Dissociable influences of *APOE* $\epsilon 4$ and polygenic risk of AD dementia on amyloid and cognition

Tian Ge, PhD, Mert R. Sabuncu, PhD, Jordan W. Smoller, MD, ScD, Reisa A. Sperling, MD, and Elizabeth C. Mormino, PhD, For the Alzheimer's Disease Neuroimaging Initiative

Neurology® 2018;90:e1605-e1612. doi:10.1212/WNL.0000000000005415

Correspondence

Dr. Mormino

bmormino@stanford.edu

Abstract

Objective

To investigate the effects of genetic risk of Alzheimer disease (AD) dementia in the context of β -amyloid ($A\beta$) accumulation.

Methods

We analyzed data from 702 participants (221 clinically normal, 367 with mild cognitive impairment, and 114 with AD dementia) with genetic data and florbetapir PET available. A subset of 669 participants additionally had longitudinal MRI scans to assess hippocampal volume. Polygenic risk scores (PRSs) were estimated with summary statistics from previous large-scale genome-wide association studies of AD dementia. We examined relationships between *APOE* $\epsilon 4$ status and PRS with longitudinal $A\beta$ and cognitive and hippocampal volume measurements.

Results

APOE $\epsilon 4$ was strongly related to baseline $A\beta$, whereas only weak associations between PRS and baseline $A\beta$ were present. *APOE* $\epsilon 4$ was additionally related to greater memory decline and hippocampal atrophy in $A\beta+$ participants. When *APOE* $\epsilon 4$ was controlled for, PRS was related to cognitive decline in $A\beta+$ participants. Finally, PRSs were associated with hippocampal atrophy in $A\beta-$ participants and weakly associated with baseline hippocampal volume in $A\beta+$ participants.

Conclusions

Genetic risk factors of AD dementia demonstrate effects related to $A\beta$, as well as synergistic interactions with $A\beta$. The specific effect of faster cognitive decline in $A\beta+$ individuals with higher genetic risk may explain the large degree of heterogeneity in cognitive trajectories among $A\beta+$ individuals. Consideration of genetic variants in conjunction with baseline $A\beta$ may improve enrichment strategies for clinical trials targeting $A\beta+$ individuals most at risk for imminent cognitive decline.

From the Psychiatric and Neurodevelopmental Genetics Unit (T.G., J.W.S.), Center for Genomic Medicine, Massachusetts General Hospital; Departments of Psychiatry (T.G., J.W.S.) and Neurology (R.A.S.), Massachusetts General Hospital, Harvard Medical School, Boston; Athinoula A. Martinos Center for Biomedical Imaging (T.G., M.R.S.), Massachusetts General Hospital, Harvard Medical School, Charlestown; School of Electrical and Computer Engineering and Nancy E. and Peter C. Meinig School of Biomedical Engineering (M.R.S.), Cornell University, Ithaca, NY; Center for Alzheimer Research and Treatment (R.A.S.), Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and Department of Neurology and Neurological Sciences (E.C.M.), Stanford University School of Medicine, Palo Alto, CA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at links.lww.com/WNL/A406.

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CN** = clinically normal; **GWAS** = genome-wide association studies; **LMM** = linear mixed-effects model; **MCI** = mild cognitive impairment; **PRS** = polygenic risk score; **SNP** = single nucleotide polymorphism.

Common genetic variants explain a large proportion of the heritability of sporadic Alzheimer disease (AD) dementia.^{1,2} However, the mechanisms underlying these genetic risk factors are unclear, and it is likely that multiple pathways are involved. Previous work has identified limited associations between genetic risk and β -amyloid (A β) accumulation^{3,4} and has suggested mechanistic pathways not directly linked to abnormal A β accumulation such as inflammatory pathways.^{5–7} Thus, genetic risk variants associated with AD dementia may not solely confer risk by promoting A β aggregation but may make an individual more likely to decline when faced with A β accumulation.

A synergistic effect between genetic risk and A β is consistent with a framework in which A β may be necessary but insufficient for clinical symptoms of AD dementia⁸ and may offer an explanation for the presence of clinically normal (CN) older individuals who have high levels of A β .⁹ Along these lines, it is known that although A β + CN individuals show group-level reductions in cognitive performance over time,^{3,10–12} many A β + individuals remain cognitively normal even after extended follow-up.¹³ Heterogeneity in cognitive decline has also been reported in symptomatic patients with AD dementia, which may be related to differences in genetic risk factors. For instance, although the *APOE* ϵ 4 allele is consistently associated with abnormal accumulation of A β ,¹⁴ A β + individuals without dementia who are also *APOE* ϵ 4 carriers show faster rates of cognitive decline than A β + individuals who are *APOE* ϵ 4 noncarriers.^{15,16} A similar effect modification has been shown for the *BDNF* gene such that A β + individuals with the *BDNF* Met allele show faster cognitive decline than A β + individuals without the Met allele.¹⁷ Given that these a priori genetic risk factors have been shown to influence cognitive decline among A β + individuals, it is possible that other established genetic risk factors have a similar influence.

