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Pharmacogenomics and therapeutic prospects in dementia

Abstract Dementia is a major problem of health in developed countries. Alzheimer's disease (AD) is the main cause of dementia, accounting for 50–70% of the cases, followed by vascular dementia (30–40%) and mixed dementia (15–20%). Approximately 10–15% of direct costs in dementia are attributed to pharmacological treatment, and only 10–20% of the patients are moderate responders to conventional anti-dementia drugs, with questionable cost-effectiveness. Primary pathogenic events underlying the dementia process include genetic factors in which more than 200 different genes distributed across the human genome are involved, accompanied by progressive cerebrovascular dysfunction and diverse environmental factors. Mutations in genes directly associated with the amyloid cascade (APP, PS1, PS2) are only present in less than 5% of the AD population; however, the presence of the APOE-4 allele in the apolipoprotein E (APOE) gene represents a major risk factor for more than 40% of patients with dementia. Genotype–phenotype correlation studies and functional genomics studies have revealed the association of specific mutations in primary loci (APP, PS1, PS2) and/or APOE-related polymorphic variants with the phenotypic expression of biological traits. It is estimated that genetics accounts for 20–95% of variability in drug disposition and pharmacodynamics. Recent studies indicate that the therapeutic response in AD is genotype-specific depending upon genes associated with AD pathogenesis and/or genes responsible for drug metabolism (CYPs). In monogenic-related studies, APOE-4/4 carriers are the worst responders. In trigenic (APOE-PS1-PS2 clusters)-related studies the best responders are those patients carrying the 331222-, 341122-, 341222-, and 441112-genomic profiles. The worst responders in all genomic clusters are patients with the 441122+ genotype, indicating the powerful, deleterious effect of the APOE-4/4 genotype on therapeutics in networking activity with other AD-related genes. Cholinesterase inhibitors of current use in AD are metabolized via CYP-related enzymes. These drugs can interact with many other drugs which are substrates, inhibitors or inducers of the cytochrome P-450 system; this interaction elicits liver toxicity and other adverse drug reactions. CYP2D6-related enzymes are involved in the metabolism of more than 20% of CNS drugs. The distribution of the CYP2D6 genotypes differentiates four major categories of CYP2D6-related metabolyzer types: (a) Extensive Metabolizers (EM)(*1/*1, *1/*10)(51.61%); (b) Intermediate Metabolizers (IM) (*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10) (32.26%); (c) Poor Metabolizers (PM) (*4/*4, *5/*5) (9.03%); and (d) Ultra-rapid Metabolizers (UM) (*1xN/*1, *1xN/*4, Dupl) (7.10%). PMs and UMs tend to show higher transaminase activity than EMs and IMs. EMs and IMs are the best responders, and PMs and UMs are the worst responders to pharmacological treatments in AD. It seems very plausible that the pharmacogenetic response in AD depends upon the interaction of genes involved in drug metabolism and genes associated with AD pathogenesis. The establishment of clinical protocols for the practical application of pharmacogenetic strategies in AD will foster important advances in drug development, pharmacological optimization and cost-effectiveness of drugs, and personalized treatments in dementia.

Key words dementia · Alzheimer's disease · APOE · CYP2D6 · pharmacogenetics · pharmacogenomics · multifactorial treatments

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Introduction

Senile dementia is becoming a major problem of health in developed countries, and the primary cause of disability in the elderly. Alzheimer's disease (AD) is the most frequent form of dementia (50–70%), followed by vascular dementia (30–40%), and mixed dementia (15–20%). These prevalent forms of age-related neurodegeneration affect more than 25 million people at present, and probably more than 75 million people will be at risk in the next 20–25 years worldwide. The prevalence of dementia increases exponentially from approximately 1% at 60–65 years of age to more than 30–35% in people older than 80 years. The vast majority of older cases (>75–80 years) are of the mixed type with a prominent vascular component [23]. The average annual cost per person with dementia ranges from US$ 15,000 to US$ 50,000, depending upon disease stage and country, with a lifetime cost per patient of more than US$ 175,000. About 10–20% of the costs in dementia are attributed to pharmacological treatment, including anti-dementia drugs, psychotropics, and other drugs currently prescribed in the elderly. In addition, during the past 20 years more than 300 drugs have been partially or totally developed for AD, with subsequent costs for the pharmaceutical industry, and only 5 drugs with moderate-to-poor efficacy and questionable cost-effectiveness have been approved in developed countries [22, 40, 53].

The application of pharmacogenetic procedures to the therapeutics of dementia

Pharmacogenetics/pharmacogenomics is a novel science that refers to the genomic conditions by which different genes determine the behavior and sensitivity of drugs on a specific organism or genotype. Pharmacogenomics relates to the application of genomic technologies, such as genotyping, gene sequencing, gene expression, genetic epidemiology, transcriptomics, proteomics, metabolomics and bioinformatics, to drugs in clinical development and on the market, applying the large-scale systematic approaches of genomics to speed the discovery of drug response markers, whether they act at the level of drug target,

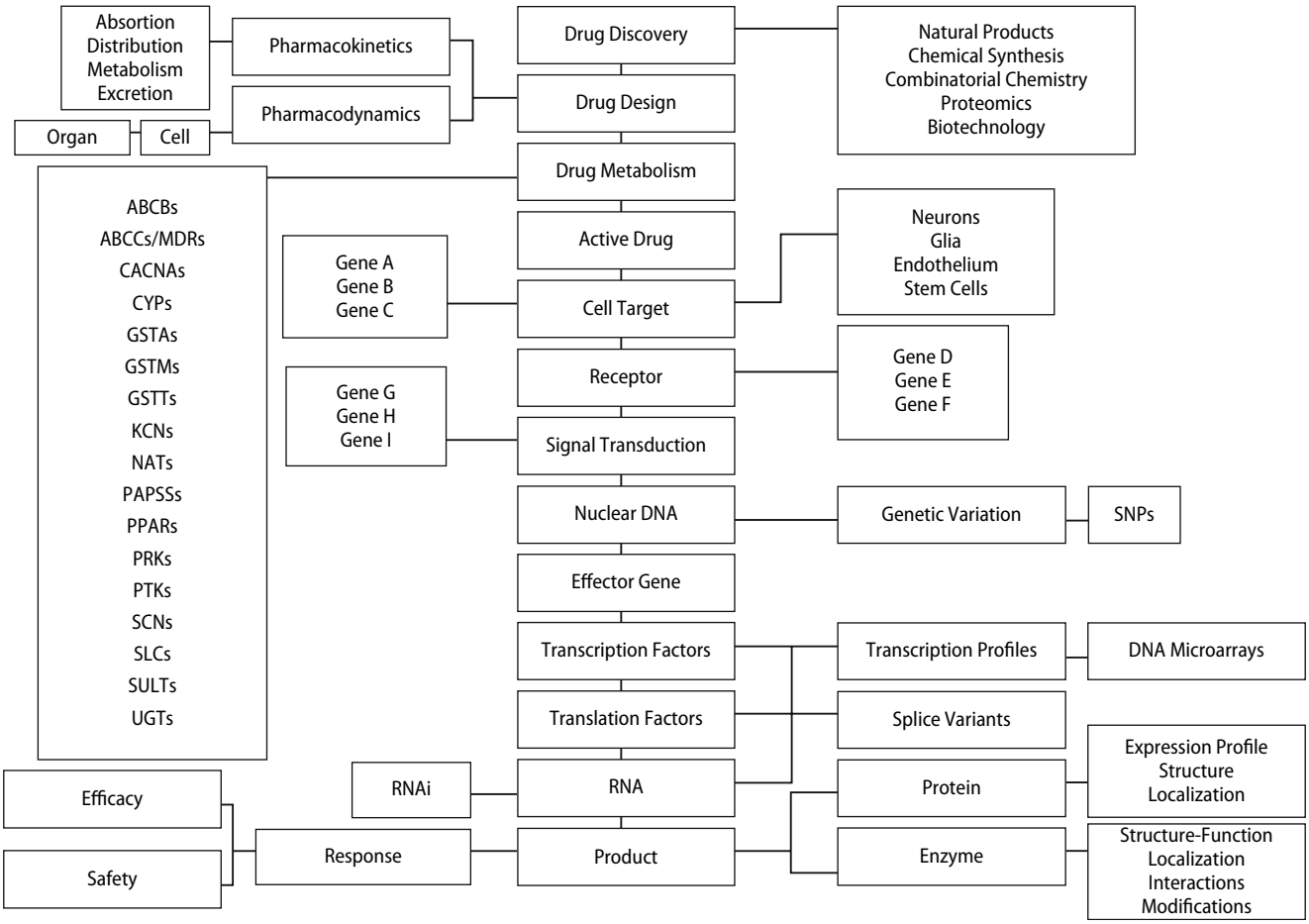


Fig. 1 Sequential processing in drug development and drug evaluation. Pharmacogenomics procedures and targets in CNS disorders (adapted from Cacabelos [16, 18, 29])

