

Genetic Haplotypes and Family History of Alzheimer's disease Modify Homocysteine and Influence Neurovascular Pathology

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Abstract

Objective: To delineate novel relationships between Alzheimer disease factors, TOMM40 genotype, AD family history (FH), vascular risk factors, and vascular neuropathology we used linear mixed model regression on imaging and biomarker data of 210 adults with 1 or 2 Apolipoprotein ε4 alleles from the Alzheimer's Disease Neuroimaging Initiative cohort.

Methods: Main effects and interactions between TOMM40 and FH were conducted on white matter hyperintensities, infarctions, and total intracranial volume, homocysteine and cholesterol adjusting for age, gender, BMI and hyperglycemia status.

Results: FH*TOMM40 interactions showed that L/L and L/VL genotypes exercised "beneficial" effects for FH negative (FH-) and "detrimental" effects for FH positive (FH+) participants

Introduction

Alzheimer's disease (AD) has been linked with genetic variants that may be influenced by family history (FH) of AD. The apolipoprotein E ε4 (APOE4) gene is the strongest replicated genetic factor causing increased risk for late onset AD (LOAD) that also functions in cholesterol transport. The Translocase of the outer mitochondrial membrane kD 40 (TOMM40) gene is in linkage disequilibrium with APOE and may contribute to LOAD risk. TOMM40 facilitates mitochondrial protein transport where upon dysfunction may underlie changes in neurovascular pathology. Among APOE4's, a "long" (L) or "very long" (VL) vs. "Short" (S) TOMM40 polyT polymorphism at rs10524523 ('523) has been associated with memory decline, but current findings are mixed.

Objective

To delineate novel relationships between Translocase of the Outer Mitochondrial Membrane - kD 40 (TOMM40) genotype, AD family history (FH), homocysteine, and vascular neuropathology.

Materials & Methods

Data used in the preparation of this poster were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public private partnership. We performed linear mixed model regression on longitudinal imaging and biomarker data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Among 210 healthy adults with 1 or 2 Apolipoprotein ε4 (APOE4) alleles (mean age 73.8), we stratified by TOMM40 genotypes S/L (n=84), L/L (n=49), L/VL (n=68). Main effects and interactions between TOMM40 and FH were conducted on neurovascular outcomes, including white matter hyperintensities (WMH), infarctions, as well as total intracranial volume. Vascular risk factors were similarly tested, including homocysteine and total cholesterol. Models were adjusted for age, gender, body mass index and hyperglycemia status.

Results

FH * TOMM40 interactions showed that L/L and L/VL genotypes respectively exercised "beneficial" effects for FH negative (FH-) and "detrimental" effects for FH positive (FH+) participants. In FH-, beneficial alleles were associated with lower serum homocysteine (P=0.024) indicated in Figure 1, lower total cholesterol (P=0.005), infarction occurrence (P=0.045). FH + risk alleles showed smaller total intracranial volume (P<0.001) and greater WMH burden (P = 0.032) in Figure 2. We propose homocysteine mediates FH * TOMM40 associations with neurovascular measures.

Figure 1

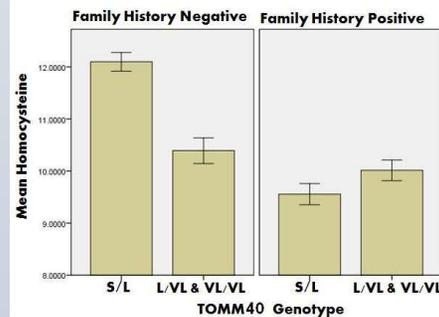
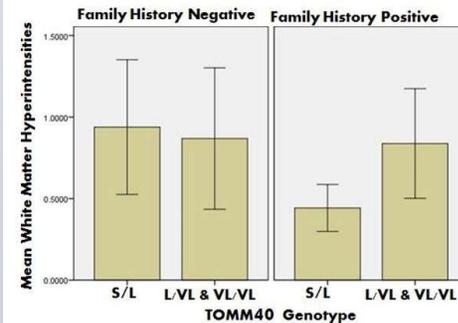


Figure 2



Conclusion

These results suggest FH modulates TOMM40's effects on vascular markers and AD neurovascular pathology in APOE4 individuals. These interactions on neurovascular pathology may be mediated by homocysteine suggesting TOMM40 genotype could serve as a novel predictor for AD and homocysteine may be a potential mechanism. Understanding how FH, IR & Genes affect neural-metabolism may lead to improved medical care prior to diagnosis, allowing earlier detection of disease symptoms, correcting insulin defects, preventing or delaying cognitive decline.

References

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