The overall goal of the present study was to investigate whether *APOE* ϵ 4 and polygenic risk of AD dementia influence A β , cognition, and hippocampal volume measurements and to determine whether their associations with cognition and hippocampal volume are modified by A β status.

Methods

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI;adni.loni.usc.edu) as of March 25, 2017. This study used 702

ADNI-GO/2 participants (221 CN, 367 with mild cognitive impairment [MCI], and 114 with AD dementia) of European ancestry who had florbetapir PET images, longitudinal neuropsychological assessment, and genome-wide single nucleotide polymorphisms (SNPs). Of the 702 participants, 669 additionally had longitudinal brain MRI scans that passed quality control. Given that florbetapir PET was introduced midstudy, longitudinal neuropsychological and hippocampal volume measurements taken >1 year before the baseline PET scan were discarded from the analyses.

Standard protocol approvals, registrations, and patient consents

Institutional review boards approved study procedures across ADNI participating sites. Written informed consent for research was obtained from all participants.

A β imaging

Global standardized uptake value ratio florbetapir index values were averaged across 4 large bilateral regions (frontal, cingulate, parietal, and lateral temporal) and normalized by the whole cerebellum.^{18,19} A 1.11 cutoff of the baseline standardized uptake value ratio value was used to classify participants as A β + and A β -.^{18,20}

Neuropsychological assessments

Composite scores of memory²¹ and executive function²² were developed previously by using sophisticated neuropsychometric approaches (confirmatory factor analyses and item response theory) to account for different distributions and formats of individual scores, missing items, and different versions of neuropsychological tests.

Structural MRI

The 3T T1 structural brain MRI scans were processed with the FreeSurfer version 5.3 longitudinal pipeline and used to define bilateral hippocampal volume.²³ We processed the MRI scans locally rather than using the imaging measurements from the ADNI website because this led to more longitudinal time points and the use of a more recent FreeSurfer version.

Processing of genetic data

Genome-wide SNP data from 793 ADNI-GO/2 participants were processed following standard pipelines.²⁴ Non-European participants, population outliers, and closely related participants were removed. Genotype imputation was performed with the MaCH software.²⁵ SNPs that had poor imputation quality, high missing rate (>2%), low minor allele frequency (<1%), or significant deviation from Hardy-Weinberg equilibrium ($p < 1e-6$) and participants who had

a high missing genotype rate (>2%) were filtered out. Seven hundred sixteen participants with 7,694,586 autosomal SNPs remained after quality control. Of the 716 participants, 702 had florbetapir PET and longitudinal neuropsychological assessments.

Calculation of polygenic risk score

Polygenic risk score (PRS) was computed on the basis of the summary statistics from the stage 1 analysis of the International Genomics of Alzheimer's Project, the largest-to-date case-control genome-wide association studies (GWAS) (17,008 cases with AD and 37,154 CN controls) of AD dementia diagnosis,²⁶ with the software package PRSice.²⁷ Specifically, imputed genome-wide SNPs were pruned by use of p value informed clumping. PRS was computed as the sum of individual SNPs below a p value threshold, weighted by the log of the odds ratio estimated by the GWAS. PRS thus summarizes genetic effects among an ensemble of variants spanning the genome that may not individually achieve GWAS-level significance. A range of p value thresholds from $p < 1e-7$ to $p < 1e-2$ were used in this study.

Statistical analysis

The influences of *APOE* $\epsilon 4$ status and PRS on baseline florbetapir values and binary $A\beta +/ -$ groups were examined in the whole sample with linear regression and logistic regression, respectively, with adjustment for top 4 principal components of the genotype data, baseline diagnosis, baseline age, sex, and education. When assessing the effect of PRS, we included *APOE* $\epsilon 4$ status in the model.

