REVIEW

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Genomics and Pharmacogenomics of Dementia

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SUMMARY

Dementia is a major problem of health in developed countries, and a prototypical paradigm of chronic disability, high cost, and social-family burden. Approximately, 10–20% of direct costs in this kind of neuropathology are related to pharmacological treatment, with a moderate responder rate below 30% and questionable cost-effectiveness. Over 200 different genes have been associated with the pathogenesis of dementia. Studies on structural and functional genomics, transcriptomics, proteomics and metabolomics have revealed the paramount importance of these novel technologies for the understanding of pathogenic cascades and the prediction of therapeutic outcomes in dementia. About 10–30% of Western populations are defective in genes of the *CYP* superfamily. The most frequent *CYP2D6* variants in the Iberian peninsula are the *1/*1 (57.84%), *1/*4 (22.78%), *1×N/*1 (6.10%), *4/*4 (2.56%), and *1/*3 (2.01%) genotypes, accounting for more than 80% of the population. The frequency of extensive (EMs), intermediate (IMs), poor (PMs), and ultra-rapid metabolizers (UMs) is about 59.51%, 29,78%, 4.46%, and 6.23%, respectively, in the general population, and 57.76, 31.05%, 5.27%, and 5.90%, respectively, in AD cases. 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, with *1*1-*1*1-*1*1 (25.70%), *1*1-*1*2-*1*2 (10.66%), *1*1-*1*1-*1*1 (10.45%), *1*4-*1*1-*1*1 (8.09%), *1*4-*1*2-*1*1 (4.91%), *1*4-*1*1-*1*2 (4.65%), and *1*1-*1*3-*1*3 (4.33%), as the most frequent genotypes. Only 26.51% of AD patients show a pure 3EM phenotype, 15.29% are 2EM1IM, 2.04% are pure 3IM, 0% are pure 3PM, and 0% are 1UM2PM. EMs and IMs are the best responders, and PMs and UMs are the worst responders to a combination therapy with cholinesterase inhibitors, neuroprotectants, and vasoactive substances. The pharmacogenetic response in AD appears to be dependent upon the networking activity of genes involved in drug metabolism and genes involved in AD pathogenesis (e.g., *APOE*). AD patients harboring the *APOE-4/4* genotypes are the worst responders to conventional antidementia drugs. To achieve a mature discipline of pharmacogenomics in CNS disorders and dementia it would be convenient to accelerate the following processes: (i) to educate physicians and the public on the use of genetic/genomic screening in daily clinical practice; (ii) to standardize genetic testing for major categories of drugs; (iii) to validate pharmacogenomic information according to drug category and pathology; (iv) to regulate ethical, social, and economic issues; and (v) to incorporate pharmacogenomic procedures both to drugs in development and drugs on the market in order to optimize therapeutics.

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 over 25 million people at present, and probably over 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 over 30–35% in people older than 80 years. It is very likely that in those patients older than 75–80 years of age most cases of dementia are mixed in nature (degenerative + vascular), whereas pure AD cases are very rare after 80 years of age. The average annual cost per person with dementia ranges from €10,000 to €40,000, depending

upon disease stage and country, with a lifetime cost per patient of more than €150,000. In some countries, approximately 80% of the global costs of dementia (direct + indirect costs) are assumed by the patients and/or their families. About 10–20% of the costs in dementia are attributed to pharmacological treatment, including antidementia drugs, psychotropics (antidepressants, neuroleptics, and anxiolytics), and other drugs currently prescribed in the elderly (antiparkinsonians, anticonvulsants, vasoactive compounds, antiinflammatory drugs, etc.). In addition, during the past 20 years over 300 drugs have been partially or totally developed for AD, with the 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 [1–3].

