proteins (*MRP1*/*ABCC1*, *MRP2*/*ABCC2*, *MRP3*/*ABCC3*, *MRP4*/*ABCC4*, *MRP5*/*ABCC5*, *MRP6*/*ABCC6*, *MRP7*/*ABCC10*, *MRP8*/*ABCC11* and *MRP9*/*ABCC12*), which belong to the ABCC family integrated by 13 members. Other genes encoding transporter proteins are genes of the solute carrier superfamily (SLC) and solute carrier organic (SLCO) transporter family, responsible for the transport of multiple endogenous and exogenous compounds.

(v) Pleiotropic genes involved in multifaceted cascades and metabolic reactions.[10–13]

All these genes are under the influence of the epigenetic machinery conditioning their expression and the efficiency of their drug-metabolizing products (enzymes, transporters).[13–16]

Although the *APP*, *PSEN1*, *PSEN2* and *MAPT* genes are considered major pathogenic genes for AD and classic tauopathies,[57] mutations in these genes represent less than 5% of the AD population and, consequently, their influence on AD pharmacogenetics associated with conventional anti-dementia drugs is quantitatively negligible; not so in the case of immunotherapy addressing Aβ deposition. Most anti-AD vaccines (active and passive immunization) are based on transgenic models with *APP*, *PSEN1* and *PSEN2* mutants.[61,62] In general, most pharmacogenetic studies in AD have been performed with susceptibility genes (*APOE*) and metabolic genes (CYPs).[11,18,63–65]

5.3.1 APOE-TOMM40

To date, the most influential gene in AD pharmacogenetics is the *APOE* gene.[4,5,11,13,63–66] *APOE* is a pleiotropic gene with multifaceted activities in physiological and pathological conditions, and the presence of the *APOE*-4 allele is determinant in AD pathogenesis.[53] *APOE-4* may influence AD pathology by interacting with APP metabolism and Aβ accumulation, enhancing hyperphosphorylation of tau protein and neurofibrillary tangle 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 and premature neuronal death.[10,53] Multiple studies over the past two decades have demonstrated that *APOE* variants may affect the therapeutic response to anti-dementia drugs.[6,10,11,13,18,53,63–70] At least 20 major phenotypic features 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.[10,11,23,65–67,70]

In over 100 clinical trials for dementia, *APOE* has been used as the only gene of reference for the pharmacogenomics of AD. Several studies indicate that the presence of the *APOE-4* allele differentially affects the quality and extent of drug responsiveness in AD patients treated with cholinergic enhancers, neuroprotective compounds, endogenous nucleotides, immunotrophins,