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The functional role of an Alzheimer's disease associated poly-T variant in TOMM40 gene

Ornit Chiba-Falek[1], **William Gottschalk**[1], **Michael W Lutz**[1] and **Allen D Roses**[1,2]
[1]Duke University Medical Center, Durham, USA
[2]Zinfandel Pharmaceuticals, USA

We investigated the TOMM40-APOE genomic region that has been associated with the risk and age of onset of late-onset Alzheimer's disease (LOAD) and with cognitive function in healthy aging to determine if a highly polymorphic, intronicpoly-T within this region (rs10524523, hereafter 523) affects expression of the APOE and TOMM40 genes. Alleles of this locus are classified: Short-S, long-L, very long-VL based on the number of T-residues. We analyzed two brain regions from Caucasian donors,APOEε3/3 and APOEε3/4autopsy-confirmed LOAD cases and APOEε3/3 normal controls. Differences in APOE-mRNA and TOMM40-mRNA levels were evaluated as a function of 523-genotype. The expression of both genes was significantly increased with disease. Mean expression of APOE-and TOMM40-mRNA levels were higher in VL-homozygotes compared to S-homozygotes in temporal and occipital cortexes from Normal and LOAD carriers of APOEε3/3 haplotype. Similarly, among APOEε3/4 LOAD subjects APOE and TOMM40-mRNAs expression were increased in VL-heterozygotes compared to S-heterozygotes brains.We further investigated the effect of the 523 locus in its native genomic context using a luciferase reporter system.The results were consistent with the human brain mRNA analysis: The 523-VL resulted in significantly higher expression than the S in both HepG2 hepatoma and SH-SY5Y neuroblastoma cell-lines. Collectively, these results suggested that the 523 locus may contribute to LOAD susceptibility by modulating the expression of TOMM40 and or APOE transcription.In conclusion, our study elucidated the mechanism of action of TOMM40-523, a genetic risk factor for LOAD and provides functional support for the role of the 523 locus in the pathogenesis of LOAD.

Biography

Ornit Chiba-Falek is an Associate Professor at the Department of Neurology at Duke University. Her lab has been studying the genetic factors and molecular mechanisms underlying neurodegenerative diseases in aging with a focus on the functional consequences of non-coding variants in dementia and Lewy body-related disorders. She has received her PhD from the Hebrew University in Jerusalem before pursuing her postdoctoral training at the NIH; she was a recipient of the Ellison Medical Foundation New Scholar Program in Aging Award in 2008. She is an Academic Editor for *PLoS ONE* and serves on the Editorial Boards of *JPAand AIMS-Genetics*.

o.chibafalek@duke.edu

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