Genomics of Dementia

The genetic defects identified in AD can be classified into three main categories:

(a) Mendelian or mutational defects in genes directly linked to AD, including (i) 32 mutations in the amyloid beta (Aβ) (ABP) precursor protein (*APP*) gene (21q21)(AD1); (ii) 165 mutations in the presenilin 1 (*PSEN1*) gene (14q24.3)(AD3); and (iii) 12 mutations in the presenilin 2 (*PSEN2*) gene (1q31–q42) (AD4) [4–6]. PSEN1 and PSEN2 are important determinants of γ-secretase activity responsible for proteolytic cleavage of APP and NOTCH receptor proteins. Mendelian mutations are very rare in AD (1:1000). Mutations in exons 16 and 17 of the *APP* gene appear with a frequency of 0.30% and 0.78%, respectively, in AD patients. Similarly, *PSEN1*, *PSEN2*, and microtubule-associated protein Tau (*MAPT*)(17q21.1) mutations are present in less than 2% of the cases. Mutations in these genes confer specific phenotypic profiles to patients with dementia: amyloidogeneic pathology associated with *APP*, *PSEN1* and *PSEN2* mutations; and tauopathy associated with *MATP* mutations, representing the two major pathogenic hypotheses for AD [4,7–9].

(b) Multiple polymorphic risk variants characterized in over 200 different genes can increase neuronal vulnerability to premature death(Table 1) [4]. 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, whereas carriers of the *APOE-2* allele might be protected against dementia [4]. APOE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD. Other genes of this category are included in Table 1.

One of the newest members of the AD-gene family is *SORL1*, a gene which encodes a mosaic protein with a domain structure which suggests it is a member of both the vacuolar protein sorting-10 (Vps10) domain-containing receptor family and the low density lipoprotein receptor (LDLR). Inherited variants of the SORL1 neuronal sorting receptor are associated with late-onset AD. Polymorphisms in two different clusters of intronic sequences within the *SORL1* gene may regulate tissue-specific expression of SORL1, which directs trafficking of APP into recycling pathways. When SORL1 is underexpressed, APP is sorted into Aβ-generating compartments leading to amyloid accumulation in neuronal tissues [10]. As with many other potential AD-related genes, the association of *SORL1* with AD [10,11] could not be replicated in other studies [12]. Another interesting gene is *DHCR24* (3β-hydroxysterol-δ-24-reductase) or *Seladin-1*, a key element in the cholesterologenic pathway in which the DHCR24 enzyme catalyzes the transformation of desmosterol into cholesterol [13,14]. *Seladin-1* was originally identified as a gene whose expression was downregulated in the AD brain, demonstrating a neuroprotective effect against neurodegeneration. Recent studies indicate that *Seladin-1/DHCR24* is an LXR (liver X nuclear hormone receptor) target gene potentially involved in the regulation of lipid raft formation [13]. Another gene, with potential therapeutic interest as a tau kinase, might be the *GSK3* gene. Analysis of the promoter and all 12 exons revealed that an intronic polymorphism (IVS2-68G>A) occurred at over twice the frequency among patients with frontotemporal dementia (10.8%) and patients with AD (14.6%) than in aged healthy subjects (4.1%). This is the first evidence that a gene known to be involved in tau phosphorylation is associated with risk for primary neurodegenerative dementias [15]. Promoter polymorphisms modulating *HSPA5* expression might also increase susceptibility to AD. Endoplasmic reticulum chaperone heat shock 70 kDa protein 5 (HSPA5/GRP78) is known to be involved in APP metabolism and neuronal death in AD. Of the three major polymorphisms (–415G/A (rs391957), –370C/T (rs17840761), and –180del/G (rs3216733)), the HSPA5-415G/A and –180del/G variants showed significant differences between AD cases and controls. Subjects harboring the –415AA/–180GG genotype or the –415A/–180G allele might be less susceptible to develop AD [16]. The rs5952C and rs1568566T alleles of the *APOD* rs5952T/C and rs1568566C/T variants increase the risk for AD, whereas the rs5952T-rs1568566C haplotype reduces it [17]. ApoD is a lipoprotein-associated glycoprotein which is increased in the hippocampus and CSF of AD patients [17]. *CALHM1* encodes a multipass transmembrane glycoprotein that controls cytosolic Ca^{2+} concentrations and Aβ levels. The *CALHM1* P86L polymorphism (rs2986017) has been associated with AD [18], but this association could not be replicated in other studies.

Harold et al. [19] undertook a two-stage genome-wide association study (GWAS) of AD involving over 16,000 individuals, and found association with SNPs at two loci not previously associated with the disease, at the *CLU* (Clusterine, APOJ) gene (rs11136000) and 5′ to the *PICALM* gene (rs3851179). In another GWAS with patients from France, Belgium, Finland, Italy and Spain, Lambert et al. [20] found association with *CLU* and with the *CR1* gene, encoding the complement component (3b/4b) receptor 1, on chromosome 1 (rs6656401).

