Alzheimer's disease susceptibility genes APOE and TOMM40, and brain white matter integrity in the Lothian Birth Cohort 1936

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ABSTRACT

Apolipoprotein E (APOE) ε genotype has previously been significantly associated with cognitive, brain imaging, and Alzheimer's disease-related phenotypes (e.g., age of onset). In the TOMM40 gene, the rs10524523 ("523") variable length poly-T repeat polymorphism has more recently been associated with similar phenotypes, although the allelic directions of these associations have varied between initial reports. Using diffusion magnetic resonance imaging tractography, the present study aimed to investigate whether there are independent effects of apolipoprotein E (APOE) and TOMM40 genotypes on human brain white matter integrity in a community-dwelling sample of older adults, the Lothian Birth Cohort 1936 (mean age = 72.70 years, standard deviation = 0.74, N approximately = 640–650; for most analyses). Some nominally significant effects were observed (i.e., covariate-adjusted differences between genotype groups at p < 0.05). For APOE, deleterious effects of ε4 “risk” allele presence (vs. absence) were found in the right ventral cingulum and left inferior longitudinal fasciculus. To test for biologically independent effects of the TOMM40 523 repeat, participants were stratified into APOE genotype subgroups, so that any significant effects could not be attributed to APOE variation. In participants with the APOE ε3/4 genotype, effects of TOMM40 523 status were found in the left uncinate fasciculus, left rostral cingulum, left ventral cingulum, and a general factor of white matter integrity. In all 4 of these tractography measures, carriers of the TOMM40 523 "short" allele showed lower white matter integrity when compared with carriers of the "long" and "very-long" alleles. Most of these effects survived correction for childhood intelligence test scores and vascular disease history, though only the effect of TOMM40 523 on the left ventral cingulum integrity survived correction for false discovery rate. The effects of APOE in this older population are more specific and restricted compared with those reported in previous studies, and the effects of TOMM40 on white matter integrity appear to be novel, although replication is required in large independent samples.

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APOE plays a role in the transport and metabolism of lipids in the human body and brain (Bu et al., 2009; Corder et al., 1994). The ε4 allele of APOE is the “risk” variant for several phenotypes compared with ε3 (“neutral”), and ε2 (generally considered “protective”, although less consistently). These phenotypes include risk of Alzheimer’s disease (AD) (Corder et al., 1994), less successful cognitive aging (Deary et al., 2004; Wisdom et al., 2011), differences in brain structure (e.g., atrophy; Biffi et al., 2010), and functional connectivity (Trachtenberg et al., 2012); vascular pathologies such as hyperlipidemia, coronary heart disease and stroke (Lahoz et al., 2009). Of these, the ε4 allele, with several SNPs in the TOMM40 region including 15 TOMM40 SNPs; average D’ = 0.91, r² = 0.22, n = 1262 (Yu et al., 2007). The TOMM40 locus encodes for a channel-forming subunit of the translocase of the outer mitochondrial membrane complex (Humphries et al., 2005). This complex imports precursor proteins into mitochondria (Koehler et al., 1999). Mitochondrial dysfunction may play a significant role in cognitive decline and AD-related pathology (“The mitochondrial cascade hypothesis”; Swerdlow and Kahn, 2004). APOE and TOMM40 may interact to affect aspects of mitochondrial function although mechanistically it is unclear exactly how (Roses et al., 2010).

The rs10524523 locus (hereafter “523”) in the TOMM40 gene is characterized by a variable number of T residues (“poly-T repeats”) that can be classified into 3 different lengths: “short” (<20); “S”, “long” (20–29; “L”), and “very-long” (>30; “VL”); Lutz et al., 2010). Roses et al. (2010) showed with phylogenetic mapping analyses that TOMM40 523 poly-T repeat length was strongly linked to APOE ε4 genotypes in humans: ε4 is most commonly linked to the 523 L allele, with ε3 linked to either S or VL alleles in different evolutionary clades. The rarer ε2 allele appeared similar to ε3 although further research is required in large samples (Roses et al., 2010).