The influences of *APOE* $\epsilon 4$ status and PRS on the baseline and longitudinal change in florbetapir values, neuropsychological composite scores, and hippocampal volume measurements were examined with longitudinal linear mixed-effects models (LMMs). All models included an intercept, time from baseline, top 4 genotype principal components, baseline diagnosis, baseline age, sex, education, and the interactions between baseline diagnosis, baseline age, sex, education, and time (i.e., baseline diagnosis $\times$ time, baseline age $\times$ time, etc) as fixed-effect covariates. Throughout the article, the calculation of PRS included the *APOE* $\epsilon 4$ allele, but when assessing the association between PRS and longitudinal change, we included *APOE* $\epsilon 4$ and its interaction with time in the model to assess the effect of PRS above and beyond *APOE* $\epsilon 4$ status. When analyzing hippocampal volume, we additionally adjusted for intracranial volume and its interaction with time as covariates. Random intercept and slopes were included in each LMM. All analyses were repeated in $A\beta +$ and $A\beta -$ participants separately. All p values reported in this article are 2-sided uncorrected p values.

To compute a metric of variance explained, we extended the classic adjusted R^2 statistic in multiple regression analysis to the context of LMM. Specifically, we assume that the unbiased estimate of the variance of the random

slope in the full LMM is V_{full} and the unbiased estimate of the variance of the random slope in a reduced model without genetic risk factors (*APOE* $\epsilon 4$ or PRS) is V_{reduced} . The reduced model contained all covariates and their interactions with time. Then, variation in the rate of decline explained by each genetic risk factor is defined as $R^2_{\text{slope}} = 1 - V_{\text{full}}/V_{\text{reduced}}$. R^2_{slope} measures the proportion of interparticipant variation in the slope that can be explained by adding the genetic risk factor into the model. R^2_{slope} was calculated for *APOE* $\epsilon 4$ by adding *APOE* $\epsilon 4$ to the reduced model. PRS was then added to this model to estimate R^2_{slope} for PRS. Variance explained in baseline measurements by genetic factors can be defined similarly.

Data availability

All imaging, genetic, demographics, and neuropsychological composite scores used in this article are publicly available and were downloaded from the ADNI website (adni.loni.usc.edu). Structural MRI data and GWAS data were downloaded and used to derive the measurements used here (hippocampus volume and PRS). The authors will provide a list of ADNI participant identifications on request for replication purposes.

Results

PRS, baseline $A\beta$, and clinical diagnosis

Table 1 summarizes the participant characteristics. In general, PRS was greater in the $A\beta +$ compared to the $A\beta -$ group (2-sample t test $p < 0.05$ across diagnosis and PRS thresholds; figure 1). However, the associations between PRS and baseline $A\beta$ were weak, regardless of whether $A\beta$ is treated as a continuous variable or as a binary variable (table e-1, [links. lwww.com/WNL/A405](http://www.com/WNL/A405)). For instance, the most significant relationship between PRS and continuous $A\beta$ explained only 0.75% of the $A\beta$ variation ($p = 0.013$). As expected, *APOE* $\epsilon 4$ was strongly associated with elevated continuous $A\beta$ at baseline, explaining 17.94% of the variance.

PRS was associated with clinical diagnosis, even in the $A\beta +$ group (PRS was higher in $A\beta +$ patients with MCI and $A\beta +$ patients with AD compared to $A\beta +$ controls; figure 1). This pattern was present for the majority of PRS thresholds (1-way analysis of variance $p < 0.05$). There were no significant diagnostic difference in PRS among the $A\beta -$ group (figure 1). Diagnosis and its interaction with time were controlled for in all subsequent analyses to ensure that results related to cognitive decline were independent of diagnosis.

Genetic risk factors and $A\beta$ accumulation

We next examined the associations between genetic risk factors and longitudinal accumulation of $A\beta$ over time. Given the slow rates of $A\beta$ accumulation, longitudinal $A\beta$ was treated as a continuous variable and examined separately in the $A\beta -$ and $A\beta +$ groups (defined at baseline). We found that $A\beta -$ *APOE* $\epsilon 4$ carriers had faster $A\beta$ accumulation over time than $A\beta -$ noncarriers ($p = 0.005$). There was no effect of *APOE* $\epsilon 4$ on $A\beta$ accumulation in the $A\beta +$ group. PRS had no influence on

