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Molecular signatures of Alzheimer's disease and aging in the *TOMM40-APOE-APOC1* locus

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Motivation and Aim: Enduring interest to the apolipoprotein E (*APOE*) region is driven by remarkably strong associations of variants from this region with Alzheimer's diseases (AD) and pleiotropic associations with multiple aging-related traits. The role of this region in pathogenesis of AD and aging remains, however, poorly understood. Elucidating genetic predisposition to aging-related traits characteristic for post-reproductive period is hampered by the uncertain role of evolution in establishing their molecular mechanisms. This uncertainty is inevitable source of natural-selection-free genetic heterogeneity in predisposition to AD and aging-related traits.
Methods and Algorithms: We examined linkage disequilibrium (LD) structures characterized by nine single nucleotide polymorphisms (SNPs) from *TOMM40-APOE-APOC1* locus, including rs429358 and rs7412 SNPs coding the *APOE* ε4 and ε2 alleles, in 2,661 AD-affected and 16,079 AD-unaffected subjects and in 570 short-lived (<75 years, SL) and 1,999 long-living (85+ years, LL) subjects from four independent studies.
Results: The LD structures, being heterogeneous, are significantly different in subjects with and without AD, $p < 2 \times 10^{-4}$. The pattern of the significant difference represents molecular signature of AD comprised of SNPs from these genes. We identified 31 of 36 SNP pairs with pair-wise estimates of the LD difference between subjects with and without AD significant after Bonferroni correction, $p < 1.3 \times 10^{-3}$. In contrast, differences in LD between SL and LL subjects attained only marginal Bonferroni-adjusted significance ($p = 3.5 \times 10^{-3}$) for one SNP pair (rs405509 [*APOE*] and rs439401 [intergenic]), nominal significance ($p < 5 \times 10^{-2}$) for three pairs and suggestive significance ($p < 10^{-1}$) for three more pairs. For all these seven SNP pairs, LD changed in the same directions in AD/no-AD and LL/SL groups.
Conclusion: Significant and highly heterogeneous molecular signature of AD provides evidence on complex polygenetic predisposition to AD in the *TOMM40-APOE-APOC1* locus. Significant differences in pair-wise LD in subjects with and without AD indicate SNPs, or their proxies, likely involved in AD pathogenesis. The same directions of the LD differences in AD/no-AD and LL/SL groups suggests heterogeneous, partly overlapping molecular mechanisms for AD and aging, defined as survival to old ages, in the *APOE* region.
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