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Genotype-related vascular phenotype in dementia: Impact on the pharmacogenetic outcome

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Over 80% of patients with dementia older than 75 years of age exhibit a clear cerebrovascular component characterized by brain hemodynamic alterations, microinfarcts or ischemic signs. In Alzheimer's disease (AD) patients, hypertension (>25%), overweightness (>40%) or obesity (>20%), diabetes (25%), hypercholesterolemia (>40%), hypertriglyceridemia (20%), cardiovascular disorders (>40%), atherosclerosis (>60%) and metabolic deficits (>20%) are common concomitant disorders contributing to premature neurodegeneration. In a cohort of 1803 patients with AD and 1096 controls, several SNPs in genes associated with lipid metabolism (*APOE, APOB, APOC3, CETP, LPL*), endothelial function and hypertension (*NOS3, ACE, AGT*), immune response and inflammation (*IL1B, IL6, IL6R, TNFA*) and thrombosis (*F2, F5, MTHFR*) were investigated. Although no significant differences were found between AD and controls, except in the case of *APOE* ($p<0.0001$), different SNPs in these genes exert a pathogenic influence in vulnerable patients. The therapeutic response to conventional drugs in AD is genotype-specific. The *APOE-TOMM40* region is a reference locus in the pharmacogenetics of AD. *APOE-4* carriers are the worst responders and *APOE*-3 carriers are the best responders to drugs. *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. 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. *CYP2D6, CYP2C9, CYP2C19* and *CYP3A4/5* variants also influence the pharmacogenetic outcome in AD. Polypharmacy in AD requires a personalized intervention to optimize therapeutics.

Biography

Ramon Cacabelos is a Professor of Genomic Medicine at Camilo Jose Cela University, Spain and President of the EuroEspes Biomedical Research Center, Spain. He has received his MD from Oviedo University, PhD from Santiago University and DMSci in Psychiatry from Osaka University Medical School, Japan. After a decade at the Department of Psychiatry in Osaka, he returned to Spain and focused his research activity on the genomics and pharmacogenomics of neurodegenerative disorders. He has published over 600 papers and 24 books and is an Editor-in-Chief of the first World Guide for Drug Use and Pharmacogenomics and President of the World Association of Genomic Medicine.

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