SciForschen
Open HUB for Scientific Research

ISSN 2471-4968

International Journal of Molecular Genetics and Gene Therapy

Research Article | Volume: 1.1 | Open Access

Gene Interactions in the Pharmacogenomics of Alzheimer's Disease

Ramón Cacabelos[1,2,*], Dmitry Goldgaber[3], Allen D Roses[4,5], Alexander Vostrov[3], Hideyuki Matsuki[3], Clara Torrellas[1,2], Pablo Cacabelos[1,2], Dolores Corzo[1,2], Juan Carlos Carril[1,2], Lucía F Novoa[2] and Iván Carrera[1,2]

[1]*Chair of Genomic Medicine, Camilo José Cela University, Madrid, Spain*
[2]*EuroEspes Biomedical Research Center, Institute for Medical Science and Genomic Medicine, Corunna, Spain*
[3]*Department of Psychiatry and Behavioral Science, Stony Brook University, New York, NY, USA*
[4]*Zinfandel Pharmaceuticals, Inc., Durham, NC, USA*
[5]*Duke University Medical Center, Department of Neurology, Durham, NC, USA*

[*]**Corresponding author:** Dr. Ramón Cacabelos, Chair of Genomic Medicine, Camilo José Cela University, Castillo de Alarcón, 49, Urb. Villafranca del Castillo, Villanueva de la Cañada, 28692-Madrid, Spain, **E-mail:** rcacabelos@ucjc.edu

Received date: 2 July 2015; **Accepted date:** 15 August 2015; **Published date:** 22 August 2015.

Citation: Cacabelos R, Goldgaber D, Roses AD, Vostrov A, Matsuki H, et al. (2015) Gene Interactions in the Pharmacogenomics of Alzheimer's Disease. Int J Mol Genet Gene Ther 1(1): doi http://dx.doi.org/10.16966/2471-4968.102

Abstract

Multiple gene-gene interactions, in conjunction with epigenetic changes and drug metabolism features, are responsible for the efficacy and safety outcomes of most pharmacological treatments. The genes involved in the pharmacogenomic response to drugs in Alzheimer's Disease (AD) fall into five major categories: (i) genes associated with AD pathogenesis and neurodegeneration; (ii) genes associated with the mechanism of action of drugs; (iii) genes associated with drug metabolism (phase I and phase II reactions); (iv) genes associated with drug transporters; and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions. Changes in DNA methylation, histone modifications, chromatin remodeling, and ncRNA dysregulation can affect pathogenic and metabolic AD-related gene expression, influencing the response to drugs. Only 25% of the Caucasian population are normal metabolizers of drugs which are metabolized via CYP2D6-CYP2C9-CYP2C19 enzymes. *APOE*-4 carriers are the worst responders and *APOE*-3 carriers are the best responders to conventional treatments. *TOMM40* poly T-S/S carriers are the best responders, VL/VL and S/VL carriers are intermediate responders, and L/L carriers are the worst responders to treatment. Patients harboring a large (L) number of poly T repeats in intron 6 of the *TOMM40* gene (L/L or S/L genotypes) in haplotypes associated with *APOE*-4 are the worst responders to treatment. Patients with short (S) *TOMM40* poly T variants (S/S genotype), and to a lesser extent S/VL and VL/VL carriers, in haplotypes with *APOE*-3 are the best responders to treatment. In 100% of the cases, the L/L genotype is exclusively associated with the *APOE*-4/4 genotype, and this haplotype (4/4-L/L) is probably responsible for early onset of the disease, a faster cognitive decline, and a poor response to different treatments.

Keywords: Alzheimer's disease; APOE; TOMM40; Cytochrome P450 family; ABCB1; Anti-dementia drugs; Epigenetics; Pharmacogenomics

Introduction

Alzheimer's Disease (AD) is a polygenic/complex disorder in which hundreds of polymorphic variants distributed across the human genome are potentially involved, in conjunction with epigenetic phenomena, cerebrovascular disorders and environmental factors, leading to premature neuronal death and concomitant cognitive decline [1-4]. AD shares pathogenic features with conformational disorders in which the abnormal expression of genes generates conformational changes in key proteins (Amyloid beta (Aβ), hyperphosphorylation of MAPT-Tau), contributing to the formation of senile plaques and neurofibrillary tangles [1]. The pharmacological treatment of AD with conventional drugs (donepezil, rivastigmine, galantamine, memantine) is not cost-effective and many novel therapeutic strategies are under development worldwide [3]. Furthermore, AD patients may take 6-12 different drugs/day for the treatment of dementia-related symptoms, including memory decline (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 1,600 FDA-approved drugs for their ability to modulate Aβ activity; 559 drugs of the 1,600 had no effect on amyloid precursor protein (APP) processing or were toxic to neurons at the testing concentration, 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 over 30%; 241 drugs could potentially promote Aβ accumulation, including 26 drugs that could increase the level of Aβ by more than 30% [5]. 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 assessment of the prevalence of Potentially Inappropriate Medication (PIM) in French patients with mild-to-moderate AD showed that 46.8% of the patients had at least one PIM [6]. "Cerebral vasodilators" were 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. The principal causes of these iatrogenic effects are (i) the inappropriate combination of drugs, and (ii) the genomic background of the patient, responsible for his/her pharmacogenomic outcome.

Pharmacogenomics accounts for 30-90% variability in pharmacokinetics and pharmacodynamics. The pharmacogenetic outcome is the result of multiple gene interactions and their respective gene products potentially involved in the therapeutic effect and/or toxicity of drugs [3]. In addition, drug-drug interactions, concomitant pathologies, and epigenetic changes in genes linked to the pharmacogenetic network associated with efficacy and safety issues of a particular drug also affect the final pharmacogenetic outcome [2-4].

The genes involved in the pharmacogenomic response to drugs in AD fall into five major categories: (i) genes associated with AD pathogenesis and neurodegeneration (*APP*, *PSEN1*, *PSEN2*, *MAPT*, *PRNP*, *APOE* and others); (ii) genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers); (iii) genes associated with drug metabolism (phase I (*CYPs*) and phase II reactions (*UGTs*, *NATs*); (iv) genes associated with drug transporters (*ABCs*, *SLCs*); and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions (*APOs*, *ILs*, *MTHFR*, *ACE*, *AGT*, *NOS*, etc) [7,8].

Pathogenic Genes

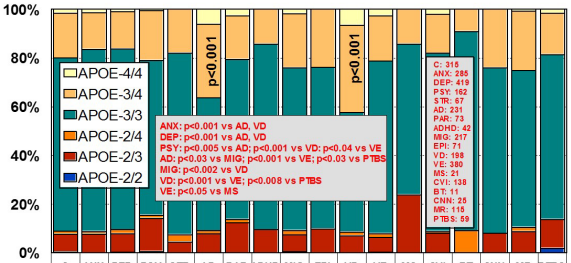
The genetic and epigenetic defects identified so far in AD include Mendelian mutations, susceptibility Single-Nucleotide Polymorphisms (SNPs), mitochondrial DNA (mtDNA) mutations, and epigenetic changes. Mendelian mutations affect genes directly linked to AD, including mutations in the *APP* gene (21q21) (*AD1*), mutations in the presenilin 1 (*PSEN1*) gene (14q24.3) (*AD3*), and mutations in the presenilin 2 (*PSEN2*) gene (1q31-q42) (*AD4*) [1, 9-13]. *PSEN1* and *PSEN2* are important determinants of γ-secretase activity responsible for the proteolytic cleavage of APP and NOTCH receptor proteins. Mendelian mutations are very rare in AD (1:1,000). 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. In the Alzgene database [9] there are over 600 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* (11q12.1), *CD33* (19q13.3), *MS4A4E* (11q12.2), and *CD2AP* (6p12). 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), 21 (4.76%; 2,289,15 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) [3]. 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*, *CRMP1*, *DMRT1*, *EPHA5*, *EPHA6*, *ERMP1*, *EVC*, *EVC2*, *FLJ35024* and *VLDLR*) have also been identified [3].

Multiple polymorphic risk variants can increase neuronal vulnerability to premature death. Among these susceptibility genes, the apolipoprotein E (*APOE*) gene (19q13.2) (*AD2*) is the most prevalent as a risk factor for AD, especially in those subjects harboring the *APOE-4* allele [14], whereas carriers of the *APOE-2* allele are prone to longevity [15] and might be protected against dementia [16-18].

APOE is the prototypical paradigm of a pleiotropic gene with multifaceted activities in physiological and pathological conditions [1,19]. ApoE is consistently associated with the amyloid plaque marker for AD. *APOE-4* may influence AD pathology by interacting with APP metabolism and Aβ accumulation, enhancing hyperphosphorylation of tau protein and Neurofibrillary Tangle (NFT) formation, reducing choline acetyltransferase activity, increasing oxidative processes, modifying inflammation-related neuroimmunotrophic activity and glial activation, altering lipid metabolism, lipid transport and membrane biosynthesis in sprouting and synaptic remodeling, and inducing neuronal apoptosis [1,19-22]. In addition, multiple studies over the past two decades have demonstrated that *APOE* variants may affect the therapeutic response to anti-dementia drugs [21-30].

The distribution of *APOE* genotypes in the Iberian peninsula is as follows: *APOE-2/2* 0.32%, *APOE-2/3* 7.3%, *APOE-2/4* 1.27%, *APOE-3/3* 71.11%, *APOE-3/4* 18.41%, and *APOE-4/4* 1.59% [7] (Figure 1). These frequencies are very similar in Europe and in other Western societies. There is a clear accumulation of *APOE-4* carriers among patients with AD (*APOE-3/4* 30.30%; *APOE-4/4* 6.06%) and VD (*APOE-3/4* 35.85%, *APOE-4/4* 6.57%) as compared to controls (Figure 1).

From studies designed to define *APOE*-related AD phenotypes, several conclusions can be drawn: (i) the age-at-onset is 5-10 years earlier in approximately 80% of AD cases harboring the *APOE-4/4* genotype; (ii) the serum levels of ApoE are lowest in *APOE-4/4*, intermediate in *APOE-3/3* and *APOE-3/4*, and highest in *APOE-2/3* and *APOE-2/4*; (iii) serum cholesterol levels are higher in *APOE-4/4* than in the other genotypes; (iv) HDL-cholesterol levels tend to be lower in *APOE-3* homozygotes than in *APOE-4* allele carriers; (v) LDL-cholesterol levels are systematically higher in *APOE-4/4* than in any other genotype; (vi) triglyceride levels are significantly lower in *APOE-4/4*; (vii) nitric oxide levels are slightly lower in *APOE-4/4*; (viii) serum and cerebrospinal fluid (CSF) Aβ levels tend to differ between *APOE-4/4* and the other most frequent genotypes (*APOE-3/3*, *APOE-3/4*); (ix) blood histamine levels are dramatically reduced in *APOE-4/4* as compared with the other genotypes; (x) brain atrophy and AD neuropathology is markedly increased in *APOE-4/4>APOE-3/4>APOE-3/3*; (xi) brain mapping activity shows a significant increase in slow wave activity in *APOE-4/4* from early stages of the disease; (xii) brain hemodynamics, as reflected by reduced brain blood flow velocity and increased pulsatility and resistance indices, is significantly worse in *APOE-4/4* (and in *APOE-4* carriers in general, as compared with *APOE-3* carriers); brain hypoperfusion and neocortical oxygenation is also more deficient in *APOE-4* carriers; (xiii) lymphocyte apoptosis is markedly enhanced in *APOE-4* carriers; (xiv) cognitive deterioration is faster in *APOE-4/4* patients than in carriers of any other *APOE* genotype; (xv) in approximately 3-8% of the AD cases, the presence of some dementia-related metabolic dysfunctions accumulates more in *APOE-4* carriers than in *APOE-3* carriers; (xvi) some behavioral disturbances, alterations in circadian rhythm patterns, and mood disorders are slightly more frequent



	C	ANX	DEP	PSY	STR	AD	PAR	ADHD	MIG	EPI	VD	VE	MS	CVI	BT	CNN	MR	PTBS
APOE-4/4	1,59	1,4	0,96	0,62	0	6,06	2,74	0	1,84	0	6,57	2,64	0	2,17	0	0	0,87	1,69
APOE-3/4	18,41	15,09	15,27	20,37	17,91	30,3	17,81	14,29	22,13	23,94	35,85	18,68	14,29	15,94	9,09	24	24,35	16,96
APOE-3/3	71,11	74,74	74,22	63,58	74,63	54,55	65,75	76,19	66,82	66,2	48,99	70,79	61,9	73,19	81,82	68	64,34	67,8
APOE-2/4	1,27	1,05	1,67	1,23	2,98	1,3	1,37	0	1,84	0	1,52	1,58	0	0,73	9,09	0	1,74	0
APOE-2/3	7,3	7,72	7,64	13,58	4,48	7,79	12,33	9,52	6,91	9,86	7,07	6,05	23,81	7,97	0	8	8,7	11,86
APOE-2/2	0,32	0	0,24	0,62	0	0	0	0	0,46	0	0	0,26	0	0	0	0	0	1,89

Figure 1: Distribution and frequency of *APOE* genotypes in CNS disorders.
(C: Controls, N=315; ANX: Anxiety, N=285; DEP: Depression, N=419; PSY: Psychosis, N=162; STR: Stroke, N=67; AD: Alzheimer's disease, N=231; PAR: Parkinson's disease, N=73; ADHD: Attention Deficit Hyperactivity Disorder, N=42; MIG: Migraine, N=217; EPI: Epilepsy, N=71; VD: Vascular dementia, N=198; VE: Vascular encephalopathy, N=380; MS: Multiple sclerosis, N=21; CVI: Cerebrovascular insufficiency, N=138; BT: Brain tumor, N=11; CNN: Cranial nerve neuropathy, N=25; MR: Mental retardation, N=115; PTBS: Post-traumatic brain syndrome, N=59). Significant differences (p<0.001) in the frequency of *APOE* genotypes with respect to controls were only found in patients with Alzheimer's disease and vascular dementia. Significant differences were also found between ANX *vs*. AD and VD (p<0.001), DEP *vs*. AD and VD (p<0.001), PSY *vs*. AD (p<0.005), PSY *vs*. VD (p<0.001), PSY *vs*.VE (p<0.04), AD *vs*. MIG (p<0.03), AD *vs*. VE (p<0.001), AD *vs*. PTBS (p<0.03), MIG *vs*. VD (p<0.002), VD *vs*. VE (p<0.001), VD *vs*. PTBS (p<0.008), and VE *vs*. MS (p<0.05)[205].

in *APOE-4* carriers; (xvii) aortic and systemic atherosclerosis is also more frequent in *APOE-4* carriers; (xviii) liver metabolism and transaminase activity also differ in *APOE-4/4* with respect to other genotypes; (xix) hypertension and other cardiovascular risk factors also accumulate in *APOE-4*; and (xx) *APOE-4/4* carriers are the poorest responders to conventional drugs. These 20 major phenotypic features clearly illustrate the biological disadvantage of *APOE-4* homozygotes and the potential consequences that these patients may experience when they receive pharmacological treatment for AD and/or concomitant pathologies [1,7,19-33].

In over 100 clinical trials for dementia, *APOE* has been used as the only gene of reference for the pharmacogenomics of AD [1,7,21,22,26-28,34-38]. 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 (tacrine, donepezil, galantamine, rivastigmine), neuroprotective compounds (nootropics), endogenous nucleotides (CDP-choline), immunotrophins (anapsos), neurotrophic factors (cerebrolysin), rosiglitazone or combination therapies [39-41]; 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 treatments. When *APOE* and *CYP2D6* genotypes are integrated in bigenic 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. In addition, a clear accumulation of *APOE-4/4* genotypes is observed among *CYP2D6* poor and ultra-rapid metabolizers [26].

Different *APP* and *PSEN1* and *PSEN2* mutations may also modify the therapeutic response to drugs acting on the amyloid cascade [42].

APOE-TOMM40 association

The *TOMM40* locus is located adjacent to and in linkage disequilibrium with *APOE* on 19q13.2. A poly T repeat in an intronic polymorphism (rs10524523) (intron 6) in the *TOMM40* gene, which encodes an outer mitochondrial membrane translocase involved in the transport of Aβ and other proteins into mitochondria, has been implicated in AD [43-56], and *APOE-TOMM40* genotypes have been shown to modify disease risk and age at onset of symptoms [45,48-51,57], although the latter assumption needs replication due to contradictory results [51,58-60]. Linnertz et al. [44] defined 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). Roses et al. [50-52] reported that longer lengths of rs10524523 are associated with a higher risk for Late Onset Alzheimer's Disease (LOAD); for *APOE*-3/4 patients who developed LOAD after 60 years of age, individuals with long poly T repeats (19-39 nucleotides) linked to *APOE*-3 develop LOAD on an average of 7 years earlier than individuals with shorter poly T repeats (11-16 nucleotides) linked to *APOE*-3 [45,49,50]. A fixed-effect meta-analysis approach showed that rs4420638 at the *TOMM40/APOE/APOC1* gene locus is associated with longevity [61,62]. Two independent associations with cognitive decline were found among European-Americans in the 19q13.32 region (rs769449, *APOE* intron; and rs115881343, *TOMM40* intron); rs769449 was also associated with cognitive decline among African-Americans, but rs115881343 was not [63]. The *APOE-TOMM40* genomic region is associated with cognitive aging [64] and with pathological cognitive decline [65].

Linnertz et al. [66] investigated the genomic region spanning the *TOMM40* and *APOE* genes, to determine whether intronic poly T (rs10524523) within this region affects expression of the *APOE* and *TOMM40* genes in the brain of patients with LOAD. The expression of both genes was significantly increased with disease. Mean expression of *APOE* and *TOMM40* mRNA levels was higher in VL homozygotes compared with S homozygotes in the temporal and occipital cortexes from normal and LOAD cases. The 523 VL poly T resulted in significantly higher expression than the S poly T. These results suggest that the 523 locus may contribute to LOAD susceptibility by modulating the expression of TOMM40 and/or APOE transcription [66]. Recent studies also suggest that the *TOMM40* gene rs10524523 ("523") variable length poly T repeat polymorphism is associated to a certain extent with similar AD phenotypes as those reported for *APOE*, such as brain white matter changes [67,68] or different biomarkers [69-72]. In addition, the *TOMM40* rs2075650 G allele may be a risk factor for the development of depression [73] and sporadic inclusion body myositis [74]. Different markers at the 19q13-q13.2 chromosomal region, including the rs2075650 and rs157590 (*TOMM40*), rs1064725 (*APOC1*), and rs429358 and rs7412 (*APOE*) SNPs also show association with primary progressive aphasia and the behavioral variant frontotemporal dementia [75].

The *TOMM40/APOE/APOC1* loci have been associated with c-reactive Protein (CRP), a heritable biomarker of systemic inflammation and a predictor of Cardiovascular Disease (CVD) [76]. Genome-wide Association Studies (GWAS) have identified LDL-cholesterol-associated loci near *HMGCR*, *ABO* and *TOMM40* [77], and also an association of TOMM40 with blood lipid levels [78,79] and body mass index [80]. Genetic variants in *TOMM40/APOE-C1-C2-C4* genes have also been found to be associated with multiple cardiovascular-related traits [81-83].

We have investigated the structure of the *APOE-TOMM40* region in Spanish patients with dementia, and the influence of polymorphic variants in this genomic segment on the therapeutic response to a multifactorial treatment adapted to the pathogenic profile of the patients. The main aims of the study were: (i) structural analysis of the *APOE-TOMM40* region (distribution and frequency of major genotypes, with special emphasis on *TOMM40* poly T variants) in the Spanish population with dementia; and (ii) *APOE*- and *TOMM40* poly T1/T2-related therapeutic response to a multifactorial therapy in AD [84].

The distribution and frequency of *APOE* genotypes wereas follows: *APOE*-2/3, 8.26%; *APOE*-2/4, 1.96%; *APOE*-3/3, 51.52%; *APOE*-3/4, 33.04%; and *APOE*-4/4, 5.22%. The distribution of 6 major *TOMM40* poly T variants was: 18.37% S/S, 7.83% S/L, 38.80% S/VL, 1.52% L/L, 7.17% L/VL, and 26.31% VL/VL. The *APOE*-2/3 genotype was found to be associated with S/S (27.63%), S/VL (51.32%), and L/VL (21.05%); *APOE*-2/4 was associated with S/L (16.67%), S/VL (38.89%), L/VL (11.11%), and VL/VL (33.33%); *APOE*-3/3 was associated with S/S (29.32%), S/L (0.42%), S/VL (47.26%), L/VL (0.21%), and VL/VL (22.79%); *APOE*-3/4 was associated with S/S (2.96%), S/L (21.38%), S/VL (28.29%), L/VL (15.46%), and VL/VL (31.91%); and *APOE*-4/4 was associated with S/L (4.17%), S/VL (2.17%), L/L (29.17%), L/VL (33.33%), and VL/VL (31.25%) (Figure 2). Likewise, the S/S genotype was associated with *APOE*-2/3 (27.63%), 3/3 (29.32%), and 3/4 (2.96%); S/L with *APOE*-2/4 (16.67%), 3/3 (0.42%), 3/4 (21.38%), and 4/4 (4.17%); S/VL with *APOE*-2/3 (51.32%), 2/4 (38.89%), 3/3 (47.26%), 3/4 (28.29%), and 4/4 (2.08%); L/L was exclusively associated with *APOE*-4/4 (100%); L/VL with *APOE*-2/4 (11.11%), 3/3 (0.21%), 3/4 (15.46%), and 4/4 (33.33%); and VL/VL with *APOE*-2/3 (21.05%), 2/4 (33.33%), 3/3 (22.79%), 3/4 (31.91%), and 4/4 (31.25%) (Figure 3). S/VL and VL/VL are the only *TOMM40* poly T genotypes which interact with all major *APOE* genotypes; in contrast, the *APOE*-4/4-*TOMM40*-L/L association is unique, representing approximately 30% of *APOE*-4/4 carriers.The allele distribution of *TOMM40* poly T repeats in the Spanish population reflects a high proportion of heterozygous S/VL (39%), followed by homozygous VL (27%) and homozygous S (19%). Homozygous L/L represents 1.52% of the

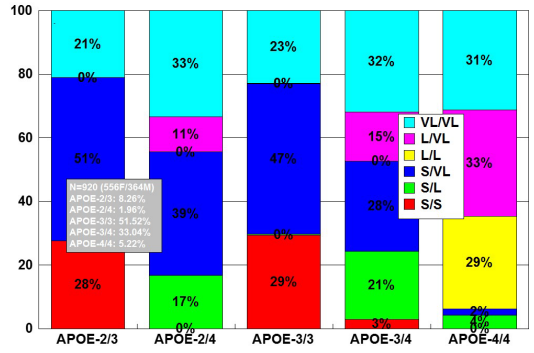


Figure 2: Distribution and frequency of *TOMM40*-Poly T variants associated with *APOE* genotypes in patients with Alzheimer's disease. Patients with Alzheimer's disease (N=920; 556 females, 364 males) were classified according to their *APOE* genotype (*APOE*-2/3, 8.26%; *APOE*-2/4, 1.96%; *APOE*-3/3, 51.52%; *APOE*-3/4, 33.04%; *APOE*-4/4, 5.22%) and the distribution and frequency of *TOMM40*-Poly T variants (VL/VL, L/VL, L/L, S/VL, S/L, S/S) were studied in each *APOE*-related group [84].

