Gene Interactions in the Pharmacogenomics of Alzheimer’s Disease

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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 worst responders, VL/VL and S/VL carriers are intermediate responders, and L/L carriers 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].

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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, transporters, 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, IIs, 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), M4A6A (11q12.1), CD33 (19q13.3), M4A4E (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%; 2,599.67 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 (AZBP1, ABAT, CDH2, CRMP1, DMRT1, EPHA5, EPHA6, ERMP1, EVC, EVC2, FLIS5024 and VDLDR) 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 pleotropic 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 neuroinflammatory 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-4 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-4/4-APOE-4/3; (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 hyperfusion and neocortical oxygenation is also more deficient in APOE-4/4 carriers; (xiii) lymphocytic 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...
In APOE-4 carriers; (xviii) 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 (anaplasos), 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 mitochondrial membrane translocase involved in the transport of Aβ and other proteins into mitochondria, has been implicated in AD [43-56], and TOMM40 mRNA levels was higher in VL homozygotes than the presence of the TOMM40 locus have been associated with primary progressive aphasia and 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), 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 were as 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 TOMM40-2/3 genotype was found to be associated with S/S (27.63%), S/VL (51.32%), and L/VL (21.05%); APOE-2/3 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%), 3/4 (47.26%), 3/4 (28.29%), and 4/4 (2.08%); L/L was exclusively associated with APOE-4/4 (100%); L/L 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%), 3/4 (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
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/L, S/L, S/VL, S/S) were studied in each APOE-related group [84].

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/L, S/L, S/VL, S/S) were studied in each APOE-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-2/4 and APOE-3/4, 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/TOMM40VL/ VL patients showed a tendency for an earlier age at onset compared to those with APOE33/TOMM40VL/S and APOE33/TOMM40S/S. TOMM40V/ VL patients had better memory performance, when compared to TOMM40S/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-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 (release, 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 monoxygenases (CYP3A4/5/7, CYP2E1, CYP2D6,
**Drug**

Name: Donepezil hydrochloride, Aricept, 120011-70-3, Donepezil HCl, BNAG, E-2020, E2020

**IUPAC Name**: 2-[(1-benzylpenicillin-4-yl)(methyl)-5,6-dimethoxy-2,3-dihydropyridin-1-yl]hydrochloride

**Molecular Formula**: C$_{22}$H$_{26}$N$_{2}$O$_{7}$

**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

**Pharmacogenetics**

Pathogenic genes: APOE, CHAT

Mechanistic genes: CHAT, ACHE, BCHE

**Drug metabolism-related genes**

- **Substrate**: CYP2D6 (major), CYP3A4 (major)
- **Inhibitor**: ACHE, BCHE

**Transporter genes**: ABCB1

**Mechanistic genes**: AKR1C1

Drug metabolism-related genes: CYP3A4 (major), UGT1A1

**Pathogenic genes**: APOE, APP

Mechanistic genes: ACHE, BCHE, CHRNA4, CHRNA7, CHRN8B

**Drug metabolism-related genes**: CYP2C19 (weak), CYP2D6 (strong), CYP2D6 (weak), CYP2E1 (weak), CYP3A4 (weak), NR1I2

**Transporter genes**: NR1I2

**Pleiotropic genes**: APOE, MAPT, MT-TK, PSEN1

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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-azaletraicyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca-6,8,10(17),15-letaen-14-ol

**Molecular Formula**: C$_{22}$H$_{26}$N$_{2}$O$_{7}$

**Molecular Weight**: 415.9529 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

**Pharmacogenetics**

Pathogenic genes: APOE, APP

Mechanistic genes: ACHE, BCHE, CHRNA4

**Drug metabolism-related genes**

- **Substrate**: CYP2D6 (major), CYP3A4 (major)
- **Inhibitor**: ACHE, BCHE

**Transporter genes**: ABCB1

**Mechanistic genes**: AKR1C1

Drug metabolism-related genes: CYP2C19 (weak), CYP2E1 (weak)

**Pathogenic genes**: APOE, APP

Mechanistic genes: ACHE, BCHE, CHRNA4

**Drug metabolism-related genes**: CYP2C19 (weak), CYP2E1 (weak), CYP3A4 (weak), NR1I2

**Transporter genes**: NR1I2

**Pleiotropic genes**: APOE, MAPT, MT-TK, PSEN1

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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$_{15}$H$_{21}$CN$_{2}$