(c) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity [4,21].

Although *APP* and *PSEN* mutations are considered causative factors for AD, the total number of mutations identified in the

Table 1. Selected human genes investigated as potential candidate genes associated with dementia and age-related neurodegenerative disorders [4–6,25].

Locus	Symbol	Aliases	Title	OMIM
1p21.3-p13.1	*SORT1*	*Gp95, NT3*	Sortilin	602458
1p31.3	*TM2D1*	*BBP*	TM2 domain containing 1	610080
1p32	*ERI3*	*PINT1; PRNPIP; MGC2683; FLJ22943*	ERI1 exoribonuclease family member 3	609917
1p32.3	*ZFYVE9*	*MADHIP, NSP, SARA, SMADIP*	Zinc finger, FYVE domain containing 9	603755
1p33-p31.1	*DHCR24*	*KIAA0018, Nbla03646, SELADIN1, seladin-1*	24-dehydrocholesterol reductase	606418
1p34	*LRP8*	*APOER2, HSZ75190, MCI1*	Low density lipoprotein receptor-related protein 8, apolipoprotein e receptor	602600
1p36.3	*MTHFR*		5,10-methylenetetrahydrofolate reductase (NADPH)	607093
1q21	*S100A1*	*S100, S100-alpha, S100A*	S100 calcium-binding protein A1	176940
1q21.2-q21.3	*LMNA*	*RP11-54H19.1, CDCD1, CDDC, CMD1A, CMT2B1, EMD2, FPL, FPLD, HGPS, IDC, LDP1, LFP, LGMD1B, LMN1, LMNC, PRO1*	Lamin A/C	150330
1q21.3	*CHRNB2*	*EFNL3, nAChRB2*	Cholinergic receptor, nicotinic, beta 2 (neuronal)	118507
1q21-q23	*APCS*	*MGC88159, PTX2, SAP*	Amyloid P component, serum	104770
1q22-q23	*NCSTN*	*RP11-517F10.1, APH2, KIAA0253*	Nicastrin	605254
1q25	*SOAT1*	*RP11-215I23.1, ACACT, ACAT, ACAT1, RP11-215I23.2, SOAT, STAT*	Sterol O-acyltransferase 1	102642
1q31-q42	*AD4*	*AD3L, AD4, PS2, STM2*	Presenilin 2 (alzheimer disease 4)	600759
1q32	*CR1*	*C3BR, C4BR, CD35, KN*	Complement component (3b/4b) receptor 1 (Knops blood group)	120620
1p36.13-q31.3	*APH1A*	*RP4-790G17.3, 6530402N02Rik, APH-1, APH-1A, CGI-78*	Anterior pharynx defective 1 homolog A (C. elegans)	607629
1q42-q43	*AGT*	*ANHU, FLJ92595, FLJ97926, SERPINA8*	Angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	106150
2p16.3	*RTN4*	*ASY, NI220/250, NOGO, NOGO-A, NOGOC, NSP, NSP-CL, Nbla00271, Nbla10545, Nogo-B, Nogo-C, RTN-X, RTN4-A, RTN4-B1, RTN4-B2, RTN4-C*	Reticulon 4	604475
2p25	*ADAM17*	*ADAM18, CD156B, CSVP, MGC71942, TACE*	ADAM metallopeptidase domain 17	603639
2q14	*IL1A*	*IL-1A, IL1, IL1-ALPHA, IL1F1*	Interleukin-1-Alpha	147760
2q21.1	*KCNIP3*	*CSEN, DREAM, KCHIP3, MGC18289*	Kv channel interacting protein 3, calsenilin	604662
2q21.2	*LRP1B*	*LRP-DIT, LRPDIT*	Low density lipoprotein-related protein 1B (deleted in tumors)	608766
2q34	*CREB1*	*CREB, MGC9284*	cAMP responsive element binding protein 1	123810
3q26.1-q26.2	*BCHE*	*CHE1, E1*	Butyrylcholinesterase	177400
3q32.3-q34	*CREB1*		cAMP response element-binding protein	123810
3q26.2-qter		*APOD*	Apolipoprotein D	107740
4p14-p13	*APBB2*	*DKFZp434E033, FE65L, FE65L1, MGC35575*	Amyloid beta (A4) precursor protein-binding, family B, member 2	602710
5q15	*CAST*	*BS-17, MGC9402*	Calpastatin	114090
5q31	*APBB3*	*FE65L2, MGC150555, MGC87674, SRA*	Amyloid beta (A4) precursor protein-binding, family B, member 3	602711
5q35.3	*DBN1*	*D0S117E, DKFZp434D064*	drebrin 1	126660
6p21.3	*AGER*	*DAMA-358M23.4, MGC22357, RAGE*	Advanced glycosylation end product-specific receptor	600214
6p21.3	*HFE*	*HFE1, HH, HLA-H, MGC103790, MVCD7, dJ221C16.10.1*	Hemochromatosis	235200
6p21.3	*TNF*	*DADB-70P7.1, DIF, TNF-alpha, TNFA, TNFSF2*	Tumor necrosis factor (TNF superfamily, member 2)	191160
7p21	*IL6*	*BSF2, HGF, HSF, IFNB2, IL-6*	Interleukin 6 (interferon, beta 2)	147620