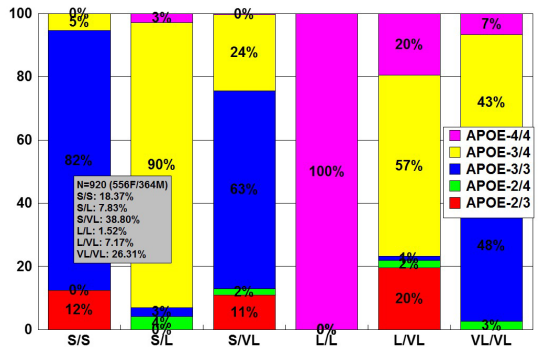


Figure 3: Distribution and frequency of *APOE* genotypes associated with *TOMM40*-Poly T variants in patients with Alzheimer's disease. Patients with Alzheimer's disease (N=920; 556 females, 364 males) were classified according to their *TOMM40*-Poly T variants (S/S, 18.37%; S/L, 7.83%; S/VL, 38.80%; L/L, 1.52%; L/VL, 7.17%; VL/VL, 26.31%) and the distribution and frequency of *APOE* genotypes were studied in each *TOMM40*-related group [84].

Spanish population, and both S/VL and L/VL genotypes conform a group of about 7-8% of the population. Potential dissimilarities with other White and Hispanic populations [44] might be due to the ancestral admixture of different cultures in the Iberian peninsula. The linkage pattern between *TOMM40*-'523' and *APOE* alleles in Whites and Hispanics reflects that the L is primarily linked to *APOE*-4, while the majority of the VL and S are linked to *APOE*-3. In African-Americans, Ghanaians and Japanese, there is an increased frequency of the '523'S-*APOE*-4 [44].

We found that patients harboring the *APOE*-4/4-L/L cluster developed dementia at an earlier age (<70 yrs) than their counterparts with other genotypes. In fact, L/L carriers were the youngest at age of onset, followed by S/S carriers. In addition, virtually 100% of L/L carriers were exclusively associated with *APOE*-4/4, representing the worst responders to our combination therapy. The *APOE*-3/3-VL/VL cluster, with an earlier age at onset (mean age ~70 yrs), was present in approximately a quarter of *APOE*-3/3 carriers (Figure 2) [84].

In terms of therapeutic response to a combination therapy, a transient profile of cognitive improvement for 6-12 months and maximum effect during the first 3 months of treatment was observed in *APOE*-2/3, *APOE*-2/4, *APOE*-3/3, *APOE*-3/4, and *APOE*-4/4 carriers, with significant effects in *APOE*-3/3 carriers for 12 months. The response rate (RR) (MMSE score after 12 months of treatment ≥ baseline MMSE score, prior to treatment) was 70% in *APOE*-3/3, 67% in *APOE*-2/3, 56% in *APOE*-2/4, 50% in *APOE*-4/4, and 45% in *APOE*-3/4 carriers, with significant differences between *APOE*-2/3 and *APOE*-3/4, *APOE*-2/3 and *APOE*-4/4, *APOE*-3/3 and *APOE*-3/4, and *APOE*-3/3 and *APOE*-4/4.The time-dependent profile of cognitive performance after treatment, according to the *TOMM40* poly T genotype, was similar to that observed in the total group or in the *APOE*-related study, with an apparent improvement during the first 3-9 months of treatment; however, significant effects were only observed in patients harboring the *TOMM40* poly T-S/S and S/VL genotypes. S/S carriers were the best responders (70%), followed by S/VL (61%), VL/VL (57%), and L/VL carriers (51%), and L/L (35%) and S/L carriers (45%) were the worst responders [84].

Bernardi et al. [57] studied the association between *TOMM40* rs10524523, age of onset, and memory performance in patients with the *PSEN1* M146L mutation in a large familial AD Calabrian kindred, and found that *APOE33/TOMM40*VL/VL patients showed a tendency for an earlier age at onset compared to those with *APOE*33/*TOMM40*VL/S and *APOE*33/*TOMM40*S/S. *TOMM40*VL/VL patients had better memory performance, when compared to *TOMM40*S/S but not to *TOMM40*VL/S patients. For Li et al. [60], *TOMM40* intron 6 poly T length may explain some of the variation in age at onset in *PSEN2* familial AD and may be associated with AD neuropathology in persons with *APOE*-3/3.

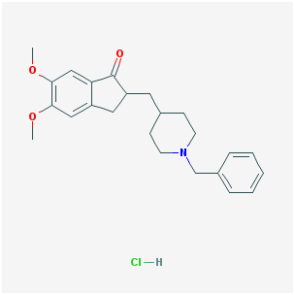
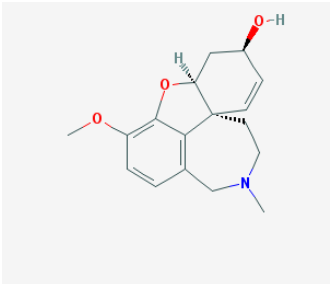
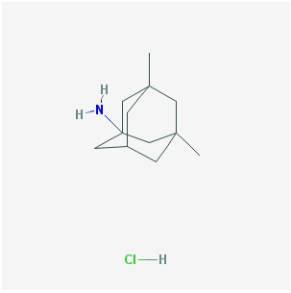
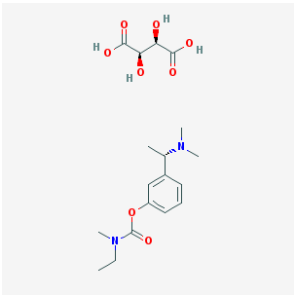
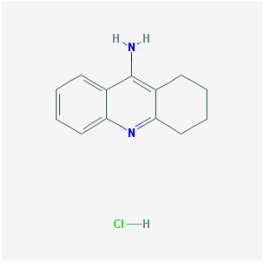
Several reports suggest that both APOE and TOMM40 influence memory performance in normal [64] and pathological conditions [65,85]. For some authors, both TOMM40 and APOE significantly influence age-related memory performance, but they appear to do so independently of each other [85]. Others suggest important *APOE*-independent associations between the *TOMM40* '523' polymorphism and specific cognitive domains of memory and executive control that are preferentially affected in early-stage AD, with S homozygotes performing better than the S/L-S/VL and the VL/L-L/VL-VL/VL genotype groups on measures associated with memory and executive function [65]. According to our data, the best mental performance (and response rate to treatment) is observed in patients harboring the *APOE*-3/3-S/S haplotype (R~70%), followed by those with the *APOE*-3/3-S/VL haplotype (R~60%). In general, S/S carriers are the best responders > S/VL (61%) > VL/VL (57%) > L/VL (51%) > S/L (45%) > L/L (35%). The presence of the L allele appears to contribute to a poor therapeutic outcome, and when the L/L genotype associates with the *APOE*-4/4 genotype, carriers of the *APOE*-4/4-S/S haplotype (30% of *APOE*-4/4 carriers) are converted into the worst responders) [84].

Genes involved in the mechanism of action of CNS drugs

Most genes associated with the mechanism of action of Central Nervous System (CNS) drugs encode receptors, enzymes, and neurotransmitters on which psychotropic drugs act as ligands (agonists, antagonists), enzyme modulators (substrates, inhibitors, inducers) or neurotransmitter regulators (releasers, reuptake inhibitors) [8]. In the case of conventional anti-dementia drugs, tacrine, donepezil, rivastigmine and galantamine are cholinesterase inhibitors; and memantine is a partial N-Methyl-D-Aspartat (NMDA) antagonist [3,86] (Table 1).

Genes involved in drug metabolism

Drug metabolism includes phase I reactions (i.e. oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e. acetylation, glucuronidation, sulphation, methylation). The principal enzymes with polymorphic variants involved in phase I reactions are the following: Cytochrome P450 monooxygenases (CYP3A4/5/7, CYP2E1, CYP2D6,

Drug	Properties	Pharmacogenetics
	**Name**: **Donepezil hydrochloride,** Aricept, 120011-70-3, Donepezil HCl, BNAG, E-2020, E2020 **IUPAC Name:** 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one;hydrochloride **Molecular Formula:**$C_{24}H_{30}ClNO_3$ **Molecular Weight:**415.9529 g/mol **Category:** Cholinesterase inhibitor **Mechanism:** Centrally active, reversible acetylcholinesterase inhibitor; increases the acetylcholine available for synaptic transmission in the CNS **Effect**:Nootropic agent, cholinesterase inhibitor, parasympathomimetic effect	**Pathogenic genes:** *APOE*, *CHAT* **Mechanistic genes:** *CHAT*, *ACHE*, *BCHE* **Drug metabolism-related genes:** **- Substrate:***CYP2D6* (major), *CYP3A4* (major), *UGTs*, *ACHE* **- Inhibitor:** *ACHE*, *BCHE* **Transporter genes:** *ABCB1*
	**Name**: **Galantamine hydrobromide**, Galanthamine hydrobromide**,** 1953-04-4, Nivalin, Razadyne, UNII-MJ4PTD2VVW, Nivaline **IUPAC Name:** (1S,12S,14R)-9-methoxy-4-methyl-11-oxa-4-azatetracyclo [8.6.1.0^{1,12}.0^{6,17}]heptadeca-6,8,10(17),15-tetraen-14-ol **Molecular Formula:**$C_{17}H_{22}BrNO_3$ **Molecular Weight:** 368.26548 g/mol **Category**: Cholinesterase inhibitor **Mechanism**: Reversible and competitive acetylcholinesterase inhibition leading to an increased concentration of acetylcholine at cholinergic synapses; modulates nicotinic acetylcholine receptor; may increase glutamate and serotonin levels **Effect:** Nootropic agent, cholinesterase inhibitor, parasympathomimetic effect	**Pathogenic genes**: *APOE, APP* **Mechanisticgenes**: *ACHE, BCHE, CHRNA4, CHRNA7, CHRNB2* **Drug metabolism-related genes:** - **Substrate**: *CYP2D6* (major), *CYP3A4* (major), *UGT1A1* - **Inhibitor**: *ACHE, BCHE*
	**Name: Memantine Hydrochloride**, 41100-52-1, Namenda, Memantine HCL, Axura, 3,5-Dimethyl-1-adamantanamine hydrochloride, 3,5-dimethyladamantan-1-amine hydrochloride **IUPAC Name:** 3,5-dimethyladamantan-1-amine;hydrochloride **Molecular Formula:** $C_{12}H_{22}ClN$ **Molecular Weight:** 215.76278 g/mol **Category:** N-Methyl-D-Aspartate receptor antagonist **Mechanism:** Binds preferentially to NMDA receptor-operated cation channels; may act by blocking actions of glutamate, mediated in part by NMDA receptors **Effect:** Dopamine agent, antiparkinson agent, excitatory amino acid antagonist, antidyskinetic	**Pathogenic genes:** *APOE, MAPT, PSEN1* **Mechanistic genes**: *CHRFAM7A, DLGAP1, FOS, GRIN2A, GRIN2B, GRIN3A, HOMER1, HTR3A* **Drug metabolism-related genes:** **-Inhibitor**:*CYP1A2* (weak), *CYP2A6* (weak), *CYP2B6* (strong), *CYP2C9* (weak), *CYP2C19* (weak), *CYP2D6* (strong), *CYP2E1* (weak), *CYP3A4* (weak), *NR1I2* **Transporter genes:** *NR1I2* **Pleiotropic genes:** *APOE, MAPT, MT-TK, PSEN1*
	**Name**: **Rivastigminetartrate**, 129101-54-8, SDZ-ENA 713, Rivastigmine hydrogentartrate, Rivastigmine Hydrogen Tartrate, ENA 713, ENA-713 **IUPAC Name:** (2R,3R)-2,3-dihydroxybutanedioic acid;[3-[(1S)-1-(dimethylamino)ethyl]phenyl] N-ethyl-N-methylcarbamate **Molecular Formula:** $C_{18}H_{28}N_2O_8$ **Molecular Weight:** 400.42352 g/mol **Category:** Cholinesterase inhibitor **Mechanism:** Increases acetylcholine in CNS through reversible inhibition of its hydrolysis by cholinesterase **Effect:** Neuroprotective agent, cholinesterase inhibitor, cholinergic agent	**Pathogenic genes:** *APOE, APP, CHAT* **Mechanistic genes:** *ACHE, BCHE, CHAT, CHRNA4, CHRNB2* **Drug metabolism-related genes:** **-Inhibitor:** *ACHE, BCHE* **Pleiotropic genes:** *APOE, MAPT*
	**Name:Tacrine Hydrochloride,** Tacrine HCl, 1684-40-8, Hydroaminacrine, tacrine.HCl, 9-AMINO-1,2,3,4-TETRAHYDROACRIDINE HYDROCHLORIDE, Tenakrin **IUPAC Name:** 1,2,3,4-tetrahydroacridin-9-amine;hydrochloride **Molecular Formula:** $C_{13}H_{15}ClN_2$ **Molecular Weight:** 234.7246 g/mol **Category:** Cholinesterase inhibitor **Mechanism:** Elevates acetylcholine in cerebral cortex by slowing degradation of acetylcholine **Effect:** Nootropic agent, cholinesterase inhibitor, Parasympathomimetic effect	**Pathogenic genes:** *APOE* **Mechanistic genes:** *ACHE, BCHE, CHRNA4, CHRNB2* **Drug metabolism-related genes:** **-Substrate***: CYP1A2 (major), CYP2D6 (minor), CYP3A4 (major)* **-Inhibitor***: ACHE, BCHE, CYP1A2 (weak)* **Transporter genes:** *SCN1A* **Pleiotropic genes***: APOE, CES1, GSTM1, GSTT1, LEPR, MTHFR*

ADH1A: Alcohol dehydrogenase 1A (class I), alpha polypeptide; **AADAC**: Arylacetamide deacetylase; **AANAT**: aralkylamine N-acetyltransferase; **ACSL1**: Acyl-CoA synthetase long-chain family member 1; **ACSL3**: Acyl-CoA synthetase long-chain family member 3; **ACSL4**: Acyl-CoA synthetase long-chain family member 4; **ACSM1**: Acyl-CoA synthetase medium-chain family member 1; **ACSM2B**: Acyl-CoA synthetase medium-chain family member 2B; **ACSM3**: Acyl-CoA synthetase medium-chain family, member 3; **ADH1B**: Alcohol dehydrogenase 1B (class I), beta polypeptide; **ADH1C**: Alcohol dehydrogenase 1C (class I), gamma polypeptide; **ADH4**: Alcohol dehydrogenase 4 (class II), pi polypeptide; **ADH5**: Alcohol dehydrogenase 5 (class III), chi polypeptide; **ADH6**: Alcohol dehydrogenase 6 (class V); **ADH7**: Alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide; **ADHFE1**: Alcohol dehydrogenase, iron containing, 1; **AGXT**: Alanine-glyoxylate aminotransferase; **AKR1A1**: Aldo-keto reductase family 1, member A1 (aldehyde reductase); **AKR1B1**: Aldo-keto reductase family 1, member B1 (aldose reductase); **AKR1C1**: Aldo-keto reductase family 1, member C1; **AKR1D1**: Aldo-keto reductase family 1, member D1; **ALDH1A1**: Aldehyde dehydrogenase 1 family, member A1; **ALDH1A2**: Aldehyde dehydrogenase family 1, subfamily A2; **ALDH1A3**: Aldehyde dehydrogenase family 1, subfamily A3; **ALDH1B1**: Aldehyde dehydrogenase 1 family, member