Table 1 Participant demographics

	Neuropsychological		Neuroimaging		A β	
	A β +	A β –	A β +	A β –	A β +	A β –
Sample size, n	380	322	355	314	380	322
Baseline CN/MCI/AD, n	78/202/100	143/165/14	71/191/93	137/164/13	78/202/100	143/165/14
Baseline age (range), y	73.9 (55.1–90.3)	71.5 (55.1–91.5)	73.5 (55.1–90.1)	71.3 (55.0–91.4)	73.9 (55.1–90.3)	71.5 (55.1–91.5)
Female, n (%)	181 (47.6)	138 (42.9)	172 (48.5)	134 (42.7)	181 (47.6)	138 (42.9)
Education (range), y	16.0 (8–20)	16.6 (12–20)	16.0 (8–20)	16.6 (12–20)	16.0 (8–20)	16.6 (12–20)
APOE ϵ 4+, n (%)	250 (65.8)	68 (21.1)	237 (66.8)	66 (21.0)	250 (65.8)	68 (21.1)
Measurements (range), n	4.16 (1–8)	4.71 (1–8)	3.92 (1–7)	4.25 (1–7)	1.71 (1–3)	2.11 (1–3)
Follow-up, mean/median (interquartile range), y	2.50/2.03 (1.02–4.01)	3.22/3.93 (2.02–4.05)	1.52/1.25 (1.00–2.08)	1.77/2.04 (1.03–2.12)	1.44/1.94 (0.00–2.04)	2.29/2.04 (1.92–3.97)

Abbreviations: A β = β -amyloid; AD = Alzheimer disease; CN = clinically normal; MCI = mild cognitive impairment. Characteristics of the A β + and A β – participants from the Alzheimer's Disease Neuroimaging Initiative.

A β accumulation in either the A β + or A β – group (figure 2 and tables e-2 and e-3, links.lww.com/WNL/A405).

Genetic risk factors and cognition

A β + APOE ϵ 4 carriers had faster memory decline than non-carriers ($p = 0.015$). There was no effect of APOE ϵ 4 on memory in the A β – group. APOE ϵ 4 was weakly associated with executive function decline in the A β – group ($p = 0.049$) but not the A β +

group. Furthermore, controlling for APOE ϵ 4, higher polygenic risk was strongly associated with higher rates of decline in memory and executive function in A β + individuals across a range of PRS p value thresholds. These associations explained approximately 8% to 10% of the variation in the rate of cognitive decline across A β + participants. PRSs were not associated with cognitive decline in A β – participants or baseline cognitive scores in either A β group (figures 2 and 3 and tables e-2 and e-3, links.lww.com/WNL/A405).

Figure 1 PRSs of AD dementia by diagnosis and A β status

Mean and standard error of the polygenic risk score (PRS) of Alzheimer disease (AD) dementia by diagnosis among (A) β -amyloid (A β)-positive and (B) A β -negative participants across PRS p value thresholds are shown. CN = clinically normal; MCI = mild cognitive impairment.

Figure 2 Associations between genetic risk factors and A β , cognition, and hippocampal volume

Variance explained by *APOE* $\epsilon 4$ and polygenic risk scores (PRSs) of Alzheimer disease dementia across longitudinal linear mixed effects models predicting (A and B) β -amyloid (A β), (C and D) memory, (E and F) executive function, and (G and H) hippocampal volume.

lww.com/WNL/A405). All results remained similar when the analysis was restricted to participants without dementia (CN and MCI combined; table e-4 and figure e-1, links.lww.com/WNL/A404). The effects of PRS on cognitive decline among A β + participants remained strong if we additionally controlled for baseline hippocampal volume and its interaction with time in the model (table e-5).

Genetic risk factors and hippocampal volume

Among A β + participants, both *APOE* $\epsilon 4$ status and polygenic risk were associated with baseline hippocampal volume. However, these effects on baseline hippocampus volume were small, accounting for <2% of the variance. Among A β -, PRS was strongly associated with longitudinal change in hippocampal volume but not hippocampal volume at baseline. PRS using the strictest threshold explained 8% of the variance in hippocampal atrophy in the A β - group (figures 2 and 3 and tables e-2 and e-3, links.lww.com/WNL/A405).

Discussion

In this study, we found that *APOE* $\epsilon 4$ and PRS of AD dementia show different patterns of associations with AD markers. Specifically, *APOE* $\epsilon 4$ was related to elevated

baseline A β and the accumulation of A β over time in A β -, whereas PRS showed minimal associations with A β but was strongly associated with faster cognitive decline in A β + participants. The influence of PRS on longitudinal cognitive trajectories was above and beyond the effect of *APOE* $\epsilon 4$ status, diagnosis, and hippocampal volume, highlighting the value of a priori genetic risk factors as a predictor of short-term decline among A β + individuals. Furthermore, polygenic risk was not related to rates of cognitive decline in the A β - group, suggesting a synergistic effect between abnormal A β and genetic risk on cognitive decline. Finally, polygenic risk showed associations with hippocampal volume across both the A β + and A β - groups, suggesting that genetic risk of AD may have an effect on non-A β pathways that influence brain structure in regions central to AD dementia.