**Molecular Weight**: 215.76278 g/mol

**Category**: N-Methyl-D-Aspartate receptor antagonist

**Mechanism**: Birds 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

**Pharmacogenetics**

Pathogenic genes: APOE, MAPT

Mechanistic genes: CHRNA4, CHRNA7, CHRN8B

**Drug metabolism-related genes**: CYP2C19 (weak), CYP2D6 (weak), CYP2E1 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP2E1 (weak), CYP3A4 (weak), NR1I2

**Transporter genes**: NR1I2

**Pleiotropic genes**: APOE, MAPT, MT-TK, PSEN1

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Name: Rivastigmine Tartrate, 129101-54-8, SDZ-ENA 713, Rivastigmine Hydrogen Tartrate, ENA 713, ENA-713

**IUPAC Name**: (2R,3R)-2,3-dihydroxybutanediol acid-[3-[15]-1, (dimethylamino)ethyl][phenyl] N-ethyl-N-methylcarbamate

**Molecular Formula**: C$_{19}$H$_{24}$N$_{2}$O$_{6}$

**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

**Pharmacogenetics**

Pathogenic genes: APOE, APP

Mechanistic genes: ACHE, BCHE, CHRNA4

**Drug metabolism-related genes**: CYP2C19 (weak), CYP2D6 (weak), CYP2E1 (weak)

**Inhibitor**: ACHE, BCHE

**Transporter genes**: ABCB1

**Pleiotropic genes**: APOE, CES1, GSTM1, GSTT1, LEPR, MTHFR

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Name: Tacrine Hydrochloride, Tacrine HCl, 168414-02-8, Hydraminacrine, tacrine.HCl, 9-AMINO-1,2,3,4- TETRAHYDROACRIDINE HYDROCHLORIDE, Tenakrin

**IUPAC Name**: 1,2,3,4-tetrahydroacridine-9-amine,hydrochloride

**Molecular Formula**: C$_{15}$H$_{21}$N$_{2}$

**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

**Pharmacogenetics**

Pathogenic genes: APOE

Mechanistic genes: ACHE, BCHE, CHRNA4, CHRN8B

**Drug metabolism-related genes**: CYP2C19 (minor), CYP3A4 (major)

**Inhibitor**: ACHE, BCHE, CYP1A2 (weak)

**Transporter genes**: ABCB1

**Pleiotropic genes**: APOE, CES1, GSTM1, GSTT1, LEPR, MTHFR

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**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), mu or sigma polypeptide; **ADHE1**: Alcohol dehydrogenase, iron containing, 1; **AGT**:Alanine-glutamylate aminotransferase; **AKR1A1**: Aldo-keto reductase family 1 member A1 (aldo reductase); **AKR1B1**: Aldo-keto reductase family 1, member B1 (aldo 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 family 1, member B1; **ALDH2**: Aldehyde dehydrogenase 2 family, member
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CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2, epoxide hydrolase, esterases, NQO1 (NADPH-quione 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), SULTs (sulfo transferases), GST-A (glutathione S-transferase A), GST-P, GST-T, GST-M, NAT-1 (N-acetyl transferase 1), NAT2, and others. Among these enzymes, CYP2D6, CYP2C9, CYP2C19, and CYP3A4 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 antidepresants 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 IID family. The cytochrome P450 proteins are 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, -1023>C>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, neuroprotetants, 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 [1,7,25-28,39].

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-3/3 55.49%; 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...
Figure 5: Distribution and frequency of CYP2D6 Extensive Metabolizers (EM), Intermediate Metabolizers (IM), Poor Metabolizers (PM) and Ultra-rapid Metabolizers (UM) in CNS disorders.

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.

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.

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 100% of homozygous APOE-2 carriers (N=20), 40% were EMs, 55% IMs, and 5% PMs (Figure 7). There is an apparent reduction in the number of PMs among 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-3/3 carriers (N=335), 64.48% were EMs, 31.34% IMs, and 4.18% PMs.

CYP2C9 association

In a sample of 566 Spanish patients with AD (APOE-2/2 0.33%; APOE-2/3 0.01%; 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-3/3 carriers (N=335), 64.48% were EMs, 31.34% IMs, and 4.18% PMs.
Distribution and frequency of APOE

Distribution and frequency of CYP3A5*3/*3

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; VT: 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 ANX showed differences with respect to PSY (p<0.02), STR 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) in patients with Alzheimer’s disease. Patients (N=566) were classified according to their genotype -2/2, 0.35%; -2/3, 9.01%; -3/3, 57.34 kDa (503 aa), 17.29 kDa (153 aa), 40.39 kDa (353 aa), and 47.99 kDa (420 aa) are identified.