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
7q36	*AD10*		Alzheimer disease-10	609636
7q36	*NOS3*	*ECNOS, eNOS*	Nitric oxide synthase 3 (endothelial cell)	163729
7q36	*PAXIP1*	*CAGF28, CAGF29, FLJ41049, PACIP1, PAXIP1L, PTIP, TNRC2*	PAX interacting (with transcription-activation domain) protein 1	608254
8p21-p12	*CLU*	*AAG4, APOJ, CLI, KUB1, MGC24903, SGP-2, SGP2, SP-40, TRPM-2, TRPM2*	Clusterin	185430
8p22	*CTSB*	*APPS, CPSB*	Cathepsin B	116810
9q13-q21.1	*APBA1*	*D9S411E, MINT1, X11, X11A, X11ALPHA*	Amyloid beta (A4) precursor protein-binding, family A, member 1	602414
9q34.1	*DAPK1*	*DAPK, DKFZp781I035*	Death-associated protein kinase 1	600831
9q33-q34.1	*HSPA5*	*BIP, FLJ26106, GRP78, MIF2*	Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	138120
10p13	*AD7*		Alzheimer disease 7	606187
10q	*AD6*		Alzheimer disease-6	605526
10q21	*TFAM*	*MtTF1, TCF6, TCF6L1, TCF6L2, TCF6L3, mtTFA*	Transcription factor A, mitochondrial	600438
10q23	*CH25H*	*C25H*	Cholesterol 25-hydroxylase	604551
10q23-q25	*IDE*	*RP11-366I13.1, FLJ35968, INSULYSIN*	Insulin-degrading enzyme	146680
10q23-q25	*SORCS1*	*RP11-446H13.1, FLJ41758, FLJ43475, FLJ44957*	Sortilin-related VPS10 domain containing receptor 1	606283
10q24	*PLAU*	*ATF, UPA, URK, u-PA*	Plasminogen activator, urokinase	191840
10q24.33	*CALHM1*	*FAM26C, MGC39514, MGC39617*	Calcium homeostasis modulator 1	612234
11p13	*BDNF*	*MGC34632*	Brain-derived neurotrophic factor	113505
11p15	*APBB1*	*FE65, MGC:9072, RIR*	Amyloid beta (A4) precursor protein-binding, family B, member 1 (Fe65)	602709
11p15.1	*SAA1*	*MGC111216, PIG4, SAA, TP53I4*	Serum amyloid A1	104750
11p15.5	*CTSD*	*CLN10, CPSD, MGC2311*	Cathepsin D	116840
11q14	*PICALM*	*CALM, CLTH, LAP*	Phosphatidylinositol binding clathrin assembly protein	603025
11q23.2-q24.2	*SORL1*	*C11orf32, FLJ21930, FLJ39258, LR11, LRP9, SORLA, SorLA-1, gp250*	sortilin-related receptor, L(DLR class) A repeats-containing	602005
11q23.2-q23.3	*BACE1*	*ASP2, BACE, FLJ90568, HSPC104, KIAA1149*	Beta-site APP-cleaving enzyme 1	604252
11q24	*APLP2*	*APPH, APPL2, CDEBP*	Amyloid beta (A4) precursor-like protein 2	104776
12p11.23-q13.12	*AD5*		Alzheimer disease 5	602096
12p12.3-p12.1	*IAPP*	*AMYLIN, DAP, IAP*	Islet amyloid polypeptide	147940
12p13.3-p12.3	*A2M*	*CPAMD5, DKFZp779B086, FWP007, S863-7*	Alpha-2-macroglobulin	103950
12q13-q14	*LRP1*	*A2MR, APOER, APR, CD91, FLJ16451, IGFBP3R, LRP, MGC88725, TGFBR5*	Low density lipoprotein-related protein 1 (alpha-2-macroglobulin receptor)	107770
14q24.3	*FOS*	*AP-1, C-FOS*	FBJ murine osteosarcoma viral oncogene homolog	164810
14q24.3	*PSEN1*	*AD3, FAD, PS1, S182*	presenilin-1	104311
14q32.1	*SERPINA3*	*AACT, ACT, GIG24, GIG25, MGC88254*	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	107280
14q32.1	*CYP46A1*	*CP46, CYP46*	Cytochrome P450, family 46, subfamily A, polypeptide 1	604087
15q22.2	*APH1B*	*APH-1B, DKFZp564D0372, FLJ33115, PRO1328, PSFL, TAAV688*	Anterior pharynx defective 1 homolog B (C. elegans)	607630
15q11-q12	*APBA2*	*D15S1518E, HsT16821, LIN-10, MGC99508, MGC:14091, MINT2, X11L*	Amyloid beta (A4) precursor protein-binding, family A, member 2	602712
16q21	*CETP*	*HDLCQ10*	Cholesteryl ester transfer protein, plasma	118470

