

# PREDICTIVE, PREVENTIVE AND PERSONALIZED MEDICINE & MOLECULAR DIAGNOSTICS

September 22-23, 2016 Phoenix, USA



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### Pharmacogenetics of Alzheimer's disease: The critical role of the *APOE-TOMM40* region

Anti-dementia drugs are not cost-effective and less than 20% of the patients respond to conventional drugs. Pharmacogenetics accounts for 60-90% variability in pharmacokinetics and pharmacodynamics. The genes involved in the pharmacogenomic response to drugs in Alzheimer's disease (AD) fall into five major categories: Pathogenic genes, mechanistic genes, metabolic genes, transporter genes and pleiotropic genes. Among pathogenic genes, *APOE* (19q13.2) is the most prevalent gene as a risk factor for AD, especially the *APOE-4* allele. Adjacent to the *APOE* gene is the *TOMM40* locus. 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 A $\beta$  and other proteins into mitochondria has been implicated in AD and *APOE-TOMM40* genotypes have been shown to modify disease risk and age at onset of symptoms. Taking the *APOE-TOMM40* region as a reference locus, pharmacogenetic studies have revealed the following: *APOE-4* carriers are the worst responders and *APOE-3* carriers are the best responders to conventional treatments. *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. Patients with short (S) *TOMM40* poly T variants (S/S genotype) in haplotypes with *APOE-3* and to a lesser extent S/VL and VL/VL carriers are the best responders to treatment. 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.

### Biography

Ramon Cacabelos is a Professor and Chairman of Genomic Medicine at Camilo Jose Cela University, Madrid and President of the EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Corunna, Spain. He has received his MD from Oviedo University, PhD from Santiago de Compostela 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 Alzheimer's disease, neurodegenerative disorders and neuropsychiatric pathology. He has published over 600 papers, 400 chapters and 24 books. One of his major contributions is the first World Guide for Drug Use and Pharmacogenomics (2012). He is the Editor-in-Chief and Member of the Editorial Board of several international journals, Member of over 30 scientific societies and President of the Spanish Society of Genomic Medicine and the World Association of Genomic Medicine.

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