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 genotype -3/3 and -4/4 carriers among AD patients (60% APOE-EMs and 40% APOE-PMs). There is a small reduction in APOE-3/3 carriers among CYP2C9-IMs, and a notable increase in APOE-3/3 carriers among CYP2C9-PMs (Figure 13).

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).

APOE-CYP2C19 association

The frequencies of CYP2C9-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), CYP2C9-EMs 50%, and CYP2C9-IMs 50%; in APOE-2/3 (N=52), CYP2C9-EMs 65.43%, CYP2C9-IMs 34.62%; in APOE-2/4 (N=7), CYP2C9-EMs 71.43%, and CYP2C9-IMs 28.57%; in APOE-3/3 (N=336), CYP2C9-EMs 75.30%, CYP2C9-IMs 23.51%, and CYP2C9-PMs 1.19%; in APOE-3/4 (N=152), CYP2C9-EMs 75.65%, CYP2C9-IMs 23.03%, and CYP2C9-PMs 1.32%; and in APOE-4/4 (N=20), CYP2C9-EMs 75%, and CYP2C9-IMs 25% (Figure 12). CYP2C9-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 CYP2C9-IMs, and a notable increase in APOE-3/3 carriers among CYP2C9-PMs (Figure 13).

CYP3A4

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 over 1,900 drugs, 1,033 acting as substrates (897 are major substrates, 136 strong inhibitors), and 241 as inducers of the CYP3A4 enzyme [86]. About 541 SNPs have been detected in the CYP3A4 gene. The frequencies of the 3 major CYP3A4 geno-phenotypes in the control population are CYP3A4-1/*1-EMs 68.54%, CYP3A4-1/*2-IMs 30.05%, and CYP3A4-2/*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).
In a series of 347 AD cases, 79.94% were found to be CYP3A5-EMs, 19.47% CYP3A4-1Ms, and 0.59% CYP3A4-RM (rapid metabolizers). The distribution of CYP3A5-EMs and 1Ms was very similar among APOE genotypes, except in APOE-2/4 carriers where the presence of 1Ms was twice higher than in carriers of the other genotypes (Figure 14). Only 2 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 (10.43%), *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...
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 glycoprotein 1/multiple drug resistance 1; Multidrug resistance 1; Doxorubicin resistance; Multidrug resistance 1; Multidrug resistance protein 1; P glycoprotein 1; P glycoprotein 1/multiple drug resistance 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’-CTGATGGG-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; ABCB1-020: 345 bp) are highly expressed in adrenal gland, Brain Blood 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. ABCB1-020: 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. 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.

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 AP06c4-determining SNP rs429358 (allele = G; 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/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’-CTGATGGG-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; ABCB1-020: 345 bp) are highly expressed in adrenal gland, Brain Blood 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. ABCB1-020: 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.

