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Genetics

Alzheimer's disease genetic risk variants beyond *APOEε4* predict mortality

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Abstract

Introduction: We hypothesized that, like apolipoprotein E (*APOE*), other late-onset Alzheimer's disease (LOAD) genetic susceptibility loci predict mortality.

Methods: We used a weighted genetic risk score (GRS) from 21 non-*APOE* LOAD risk variants to predict survival in the Adult Changes in Thought and the Health and Retirement Studies. We meta-analyzed hazard ratios and examined models adjusted for cognitive performance or limited to participants with dementia. For replication, we assessed the GRS-longevity association in the Cohorts for Heart and Aging Research in Genomic Epidemiology, comparing cases surviving to age ≥90 years with controls who died between ages 55 and 80 years.

Results: Higher GRS predicted mortality (hazard ratio = 1.05; 95% confidence interval: 1.00–1.10, $P = .04$). After adjusting for cognitive performance or restricting to participants with dementia, the relationship was attenuated and no longer significant. In case-control analysis, the GRS was associated with reduced longevity (odds ratio = 0.64; 95% confidence interval: 0.41–1.00, $P = .05$).

Discussion: Non-*APOE* LOAD susceptibility loci confer risk for mortality, likely through effects on dementia incidence.

Keywords: Alzheimer's disease; Longevity; Mortality; Survival analysis; Genetic risk score; Selection bias; Collider stratification bias; Survivor bias; Genome-wide association study (GWAS); *APOE*; Adult Changes in Thought (ACT); Health and Retirement Study (HRS); Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)

1. Introduction

Risk variants from 22 genes have been identified for late-onset Alzheimer's disease (LOAD) incidence. Of these, apolipoprotein E ε4 (*APOEε4*) has the largest effect [1].

The authors have declared that no conflict of interest exists.

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Genome-wide association studies (GWASs) of longevity in older adults have identified *APOEε4* as a risk factor for mortality [2–4]. This risk may be partially mediated through dementia incidence [5,6], as dementia is a leading cause of mortality in older adults [7]. Given the association of both *APOEε4* and dementia with mortality, we hypothesized that other genetic variants associated with LOAD incidence would also be associated with mortality in older adults. We anticipated that cognitive function and dementia incidence would mediate the relationship with mortality. In other words, we expected that LOAD genetic risk variants would increase risk for cognitive decline and LOAD dementia, which would in turn increase risk for death (Fig. 1, solid arrows).

Quantifying and explaining the link between LOAD genetic risk and mortality is critical for genetic research on determinants of LOAD incidence: severe survivor bias could make it difficult to identify genetic variants that increase disease incidence or could falsely implicate genetic variants that are not actually associated with disease incidence [8]. For example, LOAD cases who are *APOEε4* carriers may be omitted from research because they declined faster and died before study enrollment or disease ascertainment [9]. *APOE* has also been implicated in risk for other disease processes including cardiovascular disease [10], so it may influence mortality via mechanism(s) other than dementia, thereby introducing potential survivor bias in its relationship with LOAD. By assessing whether non-*APOE* genes associated with LOAD are also associated with increased mortality, we can provide researchers with tools to systematically evaluate the potential magnitude of survivor bias [11].

Here, we attempt to replicate the previously reported link between *APOEε4* and mortality and, in novel analyses, assess whether non-*APOE* loci, previously found to be associated with LOAD incidence, are also associated with mortality. Because the effect size for each non-*APOE* variant is small, we estimate the combined genetic risk that each subject had for developing LOAD by calculating a genetic risk score (GRS). In primary analyses in two longitudinal population-based prospective cohort studies, the Adult Changes in Thought (ACT) study and the Health and Retirement Study (HRS), we assessed the GRS relationship with time to death using survival analysis. In subsequent models, we tested whether cognition or dementia mediated or moderated the relationship between the GRS and mortality. We conducted a follow-up, confirmatory case-control analysis

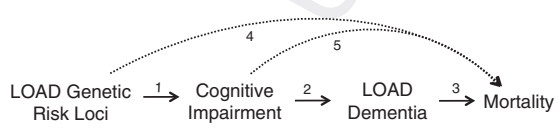

Fig. 1. Conceptual model. Solid lines indicate hypothesized path. Dashed lines indicate uncertain alternative paths. Selection bias (collider stratification bias) in LOAD genetic studies may be present if both the direct path to mortality and the indirect path through LOAD dementia exist. Abbreviation: LOAD, late-onset Alzheimer's disease.

in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), comparing the GRS among longevity cases age ≥90 years versus controls who died between ages 55 and 80 years. Our findings could suggest new genetic risk loci for longevity, add insight into how LOAD risk loci affect dementia incidence and disease course, and provide reassurance that the effect estimates of these loci on LOAD incidence do not suffer from selection bias.

2. Methods

2.1. Study populations

2.1.1. Adult Changes in Thought

The ACT cohort draws from a population base defined by the Group Health membership; the Group Health is an integrated healthcare delivery system in King County, WA. The ACT study enrolled 3392 cognitively normal community-dwelling adults 65 years or older in two enrollment phases (n = 2581 in 1994–1996 and n = 881 in 2001–2003) and initiated ongoing enrollments in 2004. After obtaining informed consent, in-person biennial interviews assessed participants' demographic, medical history, and functional status. ACT stopped assessing participants diagnosed with dementia but still obtained mortality information. For the current analyses, from 4131 individuals with ACT visits, we excluded participants who self-reported to be Hispanic or nonwhite (to avoid confounding from population stratification; n = 383) or who were not genotyped (n = 1418). This left an analytic sample of 2330 individuals.

2.1.2. Health and Retirement Study

The HRS is a nationally representative cohort study initiated in 1992 with enrollments in 1992, 1993, 1998, 2004, and 2010. The target population is all noninstitutionalized adults in the contiguous United States aged 50+ years. Biennial interviews (or proxy interviews for decedent or severely impaired participants) are available through 2012 [12]. Our analyses used a subsample with genetic data collected in 2006 or 2008. From 20,662 individuals alive in 2006 with HRS visits, we excluded participants who were not genotyped (n = 8580), who self-reported to be Hispanic or nonwhite (to avoid confounding from population stratification; n = 2894), or who were under age 65 years (to mimic ACT; n = 3224). This left an analytic sample of 5964 individuals.

2.1.3. Cohorts for Heart and Aging Research in Genomic Epidemiology

The CHARGE consortium includes participants from the following studies: Rotterdam Study, Study of Osteoporotic Fractures, Cardiovascular Health Study, Osteoporotic Fractures in Men Study, Framingham Heart Study, Health and Retirement Study, Age, Gene/Environment Susceptibility—Reykjavik Study, Religious Orders Study, Rush Memory and Aging Project, Invecchiare nel Chianti, Baltimore Longitudinal