Pharmacogenomics of Alzheimer’s Disease: Genetic Determinants of Phenotypic Variation and Therapeutic Outcome

Ramón Cacabelos*, Juan Carlos Carril, Pablo Cacabelos, Óscar Teijido and Dmitry Goldgaber#

*Chair of Genomic Medicine, Camilo José Cela University, Madrid
EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Corunna, Spain
#Department of Psychiatry and Behavioral Science, Stony Brook University

Received May 30, 2016; Accepted June 10, 2016; Published Nov 28, 2016

ABSTRACT

Alzheimer’s disease (AD) is a polygenic/complex disorder in which genomic, epigenomic, cerebrovascular, metabolic and environmental factors converge to define a progressive neurodegenerative phenotype. Conventional anti-dementia drugs are not cost-effective, and pharmacological breakthroughs have not been achieved for the past 10 years. Major determinants of therapeutic outcome in Alzheimer’s disease include age- and sex-related factors, pathogenic phenotype, concomitant disorders, treatment modality and polypharmacy, and pharmacogenetics. Different categories of genes are potentially involved in the pharmacogenetic network responsible for drug efficacy and safety. Pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes represent the major genetic determinants of response to treatment in AD. In pharmacogenetic studies, APOE-4 carriers are the worst responders and APOE-3 carriers are the best responders to conventional treatments. 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 and 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. Only 25% of the Caucasian population are extensive metabolizers for trigenic haplotypes integrating CYP2D6-CYP2C19-CYP2C9 variants. Patients harboring CYP-related poor (PM) and/or ultra-rapid (UM) geno-phenotypes display more irregular profiles in drug metabolism than extensive (EM) or intermediate (IM) metabolizers. Among 111 pentagenic (APOE-APOB-APOC3-CETP-LPL) haplotypes associated with lipid metabolism, carriers of the H26 haplotype (23-TT-CG-AG-CC) exhibit the lowest cholesterol levels and patients with the H104 haplotype (44-CC-CC-AA-CC) are severely hypercholesterolemic. Epigenetic aberrations (DNA methylation, histone modifications, miRNA dysregulation) in genes configuring the pharmacoepigenetic cascade also influence the response/resistance to drugs. Consequently, novel strategies in drug development, either preventive or therapeutic, for AD should take into consideration these pharmacogenetic determinants for treatment optimization.

Keywords: Alzheimer’s disease, anti-dementia drugs, APOE, Atorvastatin, Cholesterol, Epigenetics, CYP haplotypes, LipoEsar, Pharmacogenomics, Pharmacoepigenomics.

INTRODUCTION

Alzheimer’s disease (AD) is a major problem of health in developed countries and the most prevalent form of dementia, representing the 6th cause of death in the USA with an age-adjusted death rate of 25.4 per 100,000. Genomic, epigenomic, cerebrovascular, metabolic and environmental factors are potentially involved in the pathogenesis of AD. The age- and sex-related syndromic profile of AD reflects, at least, a tetraavalent phenotype: (i) a neuropathological component (classic hallmarks: senile plaques, neurofibrillary tangles, neuritic desarborization, neuronal loss); (ii) a
neurobehavioral component: cognitive deterioration, behavioral changes, functional decline; (iii) an age-related biological component (direct-, indirect-, and un-related biochemical, hematological and metabolic phenotypes); and (iv) gender-related phenotypes [1-3]. According to this heterogeneous, complex clinical picture, the therapeutic intervention in dementia is polymodal in order to modify the expression of all these complex phenotypes. AD patients present concomitant disorders including hypertension (20-30%), overweightness or obesity (20-40%), diabetes (20-25%), hypercholesterolemia (>40%), hypertriglyceridemia (20%); excess of urea (>80%), creatinine (6%) and uric acid (5%); alterations in transaminases (ASAT, ALAT, GGT) (>15%), alkaline phosphatase (14%), bilirubin (17%), and ions (>10%); deficits of iron (5%), ferritin (3%), folate (5%), and vitamin B12 (4%); thyroid dysfunction (5-7%), and reduced levels of RBC (3%), HCT (33%), and Hb (35%) [4]. Cardiovascular disorders (>40%), atherosclerosis (>60%), and different modalities of cerebrovascular damage (>60%) are also frequent among patients with AD. Most of these biochemical, hematological and metabolic anomalies exhibit gender differences and may contribute to accelerate the dementia process. The pharmacological treatment of these concomitant pathologies adds complexity and risks to the multifactorial therapeutic intervention in patients with dementia. Of major relevance is the treatment of diabetes, hypertension, dyslipidemia, and cardiovascular, cerebrovascular and neuropsychiatric disorders. The chronic treatment of these illnesses increases the risk of drug interactions and toxicity, aggravating the clinical condition of the demented patient. In this context, the incorporation of pharmacogenetic protocols into clinical practice is fundamental to minimize drug-drug interactions and ADRs, and to optimize the global therapeutic outcome, avoiding deleterious effects on mental function and cognition.

Major determinants of therapeutic outcome in AD include age- and sex-related factors, pathogenic phenotype, concomitant disorders, treatment modality and polypharmacy, and pharmacogenetics. Different categories of genes are potentially involved in the pharmacogenetic network responsible for drug efficacy and safety. Pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes represent the major genetic determinants of response to treatment in AD [5,6]. By-products of these genes are integrated in transcriptomic, proteomic and metabolic networks which are disrupted in AD and represent potential targets for therapeutic intervention [6,7] (Figure 1).

Figure 1. Pathogenic mechanisms and potential intervention targets for disease phenotype modification in Alzheimer’s disease.
TREATMENTS

AD patients may take 6-12 different drugs/day for the treatment of dementia-related symptoms, including memory deterioration (conventional anti-dementia drugs, neuroprotectants), behavioral changes (antidepressants, neuroleptics, sedatives, hypnotics), and functional decline, or for the treatment of concomitant pathologies (epilepsy, cardiovascular and cerebrovascular disorders, parkinsonism, hypertension, dyslipidemia, anemia, arthrosis, etc). Over 20% of dementia patients are current users of cardiovascular drugs. A high throughput screening study assessed 1600 FDA-approved drugs for their ability to modulate Aβ activity; 559 drugs of the 1600 had no effect on APP processing or were toxic to neurons at the concentration tested, while 800 drugs could reduce Aβ content by over 10% in primary neurons derived from Tg2576 mice, among which, 184 drugs were able to reduce Aβ content by more than 30%; 241 drugs could potentially promote Aβ accumulation, including 26 drugs that could increase the level of Aβ by over 30% [6]. The co-administration of several drugs may cause side-effects and adverse drug reactions in over 60% of AD patients, who in 2-10% of the cases require hospitalization. The prevalence of potentially inappropriate medication (PIM) is around 50% in some European cohorts. Cerebral vasodilators are the most widely used class of PIM, accounting for 24.0% of all prescriptions, followed by atropinic drugs and long half-life benzodiazepines. Atropinic drugs were associated with cholinesterase inhibitors in 16% of patients. In over 20% of the patients, behavioral deterioration and psychomotor function can be severely altered by polypharmacy [6]. The principal causes of these iatrogenic effects are the inappropriate combination of drugs, and the genomic background of the patient, responsible for his/her pharmacogenomic outcome.

During the past 10 years, over 1,000 different compounds have been studied as potential candidate drugs for the treatment of AD. About 50% of these substances are novel molecules obtained from natural sources. The candidate compounds can be classified according to their pharmacological properties and/or the AD-related pathogenic cascade to which they are addressed to halt disease progression. In addition to the FDA-approved drugs since 1993 (tacrine, donepezil, rivastigmine, galantamine, memantine) (Table 1), most candidate strategies fall into 6 major categories: (i) novel cholinesterase inhibitors and neurotransmitter regulators, (ii) anti-Aβ treatments (APP regulators, Aβ breakers, active and passive immunotherapy with vaccines and antibodies, β- and γ-secretase inhibitors or modulators), (iii) anti-tau treatments, (iv) pleiotropic products (most of them of natural origin), (v) epigenetic intervention, and (vi) combination therapies.

During the 2002-2012 period, 413 AD trials were performed (124 Phase 1 trials, 206 Phase 2 trials, and 83 Phase 3 trials) (78% sponsored by pharmaceutical companies). Registered trials addressed symptomatic agents (36.6%), disease-modifying small molecules (35.1%) and disease-modifying immunotherapies (18%), with a very high attrition rate (overall success rate: 0.4%; failure: 99.6%) [13]. During the past 15 years no new drugs have been approved for the treatment of AD and the available drugs are not cost-effective [14]. Therefore, the pharmacogenetics of AD is very limited, circumscribed to cholinesterase inhibitors and memantine (Table 1), remaining stuck in a primitive stage of underdevelopment due to the lack of novel therapeutic options. Although many studies on the pharmacogenetics of AD have been published since the early 2000’s [15,16], many of them are redundant and contradictory, focusing mainly on the APOE gene and, to a lesser extent, on some CYP family genes and other minor genes [17]. In this context, several considerations are pertinent regarding further steps to be followed in order to achieve a more mature profile of AD pharmacogenomics: (i) a better characterization of the roles played in drug efficacy and safety by genes involved in the pharmacogenomic network is necessary; (ii) since most genes are under the influence of the epigenetic machinery, pharmacopigenomics is becoming an attractive field which deserves special attention; (iii) drug-drug interactions represent a problematic issue in over 80% of AD patients (most patients require a multifactorial treatment with different drugs); (iv) since the neurodegenerative process underlying AD neuropathology starts 20-30 years before the onset of the disease, novel therapeutics should be addressed to prevent premature neuronal death; (v) specific biomarkers for AD are necessary in 3 different contexts: predictive markers before disease onset, early diagnosis in initial stages, and drug monitoring (in both preventive and/or therapeutic strategies); and (vi) physicians should be aware of the usefulness of pharmacogenomics to prescribe more accurately, avoid adverse reactions and optimize the limited therapeutic resources available for the treatment of dementia [12,18].