B1; **ALDH2**: Aldehyde dehydrogenase 2 family (mitochondrial); **ALDH3A1**: Aldehyde dehydrogenase 3 family, member A1; **ALDH3A2**: Aldehyde dehydrogenase 3 family, member A2; **ALDH3B1**: Aldehyde dehydrogenase 3 family, member B1; **ALDH3B2**: Aldehyde dehydrogenase 3 family, member B2; **ALDH4A1**: Aldehyde dehydrogenase 4 family, member A1; **ALDH5A1**: Aldehyde dehydrogenase 5 family, member A1; **ALDH6A1**: Aldehyde dehydrogenase 6 family, member A1; **ALDH7A1**: Aldehyde dehydrogenase 7 family, member A1; **ALDH8A1**: Aldehyde dehydrogenase 8 family, member A1; **ALDH9A1**: Aldehyde dehydrogenase 9 family, member A1; **AOX1**: Aldehyde oxidase 1; **AS3MT**: Arsenic (+3 oxidation state) methyltransferase; **ASMT**: Acetylserotonin O-methyltransferase; **BAAT**: Bile acid CoA: amino acid N-acyltransferase (glycine N-choloyltransferase); **CBR1**: Carbonyl reductase 1; **CBR3**: Carbonyl reductase 3; **CBR4**: Carbonyl reductase 4; **CCBL1**: Cysteine conjugate-beta lyase, cytoplasmic; **CDA**: Cytidine deaminase; **CEL**: Carboxyl ester lipase; **CES1**: Carboxylesterase 1; **CES1P1**: Carboxylesterase 1 pseudogene 1; **CES2**: Carboxylesterase 2; **CES3**: Carboxylesterase 3; **CES5A**: Carboxylesterase 5A; **CHST1**: Carbohydrate (keratan sulfate Gal-6) sulfotransferase 1; **CHST2**: Carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2; **CHST3**: Carbohydrate (chondroitin 6) sulfotransferase 3; **CHST4**: Carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4; **CHST5**: Carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5; **CHST6**: Carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6; **CHST7**: Carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7; **CHST8**: Carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8; **CHST9**: Carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9; **CHST10**: Carbohydrate sulfotransferase 10; **CHST11**: Carbohydrate (chondroitin 4) sulfotransferase 11; **CHST12**: Carbohydrate (chondroitin 4) sulfotransferase 12; **CHST13**: Carbohydrate (chondroitin 4) sulfotransferase 13; **COMT**: Catechol-O-methyltransferase; **CYB5R3**: Cytochrome b5 reductase 3; **CYP1A1**: Cytochrome P450, family 1, subfamily A, polypeptide 1; **CYP1A2**: Cytochrome P450, family 1, subfamily A, polypeptide 2; **CYP1B1**: Cytochrome P450, family 1, subfamily B, polypeptide 1; **CYP2A6**: Cytochrome P450, family 2, subfamily A, polypeptide 6; **CYP2A7**: Cytochrome P450, family 2, subfamily A, polypeptide 7; **CYP2A13**: Cytochrome P450, family 2, subfamily A, polypeptide 13; **CYP2B6**: Cytochrome P450, family 2, subfamily B, polypeptide 6; **CYP2C8**: Cytochrome P450, family 2, subfamily C, polypeptide 8; **CYP2C9**: Cytochrome P450, family 2, subfamily C, polypeptide 9; **CYP2C18**: Cytochrome P450, family 2, subfamily C, polypeptide 18; **CYP2C19**: Cytochrome P450, family 2, subfamily C, polypeptide 19; **CYP2D6**: Cytochrome P450, family 2, subfamily D, polypeptide 6; **CYP2D7P1**: Cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1; **CYP2E1**: Cytochrome P450, family 2, subfamily E, polypeptide 1; **CYP2F1**: Cytochrome P450, family 2, subfamily F, polypeptide 1; **CYP2J2**: Cytochrome P450, family 2, subfamily J, polypeptide 2; **CYP2R1**: Cytochrome P450, family 2, subfamily R, polypeptide 1; **CYP2S1**: Cytochrome P450, family 2, subfamily S, polypeptide 1; **CYP2W1**: Cytochrome P450, family 2, subfamily W, polypeptide 1; **CYP3A4**: Cytochrome P450, family 3, subfamily A, polypeptide 4; **CYP3A5**: Cytochrome P450, family 3, subfamily A, polypeptide 5; **CYP3A7**: Cytochrome P450, family 3, subfamily A, polypeptide 7; **CYP3A43**: Cytochrome P450, family 3, subfamily A, polypeptide 43; **CYP4A11**: Cytochrome P450, family 4, subfamily A, polypeptide 11; **CYP4A22**: Cytochrome P450, family 4, subfamily A, polypeptide 22; **CYP4B1**: Cytochrome P450, family 4, subfamily B, polypeptide 1; **CYP4F2**: Cytochrome P450, family 4, subfamily F, polypeptide 2; **CYP4F3**: Cytochrome P450, family 4, subfamily F, polypeptide 3; **CYP4F8**: Cytochrome P450, family 4, subfamily F, polypeptide 8; **CYP4F11**: Cytochrome P450, family 4, subfamily F, polypeptide 11; **CYP4F12**: Cytochrome P450, family 4, subfamily F, polypeptide 12; **CYP4Z1**: Cytochrome P450, family 4, subfamily Z, polypeptide 1; **CYP7A1**: Cytochrome P450, family 7, subfamily A, polypeptide 1; **CYP7B1**: Cytochrome P450, family 7, subfamily B, polypeptide 1; **CYP8B1**: Cytochrome P450, family 8, subfamily B, polypeptide 1; **CYP11A1**: Cytochrome P450, family 11, subfamily A, polypeptide 1; **CYP11B1**: Cytochrome P450, family 11, subfamily B, polypeptide 1: **CYP11B2**: Cytochrome P450, family 11, subfamily B, polypeptide 2; **CYP17A1**: Cytochrome P450, family 17, subfamily A, polypeptide 1; **CYP19A1**: Cytochrome P450, family 19, subfamily A, polypeptide 1; **CYP20A1**: Cytochrome P450, family 20, subfamily A, polypeptide 1; **CYP21A2**: Cytochrome P450, family 21, subfamily A, polypeptide 2; **CYP24A1**: Cytochrome P450, family 24, subfamily A, polypeptide 1; **CYP26A1**: Cytochrome P450, family 26, subfamily A, polypeptide 1; **CYP26B1**: Cytochrome P450, family 26, subfamily B, polypeptide 1; **CYP26C1**: Cytochrome P450, family 26, subfamily C, polypeptide 1; **CYP27A1**: Cytochrome P450, family 27, subfamily A, polypeptide 1; **CYP27B1**: Cytochrome P450, family 27, subfamily B, polypeptide 1; **CYP39A1**: Cytochrome P450, family 39, subfamily A, polypeptide 1; **CYP46A1**: Cytochrome P450, family 46, subfamily A, polypeptide 1; **CYP51A1**: Cytochrome P450, family 51, subfamily A, polypeptide 1; **DDOST**: Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit (non-catalytic); **DHRS1**: Dehydrogenase/reductase (SDR family) member 1; **DHRS2**: Dehydrogenase/reductase (SDR family) member 2; **DHRS3**: Dehydrogenase/reductase (SDR family) member 3; **DHRS4**: Dehydrogenase/reductase (SDR family) member 4; **DHRS7**: Dehydrogenase/reductase (SDR family) member 7; **DHRS9**: Dehydrogenase/reductase (SDR family) member 9; **DHRS12**: Dehydrogenase/reductase (SDR family) member 12; **DHRS13**: Dehydrogenase/reductase (SDR family) member 13; **DHRSX**: Dehydrogenase/reductase (SDR family) X-linked; **DLGAP1**: discs, large (Drosophila) homolog-associated protein 1; **DPEP1**: Dipeptidase 1 (renal); **DPYD**: Dihydropyrimidine dehydrogenase; **EPHX1**: Epoxide hydrolase 1, microsomal (xenobiotic); **EPHX2**: Epoxide hydrolase 2, microsomal (xenobiotic); **ESD**: Esterase D; **FMO1**: Flavin containing monooxygenase 1; **FMO2**: Flavin containing monooxygenase 2; **FMO3**: Flavin containing monooxygenase 3; **FMO4**: Flavin containing monooxygenase 4; **FMO5**: Flavin containing monooxygenase 5; **FMO6P**: Flavin containing monooxygenase 6 pseudogene; **FOS:** FBJ murine osteosarcoma viral oncogene homolog; **GAL3ST1**: Galactose-3-O-sulfotransferase 1; **GAMT**: Guanidinoacetate N-methyltransferase; **GLRX**: Glutaredoxin (thioltransferase); **GLYAT**: Glycine-N-acyltransferase; **GNMT**: Glycine N-methyltransferase; **GPX1**: Glutathione peroxidase 1; **GPX2**: Glutathione peroxidase 2 (gastrointestinal); **GPX3**: Glutathione peroxidase 3 (plasma); **GPX4**: Glutathione peroxidase 4; **GPX5**: Glutathione peroxidase 5; **GPX6**: Glutathione peroxidase 6 (olfactory); **GPX7**: Glutathione peroxidase 7; **GSR**: Glutathione reductase; **GSTA1**: Glutathione S-transferase alpha 1; **GSTA2**: Glutathione S-transferase alpha 2; **GSTA3**: Glutathione S-transferase alpha 3; **GSTA4**: Glutathione S-transferase alpha 4; **GSTA5**: Glutathione S-transferase alpha 5; **GSTCD**: Glutathione S-transferase, C-terminal domain containing; **GSTK1**: Glutathione S-transferase kappa 1; **GSTM1**: Glutathione S-transferase mu 1; **GSTM2**: Glutathione S-transferase mu 2 (muscle); **GSTM3**: Glutathione S-transferase mu 3 (brain); **GSTM4**: Glutathione S-transferase mu 4; **GSTM5**: Glutathione S-transferase mu 5; **GSTO1**: Glutathione S-transferase omega 1; **GSTO2**: Glutathione S-transferase omega 2; **GSTP1**: Glutathione S-transferase pi 1; **GSTT1**: Glutathione S-transferase theta 1; **GSTT2**: Glutathione S-transferase theta 2; **GSTZ1**: Glutathione S-transferase zeta 1; **GZMA**: Granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3; **GZMB**: Granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1); **HNMT**: Histamine N-methyltransferase; **HOMER1:** homer homolog 1 (Drosophila); **HSD11B1**: Hydroxysteroid (11-beta) dehydrogenase 1; **HSD17B10**: Hydroxysteroid (17-beta) dehydrogenase 10; **HSD17B11**: Hydroxysteroid (17-beta) dehydrogenase 11; **HSD17B14**: Hydroxysteroid (17-beta) dehydrogenase 14; **INMT**: Indolethylamine N-methyltransferase; **MAOA**: Monoamine oxidase A; **MAOB**: monoamine oxidase B; **METAP1**: Methionyl aminopeptidase 1; **MGST1**: Microsomal glutathione S-transferase 1; **MGST2**: Microsomal glutathione S-transferase 1; **MGST3**: Microsomal glutathione S-transferase 3; **NAA20**: N(alpha)-acetyltransferase 20, NatB catalytic subunit; **NAT1**: N-acetyltransferase 1 (arylamine N-acetyltransferase); **NAT2**: N-acetyltransferase 2 (arylamine N-acetyltransferase); **NNMT**: Nicotinamide N-methyltransferase; **NQO1**: NAD(P)H dehydrogenase, quinone 1; **NQO2**: NAD(P)H dehydrogenase, quinone 2; **NR1I2**:nuclear receptor subfamily 1, group I, member 2; **PNMT**: Phenylethanolamine N-methyltransferase; **PON1**: Paraoxonase 1; **PON2**: Paraoxonase 2; **PON3**: Paraoxonase 3; **POR**: P450 (cytochrome) oxidoreductase; **PTGES**: Prostaglandin E synthase; **PTGS1**: Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase); **PTGS2**: Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase); **SAT1**: Spermidine/spermine N1-acetyltransferase 1; **SMOX**: Spermine oxidase; **SOD1**: Superoxide dismutase 1, soluble; **SOD2**: Superoxide dismutase 2, mitochondrial; **SULT1A1**: Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1; **SULT1A2**: Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2; **SULT1A3**: Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3; **SULT1B1**: Sulfotransferase family, cytosolic, 1B, member 1; **SULT1C1**: Sulfotransferase family, cytosolic, 1C, member 1; **SULT1C2**: Sulfotransferase family, cytosolic, 1C, member 2; **SULT1C3**: Sulfotransferase family, cytosolic, 1C, member 3; **SULT1C4**: Sulfotransferase family, cytosolic, 1C, member 4; **SULT1E1**: Sulfotransferase family 1E, estrogen-preferring, member 1; **SULT2A1**: Sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1; **SULT2B1**: Sulfotransferase family, cytosolic, 2B, member 1; **SULT4A1**: Sulfotransferase family 4A, member 1; **SULT6B1**: sulfotransferase family, cytosolic, 6B, member 1; **TBXAS1**: Thromboxane A synthase 1 (platelet); **TPMT**: Thiopurine S-methyltransferase; **TST**: Thiopurine S-methyltransferase; **UCHL1**: Ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase); **UCHL3**: Ubiquitin carboxyl-terminal esterase L3 (ubiquitin thiolesterase); **UGT1A1**: UDP glucuronosyltransferase 1 family, polypeptide A1; **UGT1A3**: UDP glucuronosyltransferase 1 family, polypeptide A3; **UGT1A4**: UDP glucuronosyltransferase 1 family, polypeptide A4; **UGT1A5**: UDP glucuronosyltransferase 1 family, polypeptide A5; **UGT1A6**: UDP glucuronosyltransferase 1 family, polypeptide A6; **UGT1A7**: UDP glucuronosyltransferase 1 family, polypeptide A7; **UGT1A8**: UDP glucuronosyltransferase 1 family, polypeptide A8; **UGT1A9**: UDP glucuronosyltransferase 1 family, polypeptide A9; **UGT1A10**: UDP glucuronosyltransferase 1 family, polypeptide A10; **UGT2A1**: UDP glucuronosyltransferase 2 family, polypeptide A1, complex locus; **UGT2A3**: UDP glucuronosyltransferase 2 family, polypeptide A3; **UGT2B10**: UDP glucuronosyltransferase 2 family, polypeptide B10; **UGT2B11**: UDP glucuronosyltransferase 2 family, polypeptide B11; **UGT2B15**: UDP glucuronosyltransferase 2 family, polypeptide B15; **UGT2B17**: UDP glucuronosyltransferase 2 family, polypeptide B17; **UGT2B28**: UDP glucuronosyltransferase 2 family, polypeptide B28; **UGT2B4**: UDP glucuronosyltransferase 2 family, polypeptide B4; **UGT2B7**: UDP glucuronosyltransferase 2 family, polypeptide B7; **UGT3A1**: UDP glycosyltransferase 3 family, polypeptide A1; **UGT8**: UDP glycosyltransferase 8; **XDH**: Xanthine dehydrogenase.

Source [Ref.86]

Table 1: Pharmacogenomics of conventional anti-dementia drugs

CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2), epoxide hydrolase, esterases, NQO1 (NADPH-quinone oxidoreductase), DPD (dihydropyrimidine dehydrogenase), ADH (alcohol dehydrogenase), and ALDH (aldehyde dehydrogenase); and major enzymes involved in phase II reactions include UGTs (uridine 5'-triphosphate glucuronosyl transferases), TPMT (thiopurine methyltransferase), COMT (catechol-O-methyltransferase), HMT (histamine methyl-transferase), STs (sulfotransferases), GST-A (glutathione S-transferase A), GST-P, GST-T, GST-M, NAT1 (N-acetyl transferase 1), NAT2, and others. Among these enzymes, CYP2D6, CYP2C9, CYP2C19, and CYP3A4/5 are the most relevant in the pharmacogenetics of CNS drugs [8,27]. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4 [8,27]. Most CYP enzymes exhibit ontogenic-, age-, sex-, circadian-, and ethnic-related differences [8,86].

In dementia, as in any other CNS disorders, *CYP* genomics is a highly important issue, since in practice over 90% of patients with dementia are daily consumers of psychotropics. Furthermore, some acetylcholinesterase inhibitors (the most prescribed anti-dementia drugs worldwide) are metabolized via CYP enzymes (Table 1). Most CYP enzymes display highly significant ethnic differences, indicating that the enzymatic capacity of these proteins varies depending upon the polymorphic variants present in their coding *CYP* genes. The practical consequence of this genetic variation is that the same drug can be differentially metabolized according to the genetic profile of each subject, and that knowing the pharmacogenomic profile of an individual, his/her pharmacodynamic response is potentially predictable. This is the cornerstone of pharmacogenetics. In this regard, the *CYP2D6*, *CYP2C19*, *CYP2C9* and *CYP3A4/5* genes and their respective protein products deserve special consideration.

CYP2D6

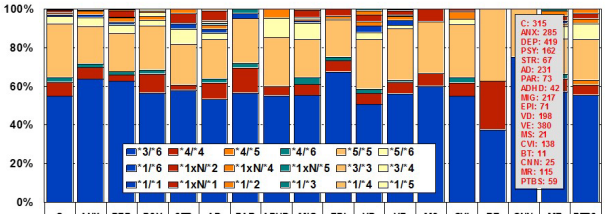
CYP2D6 is a 4.38 kb gene with 9 exons mapped on 22q13.2. Four RNA transcripts of 1190-1684 bp are expressed in the brain, liver, spleen and reproductive system where 4 major proteins of 48-55 kDa (439-494aa) are identified. This protein is a transport enzyme of the cytochrome P450 subfamily IID or multigenic cytochrome P450 superfamily of mixed-function monooxygenases. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and is known to metabolize as many as 25% of commonly prescribed drugs and over 60% of current psychotropics. Its substrates include debrisoquine, an adrenergic-blocking drug; sparteine and propafenone, both anti-arrhythmic drugs; and amitryptiline, an anti-depressant. The gene is highly polymorphic in the population. There are 141 *CYP2D6* allelic variants of which -100C>T, -1023C>T, -1659G>A, -1707delT, -1846G>A, -2549delA, -2613-2615delAGA, -2850C>T, -2988G>A, and -3183G>A represent the 10 most important variants [86-88]. Different alleles result in the extensive, intermediate, poor, and ultra-rapid metabolizer phenotypes, characterized by normal, intermediate, decreased, and multiplied ability to metabolize the enzyme's substrates, respectively. The hepatic cytochrome P450 system is responsible for the first phase in the metabolism and elimination of numerous endogenous and exogenous molecules and ingested chemicals. P450 enzymes convert these substances into electrophilic intermediates which are then conjugated by phase II enzymes (e.g. UDP glucuronosyltransferases, N-acetyltransferases) to hydrophilic derivatives that can be excreted. According to the database of the World Guide for Drug Use and Pharmacogenomics variants [86], 982 drugs are *CYP2D6*-related: 371 drugs are substrates, over 300 drugs are inhibitors, and 18 drugs are CYP2D6 inducers.

In healthy subjects, Extensive Metabolizers (EMs) account for 55.71% of the population, whereas Intermediate Metabolizers (IMs) account for 34.7%, Poor Metabolizers (PMs) 2.28%, and Ultra-rapid Metabolizers (UMs) 7.31%. Remarkable interethnic differences exist in the frequency of the PM and UM phenotypes among different societies all over the world [89-91]. On average, approximately 6.28% of the world population belongs to the PM category. Europeans (7.86%), Polynesians (7.27%), and Africans (6.73%) exhibit the highest rate of PMs, whereas Orientals (0.94%) show the lowest rate [89]. The frequency of PMs among Middle Eastern populations, Asians, and Americans is in the range of 2-3%. *CYP2D6* gene duplications are relatively infrequent among Northern Europeans, but in East Africa the frequency of alleles with duplication of *CYP2D6* is as high as 29% [92]. In Europe, there is a North-South gradient in the frequency of PMs (6-12% of PMs in Southern European countries, and 2-3% PMs in Northern latitudes) [8].

In AD, EMs, IMs, PMs, and UMs are 56.38%, 27.66%, 7.45%, and 8.51%, respectively, and in VD, 52.81%, 34.83%, 6.74%, and 5.62%, respectively (Figure 4 and Figure 5). 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 cholinesterase inhibitors, 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 [1,7,25-28,38,93].

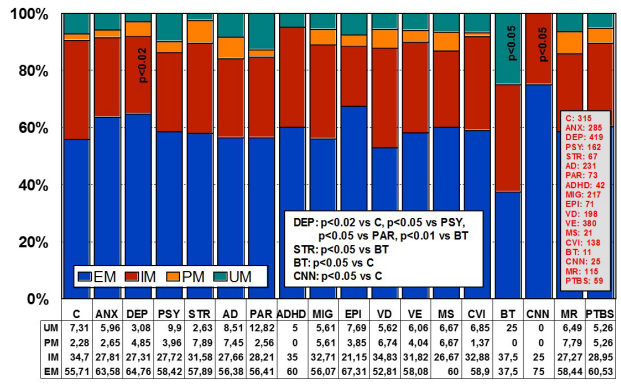
APOE-CYP2D6 association

In a population of 582 Spanish patients with AD (*APOE*-2/3 0.34%; *APOE*-2/3 9.28%; *APOE*-2/4 1.20%; *APOE*-3/359.45%; *APOE*-3/4 26.12%; *APOE*-4/4 3.61%), CYP2D6-EMs represented 60.48%, IM 28.19%, PMs 5.32%, and UMs 6.01%. In *APOE*-2/2 carriers (N=2), 50% were EMs and 50% IMs. In *APOE*-2/3 (N=54), 48.15% were EMs, 37.04% IMs, 1.85% PMs, and 12.96% UMs. In *APOE*-2/4 cases (N=7), 85.71% were EMs and 14.29% IMs. In *APOE*-3/3 (N=346), 62.14% were EMs, 28.32% IMs, 4.63% PMs, and 4.91% UMs. In *APOE*-3/4 (N=152), 61.18% were



	C	ANX	DEP	PSY	STR	AD	PAR	ADHD	MIG	EPI	VD	VE	MS	CVI	BT	CNN	MR	PTBS
*5/*6	0,46	0,66	0,44	0,99	0	0	0	0	0	0	0	0	0	0	0	0	0	0
*5/*5	0	0	0	0	0	1,06	0	0	0,93	0	0	0,51	0	0	0	0	0	0
*4/*6	0	0	0	0	0	0	2,56	0	0	0	1,12	0	0	0	0	0	1,3	0
*4/*5	0,46	0,66	0,88	0,99	2,63	0	0	0	0	0	2,25	0,51	0	0	0	0	2,6	2,63
*4/*4	1,37	0	3,08	0	5,26	5,32	0	0	3,74	3,85	3,37	2,53	6,67	1,37	0	0	2,6	2,63
*3/*6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1,3	0
*3/*4	0	0	0,44	1,98	0	0	0	0	0,93	0	0	0,51	0	0	0	0	0	0
*3/*3	0	0	0	0	0	1,06	0	0	0	0	0	0	0	0	0	0	0	0
*1xN/*5	0	0	0	0	0	1,06	0	0	0	0	0	0	0	0	0	0	0	0
*1xN/*4	0,91	1,99	2,2	1,98	0	2,12	0	5	0,93	1,92	2,25	2,02	0	4,11	0	0	1,3	2,63
*1xN/*2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
*1/*6	0,91	1,32	1,32	0	2,63	2,13	2,56	0	0,93	0	3,37	2,53	0	0	0	0	0	0
*1/*5	3,65	4,64	4,41	2,97	7,89	3,19	0	10	8,41	0	3,37	1,52	0	2,74	0	0	6,49	7,89
*1/*4	27,85	19,21	19,82	22,77	21,05	20,21	23,07	25	19,66	19,23	25,84	26,77	26,67	27,4	37,5	25	18,18	21,05
*1/*3	2,28	1,99	1,76	1,98	0	2,13	2,56	0	3,74	1,92	2,25	1,01	0	2,74	0	0	2,6	0
*1/*2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,63
*1xN/*1	7,31	5,96	3,08	9,9	2,63	8,51	12,82	5	5,61	5,77	5,62	6,06	6,67	6,85	25	0	6,49	5,26
*1/*1	54,79	63,58	62,56	56,44	57,89	53,19	56,41	55	55,14	67,31	50,56	56,06	60	54,79	37,5	75	57,14	55,26

Figure 4: Distribution and frequency of *CYP2D6* genotypes in CNS disorders.
(C: Controls, N=315; ANX: Anxiety, N=285; DEP: Depression, N=419; PSY: Psychosis, N=162; STR: Stroke, N=67; AD: Alzheimer's disease, N=231; PAR: Parkinson's disease, N=73; ADHD: Attention Deficit Hyperactivity Disorder, N=42; MIG: Migraine, N=217; EPI: Epilepsy, N=71; VD: Vascular dementia, N=198; VE: Vascular encephalopathy, N=380; MS: Multiple sclerosis, N=21; CVI: Cerebrovascular insufficiency, N=138; BT: Brain tumor, N=11; CNN: Cranial nerve neuropathy, N=25; MR: Mental retardation, N=115; PTBS: Post-traumatic brain syndrome, N=59)[205].



	C	ANX	DEP	PSY	STR	AD	PAR	ADHD	MIG	EPI	VD	VE	MS	CVI	BT	CNN	MR	PTBS
UM	7,31	5,96	3,08	9,9	2,63	8,51	12,82	5	5,61	7,69	5,62	6,06	6,67	6,85	25	0	6,49	5,26
PM	2,28	2,65	4,85	3,96	7,89	7,45	2,56	0	5,61	3,85	6,74	4,04	6,67	1,37	0	0	7,79	5,26
IM	34,7	27,81	27,31	27,72	31,58	27,66	28,21	35	32,71	21,15	34,83	31,82	26,67	32,88	37,5	25	27,27	28,95
EM	55,71	63,58	64,76	58,42	57,89	56,38	56,41	60	56,07	67,31	52,81	58,08	60	58,9	37,5	75	58,44	60,53

Figure 5: Distribution and frequency of *CYP2D6* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), Poor Metabolizers (PM) and Ultra-rapid Metabolizers (UM) in CNS disorders.
(C: Controls, N=315; ANX: Anxiety, N=285; DEP: Depression, N=419; PSY: Psychosis, N=162; STR: Stroke, N=67; AD: Alzheimer's disease, N=231; PAR: Parkinson's disease, N=73; ADHD: Attention Deficit Hyperactivity Disorder, N=42; MIG: Migraine, N=217; EPI: Epilepsy, N=71; VD: Vascular dementia, N=198; VE: Vascular encephalopathy, N=380; MS: Multiple sclerosis, N=21; CVI: Cerebrovascular insufficiency, N=138; BT: Brain tumor, N=11; CNN: Cranial nerve neuropathy, N=25; MR: Mental retardation, N=115; PTBS: Post-traumatic brain syndrome, N=59).
Significant differences were found between controls and DEP (p<0.02), BT (p<0.05), and CNN (p<0.05). Patients with DEP also showed differences with PSY (p<0.05), PAR (p<0.05), and BT (p<0.01); and patients with STR exhibited significant differences with regard to BT (p<0.05) [205].