We did not find strong evidence that an aggregate measure of genetic risk of AD dementia was directly associated with abnormal levels of amyloid, assessed either cross-sectionally or longitudinally. However, our analyses consistently showed an association between polygenic risk and cognitive decline that was specific to the A β + group. This finding is in line with previous studies that have shown that A β and *APOE* $\epsilon 4$

Figure 3 Illustration of the influences of genetic risk on cognitive decline and hippocampal atrophy in A β + participants

Model-based estimation of longitudinal changes in (A) memory, (B) executive function, and (C) hippocampal volume based on *APOE* ϵ 4 status and the polygenic risk score (PRS) of Alzheimer disease dementia computed with $p < 1 \times 10^{-5}$ as the p value threshold in β -amyloid-positive (A β +) participants. High PRS refers to the upper quartile (75%) of the PRS in the sample; low PRS refers to the lower quartile (25%) of the PRS in the sample. All fixed-effect covariates (principal components, baseline diagnosis, baseline age, sex, education, and their interactions with time) were set to the sample average.

interact to accelerate cognitive decline and hippocampal degeneration in CN individuals,^{16,17,28} highlighting synergistic interactions between genetic risk of AD and the presence of abnormal A β . Furthermore, we have previously observed that elevated PRS is associated with greater longitudinal cognitive decline in older individuals without dementia.²⁹ However, other studies investigating PRS of AD dementia have failed to identify an association with cognitive decline³⁰ or clinical progression.³¹ One source of this discrepancy may be that these previous investigations of polygenic risk did not examine decline in the context of AD biomarkers. Our results indicate that elevated PRS is associated with cognitive decline only among A β + individuals, suggesting that genetic risk factors and A β act synergistically to influence cognitive decline. Recent work from Tan et al.³² and Desikan et al.³³ also using the ADNI dataset has reported a similar pattern: cognitive decline was greatest in individuals with both abnormal CSF AD markers (amyloid and tau) and elevated genetic risk of AD as assessed with a polygenic hazard score. Although this study implemented a different methodological strategy to aggregate genetic risk across multiple genomic loci, the consistency across our study and theirs highlights a synergistic effect between genetic risk and AD pathology on cognitive trajectories. Given that genetic risk of AD has been implicated in non-A β pathways such as the immune system and cytoskeletal function,⁵⁻⁷ it is possible that the convergence of

these non-A β pathways with late-life A β accumulation is an important predictor of subsequent decline.

Whereas polygenic risk was related to decline in both memory and executive function among A β + individuals, *APOE* ϵ 4 was specifically related to decline in memory and not executive function. This finding is consistent with analyses in patients with AD dementia that have suggested that *APOE* ϵ 4 carriers tend to show memory impairment whereas patients with AD dementia who are *APOE* ϵ 4 noncarriers show impairment in executive function.³⁴ Likewise, examination of pathologically defined subtypes of AD dementia suggests that *APOE* ϵ 4 is associated with a limbic predominant presentation among late-onset AD cases.³⁵ The finding that polygenic risk influences both memory and executive function implies that polygenic risk of AD dementia may influence a more distributed set of brain regions compared to *APOE* ϵ 4. Along these lines, we previously found that polygenic risk was associated with multiple cortical regions, including frontal, parietal, and temporal cortices,³⁶ which may explain the broad effect of polygenic risk on cognitive decline. Given that calculation of polygenic risk aggregates information across many genomic loci and potentially many genetic pathways, it is unclear whether there are certain subgroups of genetic risk factors that relate to more specific brain networks and would demonstrate an effect on cognition that was domain specific.

If so, a participant's composition of these genetic risk factors may be predictive of the specific cognitive domain that is most vulnerable in an individual and provide an explanation for the heterogeneity in clinical expression of AD dementia that exists across individuals. Future work that refines polygenic risk to encapsulate variability across different cognitive domains may offer insights into the known heterogeneity of the clinical expression of AD.³⁷

In contrast to memory and executive function, we found that in A β + participants, PRS did not strongly influence longitudinal hippocampal atrophy but was associated with baseline volume, while in the A β - group, PRS was strongly associated with the longitudinal change in hippocampal volume but not its baseline measurements. This finding highlights that although polygenic risk influences hippocampal volume regardless of A β status, the time course of this effect varies. It is possible that the effect of polygenic risk on hippocampal atrophy occurs before late-life A β accumulation and that once abnormal levels of A β have occurred, there are stronger drivers of subsequent atrophy compared to polygenic risk (such as tau-mediated neurodegeneration³⁸). This framework is consistent with previous work that has shown a relationship between polygenic risk of AD dementia and hippocampal volume in young participants,^{29,39} well before the age at which abnormal A β is anticipated.⁴⁰ Thus, the effect of polygenic risk on hippocampal volume in stages preceding A β accumulation (as supported by findings in both younger participants^{29,39} and older A β - participants in the current study) may ultimately make an individual more vulnerable to cognitive decline in late life when additionally faced with A β accumulation.