PHARMACOGENOMICS

Pharmacogenomics accounts for 60-90% variability in pharmacokinetics and pharmacodynamics. The modest effect (and toxicity) of current AD drugs (Table 1) is in part due to their pharmacogenomic profile, since over 70% of AD patients are deficient metabolizers [18]. The genes involved in the pharmacogenomic response to drugs in dementia fall into five major categories:

(i) Genes associated with disease pathogenesis: Mendelian mutations affect genes directly linked to AD, including >30 mutations in the amyloid beta precursor protein (APP) gene (21q21) (AD1); >160 mutations in the presenilin 1 (PSEN1) gene (14q24.3) (AD3); and >10 mutations in the presenilin 2 (PSEN2) gene (1q31-q42) (AD4) [19-23]. PSEN1 and PSEN2 are important determinants of γ-secretase activity responsible for
Table 1. Pharmacological properties and pharmacogenomics of conventional anti-dementia drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
<th>Pharmacogenomics</th>
</tr>
</thead>
</table>
| **Donepezil hydrochloride**, Aricept, 120011-70-3, Donepezil HCl, BNAG, E-2020, E2020 | Name: Donepezil, IUPAC Name: 2-[(1-benzyl)piperidin-4-yl]methyl]-5,6-dimethoxy-2,3-dihydroxyinden-1-one-hydrochloride | Pathogenic genes: APOE, CHAT  
Mechanistic genes: CHAT, ACHE, BCHE  
Drug metabolism-related genes:  
- Substrate: CYP2D6 (major), CYP3A4 (major), UGT1A1  
- Inhibitor: ACH, BCHE  
Transporter genes: ABCB1 |
| **Memantine HCl**, 41100-52-1, Namenda, Memantine HCL, Axura, 3,5-Dimethyl-1-adamantanamine hydrochloride, 3,5-dimethyladamantan-1-amine hydrochloride | Name: Memantine Hydrochloride, IUPAC Name: (2R,3R)-2,3-dihydroxybutanedioic acid,[3-[(1S)-1-dimethylaminoethyl][phenyl]-N-ethyl-N-methylcarbamate | Pathogenic genes: APOE, APP, CHAT  
Mechanistic genes: ACHE, BCHE, CHRNA4, CHRN2, GRIN3A, HTR3A  
Drug metabolism-related genes:  
- Inhibitor: CYP1A2 (weak), CYP2B6 (weak), CYP2B2 (strong), CYP2C19 (weak), CYP2D6 (strong), CYP2E1 (weak), CYP3A4 (weak), NR1H2  
Transporter genes: NR1H2  
Pleiotropic genes: APOE, MAPT, MT-1K, PSEN1 |
| **Rivastigmine tartrate**, 129101-54-8, SDZ-ENA 713, Rivastigmine hydrogumitrate, Rivastigmine Hydrogen Tartrate, ENA 713, ENA-713 | Name: Rivastigmine tartrate, IUPAC Name: 2,3-dihydroxybutan-1-amine, N,N-dimethyl-2-(dihydroxyethyl)aniline | Pathogenic genes: APOE, APP, CHAT  
Mechanistic genes: ACHE, BCHE, CHAT, CHRNA4, CHRN2  
Drug metabolism-related genes:  
- Inhibitor: ACH, BCHE  
Pleiotropic genes: APOE, MAPT |
| **Tacrine Hydrochloride**, Tacrine HCl, 1684-40-8, Hydroxymacrine, tacrine HCl, 9-AMINO-1,2,3,4-TETRAHYDROACRIDINE HYDROCHLORIDE, Tenakrin | Name: Tacrine Hydrochloride, IUPAC Name: 1,2,3,4-tetrahydroacrid-9-aminehydrochloride | Pathogenic genes: APOE, CHAT  
Mechanistic genes: ACHE, BCHE, CHRNA4, CHRN2  
Drug metabolism-related genes:  
- Substrate: CYP1A2 (major), CYP2D6 (minor), CYP3A4 (major)  
- Inhibitor: ACH, BCHE, CYP1A2  
Transporter genes: SCN1A  
Pleiotropic genes: APOE, ACH, MTHFR, GSTM1, GSTT1, LEP, MAPT |

**ABCB1**: ATP binding cassette subfamily B member 1; **ACHE**: Acetylcholinesterase (Yt blood group); **APOE**: Apolipoprotein E; **APP**: Amyloid beta precursor protein; **BCHE**: butyrylcholinesterase; **CES1**: Carboxylesterase 1; **CHAT**: Choline O-acetyltransferase; **CHRNA4**: CHRNA4 (exons 5-10) and FAMA7A (exons A-E) fusion; **CHRNB2**: Cholinergic receptor nicotinic alpha 4 subunit; **CHRNB2**: Cholinergic receptor nicotinic alpha 7 subunit; **CYP1A2**: Cytochrome P450, family 1, subfamily A, polypeptide 2; **CYP2A6**: Cytochrome P450, family 2, subfamily A, polypeptide 6; **CYP2B6**: Cytochrome P450, family 2, subfamily B, polypeptide 6; **CYP2C9**: Cytochrome P450, family 2, subfamily C, polypeptide 9; **CYP2C19**: Cytochrome P450, family 2, subfamily C, polypeptide 19; **CYP2D6**: Cytochrome P450, family 2, subfamily D, polypeptide 6; **CYP2E1**: Cytochrome P450, family 2, subfamily E, polypeptide 1; **CYP3A4**: Cytochrome P450, family 3, subfamily A, polypeptide 4; **DLGAP1**: Discs large homolog associated protein 1; **FOS**: FBJ murine osteosarcoma viral oncogene homolog; **GRIN2A**: glutamate ionotropic receptor NMDA type subunit 2A; **GRIN2B**: glutamate ionotropic receptor NMDA type subunit 2B; **GRIN3A**: glutamate ionotropic receptor NMDA type subunit 3A; **GSTM1**: Glutathione S-transferase mu 1; **GSTT1**: Glutathione S-transferase theta 1; **HOMER1**: Homer homolog 1 (Drosophila); **HTRA1**: 5-Hydroxytryptamine receptor 3A; **LEPR**: Leptin receptor; **MAPT**: Microtubule associated protein tau; **MT-TK**: thymidine kinase 2, mitochondrial; **MTHFR**: Methylene tetrahydrofolate reductase (NAD(P)H); **NR1I2**: Nuclear receptor 1/2; **PSEN1**: Presenilin 1; **SCN1A**: Sodium voltage-gated channel alpha subunit 1; **UGT1A1**: UDP glucuronosyltransferase 1 family, polypeptide A1; **UGT2**: UDP glucuronosyitransferases. 

Source: Cacabelos et al (Ref. 10)
proteolytic cleavage of APP and NOTCH receptor proteins. Mendelian mutations are very rare in AD (1:1000). Mutations in exons 16 and 17 of the APP gene appear with a frequency of 0.30% and 0.78%, respectively, in AD patients. Likewise, PSEN1, PSEN2, and microtubule-associated protein Tau (MAPT) (17q21.1) mutations are present in less than 2% of the cases. Mutations in these genes confer specific phenotypic profiles to patients with dementia: amyloidogenic pathology associated with APP, PSEN1 and PSEN2 mutations and tauopathy associated with MAPT mutations representing the two major pathogenic hypotheses for AD.[19-25]

Multiple polymorphic risk variants can increase neuronal vulnerability to premature death. There are at least 695 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 (11q21.1), CD33 (19q13.3), MS4A4E (11q12.2), and CD2AP (6p12).[36,37] Potentially defective genes associated with AD represent about 1.39% (35,252.69 Kb) of the human genome, which is integrated by 36,505 genes (3,095,677.41 Kb). The highest number of AD-related defective genes concentrate on chromosomes 10 (5.41%; 7,337.83 Kb), 2 (5.36%; 7,022.30 Kb), 7 (1.62%; 2,584.26 Kb), 2 (1.56%; 3,799.67 Kb), 19 (1.45%; 854.54 Kb), 9 (1.42%; 2,010.62 Kb), 15 (1.23%; 1,264.4 Kb), 17 (1.19%; 970.16 Kb), 12 (1.17%; 1,559.9 Kb), and 6 (1.15%; 1,968.22 Kb).[38,39] Among susceptibility genes, the apolipoprotein E (APOE) gene (AD2) is the most prevalent as a risk factor for AD, especially in those subjects harboring the APOE-4 allele, whereas carriers of the APOE-2 allele might be protected against dementia.[40] Polymorphic variants in other genes (GRB-associated binding protein 2 (GAB2), TLR9 rs187084 variant homozygote GG, LRRK2 R1628P variant) might also be protective.[41] Ten novel private pathogenic copy number variations (CNVs) in 10 early-onset familial Alzheimer’s disease (EO-FAD) families overlapping a set of genes (A2BP1, ABAT, Cdh2, CRM1, DMRT1, EPHA5, EPHA6, ERMP1, EVC, EVC2, FLJ35024 and VLDLR) have also been identified.[42,43]

(ii) Genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers).

(iii) Genes associated with drug metabolism: (a) phase I reaction enzymes: alcohol dehydrogenases (ADH1-7), aldehyde dehydrogenases (ALDH1-9), aldo-keto reductases (AKR1A-D), amine oxidases (MAOA, MAOB, SMOX), carbonyl reductases (CBR1-4), cytochrome P450 family (CYP1-51, POR, TBXAS1), cytochrome b5 reductase (CYB5R3), dihydroxyindole dehydrogenase (DPYD), esterases (AADAC, CEL, CES1, CES1P1, CES2, CES3, CES5A, ESD, GMA, GMZB, PON1, PON2, PON3, UCHL1, UCHL3), epoxidases (EPHX1-2), flavin-containing monooxygenases (FMO1-6), glutathione reductase/ peroxidases (GPX1-7, GSR), short-chain dehydrogenases/reductases (DHR51-13, DHR5X, HSD11B1, HSD17B10, HSD17B11, HSD17B14), superoxide dismutases (SOD1-2), and xanthine dehydrogenase (XDH); and (b) phase II reaction enzymes: amino acid transferases (AGXT, BAA1, CCBL1), dehydrogenases (NQO1-2, XDH), esterases (CES1-3), glucuronosyl transferases (UGT1-8), glutathione transferases (GSTA1-5, GSTK1, GSTM1-5, GSTO1-2, GSTP1, GSTT1-2, GSTZ1, GSTCD, MGST1-3, PTGES), methyl transferases (ASMT, ASMT, COMT, GNMT, GAMT, HNMT, INMT, NNMT, PnMT, Tpmt), N-acetyl transferases (ACSL1-4, ACSM1, ACSM2B, ACSM3, AANAT, GLYAT, NA20, NAT1-2, SAT1), thiolaclient transferase (GLRX), and sulfotransferases (CHST2-13, GAL3T1, SULT1A1-3, SULT1B1, SULT1C1-4, SULT1E1, SULT2A1, SULT2B1, SULT4A1, SULT6B1, CHST1).

(iv) Genes associated with drug transporters: In humans there are 49 ABC transporter genes and the multidrug resistance associated proteins (MRP1/ABCC1, MRP2/ABCC2, MRP3/ABCC3, MRP4/ABCC4, MRP5/ABCC5, MRP6/ABCC6, MRP7/ABCC10, MRP8/ABCC11 and MRP9/ABCC12) which belong to the ABC 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.[5,6,27]

All these genes are under the influence of the epigenetic machinery conditioning their expression and the efficiency of their drug-metabolizing products (enzymes, transporters).[28-30]

GENETIC DETERMINANTS OF THE PHARMACOGENETIC OUTCOME WITH CONVENTIONAL NEUROPROTECTANTS AND ACETYL CHOLINESTERASE INHIBITORS

Although the APP, PSEN1, PSEN2 and MAPT genes are considered major pathogenic genes for AD and classic tauopathies,[23,25] 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.[31,32] In general, most pharmacogenetic studies in AD have been performed with susceptibility genes (APOE) and metabolic genes (CYPs).[6,10]
APOE-TOMM40

To date, the most influential gene in AD pharmacogenetics is the APOE gene[2,6,27,33]. 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 [19]. 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[6,9]. Multiple studies over the past two decades have demonstrated that APOE variants may affect the therapeutic response to anti-dementia drugs[3,5,6,10,15,16,19,27,33-35]. 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[5,6,15,19,33,34,38].

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, neurotrophic factors, combination therapies and other drug categories[1,3,5,35-40]; however, controversial results are frequently found due to methodological problems, study design, and patient recruitment in clinical trials. The major conclusion in most studies is that APOE-4 carriers are the worst responders to conventional treatment and[5,6,10]. When APOE and CYP2D6 genotypes are integrated in biogenic clusters and the APOE+ CYP2D6-related therapeutic response to a combination therapy is analyzed in AD patients, it becomes clear that the presence of the APOE-4/4 genotype is able to convert pure CYP2D6*1/*1 extensive metabolizers into full poor responders to conventional treatments, indicating the existence of a powerful influence of the APOE-4 homozygous genotype on the drug-metabolizing capacity of pure CYP2D6 extensive metabolizers[9]. In addition, a clear accumulation of APOE-4/4 genotypes is observed among CYP2D6 poor and ultra-rapid metabolizers[3].