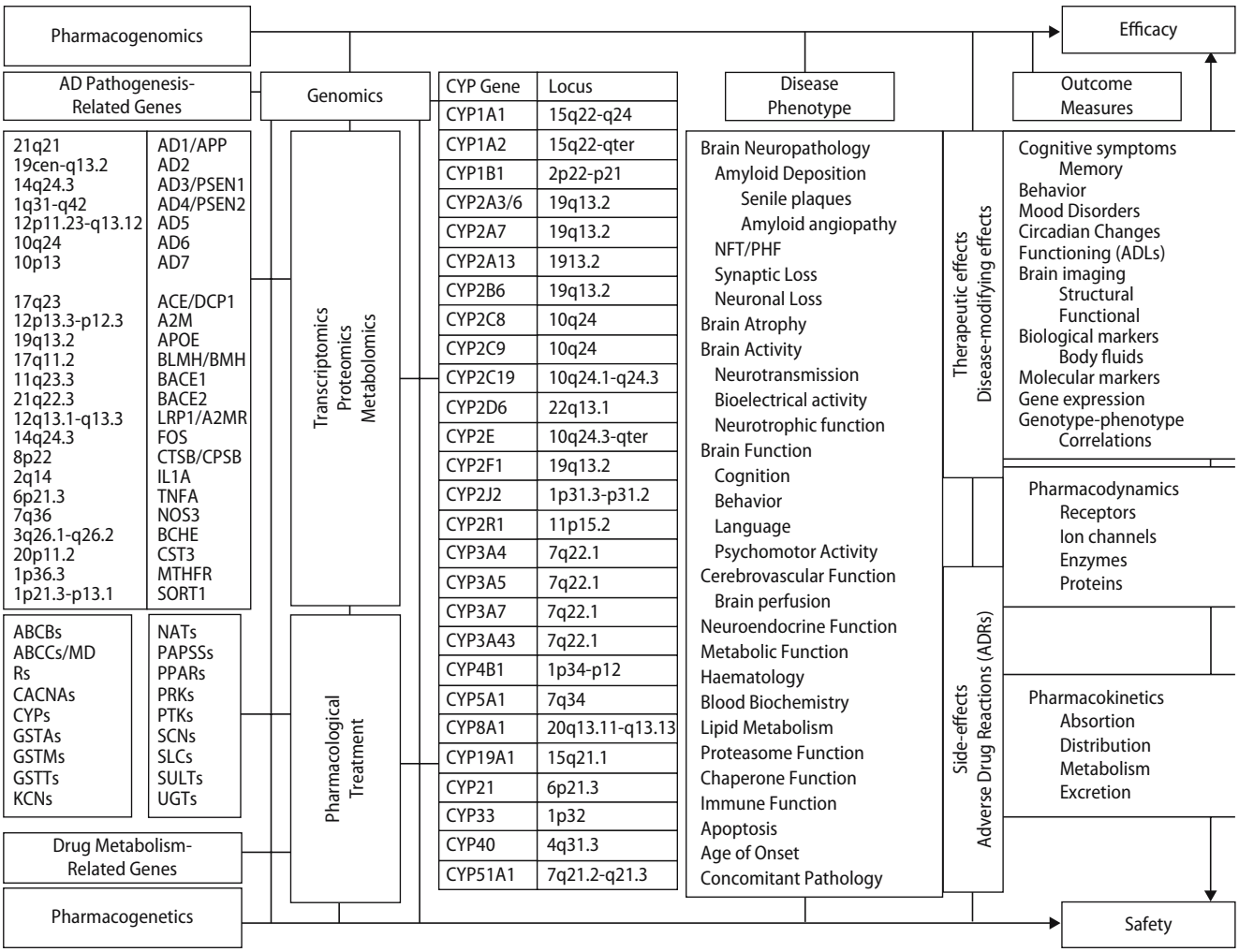


Fig. 2 Evaluation of efficacy and safety issues in Alzheimer's disease pharmacogenomics/pharmacogenetics

drug metabolism, or disease pathways [7, 18, 29, 34, 42, 90, 91]. The potential implications of pharmacogenomics in clinical trials and molecular therapeutics are that a particular disease could be treated according to genomic and biological markers, selecting medications and diseases that are optimized for individual patients or clusters of patients with a similar genomic profile [34, 91]. For many medications, interindividual differences are mainly due to single nucleotide polymorphisms (SNPs) in genes encoding drug-metabolizing enzymes, drug transporters, and/or drug targets (e.g., genome-related defective enzymes, receptors and proteins, that alter metabolic pathways leading to disease phenotype expression) [91].

With the advent of recent knowledge on the human genome and the identification and characterization of Alzheimer's disease (AD)-related genes [24], as well as novel data regarding CYP family genes and other genes whose enzymatic products are responsible for drug metabolism in the liver, it has been convincingly postulated that the incorporation of pharmacogenetic and pharmacogenomic procedures (Figs. 1, 2) in drug development might bring about substantial benefits in terms of therapeutics optimization in dementia, assuming that genetic factors are determinant for both premature neuronal death in AD and drug metabolism [7, 14–18, 21, 24, 29, 42, 73].

The therapeutic lessons obtained from pharmacogenetics in the past, as pointed out by Meyer [55], can be the following: (a) all drug effects vary from person to person and all drug effects are influenced by genes; (b) most drug responses are multifactorial; (c) genetic polymorphisms of single genes, including mutations in coding sequences, gene duplications, gene deletions and regulatory mutations affect numerous drug-metabolizing enzymes; individuals that possess these polymorphisms are at risk of experiencing documented adverse reactions or inefficacy of drugs at usual doses; (d) genetic polymorphisms of drug targets and drug transporters are increasingly recognized as those causing variation in drug responses; (e) several targets respond to treatment only in subgroups of patients who carry sensitizing mutations of these targets; (f) the frequency of variation of drug effects, whether multifactorial or genetic, varies con-

siderably in ethnically defined populations; and (g) application of response-predictive genetic profiles on clinical outcomes has, so far, been done mostly in academic centers and has not yet reached clinical practice [55].

To achieve efficient goals in pharmacogenetics and pharmacogenomics, novel interventions in drug development, diagnostics and therapeutics are required, including: (a) genetic testing of mutant genes and/or polymorphic variants of risk; (b) genomic screening, and understanding of transcriptomic, proteomic, and metabolomic networks; (c) functional genomics studies and genotype–phenotype correlation analysis; and (d) pharmacogenetics and pharmacogenomics developments, addressing drug safety and efficacy, respectively [14–18, 21, 29, 73].

The application of these procedures to dementia is a very difficult task, since dementia is a complex disorder in which more than 200 genes might be involved [24, 79] (Table 1). In addition, it is very unlikely that a single drug be able to reverse the multifactorial mechanisms associated with premature neuronal death in most dementing processes with a complex phenotype represented by memory decline, behavioral changes, and progressive functional deterioration. This clinical picture usually requires the utilization of different drugs administered simultaneously, including memory enhancers such as the conventional anti-dementia drugs (tacrine, donepezil, rivastigmine, galantamine, memantine), psychotropics (antidepressants, neuroleptics, anxiolytics), anticonvulsants, antiparkinsonians, and also other types of drugs of current use in the elderly due to the presence of concomitant ailments. In fact, the average number of drugs taken by patients suffering from dementia ranges from 6 to more than 10 per day depending upon their physical and mental conditions. Under these circumstances, therapeutics optimization is a major goal in the elderly population, and novel pharmacogenetic and pharmacogenomic procedures may help in this endeavour [18, 29].

Genetics and pathogenesis of Alzheimer's disease

Advances in molecular genetics during the past three decades allowed the identification of several genetic loci associated with AD (Table 1) and the genetic classification of AD (AD1 to ADn) as depicted in the OMIM database [24, 101]. The genetic defects identified in AD during the past 25 years can be classified into three main categories: (a) Mendelian or mutational defects in genes directly linked to AD, including (1) 32 mutations in the amyloid beta (Aβ)(ABP) precursor protein (APP) gene (21q21); (2) 165 mutations in the presenilin 1 (PS1) gene (14q24.3); and (3) 12 mutations in the presenilin 2 (PS2) gene (1q31-q42) [24, 79, 100, 101] (Table 1). (b) Multiple polymorphic variants of risk characterized in more than 200 different genes distributed across the human genome can increase neuronal vulnerability to premature death [24](Table 1). Among these genes of susceptibility, the apolipoprotein E (APOE) gene (19q13.2) is the most prevalent as a risk factor for AD, especially in those subjects harboring the APOE-4 allele, whereas carriers of the APOE-2 allele might be protected against dementia [24, 29]. APOE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD [14–18, 21, 23, 24, 26, 29, 73]. (c) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity [24, 99]. It is also likely that defective functions of genes associated with longevity may influence premature neuronal survival, since neurons are potential pacemakers defining life span in mammals [24]. All these genetic factors may interact in still unknown genetic networks leading to a cascade of pathogenic events characterized by abnormal protein processing and misfolding with subsequent accumulation of abnormal proteins [extracellular ABP deposition in senile plaques and vessels (amyloid angiopathy), intracellular neurofibrillary tangle (NFT) formation due to hyperphosphorylation of tau protein], ubiquitin-proteasome system dysfunction, excitotoxic reactions, oxidative and nitrosative stress, mitochondrial injury, synaptic failure due to dendritic desarborization and synaptic loss with dysfunction of axonal and dendritic transport, alterations in cholesterol metabolism and lipid rafts, deficiencies in neurotransmitter and neurotrophic factor function, altered metal homeostasis, and chaperone misoperation [24, 29, 41, 79, 84]. These pathogenic events, as potential therapeutic targets (Figs. 3, 4), may exert an additive effect, converging in final pathways leading to premature neuronal death with the participation of cerebrovascular factors, epigenetic factors (DNA methylation) and environmental conditions (nutrition, toxicity, social factors, etc.) [18, 24, 29, 48, 52, 85]. The higher the number of genes involved in AD pathogenesis, the earliest the onset of the disease, the faster its clinical course, and the poorer its therapeutic outcome [14–16, 18, 21, 29, 55].

Therapeutic targets

Modern therapeutic strategies in AD are addressed to interfere with the main pathogenic mechanisms potentially involved in AD. Major pathogenic events (drug targets) and their respective therapeutic alternatives (Figs. 3, 4) include the following: (a) genetic defects: gene therapy and gene silencing (RNAi); (b) β-amyloid deposition: β-secretase inhibitors, γ-secretase inhibitors, α-secretase activators, Aβ-fibrillation and aggregation inhibitors, amyloid immunotherapy (active and passive vaccination), copper

Table 1 Selected human genes investigated as potential candidate genes associated with dementia and age-related neurodegenerative disorders