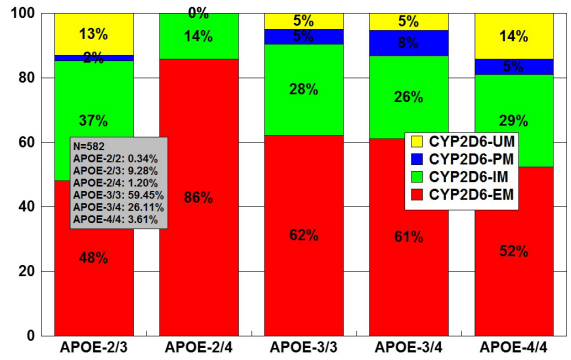


Figure 6: Distribution and frequency of *CYP2D6* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), Poor Metabolizers (PM) and Ultra-Rapid Metabolizers (UM) associated with *APOE* genotypes in patients with Alzheimer's disease.
Patients (N=582) were classified according to their *APOE* genotype (*APOE*-2/2, 0.34%; *APOE*-2/3, 9.28%; *APOE*-2/4, 1.20%; *APOE*-3/3, 59.45%; *APOE*-3/4, 26.12%; *APOE*-4/4, 3.61%) and the distribution and frequency of *CYP2D6*-EMs, IMs, PMs and UMs were studied in each *APOE*-related group. Significant differences were found between *APOE*-3/3 and *APOE*-2/3 (p<0.003), and a different pattern of *CYP2D6* variants was also observed between *APOE*-3/3 and *APOE*-4/4 carriers (p<0.06).

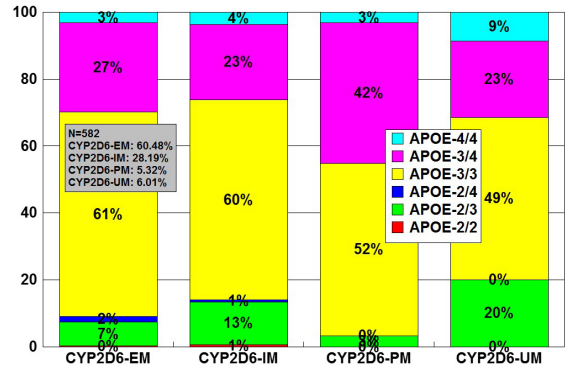


Figure 7: Distribution and frequency of *APOE* genotypes associated with *CYP2D6* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), Poor Metabolizers (PM) and Ultra-Rapid Metabolizers (UM) in patients with Alzheimer's disease.
Patients (N=582) were classified according to their *CYP2D6* profile (EMs: 60.48%, IMs: 28.19%; PMs: 5.32%; UMs: 6.01%), and the distribution and frequency of *APOE* genotypes were studied in each *CYP2D6*-related geno-phenotype.

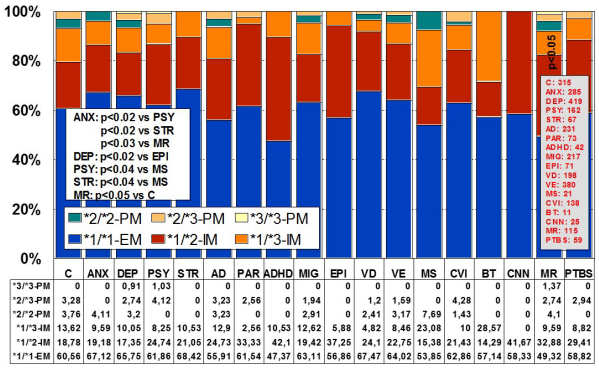
EMs, 26.66% IMs, 7.90% PMs, and 5.26% UMs. In *APOE*-4/4 (N=21), 52.38% were EMs, 28.57% IMs, 4.76% PMs, and 14.29% UMs (Figure 6). Significant differences were found in the distribution of *CYP2D6* variants between *APOE*-3/3 and *APOE*-2/3 carriers (p<0.01), and to a lesser extent between *APOE*-3/3 and *APOE*-4/4 carriers (p: 0.06). A tendency toward the accumulation of PMs and UMs in *APOE*-4 carriers was also observed (Figure 7). The presence of *CYP2D6* PMs and UMs in *APOE*-4 carriers may account for the poor response to conventional treatments currently observed in those patients harboring the *APOE*-3/4 and *APOE*-4/4 genotypes [3].

CYP2C9

CYP2C9 is a gene (50.71 kb) with 9 exons mapped on 10q24. An RNA transcript of 1860 bp is mainly expressed in hepatocytes where a protein of 55.63 kDa (490 aa) can be identified. 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 [86]. There are 481 *CYP2C9* SNPs. By phenotypes, in the control population, PMs represent 7.04%, IMs 32.39%, and EMs 60.56%. In AD, PMs, IMs, and EMs are 6.45%, 37.64%, and 55.91% respectively, and in VD are 3.61%, 28.92%, and 67.47% respectively [7] (Figure 8).

APOE-CYP2C9 association

In a sample of 566 Spanish patients with AD (*APOE*-2/2 0.35%; *APOE*-2/39.01%; *APOE*-2/4 1.24%; *APOE*-3/3 59.10%; *APOE*-3/4 26.68%; *APOE*-4/4 3.53%), 59.54% were *CYP2C9*-EMs, 35.34% *CYP2C9*-IMs, and 5.12% *CYP2C9*-PMs. By *APOE* genotype, 100% of homozygous *APOE*-2 (N=2) were EMs; in *APOE*-2/3 carriers (N=51), 43.14% were EMs, 49.02% IMs, and 7.84% PMs. In *APOE*-2/4 carriers (N=7), 28.57% were EMs and 71.43% IMs; there were no PMs in the sample. In *APOE*-3/3 carriers (N=335), 64.48% were EMs, 31.34% IMs, and 4.18% PMs. In *APOE*-3/4 carriers (N=151), 57.62% were EMs, 35.76% IMs, and 6.62% PMs; and in *APOE*-4/4 carriers (N=20), 40% were EMs, 55% IMs, and 5% PMs (Figure 9). There is an apparent reduction in the number of EMs among *APOE*-2/3, *APOE*-3/4, and *APOE*-4/4 carriers, as compared with *APOE*-3/3 carriers, and a correlative increase of IMs. The number of *CYP2C9*-PMs is similar, ranging from 4.18% in *APOE*-3/3 carriers to 5% in *APOE*-4/4, 6.62% in *APOE*-3/4, and 7.84% in *APOE*-2/3 carriers. There is a clear accumulation of *APOE*-3/3 genotypes in *CYP2C9*-EMs, and of *APOE*-3/4 genotypes in *CYP2C9*-PMs, suggesting that the latter association might also contribute to a poor pharmacogenetic outcome in AD patients, as previously reported [3] (Figure10).



	C	ANX	DEP	PSY	STR	AD	PAR	ADHD	MIG	EPI	VD	VE	MS	CVI	BT	CNN	MR	PTBS
*3/*3-PM	0	0	0,91	1,03	0	0	0	0	0	0	0	0	0	0	0	0	1,37	0
*2/*3-PM	3,28	0	2,74	4,12	0	3,23	2,56	0	1,94	0	1,2	1,59	0	4,28	0	0	2,74	2,94
*2/*2-PM	3,76	4,11	3,2	0	0	3,23	0	0	2,91	0	2,41	3,17	7,69	1,43	0	0	4,1	0
*1/*3-IM	13,62	9,59	10,05	8,25	10,53	12,9	2,56	10,53	12,62	5,88	4,82	8,46	23,08	10	28,57	0	9,59	8,82
*1/*2-IM	18,78	19,18	17,35	24,74	21,05	24,73	33,33	42,1	19,42	37,25	24,1	22,75	15,38	21,43	14,29	41,67	32,88	29,41
*1/*1-EM	60,56	67,12	65,75	61,86	68,42	55,91	61,54	47,37	63,11	56,86	67,47	64,02	53,85	62,86	57,14	58,33	49,32	58,82

Figure 8: Distribution and frequency of *CYP2C9* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) in CNS disorders.
(C: Controls, N=315; ANX: Anxiety, N=285; DEP: Depression, N=419; PSY: Psychosis, N=162; STR: Stroke, N=67; AD: Alzheimer's disease, N=231; PAR: Parkinson's disease, N=73; ADHD: Attention Deficit Hyperactivity Disorder, N=42; MIG: Migraine, N=217; EPI: Epilepsy, N=71; VD: Vascular dementia, N=198; VE: Vascular encephalopathy, N=380; MS: Multiple sclerosis, N=21; CVI: Cerebrovascular insufficiency, N=138; BT: Brain tumor, N=11; CNN: Cranial nerve neuropathy, N=25; MR: Mental retardation, N=115; PTBS: Post-traumatic brain syndrome, N=59).
Significant differences were found between controls and patients with MR ($p<0.05$), but not with other CNS disorders; however, patients with ANX showed differences with respect to PSY ($p<0.02$), STR ($p<0.02$), and MR ($p<0.03$). Other significant differences were found between DEP and EPI ($p<0.02$), PSY and MS ($p<0.04$), and STR and MS ($p<0.05$) [205].

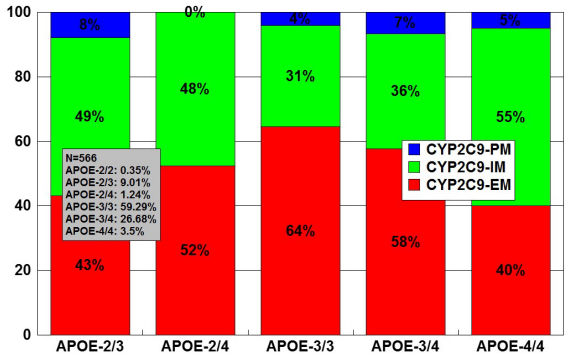


Figure 9: Distribution and frequency of *CYP2C9* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) associated with *APOE* genotypes in patients with Alzheimer's disease. Patients (N=566) were classified according to their *APOE* genotype (*APOE*-2/2, 0.35%; *APOE*-2/3, 9.01%; *APOE*-2/4, 1.24%; *APOE*-3/3, 59.19%; *APOE*-3/4, 26.68%; *APOE*-4/4, 3.53%) and the distribution and frequency of *CYP2C9* variants were studied in each *APOE*-related group. Significant differences were found between *APOE*-3/3 and *APOE*-2/3 ($p<0.001$), and a different pattern of *CYP2C9* variants was also observed between *APOE*-3/3 and *APOE*-4/4 carriers ($p<0.08$).

CYP2C19

CYP2C19 is a gene (90.21 kb) with 9 exons mapped on 10q24.1q24.3. RNA transcripts of 1901 bp, 2395 bp, and 1417 bp are expressed in liver cells where a protein of 55.93 kDa (490 aa) is identified. 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 [86]. About 541 SNPs have been detected in the *CYP2C19* gene. The frequencies of the 3 major *CYP2C19* geno-phenotypes in the control population are *CYP2C19-*1/*1*-EMs 68.54%, *CYP2C19-*1/*2*-IMs 30.05%, and *CYP2C19-*2/*2*-PMs 1.41%. EMs, IMs, and PMs account for 69.89%, 30.11%, and 0%, respectively, in AD, and 66.27%, 30.12%, and 3.61%, respectively, in VD [7] (Figure 11).

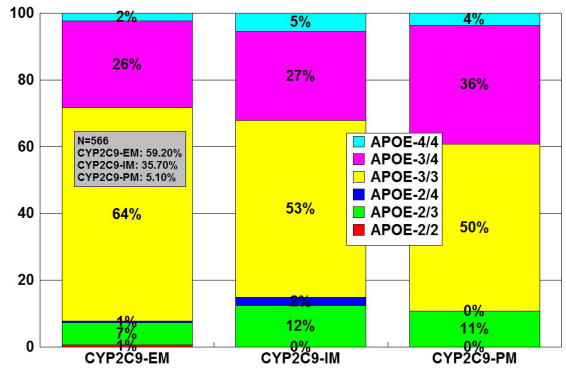


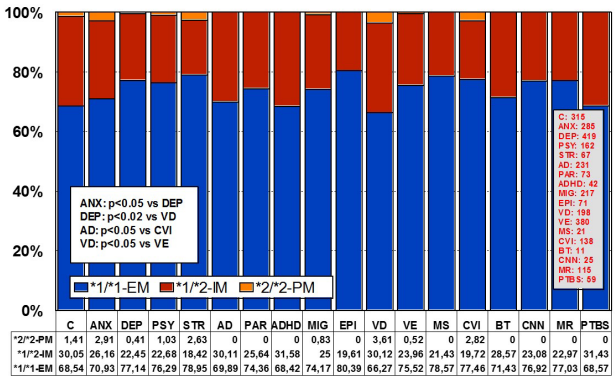
Figure 10: Distribution and frequency of *APOE* genotypes associated with *CYP2C9* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) in patients with Alzheimer's disease. Patients (N=566) were classified according to their *CYP2C9* geno-phenotype (EMs: 59.20%; IMs: 35.70%; PMs: 5.10%) and the distribution and frequency of *APOE* genotypes were studied in each *CYP2C9*-related group.

APOE-CYP2C19 association

The frequencies of *CYP2C19*-EMs, IMs, and PMs in a sample of 569 patients were 74.34%, 24.78%, and 0.88%, respectively. The distribution of *APOE*-associated *CYP2C19* geno-phenotypes was as follows: in *APOE*-2/2 (N=2), *CYP2C19*-EMs 50%, and *CYP2C19*-IMs 50%; in *APOE*-2/3 (N=52), *CYP2C19*-EMs 65.43%, *CYP2C19*-IMs 34.62%; in *APOE*-2/4 (N=7), *CYP2C19*-EMs 71.43%, and *CYP2C19*-IMs 28.57%; in *APOE*-3/3 (N=336), *CYP2C19*-EMs 75.30%, *CYP2C19*-IMs 23.51%, and *CYP2C19*-PMs 1.19%); in *APOE*-3/4 (N=152), *CYP2C19*-EMs 75.65%, *CYP2C19*-IMs 23.03%, and *CYP2C19*-PMs 1.32%; and in *APOE*-4/4 (N=20), *CYP2C19*-EMs 75%, and *CYP2C19*-IMs 25% (Figure 12). *CYP2C19*-PMs are very rare among AD patients (60% *APOE*-3/3 and 40% *APOE*-3/4). There is a small reduction in *APOE*-3/3 carriers among *CYP2C19*-IMs, and a notable increase in *APOE*-3/4 carriers among *CYP2C19*-PMs (Figure 13).

CYP3A4/5

CYP3A4 is a gene (27.2 kb) with 13 exons mapped on 7q21.1. RNA transcripts of 2153 bp, 651 bp, 564 bp, 2318 bp and 2519 bp are expressed in intestine, liver, prostate and other tissues where 4 protein variants of 57.34 kDa (503 aa), 17.29 kDa (153 aa), 40.39 kDa (353 aa), and 47.99 kDa (420 aa) are identified. The human *CYP3A* locus contains the three *CYP3A* genes (*CYP3A4*, *CYP3A5* and *CYP3A7*), three pseudogenes, as well as a novel *CYP3A* gene termed *CYP3A43*. The gene encodes a putative protein with between 71.5% and 75.8% identity to the other CYP3A proteins. The predominant hepatic form is CYP3A4, but CYP3A5 contributes significantly to the total liver CYP3A activity. This enzyme metabolizes over 1,900 drugs, 1,033 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 [86]. About 347 SNPs have been identified in the *CYP3A4* gene (*CYP3A4*1A*: Wild-type), 25 of which are of clinical relevance. Concerning *CYP3A4/5* polymorphisms in AD, 82.75% of the cases are EMs (*CYP3A5*3/*3*),



	C	ANX	DEP	PSY	STR	AD	PAR	ADHD	MIG	EPI	VD	VE	MS	CVI	BT	CNN	MR	PTBS
*2/*2-PM	1,41	2,91	0,41	1,03	2,63	0	0	0	0,83	0	3,61	0,52	0	2,82	0	0	0	0
*1/*2-IM	30,05	26,16	22,45	22,68	18,42	30,11	25,64	31,58	25	19,61	30,12	23,96	21,43	19,72	28,57	23,08	22,97	31,43
*1/*1-EM	68,54	70,93	77,14	76,29	78,95	69,89	74,36	68,42	74,17	80,39	66,27	75,52	78,57	77,46	71,43	76,92	77,03	68,57

Figure 11: Distribution and frequency of *CYP2C19* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) in CNS disorders.
(C: Controls, N=315; ANX: Anxiety, N=285; DEP: Depression, N=419; PSY: Psychosis, N=162; STR: Stroke, N=67; AD: Alzheimer's disease, N=231; PAR: Parkinson's disease, N=73; ADHD: Attention Deficit Hyperactivity Disorder, N=42; MIG: Migraine, N=217; EPI: Epilepsy, N=71; VD: Vascular dementia, N=198; VE: Vascular encephalopathy, N=380; MS: Multiple sclerosis, N=21; CVI: Cerebrovascular insufficiency, N=138; BT: Brain tumor, N=11; CNN: Cranial nerve neuropathy, N=25; MR: Mental retardation, N=115; PTBS: Post-traumatic brain syndrome, N=59).
No significant differences between controls and patients with CNS disorders were found; however, differences were found between ANX and DEP ($p<0.05$), DEP and VD ($p<0.02$), AD and CVI ($p<0.05$), and VD and VE ($p<0.05$) [205].

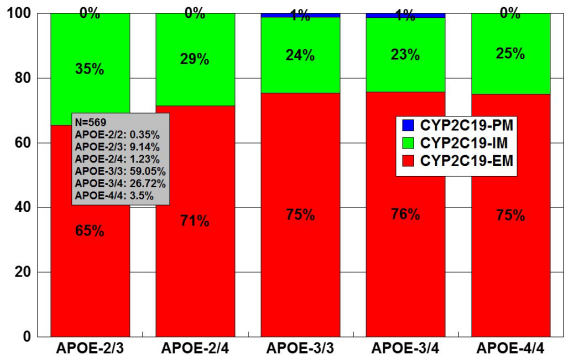


Figure 12: Distribution and frequency of *CYP2C19* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) associated with *APOE* genotypes in patients with Alzheimer's disease.
Patients (N=569) were classified according to their *APOE* genotype (*APOE*-2/2,0.35%; *APOE*-2/3, 9.14%; *APOE*-2/4, 1.23%; *APOE*-3/3, 59.05%; *APOE*-3/4, 26.72%; *APOE*-4/4, 3.51%) and the distribution and frequency of *CYP2C19* geno-phenotypes were studied in each *APOE*-related group.

15.88% are IMs (*CYP3A5*1/*3*), and 1.37% are UMs (*CYP3A5*1/*1*). Unlike other human P450s (*CYP2D6*, *CYP2C19*) there is no evidence of a 'null' allele for *CYP3A4* [86].

APOE-CYP3A4/5 interaction

In a series of 347 AD cases, 79.94% were found to be *CYP3A5*-EMs, 19.47% *CYP3A4*-IMs, and 0.59% *CYP3A4*-RM (rapid metabolizers). The distribution of *CYP3A5*-EMs and IMs was very similar among *APOE* genotypes, except in *APOE*-2/4 carriers where the presence of IMs was twice higher than in carriers of the other genotypes (Figure 14). Only 2

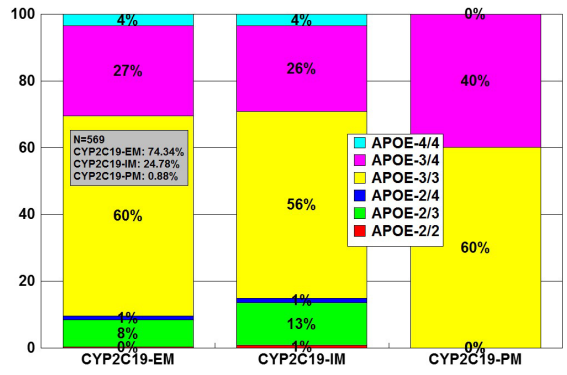


Figure 13: Distribution and frequency of *APOE* genotypes associated with *CYP2C19* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizers (PM) in patients with Alzheimer's disease.
Patients (N=569) were classified according to their *CYP2C19* geno-phenotypes (*CYP2C19*-EM, 74.34%; *CYP2C19*-IM, 24.78%; *CYP2C19*-PM, 0.88%) and the distribution and frequency of *APOE* genotypes were studied in each *CYP2C19*-related group.