Adjacent to the APOE locus (19q13.2) and in linkage disequilibrium with APOE is the TOMM40 gene. 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 Aβ and other proteins into mitochondria, has been implicated in AD[41-54]. APOE-TOMM40 genotypes have been shown to modify disease risk and age at onset of symptoms[42,47,55]. The rs4420638 at the TOMM40/APOE/APOC1 gene locus is associated with longevity[56,57]. The APOE-TOMM40 genotypic region is associated with cognitive aging[58] and with pathological cognitive decline[59]. There are 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)[60]. Longer lengths of rs10524523 are associated with a higher risk for late-onset AD (LOAD)[43-47]. Intronic poly T (rs10524523) within this region affects expression of the APOE and TOMM40 genes in the brain of patients with LOAD[60]. The 523 VL poly T shows higher expression than the S poly T, indicating that the 523 locus may contribute to LOAD susceptibility by modulating the expression of TOMM40 and/or APOE transcription[60]. S/VL and VL/VL are the only TOMM40 poly T genotypes which interact with all major APOE genotypes; in contrast, the APOE-4/-/TOMM40-L/L association is unique, representing approximately 30% of APOE-4/- carriers[61] (Figure 2). The first pharmacogenetic study of the APOE-TOMM40 region in AD patients receiving a multifactorial treatment revealed that: (i) APOE-4 carriers are the worst responders (Figures 3-4) and APOE-3 carriers are the best responders to conventional treatments (Figures 3-4); (ii) TOMM40 poly T/S carriers are the best responders (Figures 3-4), VL/VL and S/VL carriers are intermediate responders, and L/L carriers are the worst responders to treatment (Figures 3-4); (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 (Figure 2), 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[8,61].

Other recent pharmacogenetic studies with pathogenic or mechanistic genes indicate that the response to AChEIs is associated with 2 SNPs in the intronic region of CHAT rs2177370 and rs3793790[62]. The CHRNA7 T allele (rs6494223) also associates with a better response to AChEIs and there is further confirmation that APOE-4 carriers are the worst responders to conventional AChEIs[63].
CYPs

Over 70% of AD patients are deficient metabolizers for the CYP2D6/2C19/2C9 trigenic cluster; and for the CYP2D6/2C19/2C9/3A4 tetragenic cluster, more than 80% of the patients exhibit a deficient metabolizer geno-phenotype\(^3\). These four CYP genes encode enzymes responsible for the metabolism of 60-80% of drugs of current use, showing ontogenic-, age-, sex-, circadian- and ethnic-related differences\(^5,6,33,64\). According to the database of the World Guide for Drug Use and Pharmacogenomics\(^38\), 982 drugs are CYP2D6-related: 371 drugs are substrates, over 300 drugs are inhibitors, and 18 drugs are CYP2D6 inducers. Over 600 drugs are CYP2C9-related, 311 acting as substrates (177 are major substrates, 134 are minor substrates), 375 as inhibitors (92 weak, 181 moderate, and 102 strong inhibitors), and 41 as inducers of the CYP2C9 enzyme\(^38\). Nearly 500 drugs are CYP2C19-related, 281 acting as substrates (151 are major substrates, 130 are minor substrates), 263 as inhibitors (72 weak, 127 moderate, and 64 strong inhibitors), and 23 as inducers of the CYP2C19 enzyme\(^38\). The CYP3A4/5 enzyme metabolizes over 1900 drugs, 1033 acting as substrates (897 are major substrates, 136 are minor substrates), 696 as inhibitors (118 weak, 437 moderate, and 141 strong inhibitors), and 241 as inducers of the CYP3A4 enzyme\(^38\).

The distribution and frequency of CYP2D6 genotypes are very similar in the general population (GP) (N=3232) and in AD (N=1289), with the exception of the CYP2D6-*3/*4 genotype (p<0.05) which is absent in AD samples (Figure 5). In the GP, CYP2D6 extensive metabolizers (EMs) account for 58.85%, whereas intermediate metabolizers (IMs) account for 31.11%, poor metabolizers (PMs) 4.49%, and ultra-rapid metabolizers (UMs) 5.55%\(^6,10\) (Figure 5). In AD, EMs, IMs, PMs, and UMs are 57.54%, 31.01%, 5.49%, and 5.96%, respectively. There is an accumulation of AD-related genes of risk in PMs and UMs. EMs and IMs are the best responders, and PMs and UMs are the worst responders to a combination therapy with AChEIs, neuroprotectants, and vasoactive substances. The pharmacogenetic response in AD appears to be dependent upon the networking activity of genes involved in drug metabolism and genes involved in AD pathogenesis\(^5,6,10,33,34,65-67\). By phenotypes, in the GP, CYP2C9-PMs represent 4.82%, IMs 33.83%, and EMs 61.35%. In AD, PMs, IMs, and EMs are 4.76%, 34.87%, and 60.37%, respectively\(^6,38\) (Figure 6). The frequencies of the CYP2C19 geno-phenotypes in the GP are: CYP2C19-EMs 74.11%, CYP2C19-IMs 24.43%, and CYP2C19-PMs 1.46% (Figure 7). EMs, IMs, and PMs account for 75.41%, 23.56%, and 1.03%, respectively, in AD\(^6,38\) (Figure 7) Concerning CYP3A4/5 polymorphisms in AD, 83.84% of the cases are EMs (CYP3A5*3/*3), 14.62% are IMs (CYP3A5*1/*3), and
1.54% are RMs (CYP3A5*1/*1) (Figure 8), whereas in the GP, EMs, IMs and RMs represent 82.17%, 16.48%, and 1.35%, respectively (Figure 8).

Tetragenic haplotypes integrating CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 variants yield 156 genotypes (Figure 9). The most frequent haplotype is H3 (1/1-1/1-1/1-3/3)(20.87%), representing full extensive metabolizers, and only 17 haplotypes exhibit a frequency higher than 1% in the Spanish population (Figure 10). In addition to H3, the most frequent haplotypes (>2%) are H55 (1/4-1/1-1/1-1/3)(8.41%), H26 (1/1-1/2-1/1-3/3)(8.07%), H4 (1/1-1-1/1-3/3)(8.07%), H58 (1/4-1/1-1/2-3/3)(3.99%), H72 (1/4-1/2-1/1-1/3-3/3)(3.82%), H2 (1/1-1/1-1/1-1/3)(3.74%), H9 (1/1-1/1-1/1-1/1-1/3)(3.57%), and H38 (1xN/1-1/1-1/1-1/1-3/3)(2.46%) (Figure 10). This indicates that in the Spanish GP about 80% of the population is deficient for the biotransformation of current drugs which are metabolized via CYP2D6-2C9-2C19-3A4 enzymes.

Most anti-dementia drugs are metabolized via CYP enzymes. Donepezil is a major substrate of CYP2D6, CYP3A4, ACHE, and UGTs, inhibits ACHE and BCHE, and is transported by ABCB1 [2,6,17,33,34,38,65,67-69] (Table 1). CYP2D6 variants affect donepezil efficacy and safety in AD [2,6,17,33,34,38,65,66,69]. The common variant rs1080985 of CYP2D6 is associated with poor response to donepezil [30,71]. A higher frequency of mutated CYP2D6 allele *2A was found in responder than in non-responder patients (75.38% vs 43.48%) [72]. In an Italian study, 67% of patients were responders and 33%

Figure 3. APOE- and TOMM40-related therapeutic response to a multifactorial treatment in patients with Alzheimer’s disease.
(Adapted from Cacabelos et al [61])
were non-responders to donepezil treatment, with abnormal enzymes accumulating in responders\textsuperscript{[73]}. Chinese AD patients with the mutant allele \textit{CYP2D6*10} may respond better (58% responders) to donepezil than those with wild allele \textit{CYP2D6*1}\textsuperscript{[74]}. In contrast, other studies revealed that CYP2D6-PMs and UMs tend to be poor responders to conventional doses of donepezil as compared to EMs and IMs\textsuperscript{[2,6,17,34,38,69,75-77]}. In Italian patients, no association was found between \textit{CYP3A4} or \textit{CYP3A5} genotypes and plasma donepezil concentrations, or between genotypes and clinical response. The most common \textit{ABCB1} haplotypes were 1236C/2677G/3435C (46%) and 1236T/2677T/3435T (41%), and patients homozygous for the T/T/T haplotype had lower plasma donepezil concentration-to-dose ratios and better clinical response than patients with other genotypes\textsuperscript{[78]}. In Brazilian patients treated with AChEIs

---

**Figure 4.** APOE- and TOMM40-related response rate to a multifactorial treatment in patients with Alzheimer’s disease. (Adapted from Cacabelos et al \textsuperscript{[61]})

---

**CYP2D6 Gene Variants**

\textbf{General Population vs Alzheimer's disease}

---

**Figure 5.** Distribution and frequency of 
\textit{CYP2D6} gene variants and extensive (EM), intermediate (IM), poor (PM) and ultra-rapid metabolizers (UM) in the Spanish general population vs Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
Figure 6. Distribution and frequency of CYP2C9 gene variants and extensive (EM), intermediate (IM), and poor metabolizers (PM) in the Spanish general population vs Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.

Figure 7. Distribution and frequency of CYP2C19 gene variants and extensive (EM), intermediate (IM), and poor metabolizers (PM) in the Spanish general population vs Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
the response rate was 27.8%, with no apparent effect of APOE and/or CYP2D6 polymorphic variants\(^7\). The effects of galantamine are potentially influenced by APOE, APP, ACHE, BCHE, CHRNA4, CHRNA7, CHRNB2 variants. This drug is a major substrate of CYP2D6, CYP3A4, and UGT1A1, and an inhibitor of ACHE and BCHE\(^{38,68,90,82}\) (Table 1). Major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization\(^{83}\). Galantamine is extensively metabolized by the enzymes CYP2D6 and CYP3A and is a substrate of the P-gp. CYP2D6 variants are determinant for galantamine pharmacokinetics. CYP2D6-PMs exhibit higher dose-adjusted galantamine plasma concentrations than heterozygous and homozygous CYP2D6-EMs\(^{82}\); however, these pharmacokinetic changes might not substantially affect pharmacodynamics\(^{80}\). The co-administration of galantamine with paroxetine (a CYP2D6 strong inhibitor), ketoconazole (a CYP3A4 strong inhibitor) and erythromycin increases its bioavailability\(^{80,87}\). Interaction with foods and nutritional components may alter galantamine bioavailability and therapeutic effects\(^{88}\).

APOE, APP, CHAT, ACHE, BCHE, CHRNA4, CHRNA7, CHRNB2 and MAPT variants may affect rivastigmine pharmacokinetics and pharmacodynamics, but CYP enzymes are not involved in the metabolism of rivastigmine\(^{38,68,90,82}\). UGT2B7-PMs show higher rivastigmine levels with a poor response to treatment\(^{80}\).

