −0.85, p = 0.046). Notably, this association was no longer statistically significant when we excluded one participant with rs3846455^{GG} genotype from Table 2 model 4 (β = −42.9mm^3/year, 95% CI −90.1 to 4.3, p = 0.075). We note that in a *post-hoc* analysis only assuming random intercepts (i.e., not allowing random slopes) in Table 2 model 4, we observed an association between rs3846455^{G} and longitudinal HV, even when the rs3846455^{GG} participant was excluded (β = −52.3mm^3/year, 95% CI −95.0 to −9.6, p = 0.017).

Finally, we performed a *post-hoc* mediation analysis to assess whether the association between rs3846455^{G} and hippocampal volume loss (Table 2 model 4) mediates the more rapid PACC decline observed with the rs3846455^{G} allele (Table 2 model 2). In this mediation model with rs3846455^{G} as the independent variable, HV slope as the mediator variable, and PACC slope as the dependent variable, the effect of rs3846455^{G} on PACC decline was partially mediated by faster progression of hippocampal atrophy in rs3846455^{G} carriers (mediated effect on PACC slope = −0.014, 95% CI −0.032 to -6.0×10^{-4}, p = 0.039; Fig. 2). The direct effect of rs3846455^{G} on PACC decline not mediated through HV slope was not statistically significant (p = 0.29; Fig. 2).

DISCUSSION

In this study, leveraging neuroimaging data from HABS, we replicated the previous finding from clinical-pathologic cohorts (the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP)) that an *UNC5C* haplotype captured by rs3846455^{G} is associated with worse cognitive trajectories in older adults, even after controlling for measurable neuropathology burden [2]. As HABS and ROS-MAP are independent, nonoverlapping observational studies of cognitive aging, our study provides an independent validation of a role of the *UNC5C* rs3846455^{G} haplotype in interpersonal variability in cognitive decline, and demonstrates the utility of neuroimaging biomarkers in the ante-mortem studies of genetically determined susceptibility to age-related cognitive decline.

UNC5C is a gene with roles in axon guidance during development [17, 18] and apoptosis regulation [19]. UNC5C is a functional dependence receptor that can induce apoptosis in the absence of its ligand (netrin) [19] and has an enriched expression in adult human and rodent hippocampus [3, 5]. Overexpression of UNC5C increased susceptibility of cultured rat hippocampal neurons to various neurotoxic insults [3], suggesting the role of UNC5C in modulating hippocampal susceptibility to neurodegeneration. Moreover, the previously observed association of rs3846455^{G} with cognitive decline was specific to the episodic memory domain that depends on hippocampus [2], further implicating *UNC5C* in hippocampal susceptibility to neurodegeneration.

In this context, our hypothesis-driven characterization of a candidate polymorphism shows that the *UNC5C* rs3846455^{G} haplotype is associated with accelerated hippocampal atrophy in older adults who were clinically normal at baseline. This association partially mediated the association of rs3846455^{G} with accelerate cognitive decline, in a *post-hoc* mediation modeling. This finding is line with previous experimental and clinical-pathologic studies of *UNC5C* [2, 3], and expands our understanding of the rs3846455^{G} haplotype. However, our

study has a modest sample size, and the association between rs3846455^{G} carrier status and accelerated hippocampal atrophy was no longer statistically significant after excluding the single participant that is homozygous for the risk allele (rs3846455^{GG} genotype) ($p = 0.075$). Therefore, the previously unreported association between rs3846455^{G} and accelerated hippocampal atrophy requires further validation by replication studies with larger sample size.

UNC5C rs3846455^{G} haplotype was not associated with baseline Aβ, hippocampal volume, or cognition in our study. This is consistent with the previous clinical-pathologic study with close to 1,000 participants that did not find a significant relationship of rs3846455^{G} with any of the measured post-mortem neuropathologies or baseline cognition [2], as well as a large GWAS meta-analysis on a cross-sectional mid-adulthood hippocampal volume in more than 26,000 participants [20]. Thus, the clinical implication of the haplotype captured by rs3846455^{G} is likely specific to the older adults at risk of cognitive decline.

