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Editorial Open Access

The Pathogenic Component of the APOE-TOMM40 Region in Alzheimer's disease: Its Implications in Metabolomics and Pharmacogenomics

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Editorial

The genetic and epigenetic defects identified so far in Alzheimer's disease (AD) include Mendelian mutations, susceptibility single-nucleotide polymorphisms (SNPs), mitochondrial DNA (mtDNA) mutations, and epigenetic changes. Mendelian mutations affect genes directly linked to AD, including mutations in the amyloid beta precursor protein (*APP*) gene (21q21) (AD1), mutations in the presenilin 1 (*PSEN1*) gene (14q24.3) (*AD3*), and mutations in the presenilin 2 (*PSEN2*) gene (1q31-q42) (*AD4)* [1-2]. There are over 600 genes potentially associated with AD, of which the top ten are *APOE* (19q13.2), *BIN1* (2q14), *CLU* (8p21-p12), *ABCA7* (19p13.3), *CR1* (1q32), *PICALM* (11q14), *MS4A6A* (11q12.1), *CD33* (19q13.3), *MS4A4E* (11q12.2), and *CD2AP* (6p12).

Among susceptibility genes, the apolipoprotein E (*APOE*) gene (19q13.2) (*AD2*) is the most prevalent as a risk factor for AD, especially in those subjects harboring the *APOE-4* allele [3], whereas carriers of the *APOE-2* allele are prone to longevity [4] and might be protected against dementia [5].

APOE is the prototypical paradigm of a pleiotropic gene with multifaceted activities in physiological and pathological conditions [1,6]. ApoE is consistently associated with the amyloid plaque marker for AD. *APOE-4* may influence AD pathology by interacting with APP metabolism and Aβ accumulation, enhancing hyperphosphorylation of tau protein and neurofibrillary tangle (NFT) formation, reducing choline acetyltransferase activity, increasing oxidative processes, modifying inflammation-related neuroimmunotrophic activity and glial activation, altering lipid metabolism, lipid transport and membrane biosynthesis in sprouting and synaptic remodeling, and inducing neuronal apoptosis [1,6-8]. In addition, multiple studies over the past two decades have demonstrated that APOE variants may affect the therapeutic response to anti-dementia drugs [9-17].

From studies designed to define *APOE*-related AD phenotypes, several conclusions can be drawn: (i) the age-at-onset is 5-10 years earlier in approximately 80% of AD cases harboring the *APOE-4/4* genotype; (ii) the serum levels of ApoE are lowest in *APOE-4/4*, intermediate in *APOE-3/3* and *APOE-3/4*, and highest in *APOE-2/3* and *APOE-2/4*; (iii) serum cholesterol levels are higher in *APOE-4/4* than in the other genotypes; (iv) HDL-cholesterol levels tend to be lower in *APOE-3* homozygotes than in *APOE-4* allele carriers; (v) LDL-cholesterol levels are systematically higher in APOE-4/4 than in any other genotype; (vi) triglyceride levels are significantly lower in *APOE-4/4*; (vii) nitric oxide levels are slightly lower in *APOE-4/4*; (viii) serum and CSF Aβ levels tend to differ between *APOE-4/4* and the other most frequent genotypes (*APOE-3/3, APOE-3/4*); (ix) blood histamine levels are dramatically reduced in *APOE-4/4* as compared with the other genotypes; (x) brain atrophy and AD neuropathology is markedly increased in *APOE-4/4>APOE-3/4>APOE-3/3*; (xi) brain mapping activity shows a significant increase in slow wave activity in *APOE-4/4* from early stages of the disease; (xii) brain hemodynamics, as reflected by reduced brain blood flow velocity and increased pulsatility and resistance indices, is significantly worse in *APOE-4/4* (and in *APOE-4* carriers in general, as compared with *APOE-3* carriers); brain hypoperfusion and neocortical oxygenation is also more deficient in *APOE-4* carriers; (xiii) lymphocyte apoptosis is markedly enhanced in *APOE-4* carriers; (xiv) cognitive deterioration is faster in *APOE-4/4* patients than in carriers of any other *APOE* genotype; (xv) in approximately 3-8% of the AD cases, the presence of some dementia-related metabolic dysfunctions accumulates more in *APOE-4* carriers than in *APOE-3* carriers; (xvi) some behavioral disturbances, alterations in circadian rhythm patterns, and mood disorders are slightly more frequent in *APOE-4* carriers; (xvii) aortic and systemic atherosclerosis is also more frequent in APOE-4 carriers; (xviii) liver metabolism and transaminase activity also differ in *APOE-4/4* with respect to other genotypes; (xix) hypertension and other cardiovascular risk factors also accumulate in *APOE-4*; and (xx) *APOE-4/4* carriers are the poorest responders to conventional drugs. These 20 major phenotypic features clearly illustrate the biological disadvantage of *APOE-4* homozygotes and the potential consequences that these patients may experience when they receive pharmacological treatment for AD and/or concomitant pathologies [8-19].