ACHE, ABCB4, BCHE, CHRNA4, CHRNA7, APOE, MTHFR, CES1, LEPR, GSTM1 and GSTT1 variants may affect the therapeutic and toxic effects of tacrine (the first AChEI introduced in 1993 and stopped years later due to hepatotoxicity). Tacrine is a major substrate of CYP1A2 and CYP3A4, a minor substrate of CYP2D6, and is transported via SCN1A and ABCB4. Tacrine is an inhibitor of ACHE, BCHE, and CYP1A2\(^{38}\). Both tacrine and some tacrine-hybrids may cause an induction of CYP1A1, 2B1 and 3A2 expression\(^{91}\). Tacrine is associated with transaminase elevation in up to 50% of patients. The mechanism of tacrine-induced liver damage is influenced by genetic factors. The strongest association was found between alanine aminotransferase levels and three ABCB4 SNPs\(^{82}\).
Memantine is an N-Methyl-D-Aspartate (NMDA) receptor antagonist which binds preferentially to NMDA receptor-operated cation channels; it may act by blocking actions of glutamate, mediated in part by NMDA receptors, and is also an antagonist of GRIN2A, GRIN2B, GRIN3A, HTR3A and CHRFAM7A. Several pathogenic (APOE, PSEN1, MAPT) and mechanistic gene variants (GRIN2A, GRIN2B, GRIN3A, HTR3A, CHRFAM7A, c-Fos, Homer1b and PSD-95) may influence its therapeutic effects. Memantine is a strong inhibitor of CYP2B6 and CYP2D6, and a weak inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4[38,69,93]. In human liver microsomes (HLM), memantine inhibits CYP2B6 and CYP2D6 activities, decreases CYP2A6 and CYP2C19 activities, and has no effect on CYP1A2, CYP2E1, CYP2C9, or CYP3A4 activities[38]. The co-administration of memantine with CYP2B6 substrates elicits a 65% decrease in its metabolism. In clinical studies, NRII2 rs1523130 was identified as the unique significant genetic covariate for memantine clearance, with carriers of the NRII2 rs1523130 CT/TT genotypes presenting a 16% slower memantine elimination than carriers of the CC genotype[95].

TRANSPORTERS

Polymorphic variants in genes encoding transporter proteins may affect drug metabolism, brain penetrance and accessibility to neuronal/glial targets, and drug resistance[96,99]. Of special importance in AD are the ABC and SLC family genes[98]. ABC genes (ABCB1, ABCCC1, ABCG2), and other genes of this family encode proteins which are essential for drug metabolism and transport. Mutations in ABC transporters influence pathogenesis and therapeutics of brain disorders[98,99]. The multidrug efflux transporters (P-gp1/MDR1, multidrug-resistance associated protein 4 (MRP4), breast cancer resistance protein (BCRP)), are located on endothelial cells lining brain vasculature and play important roles in limiting movement of substances into and enhancing their efflux from the brain.

ABCB1 is one of the most important drug transporters in the brain. Over 1270 drugs have been reported to be associated with the Abcb1 transporter protein (P-gp), of which 490 are substrates, 618 are inhibitors, 182 are inducers, and 269 additional compounds which belong to different pharmacological categories of products with potential Abcb1 interaction[38]. The ABCB1 gene has 116 polymorphic sites in Caucasians and 127 in African-Americans, with a minor allele frequency greater than 5%. Common variants are 1236C>T, 2677G>A/T and the ABCB1*I3 haplotype involves the 1236, 2677 and 3435 (TTT) SNPs and 3 intronic SNPs (in intron 9, 13, and 14)[38]. The ABCB1 C1236T, G2677T/A and C3435T SNPs influence blood-brain barrier (BBB) P-glycoprotein function. AD patients with one or more T in C1236T, G2677T and C3435T have significantly higher binding potential values than patients without a T. Genetic variations in ABCB1 might contribute to the progression of Aβ deposition in the brain[100] and some ABCB1 SNPs (C1236T in exon 12, G2677T/A in exon 21 and C3435T in exon 26) and inferred haplotypes might represent novel biomarkers of AD[101]. ABCB1 directly transports Aβ from the brain into the blood circulation, whereas the cholesterol transporter ABCA1 neutralizes Aβ aggregation capacity in an APOE-dependent manner, facilitating subsequent Aβ elimination from the brain[100]. Some ABCB1 variants are frequent in AD cases over 65 years of age and among females. This association of ABCB1 2677G>T (rs2032582) is more pronounced in APOE4-negative cases[100]. Some other ABCs have shown potential association with AD[98,103]. The G allele of the ABCA7 rs11550680 SNP is associated with AD in Europeans. The effect size for the SNP in ABCA7 was comparable with that of the APOE ε4-determining SNP rs429358[104]. ABCG2 is involved in Aβ transport and is up-regulated in AD brains. The ABCG2 gene (C421A; rs2231142) (ABCG2 C/C genotype) is associated with AD and the ABCG2 C/C genotype and the APOE ε4

SciTech Central Inc.
J Genomic Med Pharmacogenomics (JGMP)
allele may exert an interactive effect on AD risk\(^ {103}\). Also of importance for AD pharmacogenomics are transporters encoded by genes of the solute carrier superfamily (SLC) and solute carrier organic (SLC0) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate (SLC19A1), urea (SLC14A1-2), monoamines (SLC29A4, SLC22A3), aminoacids (SLC1A5, SLC3A1, SLC7A3, SLC7A9, SLC1A6-7), nucleotides (SLC29A2-3), fatty acids (SLC27A1-6), neurotransmitters (SLC6A2 (noradrenaline transporter), SLC6A4 (serotonin transporter, SERT), SLC6A5-6, 9, 11, 12, 14-19), glutamate (SLC1A6-7), and others\(^ {98,106}\). Some organic anion transporters (OAT), which belong to the solute carrier (SLC) 22A family, are also expressed at the BBB, and regulate the excretion of endogenous and exogenous organic anions and cations\(^ {107}\). The transport of amino acids and di- and tripeptides is mediated by a number of different transporter families, and the bulk of oligopeptide transport is attributable to the activity of members of the SLC15A superfamily (SLC15A1-2, SLC15A2, SLC15A3-4). ABC and SLC transporters expressed at the BBB may cooperate to regulate the passage of different molecules into the brain\(^ {6,10,27,108}\).

**GENETIC DETERMINANTS ASSOCIATED WITH LIPID METABOLISM AND CHOLESTEROL RESPONSE TO HYPOLIPEMIC DRUGS IN HYPERCHOLESTEROLEMIC PATIENTS WITH AD**

Among hundreds of genes potentially involved in AD pathogenesis and concomitant disorders (cardiovascular and cerebrovascular disorders, hypercholesterolemia), at least 4 categories of genes deserve special attention: (i) genes associated with lipid metabolism: APOB (OMIM 107730; rs693 [7545C>T]; risk SNP 7545T)(participates in the atherogenic process in cooperation with VLDL, IDL and LDL); APOE (OMIM 107741; rs429358/rs7412 [112T>C/158T>C, E2, E3, E4]; risk SNP 112C/158C (E4))(encodes apolipoprotein E, involved in the catabolism of triglyceride-rich lipoproteins and cholesterol homeostasis); CETP (OMIM 118470; rs708272 [+279G>A, B1/B2]; risk

---

**Figure 10.** Frequent tetragenic \( CYP \) haplotypes (>1%) in the Spanish population.
SNP +279G (B1)) (contributes to eliminate cholesterol from tissues via reverse cholesterol transport); and LPL (OMIM 609708; rs328 [1421C>G, S474X]; protective SNP 1421G) (hydrolyzes triglycerides which are part of VLDL and chylomicrons and removes lipoproteins from circulation) [28,109-112]; (ii) genes associated with endothelial function and hypertension: NOS3 (OMIM 163729; rs1799983 [894G>T]; risk SNP 894T) (encodes nitric oxide synthase 3 which synthesizes nitric oxide (NO) from the amino acid arginine); ACE (OMIM 106189; rs4332 [547C>T]; risk SNP 547T) (hydrolyzes angiotensin I to angiotensin II, a potent vasopressor and aldosterone-stimulating peptide, and inactivates bradykinin, a potent vasodilator); and AGT (OMIM 1906150; rs699 [9543A>G, T174M]; risk SNP 174M; rs4762 [9360G>A, M235T]; risk SNP 235T) (encodes angiotensinogen, which is converted into angiotensin I by renin) [28,110-112]; (iii) genes associated with immune function and inflammation: IL1B (OMIM 147720; rs1143634 [3954C>T]; risk SNP 3954T) (encodes interleukin-1β, which is involved in the modulation of the inflammatory reaction in thrombus formation); IL6 (OMIM 147620; rs1800795 [-174G>C]; risk SNP -174C; rs1800796 [-573G>C]; risk SNP -573C) (encodes interleukin-6, a pleiotropic cytokine involved in the regulation of the acute phase reaction, immune response, hematopoiesis, and platelet production); IL6R (OMIM 147880; rs8192284 [1510A>G]; risk SNP 1510C) (encodes a subunit of the IL6 receptor complex); and TNFA (OMIM 191160; rs1800629 [-308G>A]; risk SNP -308A) (encodes tumor necrosis factor, a proinflammatory cytokine that influences lipid metabolism, coagulation,
insulin resistance and endothelial function\textsuperscript{[38,117-127]}; and (iv) genes associated with thrombosis and coagulation: \(F2\) (OMIM 17693; rs1799983 [20210G>A]; risk SNP 2021A)(encodes Coagulation Factor 2 (Prothrombin), involved in blood clotting); \(F5\) (OMIM 227400; rs6025 [1691G>A]; risk SNP 1691A)(encodes Factor V Leiden, an important factor involved in blood coagulation); and \(MTHFR\) (OMIM 607093; rs1801133 [677C>T]; risk SNP 677C>T; rs1801131 [1298A>C]; risk SNP 1298A)(encodes methylenetetrahydrofolate reductase, an enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for the remethylation of homocysteine to methionine\textsuperscript{[38,128-132]}. Although differences in genotype distribution and frequencies of all these genes between patients with AD and control subjects are negligible, except in the case of \(APOE\)\textsuperscript{[133]} (Figure 11) some of them may influence the pharmacogenetic outcome in the treatment of major risk factors for dementia, such as hypercholesterolemia, cardiovascular disorders and hypertension\textsuperscript{[133-137]}. Furthermore, many of these genes interact in pathogenic cascades contributing to alter brain cholesterol and A\(\beta\) metabolism, subsequently accelerating neuronal death in AD.

**PHARMACOGENETICS OF HYPERCHOLESTEROLEMIA IN ALZHEIMER’S DISEASE**

Alterations in cholesterol (CHO) metabolism are involved in AD pathogenesis and over 40% of AD patients are hypercholesterolemic. Cognitive deterioration shows a clear age-dependent profile (Figure 12), with an average decline on 3-5 points/year (MMSE score); however, total CHO levels do not appear to affect mental deterioration in AD (Figure 13). Blood lipid levels also show a moderate age-dependent profile (Figure 14). In the GP, CHO levels tend to increase with age reaching a plateau at 60-70 years of age, declining thereafter; however, CHO levels in AD tend to diminish in an age-related fashion (Figure 15).

In a group of AD patients (\(N=920\)) recruited for pharmacogenomic studies treated with a multifactorial therapy for one year\textsuperscript{[61]}, we evaluated the effects of Sardilipin (E-SAR-94010; LipoEsar\textregistered)(500 mg/day)(nutraceutical with lipid-lowering effects and anti-atherosclerotic and neuroprotective properties, Patent ID: P9602566\textsuperscript{[6,38,138]}) (whole group), and atorvastatin (10 mg/day)(patients with hypercholesterolemia >220 mg/dL)(43.48%)(first month of treatment) on lipid metabolism (total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) according to the \(APOE\) and \(CYP\) genotypes of the patients. From these
Figure 14. Age-related blood lipid levels in the general population. Source: R. Cacabelos. CIBE DataBase, 2016.