The molecular mechanism by which the *UNC5C* haplotype captured by rs3846455^{G} increases the susceptibility to cognitive decline in older adults remains unclear. As cellular overexpression of wild-type UNC5C increases apoptosis in cultured hippocampal neurons [3], it is plausible to hypothesize that functional variants increasing *UNC5C* expression in hippocampus could lead to accelerated hippocampal neurodegeneration. *UNC5C* rs3846455^{G} is an intronic SNP within an enhancer region in human hippocampus, per the ChromHMM core 15-chromatin state prediction [21] based on the Roadmap Epigenomics Project [22]. This functional prediction suggests that the SNP might alter *UNC5C* gene expression in the hippocampus, but rs3846455 was not significantly associated with hippocampal *UNC5C* mRNA expression in the Genotype-Tissue Expression database ($n = 111$) [22]. Given the SNP's relatively low MAF (0.06), larger number of hippocampal samples from older adults will be required to examine the expression quantitative trait locus association.

Our study has several important limitations. First and foremost, we had a very limited sample size for a genetic association study ($n = 177$), and the study sample included only fifteen rs3846455^{G} carriers. Therefore, our results should be interpreted with caution, and the newly found association between rs3846455^{G} and accelerated hippocampal atrophy as well as the subsequent mediation analysis requires further validation. Also, due to our limited sample size, we could not assess interactive association of Aβ and rs3846455^{G}, a potential genetic risk factor of hippocampal neurodegeneration, despite multiple previous reports that Aβ and neurodegeneration have synergistic predictive value for cognitive decline among clinically normal older adults [23-25]. Nonetheless, our study is an independent replication of the previously reported link between rs3846455^{G} and cognitive decline [2], and the link between rs3846455^{G} and hippocampal neurodegeneration was found through a hypothesis-driven candidate polymorphism analysis based on previous reports [2, 3]. Thus, our results are likely capturing a true effect rather than spurious associations. Second, our analyses were restricted to participants from European ancestry, and the results cannot be easily extrapolated to people of non-European ancestry. Third, HABS participants are highly educated and in good physical and cognitive health at the time of enrollment. As such, they are not entirely representative of the general population of older adults. Still, MAF of

rs3846455^{G} in our participants was not significantly different from the reference panel [15, 16], indicating a genetically representative sampling. Fourth, there were only 14% of *APOE ε*4 carriers among the rs3846455^{G} carriers, while 31% of the rs3846455^{C} homozygotes were *APOE ε*4 carriers. Although this imbalance did not reach statistical significance, it might have led to a slight underestimation of the effect of the rs3846455^{G} allele on hippocampal atrophy and cognitive decline. Finally, the mediation analysis should be interpreted cautiously, given that this was a simplified *post-hoc* model assuming a linear relationship among rs3846455^{G} carrier status, HV change, and PACC change.

In conclusion, leveraging longitudinal data with approximately five-year average follow-up, we validated the previously reported association of the *UNC5C* rs3846455^{G} haplotype and faster cognitive decline in older adults. Moreover, our results suggest that accelerated hippocampal atrophy might partially mediate the association between 3846455^{G} and faster cognitive decline in clinically normal older adults. This study also demonstrates the utility of modestly sized, but deeply phenotyped cohorts in investigating the genetics of complex endophenotypes such as cognitive decline not explained by neuropathology [26]. Nonetheless, neuroimaging studies with larger numbers of participants including individuals of non-European descent are required to further validate our results and understand the role of the *UNC5C* rs3846455^{G} haplotype in more diverse populations. Further investigations of the functional mechanism of the *UNC5C* rs3846455^{G} haplotype may open additional therapeutic avenues for neuroprotection in older adults at high risk of cognitive decline.