The *TOMM40* locus is located adjacent to and in linkage disequilibrium with *APOE* on 19q13.2. A poly T repeat in an intronic polymorphism (rs10524523) (intron 6) in the TOMM40 gene, which encodes an outer mitochondrial membrane translocase involved in the transport of amyloid-β and other proteins into mitochondria, has been implicated in AD [20-33], and *APOE-TOMM40* genotypes have been shown to modify disease risk and age at onset of symptoms [21-26,34]. A fixed-effect meta-analysis approach showed that rs4420638 at the *TOMM40/APOE/APOC1* gene locus is associated with longevity [35,36]. Two independent associations with cognitive decline were found among European-Americans in the 19q13.32 region (rs769449, APOE intron; and rs115881343, *TOMM40* intron); rs769449 was also associated with cognitive decline among African-Americans, but rs115881343 was not [37]. The *APOE-TOMM40* genomic region is associated with cognitive aging [38] and with pathological cognitive decline [39].

Linnertz et al. [28] defined 3 allele groups for rs10524523 ('523'), based on the number of 'T'-residues: 'Short' (S, T ≤ 19), 'Long' (L, 20 ≤ T ≤ 29) and 'Very Long' (VL, T ≥ 30). Roses et al. [22-25] reported that longer lengths of rs10524523 are associated with a higher risk for late-onset Alzheimer's disease (LOAD); for *APOE-3/4* patients who developed LOAD after 60 years of age, individuals with long poly T repeats (19-39 nucleotides) linked to *APOE-3* develop LOAD on an

average of 7 years earlier than individuals with shorter poly T repeats (11-16 nucleotides) linked to *APOE-3* [22,23,26].

Linnertz et al. [40] also investigated the genomic region spanning the *TOMM40* and *APOE* genes, to determine whether intronic poly T (rs10524523) within this region affects expression of the *APOE* and *TOMM40* genes in the brain of patients with LOAD. The expression of both genes was significantly increased with disease. Mean expression of *APOE* and *TOMM40* mRNA levels was higher in VL homozygotes compared with S homozygotes in the temporal and occipital cortexes from normal and LOAD cases. The 523 VL poly T resulted in significantly higher expression than the S poly T. These results suggest that the 523 locus may contribute to LOAD susceptibility by modulating the expression of *TOMM40* and/or *APOE* transcription [40]. Recent studies also suggest that the *TOMM40* gene rs10524523 ("523") variable length poly T repeat polymorphism is associated to a certain extent with similar AD phenotypes as those reported for *APOE*, such as brain white matter changes [41,42] or different biomarkers [43-46]. In addition, the *TOMM4*0 rs2075650 G allele may be a risk factor for the development of depression [47] and sporadic inclusion body myositis [48]. Different markers at the 19q13-q13.2 chromosomal region, including the rs2075650 and rs157590 (*TOMM40*), rs1064725 (*APOC1*), and rs429358 and rs7412 (*APOE*) SNPs also show association with primary progressive aphasia and the behavioral variant frontotemporal dementia [49].

