

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), *BINI* (2q14), *CLU* (8p21-p12), *ABCA7* (19p13.3), *CRI* (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 A β 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 A β 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 \leq 19), 'Long' (L, 20 \leq T \leq 29) and 'Very Long' (VL, T \geq 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 *TOMM40* 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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