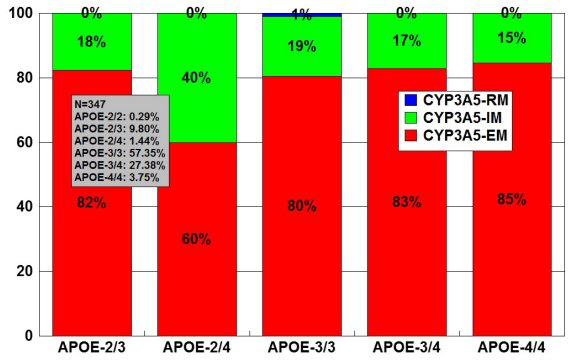


Figure 14: Distribution and frequency of *CYP3A5* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Rapid Metabolizers (RM) associated with *APOE* genotypes in patients with Alzheimer's disease.
Patients (N=347) were classified according to their *APOE* genotype (*APOE*-2/2, 0.29%; *APOE*-2/3, 9.80%; *APOE*-2/4, 1.44%; *APOE*-3/3, 57.35%; *APOE*-3/4, 27.38%; *APOE*-4/4, 3.75%) and the distribution and frequency of *CYP3A5* variants were studied in each *APOE*-related group.

cases of *CYP3A4*-RMs were found exclusively associated with *APOE*-3/3 genotypes (Figure 15).

CYP clustering

The construction of a genetic map integrating the most prevalent *CYP2D6+CYP2C19+CYP2C9* polymorphic variants in a trigenic cluster yields 82 different haplotype-like profiles. The most frequent trigenic genotypes in the AD population are **1*1-*1*1-*1*1* (25.70%), **1*1-*1*2-*1*2* (10.66%), **1*1-*1*2-*1*1* (10.45%), **1*4-*1*1-*1*1* (8.09%), **1*4-*1*2-*1*1* (4.91%), **1*4-*1*1-*1*2* (4.65%), and **1*1-*1*3-*1*3* (4.33%). These 82 trigenic genotypes represent 36 different pharmacogenetic phenotypes. According to these trigenic clusters, only 26.51% of the patients show a pure 3EM phenotype, 15.29% are 2EM1IM, 2.04% are pure 3IM, 0% are pure 3PM, and 0% are 1UM2PM (the worst possible phenotype). This implies that only one-quarter of the population processes normally the drugs which are metabolized via CYP2D6, CYP2C9 and CYP2C19 (approximately 60% of the drugs of current use) [26]. Taking into consideration the data available, it might be inferred

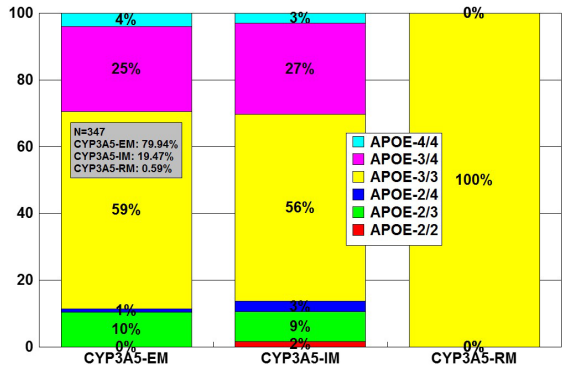


Figure 15: Distribution and frequency of *APOE* genotypes associated with *CYP3A5* Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Rapid Metabolizers (RM) in patients with Alzheimer's disease. Patients (N=347) were classified according to their *CYP3A5* geno-phenotype (*CYP3A5*-EM, 79.94%; *CYP3A5*-IM, 19.47%; *CYP3A5*-RM, 0.59%) and the distribution and frequency of *APOE* genotypes were studied in each *CYP3A5*-related group.

that at least 20-30% of the AD population may exhibit an abnormal metabolism of cholinesterase inhibitors and/or other drugs which undergo oxidation via *CYP2D6*-related enzymes. Approximately 50% of this population cluster would show an ultrarapid metabolism, requiring higher doses of cholinesterase inhibitors in order to reach a therapeutic threshold, whereas the other 50% of the cluster would exhibit a poor metabolism, displaying potential adverse events at low doses. If we take into account that approximately 60-70% of therapeutic outcomes depend upon pharmacogenomic criteria (e.g. pathogenic mechanisms associated with AD-related genes), it may be postulated that pharmacogenetic and pharmacogenomic factors are responsible for 75-85% of the therapeutic response (efficacy) in AD patients treated with conventional drugs [1,7,21,22,24-27,34-38,94].

Genes encoding drug transporters

ABC genes, especially *ABCB1* (ATP-binding cassette, subfamily B, member 1; P-glycoprotein-1, P-gp1; Multidrug Resistance 1, MDR1) (7q21.12), *ABCC1* (9q31.1), *ABCG2* (White1) (21q22.3), and other genes of this family encode proteins which are essential for drug metabolism and transport. The multidrug efflux transporters P-gp, Multidrug-Resistance Associated Protein 4 (MRP4) and Breast Cancer Resistance Protein (BCRP), located on endothelial cells lining brain vasculature, play important roles in limiting movement of substances into and enhancing their efflux from the brain. Transporters also cooperate with Phase I/Phase II metabolism enzymes by eliminating drug metabolites. Their major features are their capacity to recognize drugs belonging to unrelated pharmacological classes, and their redundancy, by which a single molecule can act as a substrate for different transporters. This ensures an efficient neuroprotection against xenobiotic invasions. The pharmacological induction of *ABC* gene expression is a mechanism of drug interaction, which may affect substrates of the up-regulated transporter, and overexpression of MDR transporters confers resistance to anticancer agents and CNS drugs [95,96].

Aberrant cholesterol trafficking and accumulation may contribute to the early onset of AD. Several ATP-Binding Cassette (ABC) transporters, such as ABCA1, ABCG1, ABCG5, and ABCG8 have been shown to play important roles in the regulation of cellular cholesterol homeostasis by mediating cholesterol efflux. Mutations in *ABC* transporters influence pathogenesis and therapeutics of brain disorders [97].

Genome-wide significance in fully adjusted models was observed for a SNP in *ABCA7* (rs115550680, allele = G; frequency, 0.09 cases and 0.06 controls), which is in linkage disequilibrium with SNPs associated with AD in Europeans. The effect size for the SNP in *ABCA7* was comparable with that of the *APOE*ε4-determining SNP rs429358 (allele = C; frequency, 0.30 cases and 0.18 controls) [98].

ABCB1

ABCB1(ATP-binding cassette, sub-family B (MDR/TAP), member 1; Doxorubicin resistance; Multidrug resistance 1; Multidrug resistance protein 1; P glycoprotein 1; P glycoprotein 1/multiple drug resistance 1; P-Glycoprotein 1; P-glycoprotein-1/multiple drug resistance-1; P-gp) is probably the most important drug transporter in the brain. The *ABCB1* gene maps on 7q21.12 spanning 209.39 kb (29 Exons) with the structure of a P-glycoprotein and a Y-box sequence 5'-CTGATTGG-3' in its cis-regulatory elements. Several transcripts/variants (*ABCB1*-001: 4645 bp; *ABCB1*-002: 3602 bp; *ABCB1*-003: 461 bp; *ABCB1*-004: 582 bp; *ABCB1*-005: 555 bp; *ABCB1*-006: 913 bp; *ABCB1*-007: 1864 bp; *ABCB1*-008: 642 bp; *ABCB1*-009: 787 bp; *ABCB1*-010: 539 bp; *ABCB1*-201: 345 bp) are highly expressed in adrenal gland, Blood Brain Barrier (BBB), brain, kidney, liver, placenta, small intestine and uterus, and low expression is present in many other tissues. These transcripts encode a protein (ABCB1-001: 141.48 kDa; 1280 aa. ABCB1-002: 5.89 kDa; 51 aa. ABCB1-003: 5.68 kDa; 48 aa. ABCB1-201: 2.52 kDa; 22 aa) of the ATP binding cassette superfamily, subfamily B (MDR/TAP) with two ATP binding and two transmembrane (2TM) domains (2 x 6 segments), acting as a transport carrier and a lipid translocase of broad specificity.

This is a large transmembrane protein which is an integral part of the BBB and functions as a drug-transport pump transporting a variety of drugs from the brain back into the blood. Functions of this protein include the following: ABC transporter, traffic ATPase, energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells; potentially implicated in cholesterol transport; may maintain neural stem/progenitor cells in an undifferentiated state and could be a neural stem/progenitor marker.

About 1630 *ABCB1* variants have been identified [86]. Of interest, *ABCB1* has approximately 116 polymorphic sites in Caucasians and 127 in African-Americans with a minor allele frequency greater than 5%. Some of the most commonly studied variants are 1236C>T, 2677G>A/T and 3435C>T and the most commonly studied haplotype involves the 1236, 2677 and 3435 (TTT) SNPs and 3 intronic SNPs (intron 9, intron 13, intron 14) named *ABCB1*13*. There are many other *ABCB1* variants such as -129C>T (5'-UTR), 61A>G (Asn21Asp) and 1199G>A (Ser400Asn) that have been studied *in vivo* and *in vitro*. To date, there is no clear consensus on the impact of any of these variants on drug disposition, response or toxicity.

Variants of the *ABCB1* gene have been associated with a diverse number of diseases and with a great variety of drugs, natural products and endogenous agents [86]. Over 1,270 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 [86].

ATP-Binding Cassette (ABC) transporters, which are localized on the surface of brain endothelial cells of the BBB and brain parenchyma, may contribute to the pathogenesis of AD. ABC transporters including ABCB1 (P-glycoprotein, P-gp), ABCG2 (breast cancer resistant protein, BCRP), ABCC1 (multidrug resistance protein 1, MRP1), and the cholesterol transporter ABCA1 play important roles in the pathogenesis of AD and Aβ peptide deposition inside the brain [99-104]. Decreased clearance of Aβ from the brain may lead to elevated Aβ levels. One of the clearance

pathways of Aβ is transport across the BBB via efflux transporters. P-glycoprotein, an efflux pump highly expressed at the endothelial cells of the BBB, has been shown to transport Aβ. The P-glycoprotein transporter at the BBB is compromised in AD, and decreased P-glycoprotein function may be involved in the pathogenesis of AD [103].

In addition to the age-related decrease in P-gp expression, $A\beta_{1-42}$ itself downregulates the expression of P-gp and other Aβ-transporters, which could exacerbate the intracerebral accumulation of Aβ and thereby accelerate neurodegeneration in AD and cerebral β- Aβ angiopathy [102]. Furthermore, amyloid efflux transporter expression at the BBB declines with aging in normal conditions [105], and expression of P-gp protein is significantly lower in the hippocampal vessels of patients with AD compared to normal individuals [106].

The Low-Density Lipoprotein Receptor-Related Protein-1 (LRP-1) and the ATP-Binding Cassette (ABC) protein ABCB1 (P-glycoprotein) are involved in the efflux of Aβ across the BBB. Other ABC proteins, such as members of the G subfamily, are also involved in the BBB clearance of Aβ. ABCG2 and ABCG4 mediate the cellular efflux of $[^3H]A\beta_{1-40}$. Probucol inhibits the efflux of $[^3H]A\beta_{1-40}$ from HEK293-abcg4 cells. GF120918 (a dual inhibitor of Abcb1 and Abcg2) strongly enhances the uptake of $[^3H]A\beta_{1-40}$ by the brains of Abcb1-deficient mice, but not by the brains of Abcb1/Abcg2-deficient mice, suggesting that Abcg2 is involved in the transport of Aβ at the mouse BBB. Abcg4 acts in concert with Abcg2 to efflux Aβ from the brain across the BBB [107].

ATP binding cassette subfamily G member 2 (ABCG2) is involved in Aβ-β transport and was found to be up-regulated in AD brains. A functional polymorphism of the *ABCG2* gene (C421A; rs2231142) (*ABCG2* C/C genotype) was associated with AD in the Hungarian population. The *ABCG2* C/C genotype and the *APOE-4* allele may also exert an interactive effect on AD risk [108].

Single-nucleotide polymorphisms in the *ABCB1* gene have been associated with altered P-glycoprotein expression and function. P-glycoprotein function at the BBB can be quantified *in vivo* using the P-glycoprotein substrate tracer (R)-[^{11}C] verapamil and Positron Emission Tomography (PET). Three different kinds of imaging probes have been described to measure ABC transporters *in vivo*: (i) radiolabeled transporter substrates, (ii) radiolabeled transporter inhibitors, and (iii) radiolabeled prodrugs which are enzymatically converted into transporter substrates in the organ of interest [109]. Van Assema et al. [110] assessed the effects of C1236T, G2677T/A and C3435T single-nucleotide polymorphisms in *ABCB1* on BBB P-glycoprotein function in healthy subjects and patients with AD. In healthy controls, binding potential did not differ between subjects without and with one or more T present in C1236T, G2677T and C3435T. In contrast, patients with AD with one or more T in C1236T, G2677T and C3435T had significantly higher binding potential values than patients without a T. There was a relationship between binding potential and T dose in C1236T and G2677T. In AD patients, C1236T, G2677T/A and C3435T SNPs may be related to changes in P-glycoprotein function at the BBB, and genetic variations in *ABCB1* might contribute to the progression of Aβ-β deposition in the brain. Kohen et al. [111] investigated a possible association between 2 common *ABCB1* polymorphisms, G2677T/A (Ala893Ser/Thr) and C3435T, AD, and CSF levels of Aβ, and no strong evidence for association was found. Frankfort et al. [112] studied *ABCB1* SNPs (C1236T in exon 12, G2677T/A in exon 21 and C3435T in exon 26) and inferred haplotypes in patients with dementia and age-matched non-demented control patients and found no differences between both groups; however, in a transcriptome analysis of leukocytes from patients with mild cognitive impairment (MCI), AD, as well as normal controls, only the *ABCB1* gene exhibited significantly positive correlation with MMSE scores, representing a novel biomarker of AD [113].

Aβ transport (flux) across the BBB is thought to contribute to the pathogenesis of AD and also the elimination of toxic amyloid from the brain by immunotherapy. Several BBB transporters have been implicated in Aβ exchange between brain parenchyma and the circulation, including efflux transporters P-glycoprotein/ABCB1 and BCRP/ABCG2. Deficiency of either of the two major efflux pumps, Abcb1 and Abcg2, implicated in Aβ trafficking across the BBB, results in increased accumulation of peripherally-injected $A\beta_{1-40}$ in the brain [114].

The drug transporter ABCB1 directly transports Aβ from the brain into the blood circulation, whereas the cholesterol transporter ABCA1 neutralizes Aβ aggregation capacity in an Apolipoprotein E (ApoE)-dependent manner, facilitating subsequent Aβ elimination from the brain [115]. Cascorbi et al. [116] genotyped selected variants in *ABCA1*, *ABCA7*, *ABCB1*, *ABCC2* and *ABCG2* in DNAs from brain tissue of 71 AD cases with Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathological stages B/C and 81 controls. The novel *ABCA7* SNP, rs3752246, tended to be associated with AD. *ABCB1* variants were significantly less frequent in AD cases older than 65 years of age and among females. This association of *ABCB1* 2677G>T (rs2032582) was more pronounced in *APOE-4* negative cases. Only *ABCC2* 3972C>T (rs3740066) was significantly associated with AD risk.

Efflux transporter P-glycoprotein (P-gp) at the BBB restricts substrate compounds from entering the brain and may thus contribute to pharmacoresistance in CNS disorders, cancer and brain infections. Positron Emission Tomography (PET) has become a promising method to study the role of P-gp at the BBB. The first PET study of P-gp function was conducted in 1998, and over the past 15 years two main categories of P-gp PET tracers have been investigated: tracers that are substrates of P-gp efflux and tracers that are inhibitors of P-gp function [117].

The ABC transporter Pgp protects the brain from accumulation of lipophilic compounds by active efflux transport across the BBB. Müllauer et al. [118] investigated the suitability of the radiolabeled Pgp inhibitors [^{11}C] elacridar and [^{11}C] tariquidar to visualize Pgp density in rat brain with PET. The small Pgp binding signals obtained with [^{11}C] elacridar and [^{11}C] tariquidar limit the applicability of these tracers to measure cerebral Pgp density.

Molecular transporters that are expressed in brain, especially at the BBB, are therapeutic targets in the treatment of AD. Some ATP-Binding Cassette (ABC) transporters, particularly P-glycoprotein (ABCB1), MRP1 (ABCC1) and BCRP (ABCG2), have been implicated in the clearance of neurotoxic polypeptides that characteristically accumulate in the brain, such as Aβ peptides. A benzopyrane derivative with P-gp stimulating properties has been proposed as a candidate agent to decrease Aβ accumulation in AD [119]. Lipid transporters of the A-branch of ABC transporters are also potentially involved in AD pathogenesis. Induction of transporters via the activation of specific nuclear receptors may represent a novel approach to restoring diminished BBB function. Transporters in the brain capillary endothelium regulate the permeation of therapeutic compounds into the brain [120,121].

Induction of the multidrug resistance protein 1 (MDR1)/P-glycoprotein (P-gp) by the Vitamin D Receptor (VDR) was investigated in isolated rat brain capillaries and rat (RBE4) and human (hCMEC/D3) brain microvessel endothelial cell lines. Incubation of isolated rat brain capillaries with the VDR ligand, 1α,25-dihydroxyvitamin D3 [$1,25OH_2D_3$] increased P-gp protein expression fourfold. Incubation with $1,25OH_2D_3$ increased P-gp transport activity by 25-30%. In RBE4 cells, *Mdr1b* mRNA was induced in a concentration-dependent manner by exposure to $1,25OH_2D_3$. Concomitantly, P-gp protein expression increased 2.5-fold and was accompanied by a 20-35% reduction in cellular accumulation of the P-gp substrates, rhodamine 6G (R6G), and HiLyte

Fluor 488-labeled human amyloid-β 1-42 ($hA\beta_{42}$). In hCMEC/D3 cells, exposure to $1,25OH_2D_3$ increased *MDR1* mRNA expression (40%) and P-gp protein; and reduced cellular accumulation of R6G and $hA\beta_{42}$ by 30%. VDR activation up-regulates Mdr1/MDR1 and P-gp protein in brain capillaries and microvascular endothelia, implicating a role for VDR in increasing the brain clearance of P-gp substrates, including $hA\beta_{42}$ in AD [122].

Since P-gp prevents the entry of compounds into the brain by an active efflux mechanism at the BBB, inhibition of P-gp may help to enhance drug penetration. New reversible inhibitors of P-gp have been developed. Some galantamine-like compounds inhibit the efflux of the fluorescent P-gp substrate rhodamine 123 in cancer cells that over-express P-gp, and also inhibit the efflux of therapeutic substrates of P-gp, such as doxorubicin, daunomycin and verapamil. These compounds modulate P-gp-mediated efflux by competing for the substrate binding sites [123]. Activation of the Liver X Receptors (LXRs) by natural or synthetic agonists decreases the amyloid burden and enhances cognitive function in transgenic murine models of AD. LXR activation may affect the transport of Aβ peptides across the BBB. LXR agonists (24S-hydroxycholesterol, 27-hydroxycholesterol and T0901317) modulate the expression of target genes involved in cholesterol homeostasis (*ABCA1*) and promote cellular cholesterol efflux to apolipoprotein A-I and high density lipoproteins. LXR stimulation increases the expression of the ABCB1 transporter, which restricts Aβ peptide influx [124].

It is also important that drugs for AD treatment optimize CNS penetration by minimizing hydrogen bond donors and reducing P-gp-mediated efflux [125-127]. The increase of P-glycoprotein expression and activity by a P-gp inducer could be an effective pharmacological strategy in slowing or halting the progression of AD. A decrease of approximately 10-35% in $^{124}I\text{-}A\beta_{1\text{-}40}$ intracellular accumulation was observed in cells treated with rifampicin, dexamethasone, caffeine, verapamil, hyperforin, β-estradiol and pentylenetetrazole (P-gp inducers) [128]. Perrone et al. [129] validated the new dye-probe β-amyloid (1-40) HiLyte Fluor™ TR-labeled (Ab-HiLyte) (Anaspec) P-gp-mediated transport in the *ex vivo* rat everted gut sac assay by using MC18 or MC266, a fully characterized P-gp inhibitor and substrate, respectively, and compared it with the commonly-used dye rhodamine, demonstrating that the new dye probe, Ab-HiLyte, could be a probe of choice to unequivocally distinguish between a P-gp substrate and an inhibitor.

Mehta et al. [121] assessed the impact of AD-associated BBB alterations on the uptake of therapeutics into the brain of triple transgenic (3×TG) AD mice. The brain uptake of passively diffusing markers, [^{3}H] diazepam and [^{3}H] propranolol, decreased 54-60% in 3×TG mice, consistent with a 33.5% increase in the thickness of the cerebrovascular basement membrane in 3×TG mice. Despite a 42.4% reduction in P-gp expression in isolated brain microvessels from a sub-population of 3×TG mice, the brain uptake of P-gp substrates ([^{3}H] digoxin, [^{3}H] loperamide and [^{3}H] verapamil) was not different between genotypes, likely due to a compensatory thickening in the cerebrovascular basement membrane counteracting any reduced efflux of these lipophilic substrates.