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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), ABC1 (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 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, Aβ1-42 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]Aβ1-42. Progol inhibits the efflux of [3H]Aβ1-42 from HEK293-abcg4 cells. GI20918 (a dual inhibitor of Abcb1 and Abcg2) strongly enhances the uptake of [3H]Aβ1-42 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; rs2381142) (ABCG2 C/C genotype) was associated with AD in the Hungarian population. The ABCG2 C/C genotype and the APOE-ε4 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)-[14C] 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 ABCR1 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, 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 Aβ1-42 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-ε4 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. Mißlaure et al. [118] investigated the suitability of the radiolabeled Pgp inhibitors [3H]cladribine and [3H]taridipine to visualize Pgp density in rat brain with PET. The small Pgp binding signals obtained with [3H]cladribine and [3H]taridipine 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), MRPI (ABCC1) and BCRP (ABCG2), have been implicated in the clearance of neurotoxic polypeptides that characteristically accumulate in the brain, such as Aβ peptides. A benzoylamine 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 D3] increased P-gp protein expression fourfold. Incubation with 1,25OH D3 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 D3. 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 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
Fluor 488-labeled human amyloid-β 1-42 (hAβ42). In hCMVEC/D3 cells, exposure to 1,25OH$_2$D$_3$ increased MDR1 mRNA expression (40%) and P-gp protein; and reduced cellular accumulation of R6G and hAβ42 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 hAβ42, 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 (245-hydroxycholesterol, 27-hydroxycholesterol and T090137) 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 123I-Aβ$_{42}$ intracellular accumulation was observed in cells treated with rifampicin, dexamethasone, caffeine, verapamil, hyperforin, β-estradiol and pentyleneterazolo (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 (3xTG) AD mice. The brain uptake of passively diffusing markers, [3H] diazepam and [3H] propranolol, decreased 54-60% in 3xTG mice, consistent with a 33.5% increase in the thickness of the cerebrovascular basement membrane in 3xTG mice. Despite a 42.4% reduction in P-gp expression in isolated brain microvessels from a sub-population of 3xTG mice, the brain uptake of P-gp substrates ([3H] digoxin, [3H] loperamide and [3H] verapamil) was not different between genotypes, likely due to a compensatory thickening in the cerebrovascular basement membrane counteracting any reduced efflux of these lipopholic 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), aminos (SLC1A5, SLC3A1, SLC7A3, SLC7A9, SLC3A1, SLC3A4, SLC3A5, SLC3A7, SLC4A2, SCLCA1), nucleosides (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 xenogenous 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 anesthetics. 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, ACH, BCHE, CHRNA4, CHRN7, CHRN12 variants may potentially influence galantamine efficacy and safety; it is a major substrate of CYP2D6, CYP3A4, and UGT1A1, and an inhibitor of ACH 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 CYP3A4 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 AUC0-∞ 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, ACH, BCHE, CHRNA4, CHRN2 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. ACH, BCHE, CHRNA4, CHRN12, 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 ACH, 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].

Mementine

Mementine is an NMDA receptor antagonist which binds preferentially to NMDA receptor-operated cation channels; it may act by blocking actions of glutamate, mediared in part by NMDA receptors, and it is also an antagonist of GRIN2A, GRIN2B, GRIN3A, HTR3A and CHRFAM7A. Several pathogenic (APOE, PS1, MAST) and mechanistic gene variants (GRIN2A, GRIN2B, GRIN3A, HTR3A, CHRFAM7A, c-Fos, Homer1b and PSD-95) may influence its therapeutic effects. Mementine is a strong inhibitor of CYP2B6 and CYP2D6, and a weak inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 [86,136,137,161] (Table 1). Mementine is beneficial for AD patients in terms of cognition and in the clinician’s global impression; however, some mementine-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 mementine 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, mementine 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 mementine 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 transcripts 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 of recent information [173,179,180] suggests that histone modifications associated with 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 hydroxymethylcytosines [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 [2,4,28,177,178]. 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 2XtG-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 acetyltransferase 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 (napPINK1, Sox2OT, 1810014B01Rik, BC200), and Huntington’s disease (HAR1F, HTTAS, DGCR5, NEAT1, TUG1) [202]. miRNAs belong to the cortical neurons of AD patients, including HAR1F, HTTAS, DGCR5, NEAT1, TUG1, miRNA-34a, miRNA-34b/c, miRNA-107, miRNA-124, miRNA-125, miRNA-137, miRNA-138, miRNA-146a, miRNA-148a, miRNA-184, miRNA-200 (miR-200a/b/200c/200d), miRNA-336, miRNA-338, miRNA-342, miRNA-343. miRNAs are involved in the regulation of AD pathogenesis. Examples of 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-200a/b/200c/200d, 1p36.33, miR-200c/141, 12p13.31) [2,4,170].

Pharmacoeigenetics

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, 2C19, 2D6, 2E1, 2J2, 2F1, 2R1, 2S1, 2W1, 3A4, 3A5, 3A7, 3A43, UGT1, GSTP1), drug transporters (ABCB1/MDR1/P-gp, ABCG2/MRP1, ABCG2/MRP8, ABCG2/BCRP, SLC19A1, SLC22A8), and nuclear receptors (RARβ2, ER1, NR112, HNF4I) has been documented in pioneering studies of pharmacoeigenetics [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 UM s 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/S 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 worst responders to treatment. In 100% of the cases, the L/L genotype is exclusively associated with the worst responders to treatment. In 100% of the cases, the L/L genotype is exclusively associated with the worst responders to treatment. In 100% of the cases, the L/L genotype is exclusively associated with the worst responders to treatment. In 100% of the cases, the L/L genotype is exclusively associated with the worst responders to treatment.

References