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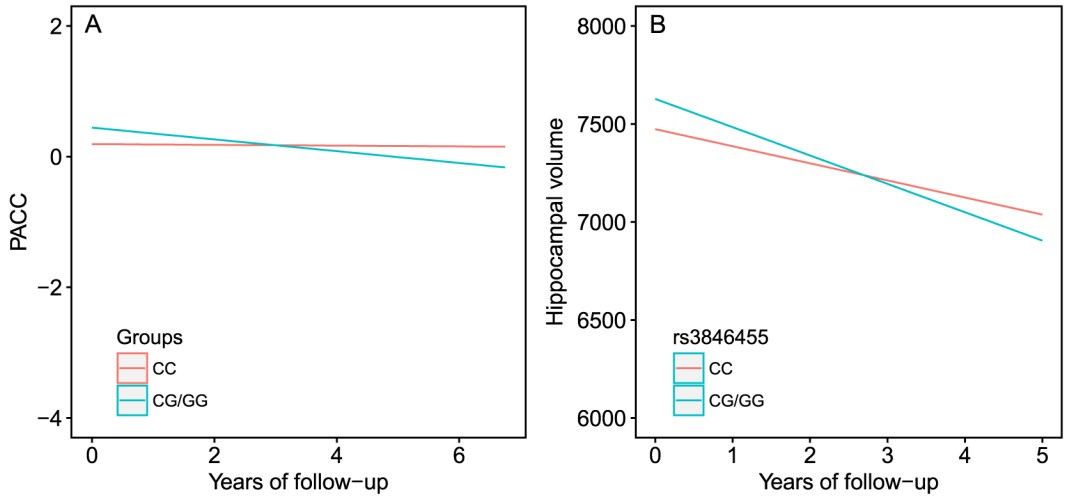

Fig. 1.

rs3846455^{G} carrier status and longitudinal changes in bilateral hippocampal volume and Preclinical Alzheimer Cognitive Composite. A) PACC change over time was predicted from a linear mixed effect model, controlling for interaction of time (years from baseline) with baseline Aβ, baseline age, sex, years of education, and EV1–3. Predicted trajectories of PACC were plotted by *UNC5C* rs3846455^{G} minor allele carrier status. B) HV change over time was predicted from a linear mixed effect model, controlling for total intracranial volume and interaction of time (years from baseline) with baseline Aβ, baseline age, sex, and EV1–3. Predicted trajectories of HV were plotted by *UNC5C* rs3846455^{G} minor allele carrier status. Aβ, baseline amyloid-β measured by Pittsburgh compound B (PiB) positron emission tomography distributed volume ratio (DVR) from composite cortical regions; EV1–3, first three principal components from the genotype covariance matrix; HV, hippocampal volume; PACC, preclinical Alzheimer cognitive composite.

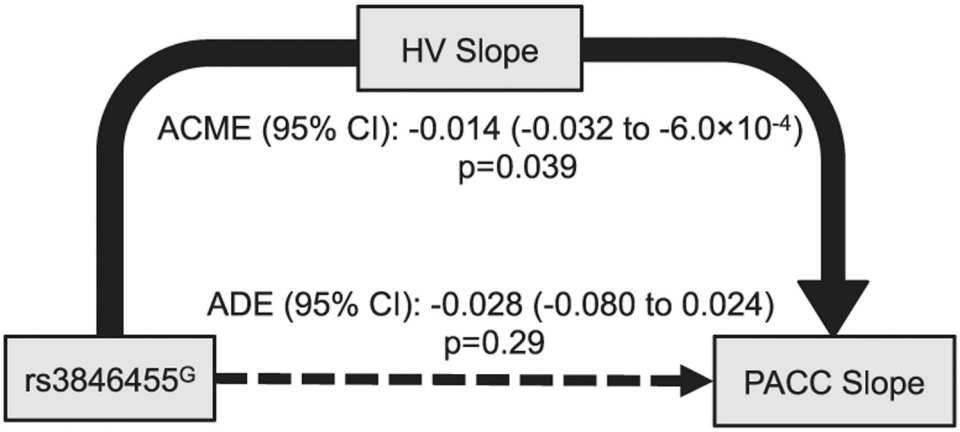

Fig. 2.

Mediation of the association of rs3846455^{G} with cognitive decline by accelerated hippocampal atrophy. Causal mediation analysis was performed using quasi-Bayesian Monte Carlo method (with 10,000 simulations), having rs3846455^{G} as an independent (causal) binary variable, HV slope (adjusted for baseline age, sex, and ICV) as a continuous mediator variable, and PACC slope (adjusted for baseline age, sex, and years of education) as the continuous outcome variable. We also adjusted for baseline Aβ and EV1–3 in the mediator and outcome models that we used for the simulation. Mediated (indirect) effect (ACME) and direct effect (ADE) were calculated. Solid arrow indicates a significant mediated effect (p <0.05), and dotted arrow indicates a direct effect that did not reach statistical significance (p = 0.29). Aβ, amyloid-β measured by Pittsburgh compound B (PiB) positron emission tomography distributed volume ratio (DVR) from composite cortical regions; ACME, average causal mediation effect (the effect of the independent variable on the outcome that is mediated through the mediator); ADE, average direct effect (the effect of the independent variable on the outcome that is independent from the mediator); EV1–3, first three principal components from the genotype covariance matrix; HV, hippocampal volume; ICV, intracranial volume; PACC, Preclinical Alzheimer Cognitive Composite.