Figure 15. Age-related blood cholesterol levels in the general population and in patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
studies we obtained interesting results which enable us to infer some conclusions with important repercussions on the pharmacogenetics of AD: (i) Body Mass Index (BMI) is not affected by total cholesterol (T-CHO) or LDL-CHO; however, there is a clear positive correlation between BMI and triglyceride (TG) levels and an inverse correlation between BMI and HDL-CHO. (ii) Liver transaminase activity is important for lipid metabolism. ASAT, ALAT and GGT exhibit different correlation patterns in relation to lipid levels. ASAT shows an inverse correlation with T-CHO and LDL-CHO; ALAT and GGT activities increase in parallel with TG levels, and tend to show an inverse correlation with HDL-CHO. (iii) Hypercholesterolemic females and males with AD show a similar response to the combination of Atorvastatin+LipoEsar, but more females (60%) are hypercholesterolemic than males (<20%). (iv) CHO levels are APOE-dependent. APOE-4/4 carriers exhibit the highest CHO levels. APOE-2/3, APOE-3/4 and APOE-4/4 carriers experience a gradual age-dependent decrease in CHO levels. (v) The therapeutic response of CHO to Atorvastatin+LipoEsar is APOE-dependent. APOE-3/3 and APOE-3/4 carriers are the best responders and APOE-2/4 and APOE-4/4 carriers are the worst responders. (vi) Basal CHO levels are similar in CYP2D6-EMs, IMs, PMs and UM. CYP2D6-EMs and IMs show a significant decrease in CHO levels in response to Atorvastatin+LipoEsar, whereas PMs and UMs exhibit a poorer CHO-lowering effect. (vii) Basal CHO levels are higher in CYP2C9-IMs and CYP2C9-EMs and IMs effectively respond to Atorvastatin+LipoEsar, with a significant reduction in CHO levels, and CYP2C9-PMs do not respond. (viii) Basal CHO levels are non-significantly higher in CYP2C19-EMs and IMs than in PMs. CYP2C19-EMs and IMs significantly respond to Atorvastatin+LipoEsar, and PMs do not show any effect. (ix) CYP3A4/5-EMs show a significant decrease in CHO levels after one month of treatment with Atorvastatin+LipoEsar. This response is similar for LDL-CHO in EMs and IMs. In hypercholesterolemic patients, over 80% of EMs respond to 20 mg of Atorvastatin + 500 mg of LipoEsar, with an almost complete normalization of CHO levels. The effect in IMs is spectacular, with over 90% of the patients experiencing a drastic reduction in CHO levels, 50% of them entering into a condition of iatrogenic hypcholesterolemia; and 60% of RMs do not respond at all.

In a larger study with 1345 hypercholesterolemic AD patients (CHO>220 mg/dL)(Figure 16) we investigated the pharmacogenetics of cholesterol response to the hypolipemic compounds Atorvastatin+LipoEsar for one month. In the whole sample, the response rate (RR) was 78.95% responders (CHO<baseline levels) and 21.04% non-responders (CHO≥baseline levels). APOE-related basal

![Individual Response to Hypolipemic Treatment](image)

**Figure 16.** Individual profile of cholesterol response to a combination treatment (Atorvastatin + LipoEsar) in patients with Alzheimer’s disease (upper panel) and correlation analysis (basal cholesterol levels vs treatment) of the response of cholesterol to a combination treatment in patients with Alzheimer’s disease (lower panel).

CHO levels are significantly different, with females showing higher CHO levels than males (Figure 17). However, females and males responded similarly to the hypolipemic treatment (Figure 18). The stratification of patients according to their APOE, APOB, APOC3, CETP, and LPL genotypes showed no genotype-related differences at basal CHO levels, except in the case of APOE carriers where the highest baseline levels of CHO were found in APOE-4/4 carriers and the lowest levels in APOE-2/2 carriers (Figure 19), in addition to a clear age-related profile (Figure 19).

In a selected group of 933 AD patients, we constructed a pentagenic haplotype integrating all possible variants of the APOE, APOB, APOC3, CETP, and LPL genes and identified 111 haplotypes (H) (Figure 20) with differential basal CHO levels (Figure 21). About 75% of these haplotypes in the AD population have a frequency below 1%, 10% have a frequency between 1% and 2%, 8% have a frequency between 2% and 5%, and only 4% of the haplotypes are present in more than 5% of AD patients (Figure 20). The haplotypes most frequently found are H55 (33-CT-CC-AG-CC)(8.79%), H58 (33-CT-CC-GG-CC) and H57 (33-CC-CC-AG-CC)(7.07%). Haplotypes H104 (44-CC-CC-AA-CC)(0.11%), H110 (44-CC-CC-GG-GG)(0.11%) and H108 (34-CC-CC-AG-GG)(0.11%) showed the highest CHO levels, and the lowest levels corresponded to haplotypes H26 (23-TT-CG-AG-CC)(0.11%), H28 (23-CC-CG-AG-CC)(0.21%), H50 (33-CC-GG-AG-CC)(0.21%), and H63 (33-CT-CG-AA-GG)(0.11%) (Figure 21).

Basal CHO levels tend to be higher in AD patients as compared to GP levels (Figures 22-23). APOE-related blood total CHO profiles are qualitatively distinct among carriers of different APOE genotypes (Figure 24). The results of APOE-related cholesterol response to hypolipemic treatment in hypercholesterolemic AD patients revealed that in absolute terms all APOE variants respond similarly (RR>70%) to treatment with a significant reduction in

Figure 17. APOE- and sex-related basal cholesterol levels in patients with Alzheimer’s disease.

Figure 18. Sex-related cholesterol response to Atorvastatin and LipoEsar in patients with Alzheimer’s disease.
CHO levels \((p<0.001)\) (Figures 25-26); however, genotype-related correlation analysis case-by-case (Figure 27) and comparative correlation analyses of APOE variants (Figure 28) show a clear differential APOE-related pattern of CHO response to treatment.

Carriers of APOB-C/C, APOB-C/T and APOB-T/T variants exhibit a similar response (RR>80%), with a significant decrease in CHO levels after treatment (Figure 29) and almost identical efficiency in comparative analyses (Figure 30). APOC3-C/C, APOC3-C/G and APOC3-G/G carriers also respond similarly \((p<0.001)\) (RR>80%) (Figure 31), with a differential comparative profile (Figure 32). CETP-A/A, CETP-A/G and CETP-G/G carriers show an identical response \((p<0.001; RR>80\%)\) (Figure 33), with insignificant variability in comparative studies (Figure 34). The same therapeutic response is observed in LPL-C/C, LPL-C/G and LPL-G/G carriers \((p<0.001; RR>80\%)\) (Figure 35), though in this case LPL-C/C carriers are the best responders, LPL-C/G carriers are intermediate responders, and LPL-G/G carriers are the most heterogeneous responders (Figure 36).
CYP haplotype-related blood total CHO levels are very heterogeneous (Figure 37), but absolute values of total CHO among the most frequent haplotypes are almost identical (Figure 38). The histograms of frequency associated with CHO levels are qualitatively different among carriers of different CYP variants (Figures 39-40). Basal CHO levels are higher in AD patients harboring the CYP2D6-*1/*1 (p<0.05) and *1xN/*1 genotypes (p<0.003) than in the corresponding GP genotypes (Figure 41), but no differences have been found according to the EM, IM, PM or UM condition (Figure 42). The therapeutic response according to SNPs of metabolic genes (CYP2D6, CYP2C9, CYP2C19, CYP3A4/5) in hypercholesterolemic patients is variable and geno-phenotype-dependent. Although all CYP2D6 variants exhibit a positive response to treatment, significant differences have only been detected in 2D6-*1/*1 (p<0.001), 2D6-*1/*4 (p<0.001) and 2D6-*1/*6 carriers (p<0.05) (Figure 43). In absolute values, CYP2D6 extensive (EM), intermediate (IM), poor (PM) and ultra-rapid (UM) metabolizers behave in a similar manner with a significant reduction in CHO levels (p<0.001) (Figure 44); however, the RR is different in EMs (81%), IMs (78%), PMs (84%), and UMs (90%) (Figure 44), indicating a variable efficiency of CYP2D6 enzymes (Figures 45-46). The comparative analysis indicates that carriers of mutant enzymes (PMs>UMs), with limitations in drug metabolism, display a more efficient response to hypolipemic treatment (Figures 45-46).

No differences are present in basal CHO levels between the AD and GP patients (Figures 47-48). CYP2C9-EMs, IMs, and PMs (Figure 49) show a similar response (p<0.001), with lower RR (75%) in PMs as compared with EMs (81%) and IMs (82%), and a clear differential comparative profile (Figure 50).

AD cases harboring the CYP2C19-*1/*2 genotype (Figure 51), corresponding to CYP2C19-IMs (Figure 52), exhibit higher basal CHO levels (p<0.05) than their homologous in the GP (Figures 51-52).

The CHO response among CYP2C19-EMs, IMs, and PMs is more variable, with PMs showing a deficient response (RR=84%) (Figure 56) in comparison to EMs (p<0.001; RR=81%), IMs (p<0.001; RR=78%), and UMs (p<0.001; RR=90%) (Figure 53), and a clearly different behavioral profile, especially in PMs and UMs (Figures 54-55).

CYP3A4/5 geno-phenotypes in AD and GP show similar basal CHO levels (Figure 56). CYP3A4/5-RMs respond poorly to hypolipemic treatment, with the worst RR (66%), whereas CYP3A4/5-EMs and IMs exhibit an excellent response (p<0.001; RR>80%) (Figures 57-58).

