Neuropathologic features of TOMM40 ’523 variant on late-life cognitive decline

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Abstract

Introduction: The study investigated the role of neuropathologies in the relationship between TOMM40 ’523 genotype and late-life cognitive decline.

Methods: Participants were community-dwelling older persons who had annual cognitive assessments and brain autopsies after death. Genotyping used DNA from peripheral blood or postmortem brain tissue. Linear mixed models assessed the extent to which the association of ’523 genotype with cognitive decline is attributable to neuropathologies.

Results: Relative to ε3/3 homozygotes with ’523-S/VL or ’523-VL/VL genotype, both ’523-L carriers and ε3/3 homozygotes with ’523-S/S genotype had faster cognitive decline. The association of ’523-L with cognitive decline was attenuated and no longer significant after controlling for Alzheimer’s and other neuropathologies. By contrast, the association of ’523-S/S was unchanged.

Discussion: There are two distinct TOMM40 ’523 signals in relation to late-life cognitive decline. One signal primarily acts through AD and other common neuropathologies, whereas the other operates through a different mechanism.

Keywords: Neuropathologies; TOMM40 ’523; Late-life cognitive decline

1. Introduction

Apolipoprotein E (APOE) is the best-known susceptibility gene for late-onset Alzheimer disease (AD) [1]. The region on chromosome 19 that harbors the APOE gene includes a large haplotype block that contains several other genes including apolipoprotein C1 (APOC1) and translocase of outer mitochondrial membrane 40 (TOMM40) [2]. Beside APOE e alleles, multiple genetic variations within the block have also been implicated in AD [3–7]. TOMM40 ’523, a poly-T polymorphism at an intronic region of TOMM40, is of particular interest. The variable length of poly-T repeat
at '523 locus is associated with age at disease onset and cognition [7–9]. Notably, the variant is in linkage disequilibrium (LD) with APOE genotype. Among Caucasians, APOE e4 is exclusively linked to the long ('523-L) poly-T repeat whereas e3 can be linked to either short ('523-S) or very long ('523-VL) poly-T repeat. This LD structure has two implications. The close linkage between e4 and '523-L raises the question whether TOMM40 '523-L is merely a proxy of e4 [10]. By contrast, three major '523 genotypes are present in APOE e3/3 homozygotes, namely '523-S/S, '523-S/VL and '523-VL/VL. An earlier study found that age at AD onset varies across these three genotypes [11], and we recently reported that '523-S/S carriers exhibit faster decline in late-life cognition compared with '523-S/VL or '523-VL/VL carriers [12]. These findings suggest that the '523 effect is not fully attributable to the LD with APOE variants. However, the neurobiologic or pathobiologic basis underlying these associations remains unclear.

Evidence suggests that the e4 allele is directly involved in the pathogenesis of AD via regulating β-amyloid accumulation, a key neuropathologic feature of the disease [13–15]. In this study, we aimed to determine whether the '523 effect was related to AD or other neuropathologies among persons with APOE e3/3.

To examine the role of common neuropathologies in the relationship between TOMM40 '523 genotype and longitudinal cognitive decline, we leveraged cognitive, genetic, and neuropathologic data from a large number of community-based older Caucasian Americans who were followed annually for up to 21 years and had undergone brain autopsy after death. We previously reported that AD pathology in general, and β-amyloid in particular, mediates the effect of APOE e4 with cognitive decline and AD dementia [16,17]. Owing to its strong linkage with APOE e4, we first confirm that the same relationship exists for TOMM40 '523-L. Then, we test the hypothesis that among persons with APOE e3/3, the '523-S/S is also associated with measures of AD pathology. Failure to find such an association, in contrast to a strong association between the APOE e4–'523-L haplotype and AD pathology, would suggest that the two genes have separate and relatively independent effects on cognition and operate through different pathologic mechanisms.

2. Methods

2.1. Study participants

Participants came from two ongoing longitudinal cohort studies of aging and dementia, the Religious Orders Study (ROS) [18] and the Rush Memory and Aging Project (MAP) [19]. ROS and MAP enroll community-dwelling older persons without known dementia. Participants were followed annually for detailed cognitive and clinical assessments; all agreed to brain donation after death. Both studies were approved by the Institutional Review Board of Rush University Medical Center, and written informed consent and an Anatomical Gift Act were provided by each participant. By early January 2017, 1501 participants of European ancestry had died, of which 1326 had undergone brain autopsy (autopsy rate = 88.3%). The present study focused on individuals who had genotype data and longitudinal cognitive assessments (N = 1114). The mean age at death was 89.4 years (standard deviation [SD] = 6.4), 66.6% were females (N = 742), and the mean education was 16.3 years (SD = 3.6).

2.2. APOE and TOMM40 '523 genotyping

DNA was extracted from peripheral blood and in some cases from frozen postmortem brain tissue. The genotyping were performed at Polymorphic DNA Technologies (Alameda, CA). The vendor was blinded to all clinical and neuropathologic information. APOE genotype was based on two polymorphisms (rs429358 and rs7412) at exon 4 of the APOE gene. TOMM40 '523 refers to rs10524523, a homopolymer length polymorphism (poly-T) at intron 6 of the TOMM40 gene (chr19:44,899,792-44,899,826, human genome reference assembly GRCh38/hg38). The '523 genotype was determined by the length of poly-T repeat, as previously described [20]. Briefly, a '523 short allele ('523-S) has poly-T repeat length less than 20, a long allele ('523-L) has poly-T repeat length between 20 and 29, and a very long allele ('523-VL) has poly-T repeat length of 30 and above.

2.3. Annual cognitive assessments

Participants underwent uniform annual cognitive assessments for up to 22 years (mean = 8.3, SD = 4.5). Cognitive performance was assessed using a battery of 17 tests [21]. Scores from each test were standardized using the baseline mean and SD of the two cohorts. The resulting z-scores were averaged across the tests to obtain a composite measure of global cognition. The composite measure minimizes the floor and ceiling artifacts that are common for individual tests, and similar approach has been applied in many other studies [22–25].

2.4. Postmortem neuropathologic evaluations

At autopsy, we quantified the burdens of common age-related neuropathologies including AD, macroscopic infarcts, microinfarcts, Lewy bodies, hippocampal sclerosis, TDP-43, cerebral amyloid angiopathy, athero-PLA Q5 Q6

sclerosis, and arteriosclerosis. β-amyloid and phosphorylated PHFtau tangles, two molecular-specific pathologic hallmarks of AD, were assessed in eight brain regions using immunohistochemistry [26]. Percent area positive for β-amyloid was computed for each region using image analysis and averaged across the regions to obtain a summary measure of β-amyloid load. Density of PHFtau tangles per mm² was computed for each region using a stereologically mapping station and averaged to obtain a summary
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