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
16q22	*NAE1*	*A-116A10.1, APPBP1, HPP1, ula-1*	NEDD8 activating enzyme E1 subunit 1	603385
17p13	*MYH13*	*MyHC-eo*	Myosin, heavy chain 13, skeletal muscle	603487
17p13.1	*TNK1*	*MGC46193*	Tyrosine kinase, non-receptor, 1	608076
17q11.2	*BLMH*	*BH, BMH*	Bleomycin hydrolase	602403
17q21.1	*MAPT*	*DDPAC, FLJ31424, FTDP-17, MAPTL, MGC138549, MSTD, MTBT1, MTBT2, PPND, TAU*	Microtubule-associated protein tau	157140
17q21.1	*STH*	*MAPTIT, MGC163191, MGC163193*	Saitohin	607067
17q21-q22	*GPSC*		Gliosis, familial progressive subcortical	221820
17q21-q23	*APPBP2*	*HS.84084, KIAA0228, PAT1*	Amyloid beta precursor protein (cytoplasmic tail) binding protein 2	605324
17q23.3	*ACE*	*ACE1, CD143, DCP, DCP1, MGC26566, MVCD3*	Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	106180
17q23.1	*MPO*		Myeloperoxidase	606989
17q24.3	*BPTF*	*FAC1, FALZ, NURF301*	Bromodomain PHD finger transcription factor	601819
18q12.1	*TTR*	*HsT2651, PALB, TBPA*	Transthyretin	176300
19p13.2-p13.1	*NOTCH3*	*CADASIL, CASIL*	Notch homolog 3 (Drosophila)	600276
19p13.2	*AD9*		Alzheimer disease 9	608907
19p13.3	*APBA3*	*MGC:15815, X11L2, mint3*	Amyloid beta (A4) precursor protein-binding, family A, member 3	604262
19p13.3-p13.2	*ICAM*	*BB2, CD54, P3.58*	Intercellular adhesion molecule 1	147840
19q13.1	*APLP1*	*APLP*	Amyloid beta (A4) precursor-like protein 1	104775
19q13.12	*PEN2*	*MDS033, MSTP064, PEN-2, PEN2*	Presenilin enhancer 2 homolog (C. elegans)	607632
19q13.2	*APOE*	*AD2, LDLCQ5, LPG, MGC1571*	Apolipoprotein E	107741
19q13.2	*APOC1*		Apolipoprotein C-I	107710
20p	*AD8*		Alzheimer disease-8	607116
20p11.21	*CST3*	*ARMD11, MGC117328*	Cystatin C	604312
20p13	*PRNP*	*ASCR, CD230, CJD, GSS, MGC26679, PRIP, PrP, PrP27-30, PrP33-35C, PrPc, prion*	Prion protein	176640
20q13.31	*PCK1*	*MGC22652, PEPCK-C, PEPCK1, PEPCKC*	Phosphoenolpyruvate carboxykinase 1 (soluble)	261680
21q21.3	*APP*	*AAA, ABETA, ABPP, AD1, APPI, CTFgamma, CVAP, PN2*	Amyloid beta (A4) precursor protein	104760
21q22.3	*BACE2*	*AEPLC, ALP56, ASP1, ASP21, BAE2, CDA13, CEAP1, DRAP*	Beta-site APP-cleaving enzyme 2	605668
22q11.21	*RTN4R*	*NGR, NOGOR*	Reticulon 4 receptor	605566
	HN		Humanin	606120