Our analyses have several limitations. First, the PRSs were calculated from summary statistics from cross-sectional case-control GWAS.²⁶ Therefore, the estimated effect sizes of genetic variants may not reflect their strength of influences on longitudinal change in AD markers, and the constructed PRS may thus be suboptimal for investigating the genetic basis of cognitive decline and AD progression. Conducting large-scale GWAS of longitudinal neuropsychological assessments and neuroimaging biomarkers of AD may improve genetic prediction of longitudinal decline. Second, although we focused on hippocampus volume, other MRI-derived neuroimaging markers of AD progression may also be relevant, especially given the association we identified between PRS and executive function. Third, although we report that $\approx 10\%$ of the variance in cognitive decline among A β + individuals can be explained by genetic risk factors, the majority of variance remains unexplained. Thus, the consideration of additional factors such as the regional deposition of tau (via PET), as well as vascular, lifestyle, and other genetic risk factors that were not captured in the International Genomics of Alzheimer's Project GWAS analysis, will be necessary to optimize our ability to predict risk at the individual participant level. Lastly, replication of the findings in this study is needed in other large cohorts with biomarker data and prospective neuropsychological follow-up.

We observed that APOE $\epsilon 4$ status and higher polygenic risk of AD dementia were associated with higher rates of decline in neuropsychological assessments of memory and executive function in A β + individuals. The effect of polygenic risk on cognitive decline was above and beyond APOE $\epsilon 4$ and specific to the A β + group, suggesting a synergistic effect between abnormal A β and genetic risk. Polygenic risk was also associated with hippocampal volume, an effect that was not dependent on A β status. These findings suggest that although this aggregate measure of genetic risk is not strongly associated with amyloid, it may moderate an individual's risk of decline once abnormal levels of amyloid are present, ultimately improving efforts to identify individuals at risk for cognitive decline.

Author contributions

Conception and design of the study: T.G., and E.C.M. Statistical analysis: T.G. Drafting the manuscript: T.G., and E.C.M. Interpretation of data: T.G., M.R.S., J.W.S., R.A.S., and E.C.M. Revising manuscript: T.G., M.R.S., J.W.S., R.A.S., and E.C.M.

Study funding

This work was funded by NIH grants K99AG054573 (T.G.); R01NS083534, R01NS070963, K25EB013649, R21AG050122, and R41AG052246 (M.R.S.); K24MH094614 and R01MH101486 (J.W.S.); and K01AG051718 (E.C.M.). J.W.S. is a Tepper Family MGH Research Scholar and was also supported in part by a gift from the Demarest Lloyd, Jr. Foundation. This research used resources provided by the Center for Functional Neuroimaging Technologies and a P41 Biotechnology Resource Grant (P41EB015896) supported by NIH. This work also involved the use of instrumentation supported by the NIH Shared Instrumentation Grant Program (S10RR023043 and S10RR023401). Data collection and sharing for this project was funded by the ADNI (NIH grant U01 AG024904) and Department of Defense ADNI (Department of Defense award W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, by the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen; Bristol-Myers Squibb Co; CereSpir, Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Co; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co Inc; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corp; Pfizer Inc; Piramal Imaging; Servier; Takeda Pharmaceutical Co; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the NIH (fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated

by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Disclosure

T. Ge received funding from K99AG054573. M. Sabuncu received funding from R01NS083534, R01NS070963, K25EB013649, R21AG050122, and R41AG052246. J. Smoller received funding from U01HG008685, R56MH110872, R01MH101486, R01MH106547, OT2OD024612, and K24MH094614. He is a Tepper Family MGH Research Scholar and was also supported in part by a gift from the Demarest Lloyd, Jr. Foundation. R. Sperling has served as a paid consultant for Abbvie, Biogen, Bracket, Genentech, Lundbeck, Roche, and Sanofi. She has served as a coinvestigator for Avid, Eli Lilly, and Janssen Alzheimer Immunotherapy clinical trials. She has spoken at symposia sponsored by Eli Lilly, Biogen, and Janssen. She receives research support from Janssen Pharmaceuticals and Eli Lilly and Co. R. Sperling received funding from P01AG036694, U01AG032438, U01AG024904, P50AG005134, U19AG010483, R01AG037497, R01AG034556, R01AG053798, R01AG027435, R01AG054029, K24AG035007, Fidelity Biosciences, Harvard NeuroDiscovery Center, and the Alzheimer's Association. E. Mormino has served as a paid consultant for Eli Lilly and Biogen. E. Mormino received funding from K01AG051718. Go to Neurology.org/N for full disclosures.