Studies have tested for association between TOMM40 523 repeat length and different brain-related phenotypes independently from APOE. For example, age of AD onset (Roses et al., 2010) and worse cognitive aging (Schiepers et al., 2012), were examined. However, reports vary in showing protective (Johnson et al., 2011, null (Chu et al., 2011), or deleterious (Cruchaga et al., 2011) effects of the S allele. See Roses et al. (2013) for a discussion of early studies.

Diffusion-tensor magnetic resonance imaging (MRI) and quantitative tractography allow examination of brain white matter microstructure in vivo in specific white matter tracts thought to relate to cognitive functions (Behrens et al., 2007; Pierpaoli et al., 1996). Diffusion-tensor imaging (DTI) measures the magnitude and directional coherence of water molecule diffusion and, because water molecule diffusion is preferentially constrained along the principal fiber direction by axonal membranes and myelin sheaths, this property can be used to assess white matter structural integrity (Behrens et al., 2007; Pierpaoli et al., 1996). Fractional anisotropy (FA) is an example of a common DTI-derived metric, and reflects the level of directional coherence of water molecule diffusion (Pierpaoli et al., 1996). Specifically, FA measures are high in healthy, structurally intact, coherently organized white matter, but fall in diseased tissue. Associations between the APOE gene and white matter integrity have been investigated previously (see Gold et al., 2012 for a review of significant findings; also Felsky and Voineskos, 2013). To our knowledge, the largest previous study had 203 participants (Westlye et al., 2012; mean age = 47.6 years, standard deviation = 14.9). That report found widespread differences in microstructural integrity depending on APOE status. Controlling for age and gender, ε3/ε4 carriers had lower white matter integrity (vs. ε3/ε3) in the brainstem, basal temporal lobe, internal capsule, anterior parts of the corpus callosum, forceps minor, superior longitudinal fasciculus, occipital, and corticospinal motor pathways (Cohen’s d range = 0.77–0.79; “medium-large effects”). We found no studies that examined the independent effects of the TOMM40 523 poly-T repeat.

The present study aims to investigate the effects of APOE and TOMM40 genotypes on brain white matter integrity as assessed using quantitative tractography in a large, age-homogeneous sample of relatively healthy older people. Fourteen major projection, commissural, and association fiber tracts were examined that have previously been significantly associated with cognitive abilities in this sample (Penke et al., 2012).

2. Methods

2.1. Sample and procedure

The LBC1936 is a cohort of 1091 generally healthy community-dwelling adults, 1028 of whom completed the Moray House Test no.12 (MHT) of verbal reasoning as part of the Scottish Mental Survey 1947 at a mean age of 11 years. The recruitment and testing of this sample has been detailed in previous protocol papers (Deary et al., 2007, 2012). All the LBC1936 participants were born in 1936 and most resided in the Edinburgh (Lothian) area of Scotland when recruited in older adulthood. In the first wave of the LBC1936 study (“wave 1”), at around the age 70 years, they were retested on the MHT in addition to other detailed cognitive, sociodemographic, and physical assessments (Deary et al., 2007). Around 3 years later, 866 members of the cohort returned for re-testing in the second wave of the study (“wave 2”). At this point, in addition to repeating the wave 1 assessments, most of the participants also underwent detailed structural brain MRI (Wardlaw et al., 2011). At both waves, participants were screened for cognitive impairment with the Mini-Mental State Examination (MMSE), with scores under 24 used to indicate possible dementia (Folstein et al., 1975). Medical history was elicited by interview, including hypertension, diabetes, stroke, hypercholesterolemia, and history of any other vascular disease (e.g., heart attack). All subjects gave written, informed consent after the nature of the procedures had been explained to them.

2.2. Cognitive assessment

Moray House Test: This was completed in 1947 at a mean age of 11 years. This test of general cognitive ability has a 45-minute time limit and has a maximum score of 76, with a predominance of verbal reasoning items, and some numerical and visuospatial items also included (Deary et al., 2007). MHT scores were adjusted for age in days at the time of assessment, and standardized to an IQ score.
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