APP, *PSEN1*, and *PSEN2* genes account for less than 3% of the cases with AD, clearly indicating that neurodegeneration associated with AD pathogenesis cannot be exclusively attributed to APP/PSEN-related cascades (amyloid hypothesis). Alterations in the ubiquitin–proteasome system and biochemical disarray in the chaperone machinery are alternative and/or complementary pathogenic events potentially leading to defects in protein synthesis, folding, and degradation with subsequent conformational changes, aggregation, and accumulation in cytotoxic deposits [4,22]. A more plausible explanation would seem to be that multiple susceptibility SNPs with a very subtle genetic variation cooperatively contribute, in concert with environmental factors and concomitant CNS vulnerability, to premature neurodegeneration in dementia.

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 [4,23]. All these genetic factors may interact in genetic networks which are still unknown, leading to a cascade of pathogenic events characterized by abnormal protein processing and misfolding with a subsequent accumulation of abnormal proteins (conformational changes), ubiquitin–proteasome system dysfunction, excitotoxic reactions, oxidative and nitrosative stress, mitochondrial injury, synaptic failure, altered metal homeostasis, dysfunction of axonal and dendritic transport, and chaperone misoperation [4,22–31]. These pathogenic events may exert an additive effect, converging in final pathways leading to premature neuronal death. Some of these mechanisms are common to several neurodegenerative

disorders which differ depending upon the gene(s) affected and the involvement of specific genetic networks, together with cerebrovascular factors, epigenetic factors (DNA methylation) and environmental conditions (nutrition, toxicity, social factors, etc.) [4,23,26–32]. The higher the number of genes involved in AD pathogenesis, the earlier the onset of the disease, the faster its clinical course, and the poorer its therapeutic outcome [4,23,26–31].

Functional Genomics

Functional genomics studies have demonstrated the influence of many genes on AD pathogenesis and phenotype expression. The study of genotype–phenotype correlations is essential for the evaluation of the actual impact of specific polymorphic variants of a particular gene on the clinical manifestation of the disease and/or biological markers reflecting the disease condition or different biological states of the individual. It has been demonstrated that mutations in the *APP*, *PSEN1*, *PSEN2*, and *MAPT* genes give rise to well-characterized differential neuropathological and clinical phenotypes of dementia [4–6]. Transgenic animals also reproduce to some extent the neuropathological hallmarks of AD in a sequential manner. The triple transgenic mouse model of AD (3×Tg-AD) harbors 3 AD-related loci: human PS1M146V, human APPswe, and human MAPTP301L. These animals develop both amyloid plaques and NFT-like pathology in a progressive and age-dependent manner in hippocampus, amygdala, and cerebral cortex, the main foci of human AD neuropathology. The evolution of AD-related transgene expression, amyloid deposition, tau phosphorylation, astrogliosis, and microglia activation throughout the hippocampus, entorhinal cortex, primary motor cortex, and amygdala over a 26-month period has been immunohistochemically documented. Intracellular Aβ accumulation is the earliest of AD-related pathologies to be detectable, followed temporally by phospho-tau, extracellular Aβ, and finally paired helical filament and NFT pathology [33]. In the same model, a decrease in neurogenesis directly associated with the presence of amyloid plaques and an increase in the number of Aβ containing neurons in the hippocampus has been demonstrated [34].