Locus	Symbol	Title/Gene	MIM
1p21.3-p13.1	SORT1	Sortilin	602458
1p31	BBP	Beta-amyloid binding protein precursor	610080
1p32	ZFYVE9; SARA; MADHIP	Zinc finger, FYVE domain containing 9; SMAD anchor for receptor activation; MADH-interacting protein	603755
1p34	LRP8; APOER2	Low-density lipoprotein receptor-related protein 8	602600
1p36	AD7CNTP	Alzheimer disease neuronal thread protein (ADNTP)	607413
1p36.3	MTHFR	Methylenetetrahydrofolate reductase	607053; 104300
1q21	S100A	S100 calcium-binding protein A1	176940
1q21-q23	APCS	Serum amyloid P component	104770
1q23	NCSTN; APH2	Nicastrin	605254
1q25	SOAT1; STAT; ACAT	Acyl-CoA: cholesterol acyltransferase; Sterol O-acyltransferase 1	102642
1q31-q42	AD4; PSEN2; STM2	Presenilin-2	600759; 104300
Chr. 1	APH1A	C. elegans anterior pharynx defective homolog	607629
2p14-p13	RTN4; NOGO	Neurite outgrowth inhibitor (reticulon 4)	604475
2p25	ADAM17; TACE	A desintegrin and metalloproteinase domain 17; Tumor necrosis factor-alpha converting enzyme	603639
2q14	IL1A	Interleukin-1-Alpha	147760
2q21.1	CSEN; DREAM; KCNIP3	Calsenilin	604662
2q21.2	LRP1B	Low-density lipoprotein receptor-related protein 1B	608766
3q26.1-q26.2	BCHE	Butyrylcholinesterase	177400
3q32.3-q34	CREB1	cAMP response element-binding protein	123810
Chr. 4	APBB2; FE65L1	Amyloid beta-A4 precursor protein-binding, family B, member 2	602710
5q15-q21	CAST	Calpastatin	114090
5q31	APBB3; FE65L2	Amyloid beta A4 precursor protein-binding, family B, member 3	602711
5q35.3	DBN1	Drebrin E	12660
6p21.3	AGER; RAGE	Advance glycosylation end product-specific receptor	600214
6p21.3	TNFA	Tumor necrosis factor-α; Cachectin	191160
7p21	IL-6; IFNB2	Interleukin-6; Beta-2 interferon	147620
7q36	NOS3	Nitric oxide synthase-3	163729
8p22	CTSB; CPSB	Cathepsin β; Amyloid precursor protein secretase	116810
9q13	APBA1; X11; MINT1; LIN10	Amyloid beta-A4 precursor protein-binding, family A, member 1	602414
10p13	AD7	Alzheimer disease-7	606187
10q23-q25	IDE	Insulin-degrading enzyme	146680
10q24	AD6	Alzheimer disease-6	605526
10q24	PLAU; URK	Plasminogen activator, urokinase	191840
11p15	APBB1; F65	Amyloid beta-A4 precursor protein-binding, family B, member 1	602709
11p15.1	SAA1	Serum amyloid A1	104750
11q23.2-q24.2	SORL1	Sortilin-related receptor 1	602005
11q23.3	BACE1; BACE	Beta-site amyloid beta A4 precursor protein-cleaving enzyme; Beta-secretase; Memapsin-2	604252
11q24	APLP2	Amyloid beta-A4 precursor-like protein 2	104776
12p11.23-q13.12	AD5	Familial AD-5	602096
12p12.3-p12.1	IAPP; IAP; DAP	Islet amyloid polypeptide; Amylin; Diabetes-associated peptide	147940
12p13.3-p12.3	A2M	Alpha-2-Macroglobulin	103950
12q13.1-q13.3	LRP1; A2MR	Low-density lipoprotein-related protein-1; Alpha-2-macroglobulin receptor	107770
14q24.3	FOS	FBJ murine osteosarcoma viral (v-fos) oncogene homolog; Oncogene Fos	164810
14q24.3	AD3; PSEN1	Presenilin-1	104311
14q32.1	SERPINA3; AACT; ACT	Alpha-1-antichymotrypsin	107280
14q32.1	CYP46; CYP46A1	Cytochrome P450; Family 46, subfamily A; polypeptide 1; cholesterol 24-hydrolase	604087
Chr. 15	APH1B	Homolog of C. elegans anterior pharynx defective 1B	607630
15q11-q12	APBA2; X11L	Amyloid beta-A4 precursor protein-binding, family A, member 2	602712
16q22	APPBP1	Amyloid beta precursor protein-binding protein 1	603385
17q11.2	BLMH; BMH	Bleomycin hydrolase	602403
17q21	STH	Saitohin	607067
17q21.1	MAPT; MTBT1; DDPAC; MST	Macrotubule-associated protein tau	157140
17q21-q22	GPSC	Familial progressive subcortical gliosis	221820
17q22-q23	APPBP2; PAT1	Amyloid beta precursor protein-binding protein 2	605324
17q23	ACE; ACE1; DCP1	Angiotensin I converting enzyme; Dipeptidyl carboxipeptidase-1	106180; 104300
17q23.1	MPO	Myeloperoxidase	254600
17q24	FALZ; FAC1	Fetal Alzheimer antigen	601819
18q11.2-q12.2	TTR; PALB	Transthyretin; Prealbumin	176300
19p13.2	NOTCH3; CADASIL; CASIL	Drosophila Notch 3 homolog	600276
19p13.2	AD8	Alzheimer disease 9	608907
19p13.3-p13.2	ICAM; CD54; BB2	Intercellular adhesion molecule 1	147840
19p13.3	APBA3; X11L2	Amyloid beta-A4 precursor protein binding, family A, member 3	604262
19q13.12	PEN2	Presenilin enhancer 2	607632
19q13.2	APOE	Apolipoprotein E	107741

Table 1 Continued

Locus	Symbol	Title/Gene	MIM
19q13.2	APOC1	Apolipoprotein C-I	107710
19cen-q13.2	AD2	Alzheimer disease-2	104310
19cen-q13.2	APLP1	Amyloid beta-A4 precursor-like protein 1	104775
19q31-qter	APPL1	Amyloid beta-A4 precursor protein-like 1	104740
20p	AD8	Alzheimer disease-8	607116
20p11.2	CST3	Cystatin 3	604312
20p11.2	CST3	Cystatin C	604312
21q21	AD1; APP; AAA; CVAP	Amyloid beta (A4) precursor protein; Amyloid of aging and Alzheimer disease; Cerebrovascular amyloid peptide; Protease nexin II	104760
21q22.3	BACE2; ALP56; DRAP	Beta-site amyloid beta A4 precursor protein-cleaving enzyme 2; Down syndrome-region aspartic protease	605668
22q11	RTN4R, NOGOR	NOGO receptor (reticulon 4 receptor)	605566
	HN	Humanin	606120

Adapted from Cacabelos et al. [24], and Cacabelos and Takeda [29]

chelating agents, solubilizers of Aβ aggregates, APP production inhibitors, and Aβ selective regulators (reticulons, chaperones); (c) tau-related pathology: phosphatase activators, GSK-3 inhibitors, Cdk5 inhibitors, p38 inhibitors, JNK inhibitors; (d) apoptosis: caspase inhibitors; (e) neurotransmitter deficits: acetylcholine enhancers (acetylcholine-release stimulants, acetylcholine reuptake inhibitors, cholinesterase inhibitors, choline-acetyl-transferase stimulants, muscarinic antagonists, nicotinic agonists), GABA modulators (inverse GABA-receptor agonists), glutamate modulators (NMDA antagonists, ampakines), dopamine reuptake inhibitors, adrenoreceptor modulators, histamine H3 antagonists, and serotonin modulators (5HT3 and 5HT1A receptor agonists, 5HT6 receptor antagonists, serotonin stimulants); (f) neurotrophic deficits: neurotrophic factors, growth factors, synthetic neuropeptides, and natural compounds with neurotrophic activity; (g) neuronal loss: neuronal stem cells, growth factors, neurite outgrowth activators, NOGO inhibitors, MOP inhibitors, GSK3 inhibitors, JNK inhibitors, and p38 inhibitors; (h) neuroinflammation: COX1 and COX2 inhibitors, complement activation inhibitors, p38 inhibitors, eNOS inhibitors, PPARα agonists, PPARγ agonists, novel NSAIDs, and cytokine inhibitors; (i) oxidative stress: antioxidants, caspase inhibitors, and antioxidating enzyme enhancers; (j) calcium dysmetabolism: calcium channel blockers; (k) neuronal hypometabolism: PPARγ agonists, and GSK3 inhibitors; (l) lipid metabolism dysfunction: HMG-CoA reductase inhibitors, PPARγ agonists, and novel biomarine lipoproteins; (m) cerebrovascular dysfunction: vasoactive substances, NO inhibitors, HIF inhibitors, dandrolene-related agents, novel lipoproteins with anti-atherosclerotic activity, and liver X receptor agonists; (n) neuronal dysfunction associated with nutritional deficits: brain metabolism enhancers, nutrigenomic agents, and nutraceuticals; and (o) a miscellany of pathogenic mechanisms potentially manageable with diverse classes of chemicals or biopharmaceuticals [18, 22, 29, 40, 53].

Pharmacogenomic strategies in dementia

For many years, it became clear the heterogeneity of AD and how apparently identical phenotypes assessed with international clinical criteria (NINCDS-ADRDA, DSM-IV, ICD-10) do not always respond to the same drugs [18, 29]. This may be due to different factors, including pharmacokinetic and pharmacodynamic properties of drugs, nutrition, liver function, concomitant medications, and individual genetic factors. In fact, the therapeutic response of AD patients to conventional cholinesterase inhibitors is partially effective in only 10–20% of the cases, with side-effects, intolerance, and non-compliance in more than 60% of the patients due to different reasons (e.g., efficacy, safety) [22, 40, 53]. Therefore, the individualization of therapy or pharmacological tailorization in AD and other CNS disorders is just a step forward of the longstanding goal of molecular pharmacology [5, 25, 35, 91] taking advantage from the information and procedures provided by the sequencing of the entire human genome [49].

In order to optimize therapeutics in AD, different pharmacogenetic/pharmacogenomic strategies can be postulated. Pharmacogenomic strategies associated with efficacy issues deal with the analysis of the influence of different genes (monogenic, bigenic, trigenic, tetragenic, polygenic clusters) on cognitive function (memory, mental performance), non-cognitive function (behavioral changes, functioning), and/or biological parameters (brain atrophy, amyloid deposition, NFT formation, etc.) during the administration of specific pharmacological treatments. Pharmacogenetic strategies associated with safety issues deal with the analysis of the influence of defined genomic profiles on pharmacokinetic and pharmacodynamic parameters and adverse drug reactions (ADRs) (Fig. 2). The candidate genes for assessment are AD-related genes involved in AD pathogenesis (Table 1) and/or genes responsible for drug metabolism (phase-I and phase-II reactions) [29] (Table 2).

Pharmacogenetics of drug metabolism in dementia

Although drug effect is a complex phenotype that depends on many factors, it is estimated that genetics account for 20–95% of variability in drug disposition and pharmacodynamics [91]. Cholinesterase inhibitors of current use in AD, such as donepezil and galantamine (and tacrine, as well) are metabolized via CYP-related enzymes. These drugs can interact with many other drugs which are substrates, inhibitors or inducers of the cytochrome P-450 system; this interaction eliciting liver toxicity and other adverse drug reactions (ADRs) [18, 29].

Alzheimer disease patients are currently treated with cholinesterase inhibitors, neuroprotective drugs, antidepressants, anxyolitics, anti-parkinsonian drugs, anticonvulsants and neuroleptics at a given time of the disease clinical course to palliate memory dysfunction, behavioral changes, sleep disorders, agitation, depression, parkinsonism, myoclonus and seizures or psychotic symptoms [19, 22, 29, 80]. Many of these substances are metabolized by enzymes known to be genetically variable. Drug metabolism includes phase I reactions (i.e., oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e., acetylation, glucuronidation, sulfation, methylation) [35]. The principal enzymes with polymorphic variants involved in phase I reactions are the following: CYP3A4/5/7, CYP2E1, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2, epoxide hydrolase, esterases, NADPH-quinone oxidoreductase (NQO1), dihydropyrimidine dehydrogenase (DPD), alcohol dehydrogenase (ADH), and aldehyde dehydrogenase (ALDH). Major enzymes involved in phase II reactions include the following: uridine 5′-triphosphate glucuronosyl transferases (UGTs), thiopurine methyltransferase (TPMT), catechol-O-methyltransferase (COMT), histamine methyltransferase (HMT), sulfotransferases (STs), glutathion S-transferase A (GST-A), GST-P, GST-T, GST-M, N-acetyl transferase (NAT2), NAT1, and others [29, 86]. Polymorphic variants in these genes can induce alterations in drug metabolism modifying the efficacy and safety of the prescribed drugs.