Most of these effects can, in part, be explained on a pharmacogenetic basis. It is obvious that a simple stratification of patients according to single genotypes is of poor value for
Table 2. Pharmacological properties and pharmacogenetics of statins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties</th>
<th>Pharmacogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG CoA reductase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong>: ATORVASTATIN CALCIUM; Lipitor; 134523-03-8; Tahor; Sorbit; CI-981&lt;br&gt;<strong>Molecular Formula</strong>: C_{38}H_{49}CaF_{2}N_{12}O_{32} &lt;br&gt;<strong>Molecular Weight</strong>: 1155.341726 g/mol &lt;br&gt;<strong>Mechanism</strong>: Inhibits HMG-CoA reductase, resulting in a compensatory increase in the expression of LDL receptors on hepatocyte membranes and a stimulation of LDL catabolism. &lt;br&gt;<strong>Effect</strong>: Anticholesteremic Agent; HMG-CoA Reductase Inhibitor; Apolipoprotein B reduction; Triglyceride reduction; Anti-atherosclerotic; Heart-health effects.</td>
<td><strong>Pathogenic genes</strong>: ABCA1, ACE, APOA1, APOA4, APOB, APOC3, APOE, CETP, FGB, GNB3, LDLR, LIPC, MMP3, MTHFR, NOS3, PON1 &lt;br&gt;<strong>Mechanistic genes</strong>: ABCB1, ABC2, APOC1, APOA1, APOA4, APOB, APOC3, APOE, CETP, CYP1B2, HMGCR, IL10, IL6, LDLR, MMP3, PON1, TFNP &lt;br&gt;<strong>Metabolic genes</strong>: Substance: CYP2C8, CYP3A4 (major), CYP2D6 &lt;br&gt;<strong>Inducer</strong>: CYP3A4 &lt;br&gt;<strong>Transporter genes</strong>: ABCA1, ABCB1, ABCB2, ABCC2, ABCD2, SLC25A1, SLC25A3, SLC41A1 &lt;br&gt;<strong>Pleiotropic genes</strong>: ACE, APOA4, APOE, NOS3, NR1H2, NR1H3, PPAR, PON1</td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong>: FLUVASTATIN SODIUM; Lescol; Fluvastatin; Fluvastatin sodium salt; 93957-55-2; Sr-42320 &lt;br&gt;<strong>Molecular Formula</strong>: C_{42}H_{45}F_{3}N_{2}O_{25} &lt;br&gt;<strong>Molecular Weight</strong>: 433.447722 g/mol &lt;br&gt;<strong>Mechanism</strong>: Acts by competitively inhibiting HMGCR, the enzyme that catalyzes reduction of HMG-CoA to mevalonate. HDL is increased while total, LDL and VLDL cholesterol, apolipoprotein B, and plasma triglycerides are decreased. &lt;br&gt;<strong>Effect</strong>: Anticholesterol Agent; HMG-CoA Reductase Inhibitor; Heart-health effects; Antineoplastic activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong>: LOVASTATIN; Mevinolin; Mevacor; 75330-75-5; Monacolin K; Altopen &lt;br&gt;<strong>Molecular Formula</strong>: C_{39}H_{49}O_{21} &lt;br&gt;<strong>Molecular Weight</strong>: 404.33964 g/mol &lt;br&gt;<strong>Mechanism</strong>: Acts by competitively inhibiting HMG-CoA reductase, enzyme which catalyzes rate-limiting step in cholesterol biosynthesis. &lt;br&gt;<strong>Effect</strong>: Anticholesterol Agent; HMG-CoA Reductase Inhibitor; Heart-health effects; Antineoplastic activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong>: PITAVASTATIN; Itavastatin; NK 104; Livalo; 147511-69-1; Nivastatin &lt;br&gt;<strong>Molecular Formula</strong>: C_{40}H_{50}F_{3}N_{2}O_{23} &lt;br&gt;<strong>Molecular Weight</strong>: 421.460763 g/mol &lt;br&gt;<strong>Mechanism</strong>: Works to control the synthesis of cholesterol via competitive inhibition of the liver enzyme, HMG-CoA reductase. As a result, a compensatory increase in LDL-receptor expression can be observed which facilitates an increase LDL catabolism. &lt;br&gt;<strong>Effect</strong>: Anticholesterol Agent; HMG-CoA Reductase Inhibitor; Heart-health effects.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong>: PRAVASTATIN SODIUM; Mevalolin; Elisor; 81131-70-6; Lipstatat; Pravachol &lt;br&gt;<strong>Molecular Formula</strong>: C_{14}H_{26}Na_{3}O_{14} &lt;br&gt;<strong>Molecular Weight</strong>: 446.509569 g/mol &lt;br&gt;<strong>Mechanism</strong>: A competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. &lt;br&gt;<strong>Effect</strong>: Anticholesterol Agent; HMG-CoA Reductase Inhibitor; Heart-health effects; Immune response modulation; MHC II suppression.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Properties</td>
<td>Pharmacogenetics</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>ABCA1</strong>: ATP binding cassette subfamily A member 1</td>
<td><strong>Pathogenic genes</strong>: ABCA1, ACE, APOA1, APOA5, APOB, APOC3, APOE, CETP, CYP7A1, FGB, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Mechanistic genes</strong>: APOA1, APOB, CETP, FGB, HMGR, LDLR, LPL, NOS3</td>
</tr>
<tr>
<td><strong>ABCB1</strong>: ATP binding cassette subfamily B member 1</td>
<td><strong>Mechanisms</strong>: Substrate: ABCB1, ABCB1, ABCB4, ABCG2, CYP2C9 (minor), CYP2C19 (minor), CYP3A4 (major), CYP3A4, POR, SLCO1B1, UGT1A3</td>
<td><strong>Inducer</strong>: CYP2C8, CYP2C9, CYP3A4</td>
</tr>
<tr>
<td><strong>ABCB11</strong>: ATP binding cassette subfamily B member 11</td>
<td><strong>Inhibitor</strong>: CYP2C9 (major), CYP3A4 (minor), CYP3A4, POR, SLCO1B1, UGT1A3</td>
<td><strong>Inducer</strong>: CYP2C8, CYP2C9, CYP3A4, SLCO4A1, SLCO1A2, SLCO1B1, SLCO3B1, SLCO2B1</td>
</tr>
<tr>
<td><strong>ABCG2</strong>: ATP binding cassette subfamily G member 2</td>
<td><strong>Inhibitor</strong>: CYP2C9 (weak), CYP2C9 (weak), CYP2C19 (strong), CYP2D6 (weak), CYP3A4 (moderate), HMGR</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>SLCO1A2</strong>, <strong>SLCO1B1</strong>, <strong>SLCO1B3</strong></td>
<td><strong>Transporter genes</strong>: ABCA1, ABCB1, ABCB11, ABCG2, SLCO1A2, SLCO1B1, SLCO1B3, SLCO2B1</td>
<td><strong>Pleiotropic effects</strong>: APOE, F2, FGB, GNB3, NOS3, PRNP, TNF, VCAM1, USP5</td>
</tr>
<tr>
<td><strong>ABCA1, ABCB1, ABCB11, ABCC2, ABCG2, SLCO1A2, SLCO1B1, SLCO1B3</strong></td>
<td><strong>Mechanistic genes</strong>: ABCA1, ABCB1, ABCB4, ABCG2, CYP2C9, CYP2C19, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Pathogenic genes</strong>: ABCA1, APOA1, APOA5, APOB, APOE, CETP, CYP7A1, FGB, GNB3, LIPC, LDLR, LPL, NOS3</td>
</tr>
<tr>
<td><strong>ABCB1, ABCB4, ABCG2, CYP2C9, CYP2C19, CYP3A4, SLCO1A2, SLCO1B1, SLCO1B3</strong></td>
<td><strong>Inhibitor</strong>: CYP2C9, CYP2C9, CYP2C19, CYP3A4, SLCO1A2, SLCO1B1, SLCO1B3, SLCO2B1</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>ABCA1, ABCB11, ABCC3, ABCG2, SLCO1B1, SLCO1B3</strong></td>
<td><strong>Transporter genes</strong>: ABCA1, ABCB1, ABCB11, ABCC2, ABCG2, SLCO1A2, SLCO1B1, SLCO1B3, SLCO2B1</td>
<td><strong>Pleiotropic effects</strong>: APOE, F2, FGB, GNB3, NOS3, PRNP, TNF, VCAM1, USP5</td>
</tr>
<tr>
<td><strong>apoB, APOC3, lipase C, hepatic</strong></td>
<td><strong>Mechanistic genes</strong>: ABCA1, ABCB1, ABCB4, ABCG2, CYP2C9, CYP2C19, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Pathogenic genes</strong>: ABCA1, APOA1, APOA5, APOB, APOC3, APOE, CETP, CYP7A1, FGB, GNB3, LIPC, LDLR, LPL, NOS3</td>
</tr>
<tr>
<td><strong>apoA-I</strong>, <strong>apoA5</strong></td>
<td><strong>Inducer</strong>: CYP2B6</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>apoA5</strong>, <strong>apoE</strong></td>
<td><strong>Inducer</strong>: CYP2B6, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>apoE</strong>, <strong>CETP</strong></td>
<td><strong>Inducer</strong>: CYP2B6, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>apoA5</strong>, <strong>apoE</strong>, <strong>CETP</strong>, <strong>CYP7A1</strong>, <strong>FGB</strong>, <strong>ITGB3</strong>, <strong>NOS3</strong></td>
<td><strong>Inducer</strong>: CYP2B6, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>apoA5</strong>, <strong>apoE</strong>, <strong>CETP</strong>, <strong>CYP7A1</strong>, <strong>FGB</strong>, <strong>ITGB3</strong>, <strong>NOS3</strong></td>
<td><strong>Inducer</strong>: CYP2B6, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
<tr>
<td><strong>apoA5</strong>, <strong>apoE</strong>, <strong>CETP</strong>, <strong>CYP7A1</strong>, <strong>FGB</strong>, <strong>ITGB3</strong>, <strong>NOS3</strong></td>
<td><strong>Inducer</strong>: CYP2B6, CYP3A4, CYP3A5, HMGCR, LDLR, LIPC, LPL, NOS3</td>
<td><strong>Inducer</strong>: CYP2B6</td>
</tr>
</tbody>
</table>
a fine interpretation of pharmacogenetic results; however, the integration of gene clusters associated with specific phenotypes yields informative haplotypes with potential utility in pharmacogenetic studies. It is likely that thousands of genes are involved in CHO metabolism, and probably not a single gene plays an absolute dominant role over the others; however, some genes exert a powerful effect on other congeners associated with a specific pathogenic cascade (e.g. \textit{APOE} in AD) or a pharmacogenetic pathway (e.g. \textit{APOE} vs \textit{CYPs} in AD treatment with donepezil)\cite{3,6,17,33,66,67}. Several pathogenic (\textit{ACE}, \textit{APOA1}, \textit{APOA5}, \textit{APOB}, \textit{AP0C3}, \textit{AP0E}, \textit{CTET}, \textit{FG8}, \textit{GNB3}, \textit{LIPC}, \textit{MMP3}, \textit{MITP}, \textit{NOS3}, \textit{PON}) and mechanistic genes (\textit{ABCB1}, \textit{ABCC1}, \textit{APOA1}, \textit{APOA3}, \textit{APOB}, \textit{APOC3}, \textit{APOE}, \textit{CRP}, \textit{CYP11B2}, \textit{HMGCGR}, \textit{IL10}, \textit{IL6}, \textit{LDLR}, \textit{MMP3}, \textit{PON1}, \textit{TNF}) are potentially influenced by atorvastatin. This statin is a major substrate of CYP2C8 and CYP3A4/5; it is a strong inhibitor of CYP2C19, a moderate inhibitor of ABCB1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and HMGCGR, and an inducer of CYP2B6 and CYP7A1. Atorvastatin is transported by ABCA1, ABCB1, ABCB11, ABC1C1, ABCD2, ABCG2, SLC01B1 and SLC01B3 proteins, and interacts with the products of various pleiotropic genes (\textit{APOA1}, \textit{APOE}, \textit{CRP}, \textit{CYP11B2}, \textit{ESR1}, \textit{GNB3}, \textit{HTR3B}, \textit{IL6}, \textit{IL10}, \textit{ITGB3}, \textit{MMP3}, \textit{TNF}, \textit{USP5})\cite{38} (Table 2). The lipid-lowering effects and the anti-atherosclerotic properties of LipoEsar are \textit{APOE}-dependent, with \textit{APOE}-3 carriers acting as the best responders and \textit{APOE}-4 carriers behaving as the worst responders\cite{3,6,17}. Sex-related changes in cholesterol response to statins have been reported in carriers of the HMGCGR-AA genotype at rs3846662, who have higher levels of total and LDL-cholesterol. The percentage reduction in LDL-cholesterol upon statin treatment is decreased in women with the AA genotype compared with women without it. In hypercholesterolemic patients, HMGR alternative splicing may explain 22-55% of the variance in statin response\cite{38}. The powerful effect of Atorvastatin in CYP3A4/5-IMs is the result of a poor metabolism of Atorvastatin by mutant CYP3A4/5 enzymes, since Atorvastatin is a major substrate of CYP3A4/5. In contrast, the lack of effect in CYP3A4/5-RMs results from a rapid destruction of the drug in the liver mediated by excessive CYP3A4/5 enzymatic activity. Therefore, the dose of statins should be adjusted to the metabolizing condition of each patient to optimize the lipid-lowering effects of statins and to avoid toxicity\cite{38}. Furthermore, the co-administration of the nutraceutical LipoEsar enhances the hypolipemic effect of Atorvastatin and facilitates a dose reduction of the statin by 50%, minimizing potential ADRs in susceptible patients.

![APOE-Related Blood Total Cholesterol Levels](figure)

**Figure 22.** \textit{APOE}-related blood cholesterol levels in the general population and in patients with Alzheimer’s disease.