Table 1

Demographic characteristics of the study participants

	All (*n* = 174)	**rs3846455^{CC} (*n* = 159)**	**rs3846455$^{GC/GG}$ (*n* = 15)**	***p*-value for difference[a]**
Baseline age, mean years, (SD)	73.4 (6.0)	73.5 (6.1)	72.9 (5.7)	0.75
Female, *n* (%)	97 (56)	90 (57)	7 (47)	0.46
Education, mean years (SD)	16.4 (2.9)	16.3 (2.9)	17.5 (2.3)	0.12
Length of f/u, mean years (SD)	4.9 (1.2)	5.0 (1.2)	4.6 (1.3)	0.21
*APOE ε*4 carriers, *n* (%)[b]	49 (29)	47 (31)	2 (14)	0.20
Aβ, mean (SD)	1.18 (0.20)	1.18 (0.20)	1.18 (0.19)	0.97
Baseline HV (SD)	7.45×10^3 (8.8×10^2)	7.45×10^3 (8.9×10^2)	7.53×10^3 (6.8×10^2)	0.72
Baseline PACC (SD)	0.123 (0.576)	0.101 (0.593)	0.354 (0.245)	0.10

[a] *p*-value for difference (either by two-sample *t*-test or chi-squared test) between two genotype groups are noted.

[b] *n* = 167. Aβ, baseline amyloid-β measured by Pittsburgh compound B (PiB) positron emission tomography distributed volume ratio (DVR) from composite cortical regions; f/u, follow-up; HV, bilateral hippocampal volume; PACC, preclinical Alzheimer Cognitive Composite; SD, standard deviation.

Table 2

UNC5C rs3846455^{G} and longitudinal change in the Preclinical Alzheimer Cognitive Composite (PACC) and hippocampal volume (HV)

Models	Predictors	Longitudinal change in PACC (/year (95% CI))	Standardized effect size
1	rs3846455^{G}*Time	−0.084 (−0.173 to 0.005), $p = 0.063$	−1.86
2	rs3846455^{G}*Time	−0.087 (−0.169 to −0.005), $p = 0.039$	−2.07
	Aβ*Time	−0.310 (−0.422 to −0.198), $p < 0.001$	−5.42
Models	**Predictors**	**Longitudinal change in HV (mm3/year (95% CI), *p*-value)**	**Standardized effect size**
3	rs3846455^{G}*Time	−57.1 (−103.0 to −11.2), $p = 0.015$	−2.45
4	rs3846455^{G}*Time	−57.3 (−102.8 to −11.9), $p = 0.014$	−2.49
	Aβ*Time	−65.3 (−129.2 to −1.5), $p = 0.045$	−2.01

In models 1 and 2, estimated effects (slopes) on longitudinal change of PACC were reported for each predictor from linear mixed effect models. In these two models, we adjusted for the interaction of time (years from baseline) with baseline age, sex, years of education, and first three principal components from genotype covariance matrix (EV1–3). In models 3 and 4, estimated effects (slopes) on longitudinal change of bilateral hippocampal volume were reported for each predictor from linear mixed effect models. In these two models, we adjusted for the total intracranial volume from the MRI of each hippocampal volume measurement, as well as the interaction of time (years from baseline) with baseline age, sex, and EV1–3. Standardized effect sizes were calculated by dividing each estimated effect ("β-value") by standard error. Aβ, baseline amyloid-β measured by Pittsburgh compound B positron emission tomography distributed volume ratio from composite cortical regions; CI, confidence interval; HV, bilateral hippocampal volume; PACC, Preclinical Alzheimer Cognitive Composite.