The CYP gene family

The typical paradigm for the pharmacogenetics of phase I drug metabolism is represented by the cytochrome P-450 enzymes, a superfamily of microsomal heme-thiolate proteins widely distributed in bacteria, fungi, plants, and animals. The P450 enzymes are encoded in genes of the CYP superfamily (Table 2) and act as terminal oxidases in multicomponent electron transfer chains which are called P450-containing monooxigenase systems. Some of the enzymatic products of the CYP gene superfamily can share substrates, inhibitors, and inducers, whereas others are quite specific for their substrates and interacting drugs [16, 18, 29, 55]. There are more than 200 P450 genes identified in different species, with more than 1,000 variants among CYP450 genes [75]. These species-specific differences are important when performing comparative pharmacogenetic studies and/or pharmacological experiments in animal models [88]. CYPs are also expressed in the CNS, and a complete characterization of constitutive and inducible CYPs in brain is essential for understanding the role of these enzymes in neurobiological functions and in age-related and xenobiotic-induced neurotoxicity [44]. The most important enzymes of the P450 cytochrome family in drug metabolism by decreasing order are CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP2A6 [29, 50, 75, 86, 97, 98] (Table 2).

The microsomal, membrane-associated, P450 isoforms CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2E1, and CYP1A2 are responsible for the oxidative metabolism of more than 90% of marketed drugs; and CYP3A4 metabolizes more drug molecules than all other isoforms together. Most of these polymorphisms exhibit geographic and ethnic differences [39, 56, 93–95]. These differences influence drug metabolism in different ethnic groups in which drug dosage should be adjusted according to their enzymatic capacity, differentiating normal or extensive metabolizers (EMs), poor metabolizers (PMs) and ultrarapid metabolizers (UMs).

CYP2D6 genotypes in Alzheimer's disease

The CYP2D6 enzyme, encoded by a gene that maps on 22q13.1-13.2, catalyzes the oxidative metabolism of more than 100 clinically important and commonly prescribed drugs such as cholinesterase inhibitors (tacrine, donepezil, galantamine), antidepressants, neuroleptics, opioids, some β-blockers, class I antiarrhythmics, analgesics and many other drug categories, acting as substrates, inhibitors or inducers with which cholinesterase inhibitors may potentially interact, thus leading to the outcome of ADRs [9, 16, 24]. The CYP2D6 locus is highly polymorphic, with more than 100 different CYP2D6 alleles identified in the general population showing deficient (PM), normal (EM) or increased enzymatic activity (UM)[98]. Most individuals (>80%) are EMs; however, remarkable interethnic differences exist in the frequency of the PM and UM phenotypes among different societies all over the world [16, 18, 29, 50, 56, 74, 94, 95]. On the 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. The frequency of PMs among Middle Eastern populations, Asians, and Americans is in the range of 2–3% [17–19, 29, 50]. CYP2D6 gene duplications are relatively infrequent among Northern

Table 2 CYP genes encoding Cytochrome P450-related enzymes involved in human pharmacogenetic activities

Gene	Locus	Name	Alternate names	Related drugs	Related diseases	OMIM phenotype	Alternate symbols
CYP1A2	15q22-qter	Cytochrome P450, subfamily (aromatic compound-inducible), polypeptide 2	P450 form 4; aryl hydrocarbon hydroxylase; cytochrome P450, subfamily 1 (aromatic compound-inducible), polypeptide 2; dioxin-inducible P3-450; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Amiodarone, caffeine, citalopram, clozapine, cyclobenzaprine, dexamethasone, Echinacea, estradiol, etoposide, fluvoxamine, haloperidol, imipramine, interferon alpha, lidocaine, mibefradil, midazolam, modafinil, naproxen, ondansetron, propranolol, ribavirin, riluzole, ropivacaine, tacrine, teniposide, theophylline, thiotepa, ticlopidine, verapamil, zolmitriptan, zoxazolamine	Chronic hepatitis C, Schizophrenia, psychosis		CP12; P3-450; P450(PA)
CYP1B1	2p21	Cytochrome P450, subfamily 1 (dioxin-inducible), polypeptide 1 (glaucoma 3, primary infantile)	Aryl hydrocarbon hydroxylase; cytochrome P450, subfamily 1 (dioxin-inducible), polypeptide 1 (glaucoma 3, primary infantile); flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Estrogens	Breast neoplasms	Primary congenital glaucoma 3A; early-onset digenic glaucoma; Peters anomaly	CP1B; GLC3A
CYP2A6	19q13.2	Cytochrome P450, family 2, subfamily A, polypeptide 6	Coumarin 7-hydroxylase; cytochrome P450, subfamily IIA (Phenobarbital-inducible), polypeptide 3; cytochrome P450, subfamily IIA (Phenobarbital-inducible), polypeptide 6; flavoprotein-linked monooxygenase; xenobiotic monooxygenase	5-Fluorouracil, dexamethasone, etoposide, fadrozole, fluorouracil, midazolam, nicotine, rifampin, teniposide	Neoplasms	Coumarin resistance, protection from nicotine addiction	CPA6; CYP2A3
CYP2B6	19q13.2	Cytochrome P450, family 2, subfamily B, polypeptide 6	Cytochrome P450, subfamily IIB (Phenobarbital-inducible), polypeptide 6	Aflatoxin B1, bupropion, cyclophosphamide, dexamethasone, etoposide, ifosfamide, midazolam, Phenobarbital, propofol, rifampin, teniposide, thiotepa, vitamin D, xenobiotics	Nicotine addiction		CPB6; CYPIIB6; P450
CYP2C19	10q24.1-q24.3	Cytochrome P450, family 2, subfamily C, polypeptide 19	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 19; flavoprotein-linked monooxygenase; mephenytoin 4′-hydroxylase; microsomal monooxygenase; xenobiotic monooxygenase	Amitriptyline, carisoprodol, citalopram, cyclophosphamide, diazepam, fluoxetine, fluvoxamine, glucorticoids, hexobarbital, lansoprazole, mephenytoin, modafinil, nelfinavir, nilutamide, omeprazole, pantoprazole, proguanil, rifampin, thiotepa, ticlopidine	Lupus nephritis, gastroesophageal reflux disease, peptic ulcer disease, visual disorders	Mephenytoin poor metabolizer	CPCJ; CYP2C; P450C2C; P450IIC19
CYP2C9	10q24	Cytochrome P450, family 2, subfamily C, polypeptide 9	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 10; cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 9; flavoprotein-linked monooxygenase; mephenytoin 4-hydroxylase; microsomal monooxygenase; xenobiotic monooxygenase	Acenocoumarol, amiodarone, celecoxib, coumadin, dexamethasone, diclofenac, etoposide, fluconazole, fluoxetine, fluvastatin, fluvoxamine, glimepiride, glipizide, glyburide, ibuprofen, irbesartan, isoniazid, losartan, midazolam, phenylbutazone, phenytoin, rifampin, teniposide, tenoxicam, thiotepa, tolbutamide, torsemide, vitamin D, warfarin	Arthritis, blood coagulation disorders, diabetes mellitus, epilepsy, hypertension, thrombolytic disease	Tolbutamide poor metabolizer, warfarin sensitivity	CPC9; CYP2C10; P450 MP-4; P450 PB-1; P450IIC9
CYP2D6	22q13.1	Cytochrome P450, family 2, subfamily D, polypeptide 6	Cytochrome P450, subfamily IID (debrisoquin, sparteine), polypeptide 6; cytochrome P450, subfamily IID (debrisoquine, sparteine)-like 1; debrisoquine 4-hydroxylase; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Amitriptyline, caffeine, cimetidine, citalopram, clomipramine, clozapine, cocaine, codeine, debrisoquine, desipramine, dextromethorphan, diltiazem, flecainide, fluoxetine, fluvoxamine, haloperidol, imipramine, interferon alpha, metoprolol, mexiletine, morphine, paroxetine, perhexiline, perphenazine, propafenone, propranolol, ribavirin, risperidone, ritonavir, sparteine, tamoxifen, thioridazine, thiotepa, timolol, tramadol, venlafaxine, xenobiotics, yohimbine, zuclopenthixol	Breast neoplasms, cystic fibrosis, depression, chronic hepatitis C, lung neoplasms, codeine dependence pain, schizophrenia, codeine dependence, psychosis	Susceptibility to parkinsonism, debrisoquine sensitivity	CPD6; CYP2D; CYP2D6; CYP2DL1; P450-DB1; P450C2D

Table 2 Continued

Gene	Locus	Name	Alternate names	Related drugs	Related diseases	OMIM phenotype	Alternate symbols
CYP2E1	10q24.3-qter	Cytochrome P450, subfamily IIE (ethanol-inducible)	Cytochrome P450, subfamily IIE (ethanol-inducible); cytochrome P450, subfamily IIE (ethanol-inducible), polypeptide 1; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Dexamethasone, ethanol, etoposide, midazolam, nicotine, teniposide, thiotepa, xenobiotics	Alcoholic liver disease, lung neoplasms, nicotine dependency		CPE1; CYP2E; CYP2E1; P450-J; P450C2E
CYP3A	7q21.3-q22.1	Cytochrome P450, family 3, subfamily A	Cytochrome P450, subfamily IIIA (nifedipine oxidase)	Dexamethasone, docetaxel, erythromycin, midazolam, rifampin, tamoxifen, thiotepa, xenobiotics	Arrhythmia, lung neoplasms		CYP3
CYP3A4	7q21.1	Cytochrome P450, family 3, subfamily A, polypeptide 4	P450-III, steroid inducible; cytochrome P450, subfamily IIIA (nifedipine oxidase), polypeptide 3; cytochrome P450, subfamily IIIA (nifedipine oxidase), polypeptide 4; glucocorticoid-inducible P450; nifedipine oxidase	Alprazolam, anthracycline, cisapride, citalopram, dexamethasone, docetaxel, epipodophyllotoxin, etoposide, glucocorticoids, interferon alpha, irinotecan, losartan, midazolam, nifedipine, omeprazole, ribavirin, rifampin, tamoxifen, teniposide, testosterone, topotecan, vitamin D, xenobiotics	Breast neoplasms, chronic hepatitis C, leukaemia, L1 acute lymphocytic leukaemia, myeloid leukaemia, neoplasms, prostatic neoplasms, helycobarcter pylori gastric ulcers		CP33; CP34; CYP3A; CYP3A3; CYP3A4; HLP; NF-25; P450C3; P450PCN1
CYP3A5	7q21.1	Cytochrome P450, family 3, subfamily A, polypeptide 5	Aryl hydrocarbon hydrolase; cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5; flavoprotein-linked monooxygenase; microsomal monooxygenase; niphedipine oxidase; xenobiotic monooxygenase	Aflatoxin B1, antrhacycline, cisapride, cyclosporine, dexamethasone, etoposide, glucocorticoids, irinotecan, midazolam, simvastatin, tacrolimus, teniposide, vitamin C, warfarin, xenobiotics	Blood coagulation disorders, L1 acute lymphocytic leukaemia, myeloid leukaemia		CYP35; CYP3A5; P450PCN3; PCN3
CYP3A7	7q21-q22.1	Cytochrome P450, family 3, subfamily A, polypeptide 7	Aryl hydrocarbon hydrolase; cytochrome P450, subfamily IIIA, polypeptide 7; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Cisapride, midazolam, vitamin D, xenobiotics			CP37; P450-HFLA
CYP4B1	1p34-p12	Cytochrome P450, subfamily IVB, polypeptide 1	Cytochrome P450, subfamily IVB, member 1; cytochrome P450, subfamily IVB, polypeptide 1; microsomal monooxygenase	Xenobiotics			P-450HP
CYP11B2	8q21-q22	Cytochrome P450, family 11, subfamily B, polypeptide 2	Steroid 11-beta/18-hydrolase; aldosterone synthase; cytochrome P450, subfamily XIB (steroid 11-beta-hydrolase), polypeptide 2; steroid 11-beta-monooxygenase; steroid 11-beta/18-hydrolase	Candesartan		Aldosterone to renin ratio raised, congenital hypoaldosteronism due to CMO I deficit, congenital hypoaldosteronism due to CMO II deficit, low renin hypertension	ALDOS; CPN2; CYP11B; CYP11BL; P-450C-18; P450aldo