The *TOMM40/APOE/APOC1* loci have been associated with C-reactive protein (CRP), a heritable biomarker of systemic inflammation and a predictor of cardiovascular disease (CVD) [50]. Genome-wide association studies (GWAS) have identified LDL-cholesterol-associated loci near *HMGCR, ABO* and *TOMM40* [51], and also an association of *TOMM40* with blood lipid levels [52,53] and body mass index [54]. Genetic variants in *TOMM40/APOE-C1-C2-C4* genes have also been found to be associated with multiple cardiovascular-related traits [55-57].

In a recent study [58], the structure of the *APOE-TOMM40* region has been investigated in Spanish patients with dementia, as well as the influence of polymorphic variants in this genomic segment on the therapeutic response to a multifactorial treatment adapted to the pathogenic profile of the patients. The distribution and frequency of APOE genotypes was the following: *APOE-2/3*, 8.26%; *APOE-2/4*, 1.96%; *APOE-3/3*, 51.52%; *APOE-3/4*, 33.04%; and *APOE-4/4*, 5.22%. The distribution of 6 major *TOMM40* poly T variants was: 18.37% S/S, 7.83% S/L, 38.80% S/VL, 1.52% L/L, 7.17% L/VL, and 26.31% VL/VL. The *APOE-2/3* genotype was found to be associated with S/S (27.63%), S/VL (51.32%), and L/VL (21.05%); *APOE-2/4* was associated with S/L (16.67%), S/VL (38.89%), L/VL (11.11%), and VL/VL (33.33%); *APOE-3/3* was associated with S/S (29.32%), S/L (0.42%), S/VL (47.26%), L/VL (0.21%), and VL/VL (22.79%); *APOE-3/4* was associated with S/S (2.96%), S/L (21.38%), S/VL (28.29%), L/VL (15.46%), and VL/VL (31.91%); and *APOE-4/4* was associated with S/L (4.17%), S/VL (2.17%), L/L (29.17%), L/VL (33.33%), and VL/VL (31.25%). Likewise, the S/S genotype was associated with *APOE-2/3* (27.63%), *3/3* (29.32%), and *3/4* (2.96%); S/L with *APOE-2/4* (16.67%), *3/3* (0.42%), *3/4* (21.38%), and *4/4* (4.17%); S/VL with *APOE-2/3* (51.32%), *2/4* (38.89%), *3/3* (47.26%), *3/4* (28.29%), and *4/4* (2.08%); L/L was exclusively associated with *APOE-4/4* (100%); L/VL with *APOE-2/4* (11.11%), *3/3* (0.21%), *3/4* (15.46%), and *4/4* (33.33%); and VL/VL with *APOE-2/3* (21.05%), *2/4* (33.33%), *3/3* (22.79%), *3/4* (31.91%), and *4/4* (31.25%). S/VL and VL/VL are the only *TOMM40* poly T genotypes which interact with all major *APOE* genotypes; in contrast, the *APOE-4/4-TOMM40-L/L* association is unique, representing approximately 30% of *APOE-4/4* carriers [58]. This pioneering study also revealed that: (i) *APOE-4* carriers are the worst responders and *APOE-3* carriers are the best responders to conventional treatments; (ii) *TOMM40 poly T-S/S* carriers are the best responders, VL/VL and S/VL carriers are intermediate responders, and L/L carriers are the worst responders to treatment; (iii) patients harboring a large (L) number of poly T repeats in intron 6 of the *TOMM40* gene (L/L or S/L genotypes) in haplotypes associated with *APOE-4* are the worst responders to treatment; (iv) patients with short (S) *TOMM40* poly T variants (S/S genotype), and to a lesser extent S/VL and VL/VL carriers, in haplotypes with *APOE-3* are the best responders to treatment; and (v) in 100% of the cases, the L/L genotype is exclusively associated with the *APOE-4/4* genotype, and this haplotype (4/4-L/L) is probably responsible for early onset of the disease, a faster cognitive decline, and a poor response to different treatments [58].

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