Received August 9, 2017. Accepted in final form February 9, 2018.

References

- Escott-Price V, Sims R, Bannister C, et al. Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain* 2015;138:3673–3684.
- Ridge PG, Mukherjee S, Crane PK, Kauwe JS. Alzheimer's disease: analyzing the missing heritability. *PLoS One* 2013;8:e79771.
- Mormino EC, Papp KV, Rentz DM, et al. Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated amyloid- β . *Alzheimer's Dement* 2017;13:1004–1012.
- Beecham GW, Hamilton K, Naj AC, et al. Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. *PLoS Genet* 2014;10:e1004606.
- Desikan RS, Schork AJ, Wang Y, et al. Polygenic overlap between C-reactive protein, plasma lipids, and Alzheimer disease. *Circulation* 2015;131:2061–2069.
- International Genomics of Alzheimer's Disease Consortium. Convergent genetic and expression data implicate immunity in Alzheimer's disease. *Alzheimer's Dement* 2015;11:658–671.
- Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. *Biol Psychiatry* 2015;77:43–51.
- Musiek ES, Holtzman DM. Three dimensions of the amyloid hypothesis: time, space and "wingmen." *Nat Neurosci* 2015;18:800–806.
- Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimer's Dement* 2016;12:292–323.
- Lim YY, Maruff P, Pietrzak RH, et al. Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease. *Brain* 2014;137:221–231.
- Petersen RC, Wiste HJ, Weigand SD, et al. Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. *JAMA Neurol* 2016;73:85–92.
- Snitz BE, Weissfeld LA, Lopez OL, et al. Cognitive trajectories associated with β -amyloid deposition in the oldest-old without dementia. *Neurology* 2013;80:1378–1384.
- Roe CM, Fagan AM, Grant EA, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology* 2013;80:1784–1791.
- Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA* 2015;313:1939–1950.
- Mormino EC, Betensky RA, Hedden T, et al. Amyloid and APOE ϵ 4 interact to influence short-term decline in preclinical Alzheimer disease. *Neurology* 2014;82:1760–1767.
- Lim YY, Villemagne VL, Pietrzak RH, et al. APOE ϵ 4 moderates amyloid-related memory decline in preclinical Alzheimer's disease. *Neurobiol Aging* 2015;36:1239–1244.
- Lim YY, Villemagne VL, Laws SM, et al. BDNF Val66Met, A β amyloid, and cognitive decline in preclinical Alzheimer's disease. *Neurobiol Aging* 2013;34:2457–2464.
- Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol* 2012;72:578–586.
- Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated β -amyloid deposition in elderly subjects. *Brain* 2009;132:1310–1323.
- Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging β -amyloid pathology. *JAMA* 2011;305:275–283.
- Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav* 2012;6:502–516.
- Gibbons LE, Carle AC, Mackin RS, et al. A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav* 2012;6:517–527.
- Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage* 2012;61:1402–1418.
- Anderson CA, Pettersson FH, Clarke GM, Cardon LR, Morris AP, Zondervan KT. Data quality control in genetic case-control association studies. *Nat Protoc* 2010;5:1564–1573.
- Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol* 2010;34:816–834.
- Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* 2013;45:1452–1458.
- Euesden J, Lewis CM, O'Reilly PF. PRSice: polygenic risk score software. *Bioinformatics* 2014;31:1466–1468.
- Lim YY, Villemagne VL, Laws SM, et al. APOE and BDNF polymorphisms moderate amyloid β -related cognitive decline in preclinical Alzheimer's disease. *Mol Psychiatry* 2015;20:1322–1328.
- Mormino EC, Sperling RA, Holmes AJ, et al. Polygenic risk of Alzheimer disease is associated with early-and late-life processes. *Neurology* 2016;87:481–488.
- Harris SE, Davies G, Luciano M, et al. Polygenic risk for Alzheimer's disease is not associated with cognitive ability or cognitive aging in non-demented older people. *J Alzheimer's Dis* 2014;39:565–574.
- Lacour A, Espinosa A, Louwersheimer E, et al. Genome-wide significant risk factors for Alzheimer's disease: role in progression to dementia due to Alzheimer's disease among subjects with mild cognitive impairment. *Mol Psychiatry* 2017;22:153–160.
- Tan CH, Fan CC, Mormino EC, et al. Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition. *Acta Neuropathol* 2017;24:1–9.
- Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. *PLoS Med* 2017;14:e1002528.
- Wolk DA, Dickerson BC, Weiner M, et al. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *Proc Natl Acad Sci USA* 2010;107:10256–10261.
- Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 2011;10:785–796.
- Sabuncu MR, Buckner RL, Smoller JW, Lee PH, Fischl B, Sperling RA. The association between a polygenic Alzheimer score and cortical thickness in clinically normal subjects. *Cereb Cortex* 2012;22:2653–2661.
- Lam B, Masellis M, Freedman M, Stuss DT, Black SE. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. *Alzheimer's Res Ther* 2013;5:1.
- Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci* 2007;8:663–672.
- Foley SF, Tansey KE, Caseras X, et al. Multimodal brain imaging reveals structural differences in Alzheimer's disease polygenic risk carriers: a study in healthy young adults. *Biol Psychiatry* 2017;81:154–161.
- Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* 1997;18:351–357.