Adapted from Cacabelos and Takeda [29]

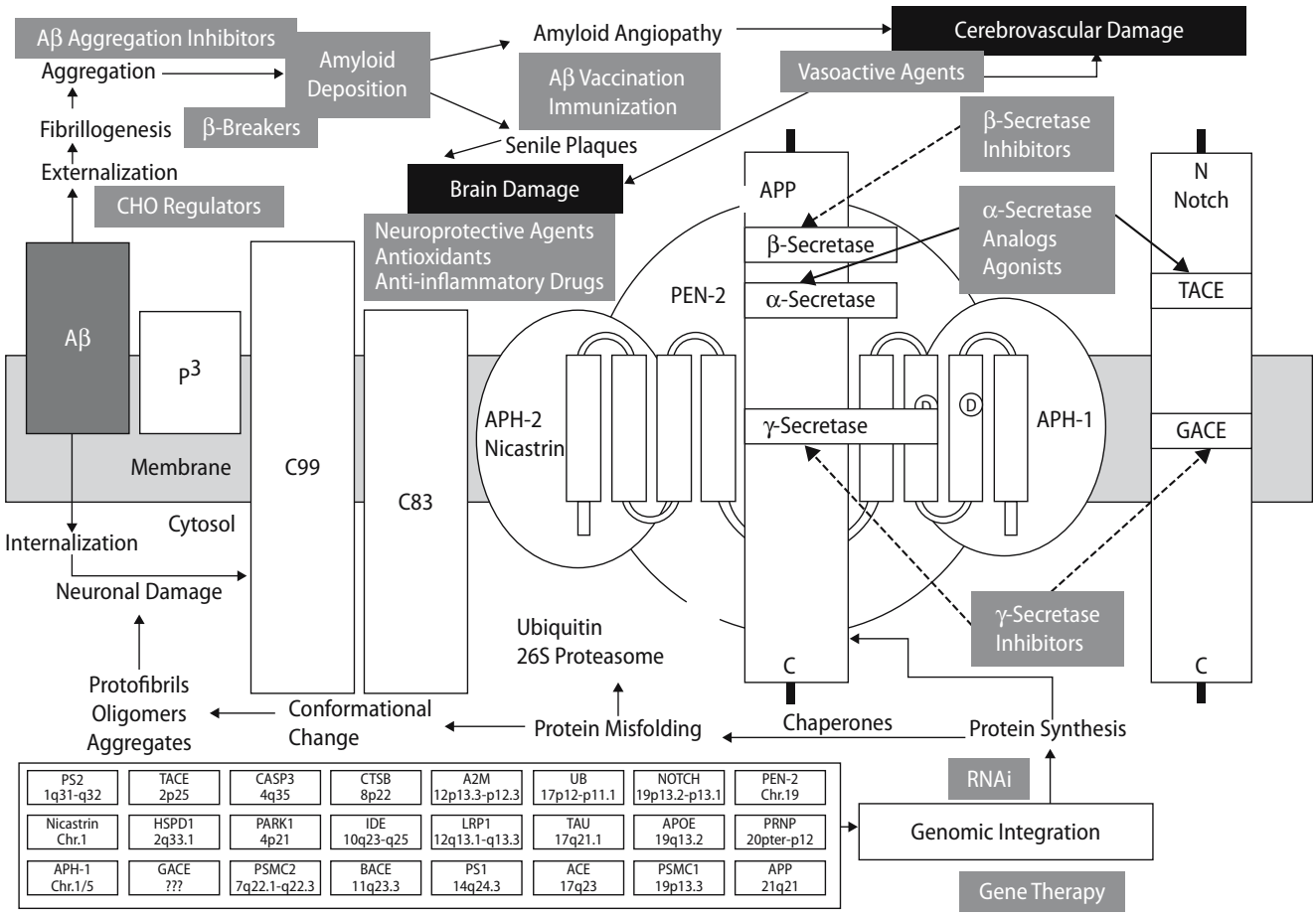


Fig. 3 Brain amyloidogenesis and potential therapeutic interventions in Alzheimer's disease (adapted from Cacabelos [18])

Europeans, but in East Africa the frequency of alleles with duplication of CYP2D6 is as high as 29% [91].

The most frequent CYP2D6 alleles in the European population are the following: CYP2D6*1 (wild-type) (normal), CYP2D6*2 (2850C > T) (normal), CYP2D6*3 (2549A > del) (inactive), CYP2D6*4 (1846G > A) (inactive), CYP2D6*5 (gene deletion) (inactive), CYP2D6*6 (1707T > del) (inactive), CYP2D6*7 (2935A > C) (inactive), CYP2D6*8 (1758G > T) (inactive), CYP2D6*9 (2613–2615 delAGA) (partially active), CYP2D6*10 (100C > T) (partially active), CYP2D6*11 (883G > C) (inactive), CYP2D6*12 (124G > A) (inactive), CYP2D6*17 (1023C > T) (partially active), and CYP2D6 gene duplications (with increased or decreased enzymatic activity depending upon the alleles involved) [10, 17–19, 29, 43].

In the Spanish population, where the mixture of ancestral cultures has occurred for centuries, the distribution of the CYP2D6 genotypes differentiates four major categories of CYP2D6-related metabolyzer types: (a) Extensive Metabolizers (EM) (*1/*1, *1/*10) (51.61%); (b) Intermediate Metabolizers (IM) (*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10) (32.26%); (c) Poor Metabolizers (PM) (*4/*4, *5/*5) (9.03%); and (d) Ultra-rapid Metabolizers (UM) (*1xN/*1, *1xN/*4, Dupl) (7.10%) [43]. The distribution of all major genotypes is the following: *1/*1, 47.10%; *1/*10, 4.52%; *1/*3, 1.95%; *1/*4, 17.42%; *1/*5, 3.87%; *1/*6, 2.58%; *1/*7, 0.65%; *10/*10, 1.30%; *4/*10, 3.23%; *6/*10, 0.65%; *7/*10, 0.65%; *4/*4, 8.37%; *5/*5, 0.65%; *1 × N/*1, 4.52%; *1 × N/*4, 1.95%; and Dupl, 0.65% [19, 20]. This distribution of CYP2D6 variants is very similar in most Caucasian populations and differs from other ethnic groups worldwide [11, 39, 50, 56, 67, 69, 75].

Although initial studies postulated the involvement of the CYP2D6B mutant allele in Lewy body formation in both Parkinson's disease and the Lewy body variant of AD, as well as in the synaptic pathology of pure AD without Lewy bodies [31], subsequent studies in different ethnic groups did not find association between AD and CYP2D6 variants [6, 30, 37, 61, 78, 92, 96]. Notwithstanding, the genetic variation between AD and controls associated with CYP2D6 genotypes is 13.35% in EMs, 15.89% in IMs, 0.38% in PMs, and 2.16% in UMs, with an absolute genetic variation of 31.78% between both groups, suggesting that this genetic difference might influence AD pathogenesis and therapeutics [19]. In addition, association studies clearly show that in PMs and UMs there is an accumulation of AD-related polymorphic variants of risk

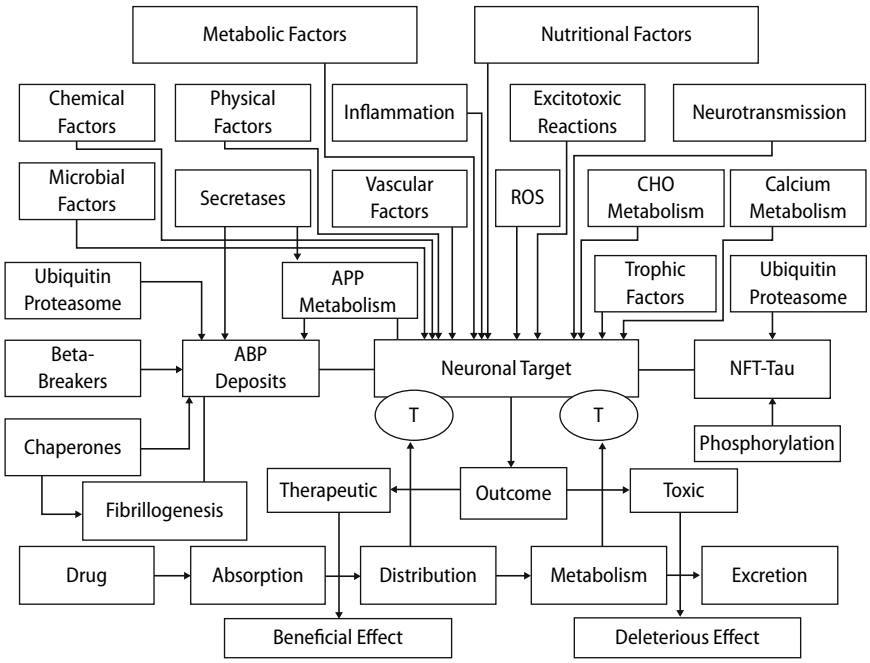


Fig. 4 Multicomponent cascade of pathogenic factors associated with efficacy and safety issues in Alzheimer's disease pharmacogenomics/pharmacogenetics