Other transporters

Also of importance for CNS pharmacogenomics are transporters encoded by genes of the solute carrier superfamily (*SLC*) and solute carrier organic (*SLCO*) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate (*SLC19A1*), urea (*SLC14A1*, *SLC14A2*), monoamines (*SLC29A4*, *SLC22A3*), aminoacids (*SLC1A5*, *SLC3A1*, *SLC7A3*, *SLC7A9*, *SLC38A1*, *SLC38A4*, *SLC38A5*, *SLC38A7*, *SLC43A2*, *SLC45A1*), nucleotides (*SLC29A2*, *SLC29A3*), fatty acids (*SLC27A1-6*), neurotransmitters (*SLC6A2* (noradrenaline transporter), *SLC6A3* (dopamine transporter), *SLC6A4* (serotonin transporter, SERT), *SLC6A5*, *SLC6A6*, *SLC6A9*, *SLC6A11*, *SLC6A12*, *SLC6A14*, *SLC6A15*, *SLC6A16*, *SLC6A17*, *SLC6A18*, *SLC6A19*), glutamate (*SLC1A6*, *SLC1A7*), and others [130]. 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 [131]. 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 (Peptide Transporters 1 and 2 [*SLC15A1* (PepT1) and *SLC15A2* (PepT2)], and Peptide/Histidine Transporters 1 and 2 [*SLC15A4* (PHT1) and *SLC15A3* (PHT2)]). ABC and SLC transporters expressed at the BBB may cooperate to regulate the passage of different molecules into the brain [132]. Polymorphic variants in *ABC* and *SLC* genes may also be associated with pathogenic events in CNS disorders and drug-related safety and efficacy complications [8,130]. For instance, an important issue to be elucidated is the role of transporters in patients under chronic treatment with psychotropic drugs or exposed to general anesthesia. Chen et al. [133] studied the potential influence of Endotracheal Tube Intubation General Anesthesia (ETGA), Intravenous Injection General Anesthesia (IVGA) or Intramuscular Injection General Anesthesia (IMGA), and heavy sedation on dementia in Taiwan and found that individuals exposed to surgery under ETGA and those exposed to surgery under IVGA or IMGA were at significantly higher risk of dementia in a dose-response relationship, whereas surgery under heavy sedation was not associated with increased risk of dementia. Subjects who had received surgery under ETGA with comorbidities such as stroke, hypertension, diabetes mellitus, and atherosclerosis could have a potential relationship with dementia risk [32]. Interestingly, the anesthetics propofol and thiopental are associated with Aβ assembly and GM1 expression on the neuronal cell surface through the γ-aminobutyric acid A receptor, and both compounds have direct and indirect inhibitory effects on Aβ fibrillogenesis [134].

Pharmacogenomics of anti-dementia drugs

Donepezil

Donepezil is a centrally active, reversible acetylcholinesterase inhibitor which increases the acetylcholine available for synaptic transmission in the CNS. The therapeutic response of donepezil is influenced by pathogenic gene variants (*APOE*, *CHAT*), as well as mechanistic gene polymorphic variants of *CHAT*, *ACHE*, and *BCHE*. Donepezil is a major substrate of CYP2D6, CYP3A4, ACHE, and UGTs, inhibits ACHE and BCHE, and is transported by ABCB1 [8,21,24,25,28,35,135-137] (Table 1). Most studies convey that *CYP2D6* variants affect donepezil efficacy and safety in AD [8,21,24,25,35,86,135-137]. The common variant rs1080985 of *CYP2D6* was found to be associated with poor response to donepezil [138,139]. A high-throughput genetic analysis of *CYP2D6* polymorphisms discriminated responders/non-responders of the *CYP2D6* allele **2A*. A higher frequency of mutated alleles was observed in responder than in non-responder patients (75.38% *vs.* 43.48%). The presence of a mutated allele of *CYP2D6* was associated with a response to CYP2D6-metabolized drugs [140]. In agreement with this criterion, in an Italian study 67% of patients were responders and 33% were non-responders to donepezil treatment. A significantly higher frequency of gene variants conferring decreased or absent enzyme activity was observed in responder than in non-responder patients (73.68% *vs.* 36.84%) [141]. Among Chinese patients, 58.3% were responders and 41.7% were non-responders to donepezil treatment. AD patients with the mutant allele *CYP2D6*10* may respond better to donepezil than those with the wild allele *CYP2D6*1*. A significantly higher frequency of patients with genotypes *CYP2D6*1/*10* and **10/*10* were found in responders than in non-responders. Patients with *CYP2D6*1/*10* and **10/*10* genotypes had higher steady-state plasma concentrations of donepezil and improved cognition scores than

those with the *CYP2D6*1/*1* genotype [142]. However, in other studies, *CYP2D6*-PMs and UMs tend to be poor responders to conventional doses of donepezil as compared to EMs and IMs [1,7,21,22,24-28,34-38,94,143-145]. In contrast, a Polish group could not find any influence of the rs1080985 SNP on response to treatment with donepezil in AD [146].

Magliulo et al. [147] evaluated the impact of *CYP3A4* (**1B*, **3*, and **4*), *CYP3A5* (**2*, **3*, and **6*), and *ABCB1* (3435C>T, 2677G>T/A, and 1236C>T) polymorphisms on donepezil disposition and clinical outcome in 54 Italian AD patients. Three patients carried one detrimental *CYP3A4* allelic variant, and 12 carried one functional *CYP3A5*1* allele. No association was found between *CYP3A4* or *CYP3A5* genotypes and plasma donepezil concentrations, or between genotypes and clinical response. The most common *ABCB1* haplotypes were 1236C/2677G/3435C (46%) and 1236T/2677T/3435T (41%). 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.

Galantamine

Galantamine is a reversible and competitive acetylcholinesterase inhibitor leading to an increased concentration of acetylcholine at cholinergic synapses. This drug also modulates nicotinic acetylcholine receptors and may increase glutamate and serotonin levels. *APOE*, *APP*, *ACHE*, *BCHE*, *CHRNA4*, *CHRNA7*, *CHRNB2* variants may potentially influence galantamine efficacy and safety; it is a major substrate of CYP2D6, CYP3A4, and UGT1A1, and an inhibitor of ACHE and BCHE [86,136,137,148-150] (Table 1). Major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization. In extensive metabolizers for CYP2D6, urinary metabolites resulting from O-demethylation represented 33.2% of the dose compared with 5.2% in poor metabolizers, which showed correspondingly higher urinary excretion of unchanged galantamine and its N-oxide. The glucuronide of O-desmethyl-galantamine represented up to 19% of the plasma radioactivity in extensive metabolizers but could not be detected in poor metabolizers [151]. Galantamine is extensively metabolized by the enzymes CYP2D6 and CYP3A and is a substrate of the P-glycoprotein. Noetzli et al. [152] studied the relationship between genetic variants of *CYP2D6*, *CYP3A4/5* and *ABCB1* with galantamine steady state plasma concentrations. The *CYP2D6* genotype seemed to be an important determinant of galantamine pharmacokinetics, with *CYP2D6* poor metabolizers presenting 45% and 61% higher dose-adjusted galantamine plasma concentrations than heterozygous and homozygous *CYP2D6* extensive metabolizers.

However, Clarke et al. [153] were unable to make inferences about an association between CYP2D6 phenotype and galantamine responsiveness.The bioavailability of galantamine is increased by co-administration with paroxetine, ketoconazole and erythromycin [154]. In healthy subjects and in AD patients, the co-administration of galantamine with ketoconazole (a CYP3A4 strong inhibitor) or paroxetine (a CYP2D6 strong inhibitor) leads to a 30% and 40% increase, respectively, in galantamine exposure compared to galantamine given alone [155]. Galantamine can interact with foods which might alter its bioavailability and therapeutic effects. Zhai and Lu [156] reported interaction between galantamine and capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide, CAP), a naturally-occurring alkaloid extracted from the fruit of *Capsicum* plant family, which is a common ingredient in spicy foods. The pretreatment of rats with capsaicin resulted in a decrease in the $AUC_{0-\infty}$ of galantamine of about 49.70% compared with the control group. After oral administration of galantamine (10 mg/kg), the apparent oral clearance of galantamine was raised by 2.05-fold by pretreatment with capsaicin, indicating that the chronic ingestion of high doses of capsaicin decreases the bioavailability of galantamine, at least in rats.

Rivastigmine

Rivastigmine is a cholinesterase inhibitor which increases acetylcholine in CNS through reversible inhibition of its hydrolysis by cholinesterase. *APOE*, *APP*, *CHAT*, *ACHE*, *BCHE*, *CHRNA4*, *CHRNB2* and *MAPT* variants may affect its pharmacokinetics and pharmacodynamics. The hepatic cytochrome P-450 (CYP-450) system is not involved in the metabolism of rivastigmine [86,136,137,154,157] (Table 1). Sonali et al. [158] studied the clinical effectiveness of *CYP2D6*, *CYP3A4*, *CYP2C9/19*, and *UGT* polymorphisms on the steady-state plasma concentrations and therapeutic outcome of rivastigmine monotherapy and combination therapy in patients with AD in India. A significant allele frequency was observed for the *CYP2D6*3* polymorphism in patients under rivastigmine combination therapy (A>del: 0.50 AD/0.20 controls), *UGT2B7* (T: 0.17 AD/0.33 C), and *UGT1A9*5* (A = 0.58 AD/0.26 C). Poor metabolizer subjects of the *UGT2B7* polymorphism in patients under rivastigmine combination therapy have higher drug levels with a poor response to treatment.

Tacrine

Tacrine was the first FDA-approved anti-dementia drug. Its use was stopped due to hepatotoxicity. Tacrine is a cholinesterase inhibitor which elevates acetylcholine in cerebral cortex by slowing degradation of acetylcholine. *ACHE*, *BCHE*, *CHRNA4*, *CHRNB2*, *APOE*, *MTHFR*, *CES1*, *LEPR*, *GSTM1*, and *GSTT1* variants may affect its therapeutic and toxic effects. Tacrine is a major substrate of CYP1A2 and CYP3A4, a minor substrate of CYP2D6, and is transported via SCN1A. Tacrine is an inhibitor of ACHE, BCHE, and CYP1A2 [86] (Table 1). Both tacrine and some tacrine-hybrids may cause an induction of CYP1A1, 2B1 and 3A2 expression [159]. 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 SNPs within ATP-binding cassette, subfamily B (MDR/TAP), member 4 (*ABCB4*) [160].

Memantine

Memantine is an 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 it 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 [86,137,161] (Table 1). Memantine is beneficial for AD patients in terms of cognition and in the clinician's global impression; however, some memantine-related major side-effects (somnolence, weight gain, confusion, hypertension, nervous system disorders, falling) [161] might be associated with pharmacogenetic factors. Micuda et al. [162] studied the drug interaction potential of memantine by elucidation of its inhibitory effects on cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) using pooled Human Liver Microsomes (HLM) and recombinant P450s. In HLM, memantine inhibited CYP2B6 and CYP2D6 activities, showed no appreciable effect on CYP1A2, CYP2E1, CYP2C9, or CYP3A4 activities, and decreased CYP2A6 and CYP2C19 activities. When co-administered with CYP2B6 substrates, a decrease in metabolism of over 65% can be expected. Noetzli et al. [163] investigated clinical and genetic factors influencing memantine disposition. A population pharmacokinetic study was performed including data from 108 patients recruited in a naturalistic setting. Patients were genotyped for common polymorphisms in renal cation transporters (*SLC22A1/2/5*, *SLC47A1*, *ABCB1*) and nuclear receptors (*NR1I2*, *NR1I3*, *RXR*, *PPAR*)

involved in transporter expression. The average clearance was 5.2 L/h with a 27% inter-individual variability. Glomerular filtration rate and sex influenced memantine clearance. *NR1I2* rs1523130 was identified as the unique significant genetic covariate for memantine clearance, with carriers of the *NR1I2* rs1523130 CT/TT genotypes presenting a 16% slower memantine elimination than carriers of the CC genotype.

Administration of NMDA receptor antagonists, such as ketamine and MK-801, may induce psychotic-like behaviors, and ketamine can exacerbate psychotic symptoms in patients with schizophrenia; in contrast, memantine, a non-competitive NMDA receptor antagonist approved for AD, may potentially display antipsychotic effects. The molecular mechanisms by which these NMDA receptor antagonists cause different neurochemical, behavioral, and clinical effects are associated with differential expression of particular genes (*Homer1a/Homer1b/PSD-95* signaling network), involved in glutamate-dependent synaptic plasticity, as well as in psychosis pathophysiology and treatment. Ketamine and MK-801 significantly induced the transcripts of immediate-early genes (*Arc, c-fos, and Homer1a*) in cortical regions, whereas they reduced *Homer1b* and *PSD-95* expression in cortical and striatal regions. Memantine did not increase Homer1a signal, whereas it induced c-fos in the somatosensory and in the medial agranular cortices, not affecting Homer1b and PSD-95 expression. When compared to ketamine and MK-801, memantine significantly increased the expression of *c-fos, Homer1b* and *PSD-95*. Overall, ketamine and MK-801 prominently increased *Homer1a/Homer1b* expression ratio, whereas memantine elicited the opposite effect. According to de Bartolomeis et al. [164], these data may support the view that ketamine, MK-801 and memantine exert divergent effects on PSD transcripts, which may contribute to their partially different behavioral and clinical effects.

Martinelli-Boneschi et al. [165] conducted a genome-wide association study in a cohort of 176 Italian AD patients treated with cholinesterase inhibitors, classifying the patients into responders (positive, stable, or ≤1 worsening of MMSE score) and non-responders (>3 points worsening in MMSE score) during a median follow-up of 0.85 years of treatment. Among the 48 SNPs screened, only 2 SNPs were associated with response to treatment: rs6720975A, and rs17798800A, an intergenic variant potentially acting as a cis-regulator of neurobeachin (NBEA), an A kinase-anchoring protein playing a substantial role in the maturation of the nervous system.

Epigenetics

Epigenetics refers to phenotypic changes with no apparent alterations in structural DNA. 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 [166].

Vertebrate genomes undergo epigenetic reprogramming during development and disease. Stable transmission of DNA methylation, transcriptomes and phenotypes from parent to clonal offspring are demonstrated in various asexual species, and clonal genotypes from natural populations show habitat-specific DNA methylation [167]. Methylation varies spatially across the genome with a majority of the methylated sites mapping to intragenic regions [168]. 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. mtDNA methylation is attracting increasing attention as a potential biomarker for the detection and diagnosis of diseases and the understanding of cellular behavior [169].

Epigenetic mechanisms and miRNAs have recently been shown to closely interact with each other, thereby creating reciprocal regulatory circuits, which appear to be disrupted in AD [170]. Brain hypoperfusion-related changes in DNA methylation may also contribute to accelerate neuronal death. Short-term, sub-lethal hypoxia results in long-lasting changes to genome-wide DNA methylation status, and some of these changes can be highly correlated with transcriptional modulation in a number of genes involved in functional pathways [171].

Memory decline is a seminal symptom in dementia. Gene expression is required for long-lasting forms of memory. Epigenetic mechanisms do not only provide complexity in the protein regulatory complexes that control coordinate transcription for specific cell function, but the epigenome encodes critical information that integrates experience and cellular history for specific cell functions as well. Epigenetic mechanisms provide a unique mechanism of gene expression regulation for memory processes. Negative regulators of gene expression, such as HDACs, have powerful effects on the formation and persistence of memory. HDAC inhibition transforms a subthreshold learning event into robust long-term memory and generates a form of long-term memory that persists beyond the point at which normal long-term memory fails [172]. Whereas increments in histone acetylation have consistently been shown to favor learning and memory, a lack thereof has been causally implicated in cognitive impairments in neurodevelopmental disorders, neurodegeneration and aging. As histone acetylation and cognitive functions can be pharmacologically restored by histone deacetylase inhibitors, this epigenetic modification might constitute a molecular memory aid on the chromatin and, by extension, a new template for therapeutic interventions against cognitive decline [173].

Neurons, due to their post-mitotic state, high metabolism, and longevity are particularly prone to the accumulation of DNA lesions. DNA damage has been suggested as a major contributor to both age-associated neurodegenerative diseases and acute neurological injury. The DNA damage response is a key factor in maintaining genome integrity. It relies on highly dynamic post-translational modifications of the chromatin and DNA repair proteins to allow signaling, access, and repair of the lesion [174]. The repair of DNA lesions, particularly oxidative DNA lesions, might be altered in AD. DNA damage is paralleled by a decrease in DNA repair activities. DNA repair proteins might be inactivated by oxidative induced post-translational modifications or degradation. Activation of DNA repair pathways might generate death signals ending with neuronal apoptosis. A link between environment-induced epigenetic modification, oxidation, and repair of AD-related genes has been proposed [175]. Early life exposure of rodents and primates to xenobiotics may enhance the expression of genes associated with AD, repress the expression of others, and increase the burden of oxidative DNA damage in the aged brain. Epigenetic mechanisms that control gene expression and promote the accumulation of oxidative DNA damage are mediated through alterations in the methylation or oxidation of CpG dinucleotides. Environmental influences occurring during brain development inhibit DNA-methyltransferases, thus hypomethylating promoters of genes associated with AD, such as *APP*. This early life imprint may sustain and trigger later in life to increase the levels of APP and Aβ. Increased Aβ levels promote the production of reactive oxygen species, which damage DNA and accelerate neurodegenerative events. These early life perturbations may result in hypomethylation as well as hypermethylation of genes. The hypermethylated genes are rendered susceptible to Aβ-enhanced oxidative DNA damage because methylcytosines restrict repair of adjacent hydroxyguanosines [176]. Many AD-related genes contain methylated CpG sites in their promoter regions, and a genome-wide decrease in DNA methylation has been reported in AD [2,4,5,177,178]. A small bulk of recent information [173,179,180] suggests that histone modifications are present in AD: (i) histone acetylation is reduced in AD brain tissues [181] and in AD transgenic models [173]; (ii) levels of HDAC6, a tau-

interacting protein and a potential modulator of tau phosphorylation and accumulation, are increased in cortical and hippocampal regions in AD [182]; mice lacking HDAC6 are cognitively normal, but reducing endogenous HDAC6 levels restores learning and memory and α-tubulin acetylation [183]; (iii) SIRT1 is decreased in the parietal cortex of AD patients, and the accumulation of Aβ and tau in AD brains might be related to the loss of SIRT1 [184], since SIRT1 may reduce Aβ production, activating the transcription of ADAM10 [185]; (iv) in the brains of twins discordant for AD, trimethylation of H3K9, a marker of gene silencing, and condensation of heterochromatin structure, are increased in the temporal cortex and hippocampus of the AD twin as compared to the twin devoid of AD neuropathology [186]; (v) phosphorylation of H3S10, a key regulator in chromatin compaction during cell division, is increased in the cytoplasm of hippocampal neurons in AD cases [187]; (vi) evidence of DNA damage, as reflected by phosphorylated H2AX at Ser139, is present in hippocampal astrocytes of AD patients [188]; (vii) Long-Term Potentiation (LTP) and memory deficits in *APP/PS1* transgenic mice might be mediated in part by decreased H4 acetylation; improving histone acetylation level restores learning after synaptic dysfunction [189]; (viii) acetylation of H3 and H4 is increased in 3xTg-AD neurons relative to non-transgenic neurons [190]; (ix) nuclear translocation of EP300 interacting inhibitor of differentiation 1 (EID1), a CBP/p300 inhibitory protein, is increased in the cortical neurons of AD patients, and overexpression of EID1 is reported to reduce hippocampal LTP and to impair cognitive function via inhibiting CBP/p300 acetyltrasferase activity and disrupting neuronal structure [191]; (x) memory formation leads to a transient increase in acetylation on lysine residues within H2B, H3, H4 [192,193]; (xi) inhibition of HDAC induces dendritic sprouting, increases synaptic number, and improves long-term memory [194]; (xii) overexpression of neuronal HDAC2 decreases dendritic spine density, synapse number, synaptic plasticity and memory formation, and HDAC2 deficiency increases synapse number and memory facilitation [195,196]; (xiii) HDAC4 is involved in learning and synaptic plasticity, and selective inhibition of HDAC4 activity may deteriorate learning and memory [197]; (xiv) treatment of hippocampal neurons with HDAC inhibitors facilitates Bdnf expression via hyperacetylation of histones at the Bdnf promoters [198,199]; (xv) histone(H3K4) methylation participates in the regulation of Bdnf expression and memory formation [200]; (xvi) histone methylation also facilitates memory consolidation coupled with histone acetylation; inhibition of HDACs with Sodium Butyrate (NaB) causes an increase in H3K4 trimethylation and a decrease in H3K9 dimethylation in the hippocampus after fear conditioning [200]; (xvii) histone H3 acetylation, methylation and phosphorylation is increased in the prefrontal cortex of Tg2576 mice, and histone H4 acetylation is increased in the hippocampal CA1 neurons of these transgenic mice [2,4,201].

Several lncRNAs are dysregulated in AD (*Sox2OT, 1810014B01Rik, BC200, BACE1-AS, NAT-Rad18, 17A, GDNFOS*), Parkinson's disease (*naPINK1, Sox2OT, 1810014B01Rik, BC200*), and Huntington's disease (*HAR1F, HTTAS, DGCR5, NEAT1, TUG1*) [202]. miRNAs belong to the class of non-coding regulatory RNA molecules of ~22 nt length and are now recognized to regulate ~60% of all known genes through post-transcriptional gene silencing (RNA interference) (RNAi). Alterations in epigenetically-regulated miRNAs may contribute to the abnormal expression of pathogenic genes in AD [170,202]. 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 (5q34), miR-148a (7p15.2), miR-184 (15q25.1), and miR-200 (miR-200b/200a/429, 1p36.33; miR-200c/141, 12p13.31) [2,4,170].

Pharmacoepigenetics

Epigenetic regulation is responsible for the tissue-specific expression of genes involved in pharmacogenetic processes, and epigenetics plays a key role in the development of drug resistance. In this regard, to optimize therapeutics with this category of drugs, it is important to understand the reciprocal effects that epigenetic drugs exert on pathogenic, mechanistic, metabolic, and transporter genes [2,3,86]. Although this is a still poorly explored field, epigenetic regulation of genes encoding drug-metabolizing enzymes (CYP1A1, 1A2, 1B1, 1A6, 2A13, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 2F1, 2R1, 2S1, 2W1, 3A4, 3A5, 3A7, 3A43, UGT1, GSTP1), drug transporters (ABCB1/MDR1/P-gp, ABCC1/MRP1, ABCC11/MRP8, ABCG2/BCRP, SLC19A1, SLC22A8), and nuclear receptors (RARB2, ESR1, NR1I2, HNF41) has been documented in pioneering studies of pharmacoepigenetics [86,203,204].