Figure 23. APOE-related comparative profile of cholesterol phenotypes in the general population and in patients with Alzheimer’s disease.
PHARMACOEPIGENOMICS

Pharmacogenetics alone does not predict all phenotypic variation in drug response\(^{[27]}\). The genes involved in the pharmacogenomic network are under the regulatory control of the epigenetic machinery (DNA methylation, histone modifications, miRNA regulation), this configuring the novel pharmacoepigenomic apparatus\(^{[27]}\). Epigenetics involves heritable alterations of gene expression, chromatin organization, and microRNA (miRNA) regulation without changes in DNA sequence. Classical epigenetic mechanisms, including DNA methylation and histone modifications, and regulation by microRNAs (miRNAs), are among the major regulatory elements that control metabolic pathways at the molecular level, with epigenetic modifications regulating gene expression transcriptionally and miRNAs suppressing gene expression post-transcriptionally\(^{[140]}\). Methylation varies spatially across the genome with a majority of the methylated sites mapping to intragenic regions\(^{[141]}\). About 70% of CpG dinucleotides within the human genome are methylated. Not only nuclear DNA (nDNA), but also mitochondrial DNA (mtDNA) may be subjected to epigenetic modifications related to disease development, environmental exposure, drug treatment and aging.

Figure 24. Histogram of frequencies of age-related cholesterol levels (central panel) and APOE-related histogram of frequencies of cholesterol levels in the general population (lateral panels).
**Figure 25.** *APOE*-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.

**Figure 26.** *APOE*- and sex-related cholesterol response to a combination treatment with Atorvastatin and LipoEsar in patients with Alzheimer’s disease.
Figure 27. APOE-related individual response of cholesterol to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.

### Table 3. Epigenetic modifications in pathogenic genes associated with Alzheimer’s disease

<table>
<thead>
<tr>
<th>Pathogenic gene</th>
<th>Locus</th>
<th>Promoter length (bp)</th>
<th>3’ UTR length (bp)</th>
<th>Defective protein</th>
<th>DNA Methylation / mRNA expression</th>
<th>Histone modifications/ chromatin remodeling</th>
<th>non-coding RNAs</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE</td>
<td>19q13.2</td>
<td>996</td>
<td>…</td>
<td>apolipoprotein E</td>
<td>Hypomethylated / Upregulated mRNA</td>
<td>Linked to AD miR-34a, miR-34b/c, miR-107, miR-124, miR-125b, miR-137</td>
<td>142,143,158-165</td>
<td></td>
</tr>
<tr>
<td>BIN1</td>
<td>2q14</td>
<td>1076</td>
<td>642</td>
<td>bridging integrator 1</td>
<td>Upregulated mRNA</td>
<td></td>
<td>23,166,167</td>
<td></td>
</tr>
<tr>
<td>CLU</td>
<td>8p21-p12</td>
<td>1094</td>
<td>1399</td>
<td>clusterin</td>
<td>Upregulated mRNA</td>
<td></td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>ABCA7</td>
<td>19p13.3</td>
<td>967</td>
<td>…</td>
<td>ATP binding cassette subfamily A member 7</td>
<td>Hypomethylated / Upregulated mRNA</td>
<td>Linked to AD let-7, miR-9, miR-132/212, miR146a, miR-148a, miR-184, miR-200, miR-200c/141</td>
<td>154,169</td>
<td></td>
</tr>
<tr>
<td>CRI</td>
<td>1q32</td>
<td>966</td>
<td>2579</td>
<td>complement component 3b/4b receptor 1</td>
<td>Upregulated mRNA</td>
<td>Reduced H3 acetylation Decreased SIRT1 Increased HDAC6 levels Increased HDAC2 levels</td>
<td>23,170,171</td>
<td></td>
</tr>
<tr>
<td>CD33</td>
<td>19q13.3</td>
<td>1190</td>
<td>387</td>
<td>CD33 molecule</td>
<td>Upregulated mRNA</td>
<td></td>
<td>5,29,142,143,160,173-175</td>
<td></td>
</tr>
<tr>
<td>APP</td>
<td>21q21.3</td>
<td>1086</td>
<td>1176</td>
<td>amyloid beta (A4) precursor protein</td>
<td>Hypomethylated / Upregulated mRNA</td>
<td>Epigenetically regulated</td>
<td>29,142,143,173</td>
<td></td>
</tr>
<tr>
<td>PSEN1</td>
<td>14q24.3</td>
<td>929</td>
<td>1198</td>
<td>presenilin 1</td>
<td>Hypomethylated / Upregulated mRNA</td>
<td></td>
<td>29,142,143,173</td>
<td></td>
</tr>
<tr>
<td>MAPT (TAU)</td>
<td>17q21.1</td>
<td>1094</td>
<td>…</td>
<td>microtubule-associated protein tau</td>
<td>Hypermethylated / Downregulated mRNA</td>
<td></td>
<td>29,142,160</td>
<td></td>
</tr>
<tr>
<td>BACE1</td>
<td>11q23.2-q23.3</td>
<td>987</td>
<td>3994</td>
<td>beta secretase 1</td>
<td>Hypomethylated / Upregulated mRNA</td>
<td></td>
<td>23,170,171</td>
<td></td>
</tr>
<tr>
<td>SORL1</td>
<td>11q23.2-q24.2</td>
<td>996</td>
<td>…</td>
<td>sortilin-related receptor</td>
<td>Downregulated mRNA</td>
<td></td>
<td>29,142,143,160,173,174</td>
<td></td>
</tr>
</tbody>
</table>
## Table 4. Epigenetic modifications in genes associated with lipid metabolism, vascular risk factors, and inflammation

<table>
<thead>
<tr>
<th>Pathogenic gene</th>
<th>Locus</th>
<th>Promoter length (bp)</th>
<th>3' UTR length (bp)</th>
<th>Defective protein</th>
<th>Epigenetic modifications</th>
<th>Pathology</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB</td>
<td>2p24.1</td>
<td>--</td>
<td>394</td>
<td>apolipoprotein B</td>
<td>miR-30 family</td>
<td>Hepatocarcinoma cell line</td>
<td>[175-179]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>miR-122</td>
<td>Fibrosis in hepatitis B infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypermethylation</td>
<td>Aberrant birth weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Upregulated mRNA</td>
<td>Risk for Alzheimer's disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOC3</td>
<td>11q23.3</td>
<td>960</td>
<td>278</td>
<td>apolipoprotein CIII</td>
<td>Hypermethylation</td>
<td>Stroke, Atherosclerosis</td>
<td>[170]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Down-regulated mRNA</td>
<td>Risk for Alzheimer's disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE</td>
<td>19q13.2</td>
<td>996</td>
<td>--</td>
<td>apolipoprotein E</td>
<td>Hypermethylation</td>
<td>Alzheimer's disease</td>
<td>[142,143,]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overexpressed mRNA</td>
<td>Ischemia in mice's heart</td>
<td>[148-165]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Up-regulated mRNA</td>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CETP</td>
<td>16q21</td>
<td>982</td>
<td>299</td>
<td>cholesteryl ester transfer protein plasma</td>
<td>Hypermethylated</td>
<td>Low HDL / vascular risk</td>
<td>[180]</td>
</tr>
<tr>
<td>LPL</td>
<td>8p22</td>
<td>1197</td>
<td>497</td>
<td>lipoprotein lipase</td>
<td>Hypermethylated</td>
<td>Low HDL / vascular risk</td>
<td>[180]</td>
</tr>
<tr>
<td>NOS3</td>
<td>7q36</td>
<td>975</td>
<td>2200</td>
<td>nitric oxide synthase</td>
<td>Histone acetylation</td>
<td>Adverse intrauterine environment</td>
<td>[181-185]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(foetal stage) mRNA upregulation</td>
<td>Adverse intrauterine environment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypermethylation / mRNA downregulation</td>
<td>Vascular disorders / hypertension</td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td>17q23.3</td>
<td>1070</td>
<td>299</td>
<td>angiotensin I converting enzyme</td>
<td>Hypermethylated</td>
<td>Major depression</td>
<td>[186,187]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypomethylated</td>
<td>Increased systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypomethylated</td>
<td>Low birth weight</td>
<td></td>
</tr>
<tr>
<td>AGT</td>
<td>1q42.2</td>
<td>803</td>
<td>698</td>
<td>angiotensinogen</td>
<td>Upregulated mRNA expression</td>
<td>Hypertension</td>
<td>[188]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Histone acetylation</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>IL1B</td>
<td>2q14</td>
<td>964</td>
<td>668</td>
<td>interleukin 1 beta</td>
<td>Hypomethylated</td>
<td>Alzheimer's disease</td>
<td>[189]</td>
</tr>
<tr>
<td>IL6</td>
<td>7p21</td>
<td>1214</td>
<td>500</td>
<td>interleukin 6</td>
<td>Hypomethylated</td>
<td>Alzheimer's disease</td>
<td>[190,191]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypomethylated</td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypomethylated</td>
<td>Lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypomethylated</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>TNFA</td>
<td>6p21.33</td>
<td>1028</td>
<td>907</td>
<td>tumor necrosis factor</td>
<td>Hypermethylated</td>
<td>Alzheimer's disease</td>
<td>[189,192,]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypomethylated</td>
<td>Parkinson's disease</td>
<td>[193]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Downregulated mRNA</td>
<td>Oxidative stress in T cells</td>
<td></td>
</tr>
<tr>
<td>MTHFR</td>
<td>1p26.32</td>
<td>959</td>
<td>--</td>
<td>methylenetetrahydrofolate</td>
<td>Hypermethylated</td>
<td>Alzheimer's disease</td>
<td>[29,142,166,]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypermethylated</td>
<td>Non-Hodgking Lymphoma</td>
<td>[194,196]</td>
</tr>
</tbody>
</table>

Alzheimer's disease

Lupus erythematosus

Hypertension
Figure 28. Comparative analysis of APOE variant-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.

APOB-Related Cholesterol Response to Hypolipemic Treatment
Alzheimer’s Disease

Figure 29. APOB-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
Figure 30. APOB-related individual response (upper panel) and comparative analysis (lower panel) of APOB-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.

Figure 31. APOC3-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
Figure 32. **APOC3**-related individual response (upper panel) and comparative analysis (lower panel) of **APOC3**-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. 

Figure 33. **CETP**-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.
CETP-related individual response (upper panel) and comparative analysis (lower panel) of CETP-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.


LPL-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.

Several pathogenic genes (Table 3) and many other AD-related susceptibility genes with direct or indirect influence on the AD phenotype (i.e. genes associated with vascular risk factors and lipid metabolism) (Table 4) contain methylated CpG sites which exhibit alterations in DNA methylation [142,143]. Different modalities of histone aberrations are present in AD [27-29,142,144,145]. Alterations in epigenetically-regulated miRNAs may contribute to the abnormal expression of pathogenic genes in AD [146,147]. Several lncRNAs are dysregulated in AD (Sox2OT, 1810014B01Rik, BC200, BACE1-AS, NAT-Rad18, 17A, GDNFOS) [147]. Examples of miRNAs directly linked to AD pathogenesis include miR-34a (1p36.22), miR-34b/c (11q23.1), miR-107 (10q23.31), miR-124 (8p23.1/8p12.3/20q13.33), miR-125b (11q24.1/21q21.1), and miR-137 (1p21.3); and examples of epigenetically-regulated miRNAs with targets linked to AD pathogenesis are let-7b (22q13.1), miR-9 (1q22/5q14.3/15q26.1), miR-132/212 (17p13.3), miR-146a (5p34), miR-148a (7p15.2), miR-184 (15q25.1), and miR-200 (miR-200b/200a/429, 1p36.33; miR-200c/141, 12p13.31) [146]. AD-related SNPs interfere with miRNA gene regulation and affect AD susceptibility. The significant interactions include target SNPs present in seven genes related to AD prognosis with the miRNAs- miR-214, -23a & -23b, -486-3p, -30e*, -143, -128, -27a & -27b, -324-5p and -422a. The dysregulated miRNA network contributes to the aberrant gene expression in AD [148-150].