Different *APOE* genotypes also confer specific phenotypic profiles to AD patients. Some of these profiles may add risk or benefit when the patients are treated with conventional drugs, and in many instances the clinical phenotype demands the administration of additional drugs, which increase the complexity of therapeutic protocols. From studies designed to define *APOE*-related AD phenotypes [4,22–31,35–41], several confirmed conclusions can be drawn: (i) the age-at-onset is 5–10 years earlier in approximately 80% of AD cases harboring the *APOE-4/4* genotype; (ii) the serum levels of ApoE are lowest in *APOE-4/4*, intermediate in *APOE-3/3* and *APOE-3/4*, and highest in *APOE-2/3* and *APOE-2/4;* (iii) serum cholesterol levels are higher in APOE-4/4 than in the other genotypes; (iv) HDL-cholesterol levels tend to be lower in *APOE-3* homozygotes than in *APOE-4* allele carriers; (v) LDL-cholesterol levels are systematically higher in *APOE-4/4* than in any other genotype; (vi) triglyceride levels are significantly lower in *APOE-4/4*; (vii) nitric oxide levels are slightly lower in *APOE-4/4*; (viii) serum Aβ levels do not 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 is markedly increased in *APOE-4/4>APOE-3/4>APOE-3/3*; (xi) brain mapping activity shows a significant increase in slow wave activity in *APOE-4/4* from early stages of the disease; (xii) brain hemodynamics, as reflected by reduced brain blood flow velocity and increased pulsatility and resistance indices, is significantly worse in *APOE-4/4* (and in *APOE-4* carriers, in general, as compared with *APOE-3* carriers); (xiii) lymphocyte apoptosis is markedly enhanced in *APOE-4* carriers; (xiv) cognitive deterioration is faster in *APOE-4/4* patients than in carriers of any other *APOE* genotype; (xv) occasionally, in approximately 3–8% of the AD cases, the presence of some dementia-related metabolic dysfunctions (e.g., iron, folic acid, vitamin B_{12} deficiencies) accumulate more in *APOE-4* carriers than in *APOE-3* carriers; (xvi) some behavioral disturbances (bizarre behaviors, psychotic symptoms), alterations in circadian rhythm patterns (e.g., sleep disorders), and mood disorders (anxiety, depression) are slightly more frequent in *APOE-4* carriers; (xvii) aortic and systemic atherosclerosis is also more frequent in *APOE-4* carriers; (xviii) liver metabolism and transaminase activity also differ in *APOE-4/4* with respect to other genotypes; (xix) blood pressure (hypertension) and other cardiovascular risk factors also accumulate in *APOE-4*; and (xx) *APOE-4/4* 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 [4,9,22–31,35–43].

Therapeutic Strategies in Dementia

Modern therapeutic strategies in AD are addressed to interfering with the main pathogenic mechanisms potentially involved in AD. Major pathogenic events (drug targets) and their respective therapeutic alternatives include the following: genetic defects, β-amyloid deposition, tau-related pathology, apoptosis, neurotransmitter deficits, neurotrophic deficits, neuronal loss, neuroinflammation, oxidative stress, calcium dysmetabolism, neuronal hypometabolism, lipid metabolism dysfunction, cerebrovascular dysfunction, neuronal dysfunction associated with nutritional and/or metabolic deficits, and a miscellany of pathogenic mechanisms potentially manageable with diverse classes of chemicals or biopharmaceuticals [4,22–31,35,36,41]. Since the early 1980s, the neuropharmacology of AD was dominated by the acetylcholinesterase inhibitors, represented by tacrine, donepezil, rivastigmine, and galantamine [2,3,44]. Memantine, a partial NMDA antagonist, was introduced in the 2000s for the treatment of severe dementia [45]; and the first clinical trials with immunotherapy, to reduce amyloid burden in senile plaques, were withdrawn due to severe ADRs [46]. During the past few years no relevant drug candidates have been postulated for the treatment of AD, despite the initial promises of β- and γ-secretase inhibitors [22].

Pharmacogenomics

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 up the discovery of drug response markers, whether they act at the level of drug target, drug metabolism, or disease pathways [23,25,31,35,47].

The potential implications of pharmacogenomics in clinical trials and molecular therapeutics is that a particular disease could be treated according to genomic and biological markers, selecting medications and diseases which are optimized for individual patients or clusters of patients with a similar genomic profile.