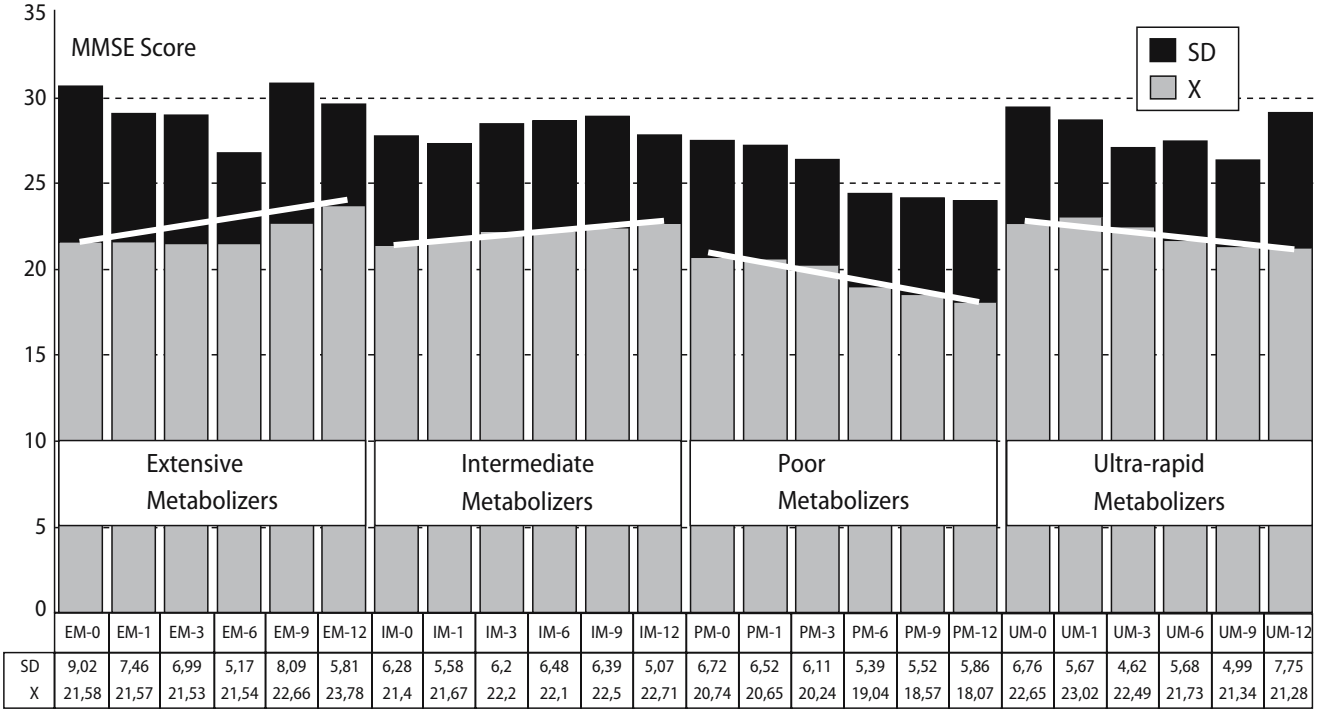
which might be responsible for the defective therapeutic responses currently seen in these AD clusters, and CYP2D6-related variants also influence liver transaminase activity [20, 27, 67, 89].

CYP2D6-related therapeutic response to a multifactorial treatment in dementia

Prospective studies in dementia with a multifactorial therapy including (a) an endogenous nucleotide and choline donor, CDP-choline (500 mg/day), (b) a nootropic substance, piracetam (1,600 mg/day), (c) a vasoactive compound, 1,6 dimethyl 8β-(5-bromonicotinoyl-oxymethyl)-10α-methoxyergoline (nicergoline)(5 mg/day), and (d) a cholinesterase inhibitor, donepezil (5 mg/day), for 1 year, have revealed a clear CYP2D6-related therapeutic response in which PMs and UMs are the worst responders [19, 20]. With this multifactorial therapeutic intervention, EMs improved their cognitive function (MMSE score) from 21.58 ± 9.02 at baseline to 23.78 ± 5.81 after 1-year treatment. IMs also improved from 21.40 ± 6.28 to 22.50 ± 5.07, whereas PMs and UMs deteriorated from 20.74 ± 6.72 to 18.07 ± 5.52, and from 22.65 ± 6.76 to 21.28 ± 7.75, respectively. According to these results, PMs and UMs were the worst responders, showing a progressive cognitive decline with no therapeutic effect, and EMs and IMs were the best responders, with a clear improvement in cognition after 1 year of treatment (Fig. 5). Among EMs, AD patients harboring the *1/*10 genotype responded better than patients with the *1/*1 genotype. The best responders among IMs were the *1/*3, *1/*6 and *1/*5 genotypes, whereas the *1/*4, *10/*10, and *4/*10 genotypes were poor responders. Among PMs and UMs, the poorest responders were carriers of the *4/*4 and *1 × N/*1 genotypes, respectively [19, 20].

CYP2D6-related pharmacogenetics in Alzheimer's disease

From reported data during the past few years we can conclude the following: (a) The most frequent CYP2D6 variants in the Spanish population are the *1/*1 (47.10%), *1/*4 (17.42%), *4/*4 (8.37%), *1/*10 (4.52%) and *1 × N/*1 (4.52%), accounting for more than 80% of the population; (b) the frequency of EMs, IMs, PMs, and UMs is about 51.61, 32.26, 9.03, and 7.10%, respectively; (c) EMs are more prevalent in AD (57.47%) than in controls (44.12%); IMs are more frequent in controls (41.18%) than in AD (25.29%), especially the *1/*4 (C: 23.53%; AD: 12.64%) and *4/*10 genotypes (C: 5.88%; AD: 1.15%); the frequency of PMs is similar in AD (9.20%) and controls (8.82%); and UMs are more frequent among AD cases (8.04%) than in controls (5.88%); (d) there is an accumulation of AD-related genes of risk in PMs and UMs; (e) PMs and UMs tend to show higher transaminase activities than EMs and IMs; (f) 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; and (g) 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 [18–20, 29].



	EM-0	EM-1	EM-3	EM-6	EM-9	EM-12	IM-0	IM-1	IM-3	IM-6	IM-9	IM-12	PM-0	PM-1	PM-3	PM-6	PM-9	PM-12	UM-0	UM-1	UM-3	UM-6	UM-9	UM-12
SD	9,02	7,46	6,99	5,17	8,09	5,81	6,28	5,58	6,2	6,48	6,39	5,07	6,72	6,52	6,11	5,39	5,52	5,86	6,76	5,67	4,62	5,68	4,99	7,75
X	21,58	21,57	21,53	21,54	22,66	23,78	21,4	21,67	22,2	22,1	22,5	22,71	20,74	20,65	20,24	19,04	18,57	18,07	22,65	23,02	22,49	21,73	21,34	21,28

Fig. 5 CYP2D6-related therapeutic response to a multifactorial treatment in Alzheimer's disease for 1-year period (adapted from Cacabelos [19])

Taking into consideration the available data, it might be inferred that at least 15% 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 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 can be postulated that pharmacogenetic and pharmacogenomic factors are responsible for 75–85% of the therapeutic response (efficacy) in AD patients treated with conventional drugs [17–19, 25, 29]. Of particular interest are the potential interactions of cholinesterase inhibitors with other drugs of current use in patients with AD, such as antidepressants, neuroleptics, antiarrhythmics, analgesics, and antiemetics which are metabolized by the cytochrome P450 CYP2D6 enzyme. Approximately 30–60% of drug failure or lack of therapeutic efficacy (and/or ADR manifestation) is not a matter of drug dosage but a problem of poor-metabolizing capacity in PMs. Additionally, inappropriate drug use is one of the risk factors for adverse drug reactions (ADRs) in the elderly. The prevalence of use of potentially inappropriate medications in patients older than 65 years of age admitted to a general medical or geriatric ward ranges from 16 to 20% [33], and these numbers may double in ambulatory patients. Overall, the most prevalent inappropriate drugs currently prescribed to the elderly are amiodarone, long-acting benzodiazepines, and anticholinergic antispasmodics; however, the list of drugs with potential risk also include antidepressant, antihistaminics, NSAIDs, amphetamines, laxatives, clonidine, indomethacin, and several neuroleptics [33], most of which are processed via CYP2D6 and CYP3A5 enzymes [16, 18, 19, 29, 77]. Therefore, pre-treatment CYP screening might be of great help to rationalize and optimize therapeutics in the elderly, by avoiding medications of risk in PMs and UMs.

Pharmacogenomics in dementia

APOE in Alzheimer's disease therapeutics

Polymorphic variants in the APOE gene (19q13.2) are associated with risk (APOE-4 allele) or protection (APOE-2 allele) for AD [24, 29]. For many years, alterations in ApoE and defects in the APOE gene have been associated with dysfunctions in lipid metabolism, cardiovascular disease, and atherosclerosis. During the past 25 years an enormous number of studies clearly documented the role of APOE-4 as a risk factor for AD, and the accumulation of the APOE-4 allele has been reported as a risk factor

for other forms of dementia and CNS disorders [24, 29].

APOE-4 may influence AD pathology interacting with APP metabolism and ABP accumulation, enhancing hyperphosphorylation of tau protein and 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 [24, 29].

APOE-related therapeutic response to cholinesterase inhibitors

Several studies indicate that the presence of the APOE-4 allele differentially affects the quality and size of drug responsiveness in AD patients treated with cholinergic enhancers (tacrine, donepezil, rivastigmine) [2, 65, 66]. For example, APOE-4 carriers show a less significant therapeutic response to tacrine (60%) than patients with no APOE-4 [66]. In another study the frequency of APOE-4 alleles was higher in responders to a single oral dose of tacrine [2]. It has been demonstrated that more than 80% of APOE-4(−) AD patients showed marked improvement after 30 weeks of treatment with tacrine, whereas 60% of APOE-4(+) carriers had a poor response [66]. Others found no differences after 6 months of treatment with tacrine among APOE genotypes, but after 12 months the CIBIC scores revealed that APOE-4 carriers had declined more than the APOE-2 and APOE-3 patients, suggesting that a faster rate of decline was evident in the APOE-4 patients probably reflecting that APOE-4 inheritance is a negative predictor of treatment of tacrine in AD [81]. It has also been shown that the APOE genotype may influence the biological effect of donepezil on APP metabolism in AD [13]. Prospective studies with galantamine in large samples of patients in Europe [1] and in USA [68] showed no effect of APOE genotypes on drug efficacy. APOE-4 non-carriers also exhibit cognitive and functional improvement to rosiglitazone, a PPARG agonist, whereas APOE-4 carriers show no improvement or some decline [72]. MacGowan et al. [54] reported that gender is likely to be a more powerful determinant of outcome of anticholinesterase treatment than APOE status in the short term. In contrast, other studies do not support the hypothesis that APOE and gender are predictors of the therapeutic response of AD patients to tacrine or donepezil [70,71]. Petersen et al. [63] showed that APOE-4 carriers exhibited a better response to donepezil. Similar results have been found by Bizzarro et al. [12]; however, Rigaud et al. [71] did not find any significant difference between APOE-4-related responders and non-responders to donepezil.

APOE-related therapeutic response to non-cholinergic strategies

An APOE-related differential response has also been observed in patients treated with other compounds devoid of acetylcholinesterase inhibiting activity (e.g., CDP-choline, anapsos, rosiglitazone) [3, 4, 72] suggesting that APOE-associated factors may influence drug activity in the brain either directly acting on neural mechanisms or indirectly influencing diverse metabolic pathways [76].