Epigenetic regulation is also responsible for the tissue-specific expression of genes involved in pharmacogenetic processes, and epigenetics plays a key role in the development of drug efficacy, safety and resistance. Epigenetic changes affect CYP expression, major transporter function, and nuclear receptor interactions [151-154]. Variable methylation patterns have been detected in genes encoding phase I-III enzymes (Table 5). Although this is a still poorly explored field, epigenetic regulation of genes encoding drug-metabolizing enzymes (CYP1A1, 1A2, 1B1, 1A6, 2A13, 2B6, 2C8, 2C9,
Figure 37. CYP haplotype-related blood total cholesterol levels. Source: R. Cacabelos. CIBE DataBase, 2016.

Figure 38. Blood cholesterol levels in subjects harboring the most frequent (>1%) CYP haplotypes in the Spanish population. Source: R. Cacabelos. CIBE DataBase, 2016.
2C18, 2C19, 2D6, 2E1, 2J2, 2F1, 2R1, 2S1, 2W1, 3A4, 3A5, 3A7, 3A43, UGT1, GSTP1), drug transporters (ABCB1/MDR1/P-gp, ABCC1/MRP1, ABCC1/MPR8, ABCG2/BCRP, SLC19A1, SLC22A8), and nuclear receptors (RARB2, ESR1, NR1I2, HNF4). Has been documented in pioneering studies of pharmacoepigenetics[27,151-154].

Epigenetic modifications are also associated with drug resistance[27,153,155]. The acquisition of drug resistance is tightly regulated by post-transcriptional regulators such as RNA-binding proteins (RBPs) and miRNAs, which change the stability and translation of mRNA-encoding factors involved in cell survival, proliferation, epithelial-mesenchymal transition, and drug metabolism[153]. In the complex cascade of pharmacoepigenetic events, the epigenetic factory may act as a promiscuous, redundant security system in which several miRNAs target genes encoding epigenetic regulators. For example, miR-29, -29c, -370, and -450 target DNMT3A, and miR-29, -148, and -29b target DNMT3B, inducing hypomethylation and expression of tumor suppressor genes; let-7a, miR-26a, -101, -138, and -124 target EZH2, decreasing histone methylation and increasing expression of tumor suppressor genes; miR-449 and -874 target HDAC1, inducing growth arrest by decreasing histone acetylation; miR-1 and -155 target HDAC4, promoting myogenesis and impairing transcriptional activity of B-cell lymphoma 6 (BCL6); miR-627 and -155 target JMJD1A, decreasing histone demethylation and hypoxic gene expression; miR-132 and -483-5p target MECP2, promoting demethylation and cell differentiation[156]. Furthermore, epigenetic drugs reverse epigenetic changes in gene expression and might open new avenues in AD therapeutics[29,30,145,157].

**Figure 39.** CYP2D6-related histogram of frequencies of cholesterol levels in the Spanish population.
Figure 40. CYP2C9-, CYP2C19-, and CYP3A4/5-related histogram of frequencies of cholesterol levels in the Spanish population.

Figure 41. CYP2D6-related blood total cholesterol levels in the general population and in patients with Alzheimer's disease.

Figure 42. CYP2D6-EM-, IM-, PM- and UM-related blood total cholesterol levels in the general population and in patients with Alzheimer’s disease.
CYP2D6-Related Therapeutic Response to Atorvastatin+LipoEsar

CYP2D6Related Cholesterol Changes

Figure 43. CYP2D6 genotype-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.

CYP2D6-Related Cholesterol Response to Hypolipemic Treatment

Alzheimer’s Disease

Figure 44. CYP2D6-EM-, IM-, PM- and UM-related response of cholesterol to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.
Figure 45. CYP2D6-EM-, IM-, PM- and UM-related individual response of cholesterol to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.

Figure 46. Comparative analysis of CYP2D6 geno-phenotype-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.
Figure 47. CYP2C9 genotype-related blood total cholesterol levels in the general population and in patients with Alzheimer’s disease.

Figure 48. CYP2C9-EM-, IM- and PM-related blood total cholesterol levels in the general population and in patients with Alzheimer’s disease.

Figure 49. CYP2C9-EM-, IM- and PM-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.


**Figure 50.** CYP2C9.- EM-, IM- and PM-related individual response (upper panel) and comparative analysis (lower panel) of CYP2C9 geno-phenotype-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.

**Figure 51.** CYP2C19 genotype-related blood total cholesterol levels in the general population and in patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
**CYP2C19-Related Blood Total Cholesterol Levels**

*General Population vs Alzheimer's disease*

Figure 52. CYP2C19-EM-, IM- and PM-related blood total cholesterol levels in the general population and in patients with Alzheimer’s disease.

**CYP2C19-Related Cholesterol Response to Hypolipemic Treatment**

*Alzheimer's Disease*

Figure 53. CYP2C19-EM-, IM-, PM- and UM-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.

Figure S54. CYP2C19-EM-, IM-, PM- and UM-related individual response of cholesterol to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease.
Figure 55. Comparative analysis of CYP2C19 geno-phenotype-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE database, 2016.

CYP3A4/5-Related Blood Total Cholesterol Levels
General Population vs Alzheimer's disease

Figure 56. CYP3A4/5 geno-phenotype-related blood total cholesterol levels in the general population and in patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE database, 2016.
CYP3A4/5-Related Cholesterol Response to Hypolipemic Treatment
Alzheimer’s Disease

Figure 57. CYP3A4/5 geno-phenotype-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.

Figure 58. CYP3A4/5 geno-phenotype-related individual response (upper panel) and comparative analysis (lower panel) of CYP3A4/5 geno-phenotype-related cholesterol response to a hypolipemic treatment in hypercholesterolemic patients with Alzheimer’s disease. Source: R. Cacabelos. CIBE DataBase, 2016.
Table 5. Methylation patterns in genes encoding Phase I and Phase II drug metabolizing enzymes and transporters

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Locus</th>
<th>Promoter length (bp)</th>
<th>Pathology</th>
<th>Methylation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I Drug Metabolism</td>
<td>ALDH1A2</td>
<td>15q21.3</td>
<td>982</td>
<td>prostate cancer</td>
<td>Hypermethylated</td>
<td>154,197,198</td>
</tr>
<tr>
<td></td>
<td>CYP1A1</td>
<td>15q24.1</td>
<td>1200</td>
<td>head and neck cancer, prostate cancer, fetal growth restriction (toxics), smoking-related</td>
<td>Hypermethylated</td>
<td>157,199,152,197,199,200</td>
</tr>
<tr>
<td></td>
<td>CYP1B1</td>
<td>2p22.2</td>
<td>1193</td>
<td>colorectal cancer, prostate cancer, hepatoma cell lines, breast cancer</td>
<td>Hypermethylated</td>
<td>29,151,154,199,202,205,206</td>
</tr>
<tr>
<td></td>
<td>CYP2A13</td>
<td>19q13.2</td>
<td>928</td>
<td>head and neck cancer</td>
<td>Hypermethylated</td>
<td>154,197,198</td>
</tr>
<tr>
<td></td>
<td>CYP2B1</td>
<td>12q14.1</td>
<td>917</td>
<td>breast cancer, choriocarcinoma, lymphoma and leukemia</td>
<td>Hypermethylated</td>
<td>20,154,199,205,212,213</td>
</tr>
<tr>
<td></td>
<td>CYP2A13</td>
<td>19q13.2</td>
<td>928</td>
<td>head and neck cancer</td>
<td>Hypermethylated</td>
<td>154,197,198</td>
</tr>
<tr>
<td></td>
<td>CYP2C19</td>
<td>10q24</td>
<td>1048</td>
<td>Drug resistance</td>
<td>Hypermethylated</td>
<td>29,154,199,205</td>
</tr>
<tr>
<td></td>
<td>CYP2E1</td>
<td>10q26.3</td>
<td>918</td>
<td>Parkinson's disease, toluene exposure</td>
<td>Hypermethylated</td>
<td>29,154,197,199,205,216</td>
</tr>
</tbody>
</table>
CONCLUSIONS

1. AD is a complex disorder with a tetravalent phenotype (neuropathological, neurobehavioral, age-related, and gender-related components).

2. Major determinants of therapeutic outcome in AD include age- and sex-related factors, pathogenic phenotype, concomitant disorders, treatment modality and polypharmacy, and pharmacogenetics.

3. Different categories of genes are potentially involved in the pharmacogenetic network responsible for drug efficacy and safety.

4. Pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes represent the major genetic determinants of response to treatment in AD.

5. The genes involved in the pharmacogenomic network are under the regulatory control of the epigenetic machinery (DNA methylation, histone modifications, miRNA regulation), this configuring the novel pharmacoepigenomic apparatus and constituting a novel source of potential therapeutic targets.

6. By-products of these genes are integrated in transcriptomic, proteomic and metabolic networks which are disrupted in AD and represent potential targets for therapeutic intervention.

7. In pharmacogenetic studies with conventional anti-dementia drugs and combination treatments, APOE-4 carriers are the worst responders and APOE-3 carriers are the best responders; 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 are the best responders to treatment; and CYP2D6 and ABCB1 variants may influence the therapeutic response to conventional treatments.

8. Over 80% of AD patients are daily consumers of different treatments for concomitant disorders. Only 20% of the Caucasian population are extensive metabolizers for the tetragenic haplotype integrated by CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 variants.

9. Tetragenic haplotypes integrating CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 variants yield 156 genotypes. The most frequent haplotype is H3 (1/1-1/1-1/1-3/3)(20.87%), representing full extensive metabolizers, and only 17 haplotypes exhibit a frequency higher than 1% in the Spanish population.

10. AD patients exhibit at least 111 pentagenic (APOE-APOB-APOC3-CETP-LPL) haplotypes associated with cholesterol levels. The highest levels of cholesterol are present in carriers of the haplotype H104 (44-CC-CC-AA-CC) and the lowest levels of cholesterol are detected in carriers of the haplotype H26 (23-TT-CG-AG-CC).

11. The response of cholesterol to specific hypolipemic treatments in hypercholesterolemic AD patients is highly efficient in over 70% of the cases and associates with CHO-related haplotypes and drug-specific CYP metabolizer geno-phenotypes.

12. Further considerations for a mature profile of AD pharmacogenomics include the following: (i) a better characterization of the roles played in drug efficacy and safety by genes involved in the pharmacogenomic network is necessary; (ii) since most genes are under the influence of the epigenetic machinery, pharmacoepigenomics is becoming an attractive field which deserves special attention; (iii) drug-drug interactions represent a problematic issue in over 80% of AD patients; (iv) since the neurodegenerative process underlying AD neuropathology starts 20-30 years before the onset of the disease, novel therapeutics should be addressed to prevent premature neuronal death; (v) specific biomarkers for AD are necessary in 3 different contexts: predictive markers before disease onset, early diagnosis in initial stages, and drug monitoring (in both preventive and/or therapeutic strategies); and (vi) physicians should be aware of the usefulness of pharmacogenomics to prescribe more accurately, avoid adverse reactions and optimize the limited therapeutic resources available for the treatment of dementia.


87 Huang F, Fu Y. (2010) A review of clinical pharmacokinetics and pharmacodynamics of galantamine, a reversible...