Conclusions

1. AD is a polygenic/complex disorder in which multiple genomic defects, epigenetic changes, and environmental factors are potentially involved.
2. The interplay of pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes is responsible for the therapeutic response in AD.
3. Epigenetic phenomena (DNA methylation, histone modifications, chromatin remodeling, and miRNA dysregulation) may also affect the pharmacogenetic outcome.
4. Different *APOE*-associated haplotypes influence the pharmacological effect (efficacy, safety) of drugs in AD.
5. Only 25% of the Caucasian population are extensive metabolizers for drugs metabolized via CYP2D6-CYP2C9-CYP2C19 enzymes.
6. *CYP2D6* poor (PM) and Ultra-Rapid Metabolizers (UM) are the worst responders to drugs in AD; and there is a tendency for the accumulation of PMs and UMs among patients harboring the *APOE*-4 allele.
7. *APOE*-4 carriers are the worst responders and *APOE*-3 carriers are the best responders to conventional treatments.
8. *TOMM40* poly T-S/S carriers are the best responders, VL/VL and S/VL carriers are intermediate responders, and L/L carriers are the worst responders to treatment.
9. 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), and to a lesser extent S/VL and VL/VL carriers, in haplotypes with *APOE*-3 are the best responders to treatment. In 100% of the cases, the L/L genotype is exclusively associated with the *APOE*-4/4 genotype, and this haplotype (4/4-L/L) is probably responsible for early onset of the disease, a faster cognitive decline, and a poor response to different treatments.

References

1. Cacabelos R, Fernandez-Novoa L, Lombardi V, Kubota Y, Takeda M (2005) Molecular genetics of Alzheimer's disease and aging. Methods Find Exp Clin Pharmacol 27: 1-573.
2. Cacabelos R, Torrellas C (2014) Epigenetic drug discovery for Alzheimer's disease. Expert Opin Drug Discov 9: 1059-1086.
3. Cacabelos R, Cacabelos P, Torrellas C, Tellado I, Carril JC (2014) Pharmacogenomics of Alzheimer's disease: novel therapeutic strategies for drug development. Methods Mol Biol 1175: 323-556.
4. Cacabelos R, Torrellas C, López-Muñoz F (2014) Epigenomics of Alzheimer's disease. J Exper Clin Med 6: 75-82.

5. Wang J, Zhao Z, Lin E, Zhao W, Qian X, et al. (2013) Unintended effects of cardiovascular drugs on the pathogenesis of Alzheimer's disease. PLoS One 8: e65232.

6. Montastruc F, Gardette V, Cantet C, Piau A, Lapeyre-Mestre M, et al. (2013) Potentially inappropriate medication use among patients with Alzheimer disease in the REAL.FR cohort: be aware of atropinic and benzodiazepine drugs! Eur J Clin Pharmacol 69: 1589-1597.

7. Cacabelos R (2011) Alzheimer's disease 2011: Where are we heading? Gen-T 8: 54-86.

8. Cacabelos R (2012) Pharmacogenomics of central nervous system (CNS) drugs. Drug Dev Res 73: 461-476.

9. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: The AlzGene database. Nat Genet 39: 17-23.

10. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297: 353-356.

11. Larner AJ (2013) Presenilin-1 mutations in Alzheimer's disease: an update on genotype-phenotype relationships. J Alzheimers Dis 37: 653-659.

12. Selkoe DJ, Podlisny MB (2002) Deciphering the genetic basis of Alzheimer's disease. Annu Rev Genomics Hum Genet 3: 67-99.

13. Suh YH, Checler F (2002) Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. Pharmacol Rev 54: 469-525.

14. Roses AD, Strittmatter WJ, Pericak-Vance MA, Corder EH, Saunders AM, et al. (1994) Clinical application of apolipoprotein E genotyping to Alzheimer's disease. Lancet 343: 1564-1565.

15. Schupf N, Barral S, Perls T, Newman A, Christensen K, et al. (2013) Apolipoprotein E and familial longevity. Neurobiol Aging 34: 1287-1291.

16. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, et al. (1994) Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 7: 180-184.

17. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, et al. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261: 921-923.

18. Li YJ, Scott WK, Hedges DJ, Zhang F, Gaskell PC, et al. (2002) Age at onset in two common neurodegenerative diseases is genetically controlled. Am J Hum Genet 70: 985-993.

19. Cacabelos R, Takeda M (2006) Pharmacogenomics, nutrigenomics and future therapeutics in Alzheimer's disease. Drugs Future 31: 5-146.

20. Cacabelos R (2003) The application of functional genomics to Alzheimer's disease. Pharmacogenomics 4: 597-621.

21. Cacabelos R (2008) Pharmacogenomics in Alzheimer's disease. Methods Mol Biol 448: 213-357.

22. Cacabelos R, Martínez-Bouza R (2011) Genomics and pharmacogenomics of dementia. CNS Neurosci Ther 17: 566-576.

23. Cacabelos R, Fernández-Novoa L, Pichel V, Lombardi V, Kubota Y, et al. (2004) Pharmacogenomic studies with a combination therapy in Alzheimer's disease. In: Takeda M, Tanaka T, Cacabelos R (eds) Molecular Neurobiology of Alzheimer Disease and Related Disorders. Karger, Switzerland 94-107.

24. Cacabelos R, Llovo R, Fraile C, Fernández-Novoa L (2007) Pharmacogenetic aspects of therapy with cholinesterase inhibitors: the role of CYP2D6 in Alzheimer's disease pharmacogenetics. Curr Alzheimer Res 4: 479-500.

25. Cacabelos R (2007) Donepezil in Alzheimer's disease: From conventional trials to pharmacogenetics. Neuropsychiatr Dis Treat 3: 303-333.

26. Cacabelos R (2009) Pharmacogenomics and therapeutic strategies for dementia. Expert Rev Mol Diagn 9: 567-611.

27. Cacabelos R, Fernández-Novoa L, Martínez-Bouza R, McKay A, Carril JC, et al. (2010) Future trends in the pharmacogenomics of brain disorders and dementia: Influence of APOE and CYP2D6 variants. Pharmaceuticals 3: 3040-3100.

28. Cacabelos R (2011) The path to personalized medicine in mental disorders. In: Ritsner MS (eds) The handbook of neuropsychiatric biomarkers, endophenotypes and genes. Springer, Netherlands 3-63.

29. Roses AD (2004) Pharmacogenetics and drug development: the path to safer and more effective drugs. Nat Rev Genet 5: 645-656.

30. Roses AD (2008) Pharmacogenetics in drug discovery and development: a translational perspective. Nat Rev Drug Discov 7: 807-817.

31. Kennedy RE, Cutter GR, Schneider LS (2014) Effect of APOE genotype status on targeted clinical trials outcomes and efficiency in dementia and mild cognitive impairment resulting from Alzheimer's disease. Alzheimers Dement 10: 349-359.

32. Sabbagh MN, Malek-Ahmadi M, Dugger BN, Lee K, Sue LI, et al. (2013) The influence of Apolipoprotein E genotype on regional pathology in Alzheimer's disease. BMC Neurol 13: 44.

33. Schiepers OJ, Harris SE, Gow AJ, Pattie A, Brett CE, et al. (2012) APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. Mol Psychiatry 17: 315-324.

34. Cacabelos R (2005) Pharmacogenomics and therapeutic prospects in Alzheimer's disease. Expert Opin Pharmacother 6: 1967-1987.

35. Cacabelos R (2005) Molecular pathology and pharmacogenomics in Alzheimer's disease: polygenic-related effects of multifactorial treatments on cognition, anxiety and depression. Methods Find Exp Clin Pharmacol 29: 1-91.

36. Cacabelos R (2005) Pharmacogenomics, nutrigenomics and therapeutic optimization in Alzheimer's disease. Aging Health 1: 303-348.

37. Cacabelos R (2008) Pharmacogenomics and therapeutic prospects in dementia. Eur Arch Psychiatry Clin Neurosci 258: 28-47.

38. Takeda M, Martínez R, Kudo T, Tanaka T, Okochi M, et al. (2010) Apolipoprotein E and central nervous system disorders: reviews of clinical findings. Psychiatry Clin Neurosci 64: 592-607.

39. Roses AD (2009) The medical and economic roles of pipeline pharmacogenetics: Alzheimer's disease as a model of efficacy and HLA-B(*)5701 as a model of safety. Neuropsychopharmacology 34: 6-17.

40. Roses AD, Saunders AM, Huang Y, Strum J, Weisgraber KH, et al. (2007) Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenic hypothesis (Alzheimer's disease). Pharmacogenomics J 7: 10-28.

41. Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, et al. (2006) Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J 6: 246-254.

42. Dimitrov M, Alattia JR, Lemmin T, Lehal R, Fligier A, et al. (2013) Alzheimer's disease mutations in APP but not γ-secretase modulators affect epsilon-cleavage-dependent AICD production. Nat Commun 4: 2246.

43. Bagnoli S, Piaceri I, Tedde A, Bessi V, Bracco L, et al. (2013) TOMM40 polymorphisms in Italian Alzheimer's disease and frontotemporal dementia patients. Neurol Sci 34: 995-998.

44. Linnertz C, Saunders AM, Lutz MW, Crenshaw DM, Grossman I, et al. (2012) Characterization of the poly-T variant in the TOMM40 gene in diverse populations. PLoS One 7: e30994.

45. Lutz MW, Crenshaw DG, Saunders AM, Roses AD (2010) Genetic variation at a single locus and age of onset for Alzheimer's disease. Alzheimers Dement 6: 125-131.

46. Ma XY, Yu JT, Wang W, Wang HF, Liu QY, et al. (2013) Association of TOMM40 polymorphisms with late-onset Alzheimer's disease in a Northern Han Chinese population. Neuromolecular Med 15: 279-287.

47. Omoumi A, Fok A, Greenwood T, Sadovnick AD, Feldman HH, et al. (2014) Evaluation of late-onset Alzheimer disease genetic susceptibility risks in a Canadian population. Neurobiol Aging 35: 936. e5-12.

48. Potkin SG, Guffanti G, Lakatos A, Turner JA, Kruggel F, et al. (2009) Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease. PLoS One 4: e6501.

49. Roses AD (2010) An inherited variable poly-T repeat genotype in TOMM40 in Alzheimer disease. Arch Neurol 67: 536-541.

50. Roses AD, Lutz MW, Amrine-Madsen H, Saunders AM, Crenshaw DG, et al. (2010) A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease. Pharmacogenomics J 10: 375-384.

51. Roses AD, Lutz MW, Crenshaw DG, Grossman I, Saunders AM, et al. (2013) TOMM40 and APOE: Requirements for replication studies of association with age of disease onset and enrichment of a clinical trial. Alzheimers Dement 9: 132-136.

52. Roses AD, Saunders AM, Lutz MW, Zhang N, Hariri AR, et al. (2014) New applications of disease genetics and pharmacogenetics to drug development. Curr Opin Pharmacol 14: 81-89.

53. Shen L, Kim S, Risacher SL, Nho K, Swaminathan S, et al. (2010) Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: A study of the ADNI cohort. Neuroimage 53: 1051-1063.

54. Takei N, Miyashita A, Tsukie T, Arai H, Asada T, et al. (2009) Genetic association study on in and around the APOE in late-onset Alzheimer disease in Japanese. Genomics 93: 441-448.

55. Valant V, Keenan BT, Anderson CD, Shulman JM, Devan WJ, et al. (2012) TOMM40 in cerebral amyloid angiopathy related intracerebral hemorrhage: comparative genetic analysis with Alzheimer's disease. Transl Stroke Res 3: 102-112.

56. Vounou M, Janousova E, Wolz R, Stein JL, Thompson PM, et al. (2012) Sparse reduced-rank regression detects genetic associations with voxel-wise longitudinal phenotypes in Alzheimer's disease. Neuroimage 60: 700-716.

57. Bernardi L, Gallo M, Anfossi M, Conidi ME, Colao R, et al. (2013) Role of TOMM40 rs10524523 polymorphism in onset of alzheimer's disease caused by the PSEN1 M146L mutation. J Alzheimers Dis 37: 285-289.

58. Cruchaga C, Nowotny P, Kauwe JS, Ridge PG, Mayo K, et al. (2011) Association and expression analyses with single-nucleotide polymorphisms in TOMM40 in Alzheimer disease. Arch Neurol 68: 1013-1019.

59. Jun G, Vardarajan BN, Buros J, Yu CE, Hawk MV, et al. (2012) Comprehensive search for Alzheimer disease susceptibility loci in the APOE region. Arch Neurol 69: 1270-1279.

60. Li G, Bekris LM, Leong L, Steinbart EJ, Shofer JB, et al. (2013) TOMM40 intron 6 poly-T length, age at onset, and neuropathology of AD in individuals with APOE ε3/ε3. Alzheimers Dement 9: 554-561.

61. Beekman M, Blanché H, Perola M, Hervonen A, Bezrukov V, et al. (2013) Genome-wide linkage analysis for human longevity: Genetics of healthy aging study. Aging Cell 12: 184-193.

62. Sebastiani P, Solovieff N, Dewan AT, Walsh KM, Puca A, et al. (2012) Genetic signatures of exceptional longevity in humans. PLoS One 7: e29848.

63. Zhang C, Pierce BL (2014) Genetic susceptibility to accelerated cognitive decline in the US Health and Retirement Study. Neurobiol Aging 35: 1512.e11-e18.

64. Davies G, Harris SE, Reynolds CA, Payton A, Knight HM, et al. (2014) A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. Mol Psychiatry 19: 76-87.

65. Hayden KM, McEvoy JM, Linnertz C, Attix D, Kuchibhatla M, et al. (2012) A homopolymer polymorphism in the TOMM40 gene contributes to cognitive performance in aging. Alzheimers Dement 8: 381-388.

66. Linnertz C, Anderson L, Gottschalk W, Crenshaw D, Lutz MW, et al. (2014) The cis-regulatory effect of an Alzheimer's disease-associated poly-T locus on expression of TOMM40 and apolipoprotein E genes. Alzheimers Dement 10: 541-551.

67. Johnson SC, La Rue A, Hermann BP, Xu G, Koscik RL, et al. (2011) The effect of TOMM40 poly-T length on gray matter volume and cognition in middle-aged persons with APOE ε3/ε3 genotype. Alzheimers Dement 7: 456-465.

68. Lyall DM, Harris SE, Bastin ME, Muñoz-Maniega S, Murray C, et al. (2014) Alzheimer's disease susceptibility genes APOE and TOMM40, and brain white matter integrity in the Lothian Birth Cohort 1936. Neurobiol Aging 35: 1513.e25-e33.

69. Bruno D, Pomara N, Nierenberg J, Ritchie JC, Lutz MW, et al. (2012) Levels of cerebrospinal fluid neurofilament light protein in healthy elderly vary as a function of TOMM40 variants. Exp Gerontol 47: 347-352.

70. Elias-Sonnenschein LS, Helisalmi S, Natunen T, Hall A, Paajanen T, et al. (2013) Genetic loci associated with Alzheimer's disease and cerebrospinal fluid biomarkers in a finnish case-control cohort. PLoS One 8: e59676.

71. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, et al. (2011) Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology 76: 69-79.

72. Silver M, Janousova E, Hua X, Thompson PM, Montana G, et al. (2012) Identification of gene pathways implicated in Alzheimer's disease using longitudinal imaging phenotypes with sparse regression. Neuroimage 63: 1681-1694.

73. McFarquhar M, Elliott R, McKie S, Thomas E, Downey D, et al. (2014) TOMM40 rs2075650 may represent a new candidate gene for vulnerability to major depressive disorder. Neuropsychopharmacology 39: 1743-1753.

74. Mastaglia FL, Rojana-udomsart A, James I, Needham M, Day TJ, et al. (2013) Polymorphism in the TOMM40 gene modifies the risk of developing sporadic inclusion body myositis and the age of onset of symptoms. Neuromuscul Disord 23: 969-974.

75. Seripa D, Bizzarro A, Pilotto A, Palmieri O, Panza F, et al. (2012) TOMM40, APOE, and APOC1 in primary progressive aphasia and frontotemporal dementia. J Alzheimers Dis 31: 731-740.

76. Ellis J, Lange EM, Li J, Dupuis J, Baumert J, et al. (2014) Large multiethnic Candidate Gene Study for C-reactive protein levels: identification of a novel association at CD36 in African Americans. Hum Genet 133: 985-995.

77. Zhou L, He M, Mo Z, Wu C, Yang H, et al. (2013) A genome wide association study identifies common variants associated with lipid levels in the Chinese population. PLoS One 8: e82420.

78. Jiang R, Brummett BH, Hauser ER, Babyak MA, Siegler IC, et al. (2013) Chronic family stress moderates the association between a TOMM40 variant and triglyceride levels in two independent Caucasian samples. Biol Psychol 93: 184-189.

79. Zhang Z, Tao L, Chen Z, Zhou D, Kan M, et al. (2011) Association of genetic loci with blood lipids in the Chinese population. PLoS One 6: e27305.

80. Guo Y, Lanktree MB, Taylor KC, Hakonarson H, Lange LA, et al. (2013) Gene-centric meta-analyses of 108 912 individuals confirm known body mass index loci and reveal three novel signals. Hum Mol Genet 22: 184-201.

81. Jeemon P, Pettigrew K, Sainsbury C, Prabhakaran D, Padmanabhan S (2011) Implications of discoveries from genome-wide association studies in current cardiovascular practice. World J Cardiol 3: 230-247.

82. Middelberg RP, Ferreira MA, Henders AK, Heath AC, Madden PA, et al. (2011) Genetic variants in LPL, OASL and TOMM40/APOE-C1-C2-C4 genes are associated with multiple cardiovascular-related traits. BMC Med Genet 12: 123.

83. Ronald J, Rajagopalan R, Ranchalis JE, Marshall JK, Hatsukami TS, et al. (2009) Analysis of recently identified dyslipidemia alleles reveals two loci that contribute to risk for carotid artery disease. Lipids Health Dis 8: 52.

84. Cacabelos R, Goldgaber D, Vostrov A, Matsuki H, Torrellas C, et al. (2014) APOE-TOMM40 in the Pharmacogenomics of dementia. J Pharmacogenomics Pharmacoproteomics 5: 135.

85. Caselli RJ, Dueck AC, Huentelman MJ, Lutz MW, Saunders AM, et al. (2012) Longitudinal modeling of cognitive aging and the TOMM40 effect. Alzheimers Dement 8: 490-495.

86. Cacabelos R (2012) World guide for drug use and pharmacogenomics. Euroespes Publishing, Corunna.

87. Preissner S1, Kroll K, Dunkel M, Senger C, Goldsobel G, et al. (2010) SuperCYP: A comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res 38: D237-D243.

88. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, et al. (2012) Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther 92: 414-417.

89. Isaza CA, Henao J, López AM, Cacabelos R (2000) Isolation, sequence and genotyping of the drug metabolizer CYP2D6 gene in the Colombian population. Methods Find Exp Clin Pharmacol 22: 695-705.

90. Mizutani T (2003) PM frequencies of major CYPs in Asians and Caucasians. Drug Metab Rev 35: 99-106.

91. Ozawa S, Soyama A, Saeki M, Fukushima-Uesaka H, Itoda M, et al. (2004) Ethnic differences in genetic polymorphisms of CYP2D6, CYP2C19, CYP3As and MDR1/ABCB1. Drug Metab Pharmacokin 19: 83-95.

92. Weinshilboum RM, Wang L (2006) Pharmacogenetics and pharmacogenomics: development, science, and translation. Annu Rev Genomics Hum Genet 7: 223-245.

93. Tayler H, Fraser T, Miners JS, Kehoe PG, Love S (2010) Oxidative balance in Alzheimer's disease: relationship to APOE, Braak tangle stage, and the concentrations of soluble and insoluble amyloid-β. J Alzheimers Dis 22: 1363-1373.

94. Cacabelos R (2007) Pharmacogenetic basis for therapeutic optimization in Alzheimer's disease. Mol Diagn Ther 11: 385-405.

95. Haufroid V (2011) Genetic polymorphisms of ATP-binding cassette transporters ABCB1 and ABCC2 and their impact on drug disposition. Curr Drug Targets 12: 631-646.

96. Marquez B, Van Bambeke F (2011) ABC multidrug transporters: target for modulation of drug pharmacokinetics and drug-drug interactions. Curr Drug Targets 12: 600-620.

97. Li G, Gu HM, Zhang DW (2013) ATP-binding cassette transporters and cholesterol translocation. IUBMB Life.

98. Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN, et al. (2013) Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ϵ4, and the risk of late-onset Alzheimer disease in African Americans. JAMA 309: 1483-1492.

99. Abuznait AH, Kaddoumi A (2012) Role of ABC transporters in the pathogenesis of Alzheimer's disease. ACS Chem Neurosci 3: 820-831.

100. Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C, et al. (2012) Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. PLoS One 7: e50976.

101. Qosa H, Abuznait AH, Hill RA, Kaddoumi A (2012) Enhanced brain amyloid-β clearance by rifampicin and caffeine as a possible protective mechanism against Alzheimer's disease. J Alzheimers Dis 31: 151-165.

102. Silverberg GD, Messier AA, Miller MC, Machan JT, Majmudar SS, et al. (2010) Amyloid efflux transporter expression at the blood-brain barrier declines in normal aging. J Neuropathol Exp Neurol 69: 1034-1043.

103. van Assema DM, Lubberink M, Rizzu P, van Swieten JC, Schuit RC, et al. (2012) Blood-brain barrier P-glycoprotein function in healthy subjects and Alzheimer's disease patients: Effect of polymorphisms in the ABCB1 gene. EJNMMI Res 2: 57.

104. Wolf A, Bauer B, Hartz AM (2012) ABC transporters and the alzheimer's disease enigma. Front Psychiatry 3: 54.

105. Brenn A, Grube M, Peters M, Fischer A, Jedlitschky G, et al. (2011) Beta-amyloid downregulates MDR1-P-glycoprotein (Abcb1) expression at the blood-brain barrier in mice. Int J Alzheimers Dis 2011: 690121.