Influence of APOE in polygenic clusters on Alzheimer's disease therapeutics

To date, few studies have addressed in a prospective manner the impact of pharmacogenetic and pharmacogenomic factors on AD therapeutics [14–19, 21, 25, 29]. Practically, all studies reported to date in the international literature are referred to monotherapies (one single drug) associated with responses to APOE variants [29]. Since many different genes (Table 1) participate in AD pathogenesis regulating neuronal function and brain amyloidogenesis, in an attempt to envision the potential influence of major AD-associated genes on the therapeutic response in AD patients, some pioneering pharmacogenomic studies have been performed using a genetic matrix model (trigenic haplotype-like model) to identify the response of a multifactorial therapy in different AD genotypes combining allelic associations of APOE + PS1 + PS2 genes [21, 25, 29]. With this strategy it has been demonstrated that the therapeutic response in AD is genotype-specific [14–19, 21, 29]. In monogenic-related studies, APOE-4/4 carriers are the worst responders (Fig. 6). PS1- and PS2-related polymorphic variants do not appear to influence the therapeutic response in AD; however, APP, PS1, and PS2 mutations may drastically modify the therapeutic response to conventional drugs. In trigenic (APOE + PS1 + PS2)-related studies the best responders are those patients carrying the 331222-, 341122-, 341222-, and 441112-genomic clusters (Fig. 7). The worst responders in all genomic clusters are patients with the 441122+ genotype (Fig. 7). In general terms, APOE-4/4 carriers show a faster disease progression and a poorer therapeutic response to all available treatments than any other polymorphic variant. Pharmacogenomic studies using trigenic, tetragenic or polygenic clusters as a harmonization procedure to reduce genomic heterogeneity are very useful to widen the therapeutic scope of limited pharmacological resources [14–19, 21, 25, 29].

Pharmacogenomics of non-cognitive symptoms

Behavioral disturbances and mood disorders are intrinsic components of dementia. The appearance of

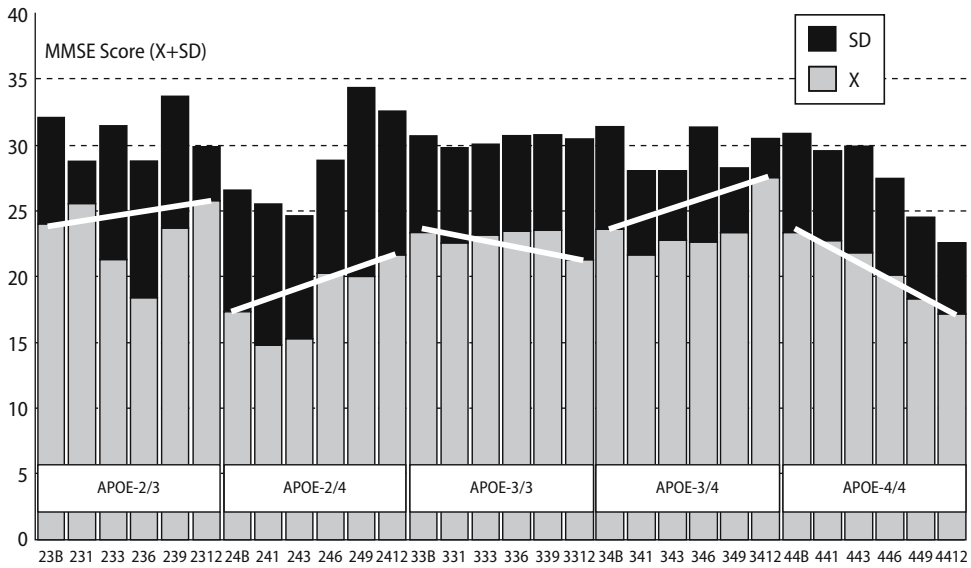


Fig. 6 APOE-related cognitive performance in patients with Alzheimer's disease treated with a combination therapy for 1 year. (adapted from Cacabelos [19])

anxiety, depression, psychotic symptoms, verbal and physical aggressiveness, agitation, wandering and sleep disorders complicate the clinical picture of dementia and add important problems to the therapeutics of AD and the daily management of patients as well. Under these conditions, psychotropic drugs (antidepressants, anxyolitics, hypnotics, and neuroleptics) are required, and most of these substances contribute to deteriorate cognition and psychomotor function. APOE polymorphic variants have been associated with mood disorders and other non-cognitive symptoms in dementia [8, 28, 32, 36, 38, 47, 57, 82, 83, 87]. Gender, age, dementia severity, APOE-4, and general medical health appear to influence the occurrence of individual neuropsychiatric symptoms in dementia, and medical comorbidity increases the risk of agitation, irritability, disinhibition, and aberrant motor behavior [83]. A positive association between APOE-4 and neuropsychiatric symptoms and depressive symptoms in AD has been reported [36, 57, 87]. APOE-4 carriers with deep white matter hyperintensities in MRI show association with depressive symptoms and vascular depression [59]. Reduced caudate nucleus volumes and genetic determinants of homocysteine metabolism accumulate in patients with psychomotor slowing and cognitive deficits [58], and older depressed subjects have persisting cognitive impairments associated with hippocampal volume reduction [45, 62]. Depressive symptoms are also associated with stroke and atherogenic lipid profile [51].

Effect of combination treatments on anxiety and depression in Alzheimer's disease

Recent evidence indicates that multifactorial therapies similar to those used to treat cognitive dysfunction (excluding psychotropic agents such as anxiolytics and/or antidepressants from the combination therapy) can be extremely effective in reducing anxiety and depression in patients with dementia [19]. With this strategy, the anxiety rate progressively declines from a baseline HRS-A score of 10.90 ± 5.69 to 9.07 ± 4.03 ($P < 0.0000000001$) at 1 month, 9.01 ± 4.38 ($P < 0.000006$) at 3 months, 8.90 ± 4.47 ($P < 0.005$) at 6 months, 7.98 ± 3.72 ($P < 0.00002$) at 9 months, and 8.56 ± 4.72 ($P < 0.01$) at 12 months of treatment [19].

Identical striking results are found in depression. Depressive symptoms gradually improve from a baseline HRS-D score of 9.45 ± 5.66 to 7.07 ± 4.68 ($P < 0.001$) after 1 year of treatment. The progressive decline in HDR-D scores is significant with respect to baseline values at 1 month (7.73 ± 4.03, $P < 0.0000000001$), 3 months (8.04 ± 4.22, $P < 0.000002$), 6 months (7.37 ± 4.18, $P < 0.000002$), 9 months (7.52 ± 3.95, $P < 0.0001$) and 12 months ($P < 0.001$) of treatment. From a global perspective, these data might suggest that improvement in mood conditions can contribute to stabilize cognitive function or that neuroprotection (with the consequent stabilization or improvement in mental performance) can enhance emotional equilibrium [19].

APOE-related therapeutic response in anxiety and depression

At baseline, all APOE variants show similar anxiety and depression rates, except the APOE-4/4 carriers who differ from the rest with significantly lower rates of anxiety and depression ($P < 0.05$) (Figs. 8, 9). Remarkable changes in anxiety are found among different APOE genotypes during the treatment period with a combination therapy (Fig. 8). All APOE variants respond with a significant diminution of anxiogenic and depressive symptoms, except patients

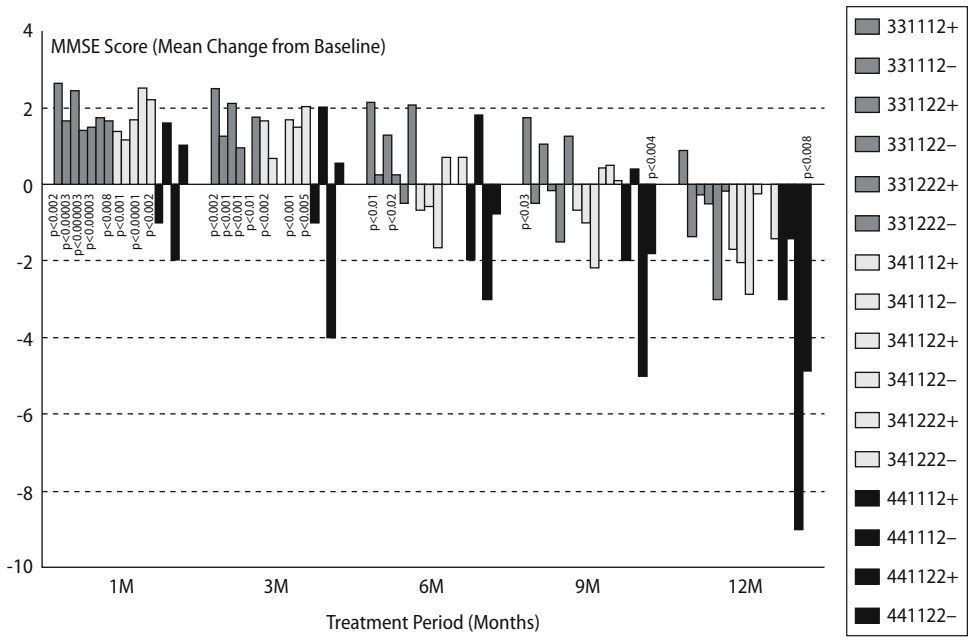


Fig. 7 Trigenic (APOE + PS1 + PS2)-related therapeutic response to a combination therapy in patients with Alzheimer's disease (adapted from Cacabelos et al. [16, 25])

with the APOE-4/4 genotype who only showed a slight improvement. The best responders are APOE-2/4 > APOE-2/3 > APOE-3/3 > APOE-3/4 carriers [19] (Figs. 8, 9). APOE-4/4 carriers are the worst responders, with results similar to those obtained in cognitive performance; however, the potential influence of APOE variants on mood disorders and cognition in AD does not show a clear parallelism, suggesting that many other complex mechanisms are involved in the onset of anxiety and depression in dementia [19].

Polygenic networking in pharmacogenomics

There is convincing evidence that genetic interactions contribute to neurodegeneration in AD [24] and that many different genes interact to elicit a pharmacogenetic outcome in patients with dementia [19, 20, 29].

APOE–CYP2D6 interactions

The apolipoprotein E influences liver function and CYP2D6-related enzymes probably via regulation of hepatic lipid metabolism [19,27]. APOE may affect liver function and drug metabolism by modifying hepatic steatosis and transaminase activity. There is a clear correlation between APOE-related triglyceride (TG) levels and GOT, GPT, and GGT activities in AD [27]. Both plasma TG levels and transaminase activity are significantly lower in AD patients harboring the APOE-4/4 genotype, probably indicating that (a) low-TG levels protect against liver steatosis, and (b) the presence of the APOE-4 allele influences TG levels, liver steatosis, and transaminase activity. Consequently, it is very likely that APOE influences drug metabolism in the liver through different mechanisms, including interactions with enzymes such as transaminases and/or cytochrome P450-related enzymes encoded in genes of the CYP superfamily [19, 27].

