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A *TOMM40* poly-T variant modulates gene expression and is associated with vocabulary ability and decline in nonpathologic aging

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ABSTRACT

The Translocase of Outer Mitochondrial Membrane 40 Homolog and Apolipoprotein E (TOMM40-APOE) locus has been associated with a number of age-related phenotypes in humans including nonpathologic cognitive aging, late-onset Alzheimer's disease, and longevity. Here, we investigate the influence of the TOMM40 intron 6 poly-T variant (rs10524523) on TOMM40 gene expression and cognitive abilities and decline in a cohort of 1613 community-dwelling elderly volunteers who had been followed for changes in cognitive functioning over a period of 14 years (range = 12–18 years). We showed that the shorter length poly-T variants were found to act as a repressor of luciferase gene expression in reporter gene constructs. Expression was reduced to approximately half of that observed for the very long variant. We further observed that the shorter poly-T variant was significantly associated with reduced vocabulary ability and a slower rate of vocabulary decline with age compared to the very long poly-T variants. No significant associations were observed for memory, fluid intelligence or processing speed, although the direction of effect, where the short variant was correlated with reduced ability and slower rate of decline was observed for all tests. Our results indicate that the poly-T variant has the ability to interact with transcription machinery and differentially modulate reporter gene expression and influence vocabulary ability and decline with age.

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1. Introduction

As human life expectancy is increasing, age-related cognitive impairment is becoming a substantial problem due to its high social (Tannenbaum et al., 2005) and economic (Comas-Herrera et al., 2007) burdens. Consequently, the identification of genetic risk factors for cognitive aging is becoming a high-priority research area that aims to prevent or slow down the progression of cognitive decline in later life. Cognitive aging can be nonpathologic (also known as normal aging) (Davies et al., 2014) or caused by pathologic diseases such as Alzheimer's disease (AD) (Bakulski et al., 2012). AD, cognitive ability, and cognitive decline are highly heritable with the strongest and most consistent associations being reported within the Translocase of Outer Mitochondrial Membrane 40 Homolog and Apolipoprotein E (TOMM40-APOE) locus which occupies an 18 kb region on chromosome 19. Twin and adoption studies suggest that additive genetic effects contribute over half of the adult population variance in intelligence (Deary et al., 2010) with between 0.40 to 0.51 of this variation being accounted for by common SNP markers (Davies et al., 2011). A lifetime (age 11 to old age) study of cognitive change estimated a narrow-sense heritability of 0.24 with the genetic correlation between intelligence at age 11 and old age to be 0.62 (Davies et al., 2014).

TOMM40 codes for the central component of the translocase of the outer mitochondrial membrane (TOM) which is a multisubunit complex made up of 6 TOM proteins (Humphries et al., 2005). TOM is a channel forming protein involved in the transport and sorting of proteins across the mitochondrial membrane. TOMM40 has been reported to be involved in the predisposition to AD and nonpathologic cognitive decline possibly through a theory known as the "mitochondrial cascade hypothesis" which proposes a genetic contribution toward mitochondrial durability and function (Swerdlow and Khan,

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2009). SNPs within the TOMM40 gene have been associated with plaque and vascular amyloid deposition (Valant et al., 2012). Several TOMM40 SNPs have been associated with non-pathologic cognitive aging (Davies et al., 2014; Greenbaum et al., 2014) but none of these have yet been shown to be functional, and the possibility remains that they may be in linkage disequilibrium with another TOMM40-APOE variant. The TOMM40 gene is 2104 base pairs from APOE, and they share the same linkage disequilibrium block (Lyall et al., 2013) making it difficult to identify discreet predisposing functional regions.