106. Wijesuriya HC, Bullock JY, Faull RL, Hladky SB, Barrand MA (2010) ABC efflux transporters in brain vasculature of Alzheimer's subjects. Brain Res 1358: 228-238.

107. Do TM, Noel-Hudson MS, Ribes S, Besengez C, Smirnova M, et al. (2012) ABCG2- and ABCG4-mediated efflux of amyloid-β peptide 1-40 at the mouse blood-brain barrier. J Alzheimers Dis 30: 155-166.

108. Fehér Á, Juhász A, László A, Pákáski M, Kálmán J, et al. (2013) Association between the ABCG2 C421A polymorphism and Alzheimer's disease. Neurosci Lett 550: 51-54.

109. Mairinger S, Erker T, Muller M, Langer O (2011) PET and SPECT radiotracers to assess function and expression of ABC transporters in vivo. Curr Drug Metab 12: 774-792.

110. van Assema DM, Lubberink M, Bauer M, van der Flier WM, Schuit RC, et al. (2012) Blood-brain barrier P-glycoprotein function in Alzheimer's disease. Brain 135: 181-189.

111. Kohen R, Shofer JB, Korvatska O, Petrie EC, Wang LY, et al. (2011) ABCB1 genotype and CSF beta-amyloid in Alzheimer disease. J Geriatr Psychiatry Neurol 24: 63-66.

112. Frankfort SV, Doodeman VD, Bakker R, Tulner LR, van Campen JP, et al. (2006) ABCB1 genotypes and haplotypes in patients with dementia and age-matched non-demented control patients. Mol Neurodegener 1:13.

113. Chen KD, Chang PT, Ping YH, Lee HC, Yeh CW, et al. (2011) Gene expression profiling of peripheral blood leukocytes identifies and validates ABCB1 as a novel biomarker for Alzheimer's disease. Neurobiol Dis 43: 698-705.

114. Zhang W, Xiong H, Callaghan D, Liu H, Jones A, et al. (2013) Blood-brain barrier transport of amyloid beta peptides in efflux pump knock-out animals evaluated by in vivo optical imaging. Fluids Barriers CNS 10: 13.

115. Elali A, Rivest S (2013) The role of ABCB1 and ABCA1 in beta-amyloid clearance at the neurovascular unit in Alzheimer's disease. Front Physiol 4: 45.

116. Cascorbi I, Flüh C, Remmler C, Haenisch S, Faltraco F, et al. (2013) Association of ATP-binding cassette transporter variants with the risk of Alzheimer's disease. Pharmacogenomics 14: 485-494.

117. Syvänen S, Eriksson J (2013) Advances in PET imaging of P-glycoprotein function at the blood-brain barrier. ACS Chem Neurosci 4: 225-237.

118. Müllauer J, Karch R, Bankstahl JP, Bankstahl M, Stanek J, et al. (2013) Assessment of cerebral P-glycoprotein expression and function with PET by combined [11C] inhibitor and [11C] substrate scans in rats. Nucl Med Biol 40: 755-763.

119. Contino M, Cantore M, Capparelli E, Perrone MG, Niso M, et al. (2012) A benzopyrane derivative as a P-glycoprotein stimulator: A potential agent to decrease β-amyloid accumulation in Alzheimer's disease. Chem Med Chem 7: 391-395.

120. Jedlitschky G, Grube M, Mosyagin I, Kroemer HK, Vogelgesang S (2014) Targeting CNS transporters for treatment of neurodegenerative diseases. Curr Pharm Des 20: 1523-1533.

121. Mehta DC, Short JL, Nicolazzo JA (2013) Altered brain uptake of therapeutics in a triple transgenic mouse model of Alzheimer's disease. Pharm Res 30: 2868-2879.

122. Durk MR, Chan GN, Campos CR, Peart JC, Chow EC, et al. (2012) 1α,25-Dihydroxyvitamin D3-liganded vitamin D receptor increases expression and transport activity of P-glycoprotein in isolated rat brain capillaries and human and rat brain microvessel endothelial cells. J Neurochem 123: 944-953.

123. Namanja HA, Emmert D, Pires MM, Hrycyna CA, Chmielewski J (2009) Inhibition of human P-glycoprotein transport and substrate binding using a galantamine dimer. Biochem Biophys Res Commun 388: 672-676.

124. Saint-Pol J, Candela P, Boucau MC, Fenart L, Gosselet F (2013) Oxysterols decrease apical-to-basolateral transport of Aβ peptides via an ABCB1-mediated process in an *in vitro* blood-brain barrier model constituted of bovine brain capillary endothelial cells. Brain Res 1517: 1-15.

125. Brodney MA, Barreiro G, Ogilvie K, Hajos-Korcsok E, Murray J, et al. (2012) Spirocyclic sulfamides as β-secretase 1 (BACE-1) inhibitors for the treatment of Alzheimer's disease: utilization of structure based drug design, WaterMap, and CNS penetration studies to identify centrally efficacious inhibitors. J Med Chem 55: 9224-9239.

126. Brodney MA, Johnson DE, Sawant-Basak A, Coffman KJ, Drummond EM, et al. (2012) Identification of multiple 5-HT_4partial agonist clinical candidates for the treatment of Alzheimer's disease. J Med Chem 55: 9240-9254.

127. Wood S, Wen PH, Zhang J, Zhu L, Luo Y, et al. (2012) Establishing the relationship between in vitro potency, pharmacokinetic, and pharmacodynamic parameters in a series of orally available, hydroxyethylamine-derived β-secretase inhibitors. J Pharmacol Exp Ther 343: 460-467.

128. Abuznait AH, Cain C, Ingram D, Burk D, Kaddoumi A (2011) Up-regulation of P-glycoprotein reduces intracellular accumulation of beta amyloid: investigation of P-glycoprotein as a novel therapeutic target for Alzheimer's disease. J Pharm Pharmacol 63: 1111-1118.

129. Perrone MG, Inglese C, Berardi F, Leopoldo M, Perrone R, et al. (2013) Comparative evaluation of two dye probes in the rat everted gut sac model for unambiguous classification of P-gp substrate and inhibitor. J Pharmacol Toxicol Methods 67: 5-8.

130. Cacabelos R (2012) The metabolomics paradigm of pharmacogenomics in complex disorders. Metabolomics 2: 5.

131. Hosoya K, Tachikawa M (2011) Roles of organic anion/cation transporters at the blood-brain and blood-cerebrospinal fluid barriers involving uremic toxins. Clin Exp Nephrol 15: 478-485.

132. Carl SM, Lindley DJ, Das D, Couraud PO, Weksler BB, et al. (2010) ABC and SLC transporter expression and proton oligopeptide transporter (POT) mediated permeation across the human blood-brain barrier cell line, hCMEC/D3 [corrected]. Mol Pharm 7: 1057-1068.

133. Chen CW, Lin CC, Chen KB, Kuo YC, Li CY, et al. (2014) Increased risk of dementia in people with previous exposure to general anesthesia: a nationwide population-based case-control study. Alzheimers Dement 10: 196-204.

134. Yamamoto N, Arima H, Sugiura T, Hirate H, Taniura H, et al. (2013) Propofol and thiopental suppress amyloid fibril formation and GM1 ganglioside expression through the γ-aminobutyric acid A receptor. Anesthesiology 118: 1408-1416.

135. Cacabelos R, Alvarez A, Lombardi V, Fernández-Novoa L, Corzo L, et al. (2000) Pharmacological treatment of Alzheimer disease: From psychotropic drugs and cholinesterase inhibitors to pharmacogenomics. Drugs Today (Barc.) 36: 415-499.

136. Jann MW, Shirley KL, Small GW (2002) Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. Clin Pharmacokinet 41: 719-739.

137. Noetzli M, Eap CB (2013) Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. Clin Pharmacokinet 52: 225-241.

138. Albani D, Martinelli Boneschi F, Biella G, Giacalone G, Lupoli S, et al. (2012) Replication study to confirm the role of CYP2D6 polymorphism rs1080985 on donepezil efficacy in Alzheimer's disease patients. J Alzheimers Dis 30: 745-749.

139. Pilotto A, Franceschi M, D'Onofrio G, Bizzarro A, Mangialasche F, et al. (2009) Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer disease. Neurology 73: 761-767.

140. Savino M, Seripa D, Gallo AP, Garrubba M, D'Onofrio G, et al. (2011) Effectiveness of a high-throughput genetic analysis in the identification of responders/non-responders to CYP2D6-metabolized drugs. Clin Lab 57: 887-893.

141. Seripa D, Bizzarro A, Pilotto A, D'Onofrio G, Vecchione G, et al. (2011) Role of cytochrome P4502D6 functional polymorphisms in the efficacy of donepezil in patients with Alzheimer's disease. Pharmacogenet Genomics 21: 225-230.

142. Zhong Y, Zheng X, Miao Y, Wan L, Yan H, et al. (2013) Effect of CYP2D6*10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease. Am J Med Sci 345: 222-226.

143. Chianella C, Gragnaniello D, Maisano Delser P, Visentini MF, Sette E, et al. (2011) BCHE and CYP2D6 genetic variation in Alzheimer's disease patients treated with cholinesterase inhibitors. Eur J Clin Pharmacol 67: 1147-1157.

144. Mannheimer B, Wettermark B, Lundberg M, Pettersson H, von Bahr C, et al. (2010) Nationwide drug-dispensing data reveal important differences in adherence to drug label recommendations on CYP2D6-dependent drug interactions. Br J Clin Pharmacol 69: 411-417.

145. Varsaldi F, Miglio G, Scordo MG, Dahl ML, Villa LM, et al. (2006) Impact of the CYP2D6 polymorphism on steady-state plasma concentrations and clinical outcome of donepezil in Alzheimer's disease patients. Eur J Clin Pharmacol 62: 721-726.

146. Klimkowicz-Mrowiec A, Wolkow P, Sado M, Dziubek A, Pera J, et al. (2013) Influence of rs1080985 single nucleotide polymorphism of the CYP2D6 gene on response to treatment with donepezil in patients with alzheimer's disease. Neuropsychiatr Dis Treat 9: 1029-1033.

147. Magliulo L, Dahl ML, Lombardi G, Fallarini S, Villa LM, et al. (2011) Do CYP3A and ABCB1 genotypes influence the plasma concentration and clinical outcome of donepezil treatment? Eur J Clin Pharmacol 67: 47-54.

148. Farlow MR (2003) Clinical pharmacokinetics of galantamine. Clin Pharmacokinet 42: 1383-1392.

149. Lilienfeld S (2002) Galantamine - a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. CNS Drug Rev 8: 159-176.

150. Zhao Q, Brett M, Van Osselaer N, Huang F, Raoult A, et al. (2002) Galantamine pharmacokinetics, safety, and tolerability profiles are

similar in healthy Caucasian and Japanese subjects. J Clin Pharmacol 42: 1002-1010.

151. Mannens GS, Snel CA, Hendrickx J, Verhaeghe T, Le Jeune L, et al. (2002) The metabolism and excretion of galantamine in rats, dogs, and humans. Drug Metab Dispos 30: 553-563.

152. Noetzli M, Guidi M, Ebbing K, Eyer S, Zumbach S, et al. (2013) Relationship of CYP2D6, CYP3A, POR, and ABCB1 genotypes with galantamine plasma concentrations. Ther Drug Monit 35: 270-275.

153. Clarke JA, Cutler M, Gong I, Schwarz UI, Freeman D, et al. (2011) Cytochrome P450 2D6 phenotyping in an elderly population with dementia and response to galantamine in dementia: A pilot study. Am J Geriatr Pharmacother 9: 224-233.

154. Bentué-Ferrer D, Tribut O, Polard E, Allain H (2003) Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. CNS Drugs 17: 947-963.

155. Huang F, Fu Y (2010) A review of clinical pharmacokinetics and pharmacodynamics of galantamine, a reversible acetylcholinesterase inhibitor for the treatment of Alzheimer's disease, in healthy subjects and patients. Curr Clin Pharmacol 5: 115-124.

156. Zhai XJ, Lu YN (2012) Food-drug interactions: Effect of capsaicin on the pharmacokinetics of galantamine in rats. Xenobiotica 42: 1151-1155.

157. Polinsky RJ (1998) Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. Clin Ther 20: 634-647.

158. Sonali N, Tripathi M, Sagar R, Velpandian T, Subbiah V (2013) Clinical effectiveness of rivastigmine monotherapy and combination therapy in Alzheimer's patients. CNS Neurosci Ther 19: 91-97.

159. Lupp A, Appenroth D, Fang L, Decker M, Lehmann J, et al. (2010) Tacrine-NO donor and tacrine-ferulic acid hybrid molecules as new anti-Alzheimer agents: hepatotoxicity and influence on the cytochrome P450 system in comparison to tacrine. Arzneimittelforschung 60: 229-237.

160. Alfirevic A, Mills T, Carr D, Barratt BJ, Jawaid A, et al. (2007) Tacrine-induced liver damage: an analysis of 19 candidate genes. Pharmacogenet Genomics 17: 1091-1100.

161. Yang Z, Zhou X, Zhang Q (2013) Effectiveness and safety of memantine treatment for Alzheimer's disease. J Alzheimers Dis 36: 445-458.

162. Micuda S, Mundlova L, Anzenbacherova E, Anzenbacher P, Chladek J, et al. (2004) Inhibitory effects of memantine on human cytochrome P450 activities: prediction of in vivo drug interactions. Eur J Clin Pharmacol 60: 583-589.

163. Noetzli M, Guidi, M, Ebbing K, Eyer S, Wilhelm L, et al. (2013) Population pharmacokinetic study of memantine: effects of clinical and genetic factors. Clin Pharmacokinet 52: 211-223.

164. de Bartolomeis A, Sarappa C, Buonaguro EF, Marmo F, Eramo A, et al. (2013) Different effects of the NMDA receptor antagonists ketamine, MK-801, and memantine on postsynaptic density transcripts and their topography: role of Homer signaling, and implications for novel antipsychotic and pro-cognitive targets in psychosis. Prog Neuropsychopharmacol Biol Psychiatry 46: 1-12.

165. Martinelli-Boneschi F, Giacalone G, Magnani G, Biella G, Coppi E, et al. (2013) Pharmacogenomics in Alzheimer's disease: a genome-wide association study of response to cholinesterase inhibitors. Neurobiol Aging 34: 1711.e7-1711.e13.

166. Szulwach KE, Jin P (2014) Integrating DNA methylation dynamics into a framework for understanding epigenetic codes. Bioessays 36: 107-117.

167. Verhoeven KJ, Preite V (2014) Epigenetic variation in asexually reproducing organisms. Evolution 68: 644-655.

168. Gavery MR, Roberts SB (2013) Predominant intragenic methylation is associated with gene expression characteristics in a bivalve mollusc. Peer J 1: e215.

169. Iacobazzi V, Castegna A, Infantino V, Andria G (2013) Mitochondrial DNA methylation as a next-generation biomarker and diagnostic tool. Mol Genet Metab 110: 25-34.

170. Van den Hove DL, Kompotis K, Lardenoije R, Kenis G, Mill J, et al. (2014) Epigenetically regulated microRNAs in Alzheimer's disease. Neurobiol Aging 35: 731-745.

171. Hartley I, Elkhoury FF, Heon Shin J, Xie B, Gu X, et al. (2013) Long-lasting changes in DNA methylation following short-term hypoxic exposure in primary hippocampal neuronal cultures. PLoS One 8: e77859.

172. White AO, Wood MA (2014) Does stress remove the HDAC brakes for the formation and persistence of long-term memory? Neurobiol Learn Mem 112: 61-67.

173. Gräff J, Tsai LH (2013) The potential of HDAC inhibitors as cognitive enhancers. Annu Rev Pharmacol Toxicol 53: 311-330.

174. Brochier C, Langley B (2013) Chromatin modifications associated with DNA double-strand breaks repair as potential targets for neurological diseases. Neurotherapeutics 10: 817-830.

175. Coppedè F, Migliore L (2010) Evidence linking genetics, environment, and epigenetics to impaired DNA repair in Alzheimer's disease. J Alzheimers Dis 20: 953-966.

176. Zawia NH, Lahiri DK, Cardozo-Pelaez F (2009) Epigenetics, oxidative stress, and Alzheimer disease. Free Radic Biol Med 46: 1241-1249.

177. Cacabelos R (2014) Epigenomic networking in drug development: from pathogenic mechanisms to pharmacogenomics. Drug Dev Res 75: 348-365.

178. Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, et al. (2011) Epigenetic mechanisms in Alzheimer's disease. Neurobiol Aging 32: 1161-1180.

179. Adwan L, Zawia NH (2013) Epigenetics: a novel therapeutic approach for the treatment of Alzheimer's disease. Pharmacol Ther 139: 41-50.

180. Wang J, Yu JT, Tan MS, Jiang T, Tan L (2013) Epigenetic mechanisms in Alzheimer's disease: implications for pathogenesis and therapy. Ageing Res Rev 12: 1024-1041.

181. Zhang K, Schrag M, Crofton A, Trivedi R, Vinters H, et al. (2012) Targeted proteomics for quantification of histone acetylation in Alzheimer's disease. Proteomics 12: 1261-1268.

182. Ding H, Dolan PJ, Johnson GV (2008) Histone deacetylase 6 interacts with the microtubule-associated protein tau. J Neurochem 106: 2119-2130.

183. Govindarajan N, Rao P, Burkhardt S, Sananbenesi F, Schlüter OM, et al. (2013) Reducing HDAC6 ameliorates cognitive deficits in a mouse model for Alzheimer's disease. EMBO Mol Med 5: 52-63.

184. Julien C, Tremblay C, Émond V, Lebbadi M, Salem N, et al. (2009) SIRT1 decrease parallels the accumulation of tau in alzheimer disease. J Neuropathol Exp Neurol 68: 48.

185. Donmez G, Wang D, Cohen DE, Guarente L (2010) SIRT1 suppresses beta-amyloid production by activating the alpha-secretase gene ADAM10. Cell 142: 320-332.

186. Ryu H, Barrup M, Kowall NW, McKee AC (2008) P3-260: Epigenetic modification in a monozygotic twin with Alzheimer's disease. Alzheimers Dement 4: T598.

187. Ogawa O, Zhu X, Lee HG, Raina A, Obrenovich ME, et al. (2003) Ectopic localization of phosphorylated histone H3 in Alzheimer's disease: a mitotic catastrophe? Acta Neuropathol 105: 524-528.

188. Myung NH, Zhu X, Kruman II, Castellani RJ, Petersen RB, et al. (2008) Evidence of DNA damage in Alzheimer disease: phosphorylation of histone H2AX in astrocytes. Age (Dordr) 30: 209-215.

189. Francis YI, Fà M, Ashraf H, Zhang H, Staniszewski A, et al. (2009) Dysregulation of histone acetylation in the APP/PS1 mouse model of Alzheimer's disease. J Alzheimers Dis 18: 131-139.

190. Walker MP, LaFerla FM, Oddo SS, Brewer GJ (2013) Reversible epigenetic histone modifications and Bdnf expression in neurons with aging and from a mouse model of Alzheimer's disease. Age (Dordr) 35: 519-531.

191. Liu R, Lei JX, Luo C, Lan X, Chi L, et al. (2012) Increased EID1 nuclear translocation impairs synaptic plasticity and memory function associated with pathogenesis of Alzheimer's disease. Neurobiol Dis 45: 902-912.

192. Koshibu K, Gräff J, Beullens M, Heitz FD, Berchtold D, et al. (2009) Protein phosphatase 1 regulates the histone code for long-term memory. J Neurosci 29: 13079-13089.

193. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, et al. (2010) Altered histone acetylation is associated with age-dependent memory impairment in mice. Science 328: 753-756.

194. Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH (2007) Recovery of learning and memory is associated with chromatin remodelling. Nature 447: 178-182.

195. Gräff J, Rei D, Guan JS, Wang WY, Seo J, et al. (2012) An epigenetic blockade of cognitive functions in the neurodegenerating brain. Nature 483: 222-226.

196. Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, et al. (2009) HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459: 55-60.

197. Kim MS, Akhtar MW, Adachi M, Mahgoub M, Bassel-Duby R, et al. (2012) An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J Neurosci 32: 10879-10886.

198. Ishimaru N, Fukuchi M, Hirai A, Chiba Y, Tamura T, et al. (2010) Differential epigenetic regulation of BDNF and NT-3 genes by trichostatin A and 5-aza-2'-deoxycytidine in Neuro-2a cells. Biochem Biophys Res Commun 394: 173-177.

199. Tian F, Marini AM, Lipsky RH (2010) Effects of histone deacetylase inhibitor Trichostatin A on epigenetic changes and transcriptional activation of Bdnf promoter 1 by rat hippocampal neurons. Ann N Y Acad Sci 1199: 186-193.

200. Gupta S, Kim SY, Artis S, Molfese DL, Schumacher A, et al. (2010) Histone methylation regulates memory formation. J Neurosci 30: 3589-3599.

201. Lithner CU, Hernandez CM, Nordberg A, Sweatt JD (2009) Epigenetic changes related to beta-amyloid-implications for Alzheimer's disease. Alzheimers Dement 5: P304.

202. Wu P, Zuo X, Deng H, Liu X, Liu L, et al. (2013) Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. Brain Res Bull 97: 69-80.

203. Cacabelos R (2014) Metabolomics of epigenetic drugs: Precautionary measures. Metabolomics 4: 2.

204. Kim IW, Han N, Burckart GJ, Oh JM (2014) Epigenetic changes in gene expression for drug-metabolizing enzymes and transporters. Pharmacotherapy 34: 140-150.

205. Cacabelos R, Martínez-Bouza R, Carril JC, Fernández-Novoa L, Lombardi V, et al. (2012) Genomics and pharmacogenomics of brain disorders. Curr Pharm Biotechnol 13: 674-725.