When APOE and CYP2D6 genotypes are integrated into bigenic clusters and the APOE + CYP2D6-related therapeutic response to a combination therapy is analyzed in AD patients after 1 year of treatment, it becomes clear that the presence of the APOE-4/4 genotype is able to convert pure CYP2D6*1/*1 EMs into full PMs, indicating the existence of a powerful influence of the APOE-4 homozygous genotype on the drug-metabolizing capacity of pure CYP2D6-EMs [19, 20].

Conclusions

The optimization of AD therapeutics requires the establishment of new postulates regarding (a) the costs of medicines, (b) the assessment of protocols for global treatment in dementia, (c) the implementation of novel therapeutics addressing causative factors, and (d) the setting-up of pharmacogenetic/pharmacogenomic strategies for drug development [14–19, 21, 24, 29, 73].

Cost-effectiveness of anti-dementia drugs

Drugs approved by the FDA and other regulatory authorities in Europe and Japan include the cholinesterase inhibitors (ChEIs) tacrine, donepezil, rivastigmine, and galantamine, and the NMDA receptor partial antagonist memantine [18, 29]. Some studies assessing the cost-effectiveness of ChEIs suggest that ChEI therapy provides benefit at every stage of disease, with better outcomes resulting from persistent,

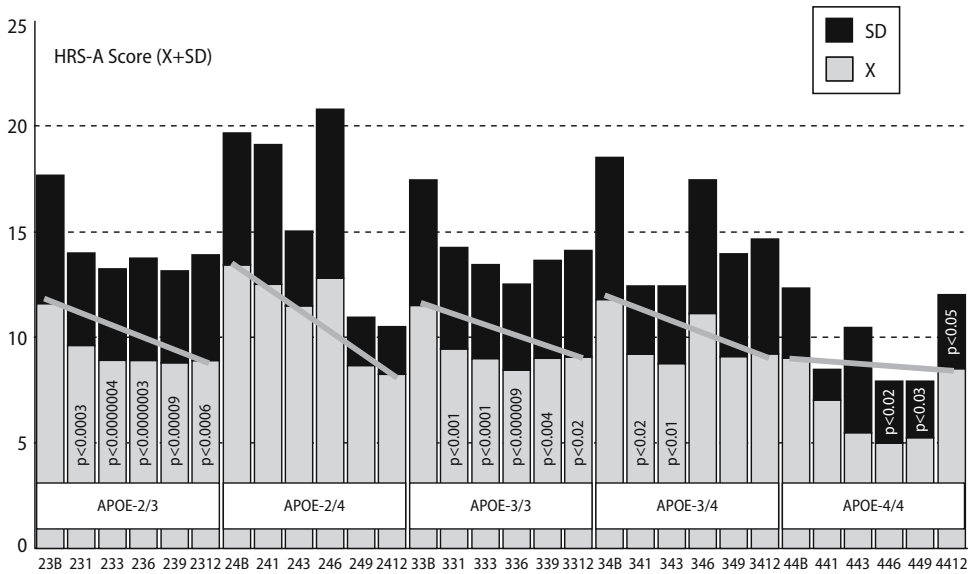


Fig. 8 APOE-related anxiety rate in patients with Alzheimer's disease treated with a combination therapy. *B* Baseline. 1-3-6-9-12: months of treatment. X: mean value. SD: Standard deviation. HRS-A: Hamilton Rating Scale for Anxiety (adapted from Cacabelos [19])

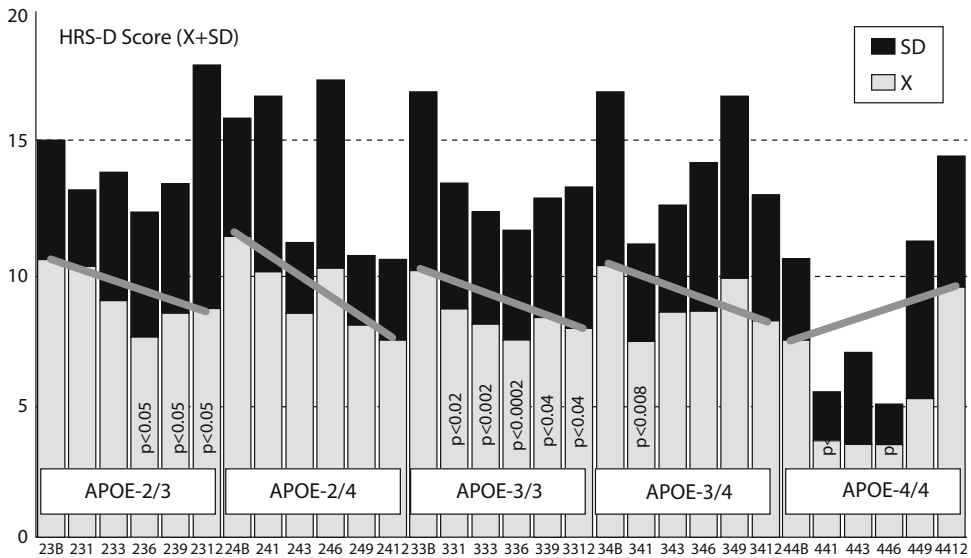


Fig. 9 APOE-related depression rate in patients with Alzheimer's disease treated with a combination therapy. *B* Baseline. 1-3-6-9-12: months of treatment. X: mean value. SD: Standard deviation. HRS-D: Hamilton Rating Scale for Depression (adapted from Cacabelos [19])

uninterrupted treatment, whereas other studies indicate that ChEIs are not cost-effective, with benefits below minimally relevant thresholds or cost-neutral [53]. Methodological limitations in some studies reduce the confidence of independent evaluators in the validity of the conclusions drawn in published reports [46]. Although the therapeutic value and cost-effectiveness of current anti-dementia treatment is very questionable [53], these drugs are of common use in AD [18,29] and still require further evaluation from a pharmacogenetic/pharmacogenomic perspective in order to avoid side-effects and unnecessary costs [29]. There is an urgent need to assess the costs of new trials with pharmacogenetics and pharmacogenomics strategies, and to implement pharmacogenetic procedures to predict drug-related adverse events [7, 17, 18, 29, 42, 73].

Cost-effectiveness analysis has been the most commonly applied framework for evaluating pharmacogenetics. Pharmacogenetic testing is potentially relevant to large populations that incur high costs. For instance, the most common drugs metabolized by CYP2D6 account for 189 million prescriptions and US$ 12.8 billion annually in expenditures in the US, which represent 5–10% of total utilization and expenditures for outpatient prescription drugs [64]. Pharmacogenomics offer great potential to improve patients' health in a cost-effective manner; however, pharmacogenetics/pharmacogenomics will not be applied to all drugs available in the market, and careful evaluations should be done on a case-by-case basis prior to investing resources in R&D of pharmacogenomic-based therapeutics and making reimbursement decisions.

Therapeutic expectations

In performing pharmacogenomic studies in AD, it is necessary to rethink the therapeutic expectations of novel drugs, redesign the protocols for drug clinical trials, and incorporate biological markers as assessable parameters of efficacy and prevention [18, 29]. In addition to the characterization of genomic profiles, phenotypic profiling of responders and non-responders to conventional drugs is also important (and currently neglected). Brain imaging techniques, computerized electrophysiology, and optical topography in combination with genotyping of polygenic clusters can help in the differentiation of responders and non-responders. The early identification of predictive risks requires genomic screening and molecular diagnosis, and individualized preventive programs will only be achieved when pharmacogenomic/pharmacogenetic protocols are incorporated into the clinical armamentarium with powerful bioinformatics support.

Another important issue in AD therapeutics is that anti-dementia drugs should be effective in covering the clinical spectrum of dementia symptoms represented by memory deficits, behavioral changes, and functional decline. It is difficult (or impossible) that a single drug be able to fulfil this criterion. A potential solution to this problem is the implementation of cost-effective, multifactorial (combination) treatments integrating several drugs, taking into consideration that traditional neuroleptics and novel antipsychotics (and many other psychotropics) deteriorate both cognitive and psychomotor functions in the elderly and may also increase the risk of stroke. Few studies with combination treatments have been reported and most of them are poorly designed. We also have to realize that the vast majority of dementia cases in people older than 75–80% are of a mixed type, in which the cerebrovascular component associated with neurodegeneration cannot be therapeutically neglected. In most cases of dementia, the multifactorial (combination) therapy appears to be the most effective strategy [14–16, 18–21, 25, 29]. The combination of several drugs (neuroprotectants, vasoactive substances, AChEIs, metabolic supplementation) increases the direct costs (e.g., medication) by 5–10%, but in turn annual global costs are reduced by approximately 18–20%, and the average survival rate increases by about 30% (from 8 to 12 years post-diagnosis)[29].

Factors associated with drug efficacy and safety

Major impact factors associated with drug efficacy and safety include the following: (a) the mechanisms of action of drugs, (b) drug-specific adverse reactions, (c) drug–drug interactions, (d) nutritional factors, (e) vascular factors, (f) social factors, and (g) genomic factors (nutrigenetics, nutrigenomics, pharmacogenetics, pharmacogenomics). Among genomic factors, nutrigenetics/nutrigenomics and pharmacogenetics/pharmacogenomics account for more than 80% of efficacy-safety outcomes in current therapeutics [18, 19, 29].

Some authors consider that priority areas for pharmacogenetic research are to predict serious adverse reactions (ADRs) and to establish variation in efficacy [60]. Both requirements are necessary in AD to cope with the efficacy and safety issues associated with conventional AD-related drugs, new drugs, and psychotropic drugs of current use in dementia. Since drug response is a complex trait, genome-wide approaches (oligonucleotide microarrays, proteomic profiling) may provide new insights into drug metabolism and drug response.

Education and training in pharmacogenetics

It seems clear that the therapeutic response in AD is genotype-specific with the involvement of multiple genes displaying a networking activity. This is particularly evident in the case of APOE and CYP2D6 as potential modulators of pharmacogenetic responses associated with multifactorial therapies capable of improving cognitive deterioration and behavioral disturbances in dementia. Pharmacogenomic studies using trigenic, tetragenic or polygenic clusters represent a useful harmonization procedure to reduce genomic heterogeneity and to optimize therapeutics in AD [14–16, 18–21, 24, 25, 29].

To achieve a mature discipline of pharmacogenetics and pharmacogenomics in CNS disorders and dementia it would be convenient to accelerate the following processes: (a) educate physicians and the public on the use of genetic/genomic screening in the daily clinical practice; (b) standardize genetic testing for major categories of drugs; (c) validate pharmacogenetic and pharmacogenomic procedures according to drug category and pathology; (d) regulate ethical, social, and economic issues; and (e) incorporate pharmacogenetic and pharmacogenomic procedures to drugs in development and drugs in the market to optimize therapeutics.

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