Dissociable influences of *APOE* ϵ 4 and polygenic risk of AD dementia on amyloid and cognition

Tian Ge, PhD, Mert R. Sabuncu, PhD, Jordan W. Smoller, MD, ScD, Reisa A. Sperling, MD, and Elizabeth C. Mormino, PhD, For the Alzheimer's Disease Neuroimaging Initiative

Cite as: *Neurology*® 2018;90:e1605-e1612. doi:10.1212/WNL.0000000000005415

Correspondence

Dr. Mormino
bmormino@stanford.edu

Study question

Do *APOE* ϵ 4 status and a polygenic risk of Alzheimer disease (AD) dementia influence β -amyloid ($A\beta$) accumulation, cognitive decline, and hippocampal volume?

Summary answer

APOE ϵ 4 status and higher polygenic risk of AD dementia were associated with higher rates of decline in memory and executive function among $A\beta$ -positive individuals. Polygenic risk was also associated with hippocampal volume.

What is known and what this paper adds

Genetic risk variants associated with AD dementia do not only confer risk by promoting $A\beta$ aggregation but may make an individual more susceptible to decline when faced with $A\beta$ accumulation. The present study showed that polygenic risk within the $A\beta$ -positive group was associated with future cognitive decline, an effect that could not be explained by *APOE* ϵ 4 status alone. This finding suggests a synergistic effect between abnormal $A\beta$ accumulation and genetic risk of AD.

Participants and setting

The study utilized data obtained from 702 participants (221 cognitively healthy controls, 367 patients with mild cognitive impairment, and 114 patients with AD dementia) of the Alzheimer's Disease Neuroimaging Initiative (adni.loni.usc.edu) as of March 25, 2017. All participants were of European ancestry and had undergone florbetapir PET, longitudinal neuropsychologic assessment, and analyses of genome-wide single nucleotide polymorphisms (SNPs).

Design, size, and duration

Global standardized uptake value ratios (SUVRs) for florbetapir imaging were averaged across the bilateral frontal, cingulate, parietal, and lateral temporal regions and normalized to values for the whole cerebellum. A cutoff of 1.11 was used to classify participants into the $A\beta$ -positive and $A\beta$ -negative groups. Composite memory and executive function scores were used to examine cognition. Polygenic risk scores (PRS) were computed based on data from the International Genomics of Alzheimer's Project (IGAP).

Main results and the role of chance

$A\beta$ -negative *APOE* ϵ 4 carriers had faster $A\beta$ accumulation over time than $A\beta$ -negative non-carriers ($p = 0.005$), although no such effect of *APOE* ϵ 4 was observed in the $A\beta$ -positive group. Controlling for *APOE* ϵ 4, higher polygenic risk was strongly associated with higher rates of decline in memory and executive function among $A\beta$ -positive individuals.

Bias, confounding, and other reasons for caution

The constructed PRS may have been suboptimal for investigating the genetic basis of cognitive decline/AD progression since it was defined by contrasting patients with AD dementia with age-matched controls in the International Genomics of Alzheimer's Project (IGAP) study.

Generalizability to other populations

The results regarding $A\beta$ accumulation may be generalizable to patients with other genetic risk factors for AD, although further research is required.

Study funding/potential competing interests

This study was supported by the NIH and the Demarest Lloyd, Jr. Foundation. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by D. Drobish, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.