Retrotransposons have been less thoroughly studied in disease states than SNPs but have recently been associated with several conditions including Rett syndrome, Ataxia telangiectasia, and schizophrenia (Coufal et al., 2011; Erwin et al., 2014). Retrotransposons, also known as mobile DNA elements, encompass up to 45% of the human genome. Their mobilization occurs via "copy and paste" mechanisms that require the presence of an RNA intermediate which is subjected to reverse transcription and integration into DNA at a locus different than the original sequence (Raiz et al., 2012). They are mobilized in the germline genome during early stages of embryonic development and in somatic cell types of the brain, leading to both de novo germline and somatic mutations (Damert et al., 2009; Erwin et al., 2014). Among them, non–long terminal repeat elements such as long-interspersed nuclear elements, short-interspersed nuclear elements (SINEs), and SINE-VNTR-Alus (SVAs) constitute approximately 34% of the genome (Bekris et al., 2012). SINEs, such as Alus, are very abundant between exons 6 and 7 of TOMM40. Particularly interesting is a block of 6 adjacent SINEs: AluSx, AluYc3, AluJb, AluJo, another AluJb, and FLAM_A. FLAM_A encompasses the poly-T variant rs10524523, henceforth "523". This block also constitutes a human block of insertions with only limited homology seen in other primates but not observed in other nonprimate species. "523" has been analyzed according to its length and is reported as having 3 variants that are short (S) <20 T residues, long (L) 20–30 T residues, and very long (VL) ≥30 T residues (Roses et al., 2010). Roses et al. have shown that the TOMM40L variant is in strong LD with APOEε4 and that the S and VL variants are in strong LD with the APOE ε3. The longer TOMM40 variants have been linked to a higher risk of developing late-onset Alzheimer's disease and an earlier age of the disease onset compared to the short variant in APOE ε3 patients (Lutz et al., 2010; Roses et al., 2010). However, other studies have either not observed this association or reported that the VL variant was associated with lower risk of AD (Cruchaga et al., 2011; Jun et al., 2012). Another study also reported that the VL variant was associated with lower risk of AD, and that the L variant was associated with increased risk (Maruszak et al., 2012). This same group also found that the L variant significantly reduced the chance of living to 100 years of age. The "523" S variant has also been associated with improved memory and executive function in several studies (Caselli et al., 2012; Greenbaum et al., 2014; Hayden et al., 2012; Johnson et al., 2011).

The location of these candidate genetic risk factors within noncoding regions of the TOMM40-APOE locus suggests the possible involvement of transcriptional and post-transcriptional regulation. Our group has previously demonstrated that SVAs can serve as transcriptional regulators in a classical reporter gene assay in vitro and in vivo (Savage et al., 2013, 2014). Here, we hypothesize that "523" variants may regulate the expression of TOMM40 and have an influence on cognitive abilities and their decline (over a mean period of 14 years) with age in a cohort of 1613 nondemented community-dwelling older volunteers.

2. Material and methods

2.1. Cohort

The University of Manchester Longitudinal Studies of Cognition in Normal Healthy Old Age documented longitudinal trajectories in cognitive function in a large sample of older adults in the North of England, UK; the Manchester and Newcastle Longitudinal Studies of Cognitive Aging Cohorts (Rabbitt et al., 2004). Recruitment took place in Newcastle and Greater Manchester between 1983 and 1992. At the start of the study, 6063 volunteers were available, 1825 men and 4238 women, with a median age of 65 years (range, 44–93 years). Over the period 1983 to 2003, 2 alternating batteries of cognitive tasks applied biennially were designed to measure fluid and crystallized aspects of intelligence. The studies have run for over 30 years and have collected a rich archive of demographic (including date and location of birth), lifestyle, health, cognitive, and emotional health data. This program of work continues at Manchester University, and it will follow subjects to death. DNA was available on 1613 volunteers. Ethical approval for all projects was obtained from University of Manchester.

2.2. Cognitive measures

Principle components analysis has been used to derive variables for memory, vocabulary ability, fluid intelligence (novel problem solving), and processing speed for the Manchester and Newcastle cohorts. The vocabulary ability (crystallized intelligence) factor was generated using tests that comprised the Mill Hill and Wais vocabulary tests (Rabbitt et al., 2004; Raven, 1965). Cognitive tests used for fluid factors were the two parts of the Alice Heim test 4 and the four subtests of the Culture Fair Test (Cattell, 1949; Heim, 1970). Speed factors were derived from the Alphabet Coding Task and the Random Letters test (Rabbitt et al., 2004; Savage, 1984). Factors for memory were generated from free recall, propositions and spatial memory tests (Rabbitt et al., 2004).

In all cases, men and women were examined, and scores were standardized separately. Longitudinal growth curve models were estimated that took the 0 point on the age scale as age 70 years and measured variation about that in units of 10 years. Data were available for up to 4 occasions (collected at roughly 5 years intervals) of measurement that spanned an average of 14 years (range, 12–18 years) for all volunteers. The fixed part of the models that described the overall pattern of change in the construct for the sample as a whole included linear and quadratic age terms. In addition, to account for possible artifactual improvement due to practice effects (a single step function), each test score was allowed to increment between the first and subsequent occasions in which each particular test was taken. Individual differences were accounted for by allowing subject-specific random effects for the intercept, describing the within-sample variation in performance at age 70 years, and for a linear growth term, describing the individual differences in the trend of cognitive decline over the period of follow-up. The random effects were assumed to be bivariate normally distributed, and the models estimated in gllamm by maximum likelihood using adaptive quadrature (www.gllamm.org). Incomplete data observations were included under an assumption that the missing scores were missing at random, allowing attrition to be selective with respect to age, sex, and observed test scores. Subject-specific intercepts and linear trends were estimated using empirical Bayes methods. The above fully describes the model in the circumstance where a single-repeated cognitive test was available. Different tests were allowed different means, scales, and error variances, but the tests were assumed to reflect a single underlying construct with a common trend.

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