The pharmacogenomic outcome depends upon many different determinant factors including (i) genomic profile, (ii) disease phenotype, (iii) concomitant pathology, (iv) genotype–phenotype correlations, (v) nutritional conditions, (vi) age and gender, (vii) pharmacological profile of the drugs, (viii) drug–drug interactions, (ix) gene expression profile, (x) transcriptomic cascade, (xi) proteomic profile, and (xii) metabolomic networking. The dissection and further integration of all these factors is of paramount importance for the assessment of the pharmacogenomic outcome in terms of safety and efficacy. Pharmacogenomic approaches based on genomewide sets of SNPs associated with drug response are now feasible and may offer the potential to personalize therapeutics [25].

Drug metabolism includes phase I reactions (i.e., oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e., acetylation, glucuronidation, sulphation, and methylation). 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, NQO1 (NADPH-quinone oxidoreductase), DPD (dihydropyrimidine dehydrogenase), ADH (alcohol dehydrogenase), and ALDH (aldehyde dehydrogenase). Major enzymes involved in phase II reactions include the following: UGTs (uridine 5′-triphosphate glucuronosyl transferases), TPMT (thiopurine methyltransferase), COMT (catechol-O-methyltransferase), HMT (histamine methyl-transferase), STs (sulfotransferases), GST-A (glutathion S-transferase A), GST-P, GST-T, GST-M, NAT2 (N-acetyl transferase), NAT1, and others [22–25].

CYPs in Dementia

In dementia, *CYP* genomics is a very important issue since in practice over 90% of patients with dementia are daily consumers of psychotropics. Furthermore, some acetylcholinesterase inhibitors (the most prescribed antidementia drugs worldwide) are metabolized via CYP enzymes [24,25,39]. CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5 deserve special consideration.

The CYP2D6 enzyme, encoded by a gene that maps on 22q13.1–13.2, catalyzes the oxidative metabolism of over 100 clinically important and commonly prescribed drugs such as cholinesterase inhibitors, antidepressants, neuroleptics, opioids, some β-blockers, class I antiarrhythmics, analgesics, and many other drug categories [48], acting as substrates, inhibitors or inducers with which many other drugs may potentially interact, this leading to the outcome of ADRs. The CYP2D6 locus is highly polymorphic, with over 100 different *CYP2D6* alleles identified in the general population showing deficient (PM), normal (EM), intermediate (IM), or increased enzymatic activity (UM) [49,50]. 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 [23,51,52]. 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. 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% [53].

CYP2D6-Related Therapeutic Response to a Multifactorial Treatment in Dementia

Few prospective clinical trials have been performed to elucidate the influence of *CYP2D6* variants on the therapeutic outcome in AD in response to cholinesterase inhibitors or other antidementia drugs. We have performed the first prospective study in AD patients who received a combination therapy with (a) an endogenous nucleotide and choline donor, CDP-choline (500 mg/day), (b) a nootropic substance, piracetam (1600 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 one year. 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-yr treatment. IMs also improved from 21.40 ± 6.28 to 22.50 ± 5.07 ($r = +0.96$), whereas PMs and UMs deteriorate from 20.74 ± 6.72 to 18.07 ± 5.52 ($r = -0.97$), and from 22.65 ± 6.76 to 21.28 ± 7.75 ($r = -0.92$), 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 one year of treatment. 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 [4,9,22,25,36–39]. In a recent study, Pilotto et al. [54] have confirmed the influence of *CYP2D6* variants (rs1080985) on the efficacy of donepezil in AD.

From all these data we can conclude the following: (i) The most frequent *CYP2D6* variants in the Southern European population (Iberian peninsula) are the *1/*1 (57.84%), *1/*4 (22.78%), *1×N/*1 (6.10%), *4/*4 (2.56%), and *1/*3 (2.01%) genotypes, accounting for more than 80% of the population; (ii) the frequency of EMs, IMs, PMs, and UMs is about 59.51%, 29,78%, 4.46%, and 6.23%, respectively, in the general population (GP), and 57.76, 31.05%, 5.27%, and 5.90%, respectively in AD cases; (iii) EMs are more prevalent in GP (59.51%) than in AD (57.76%); IMs are more frequent in AD (31.05%) than in GP (29.78%); the

frequency of PMs is slightly higher in AD (5.27%%) than in GP (4.46%); and UMs are more frequent in GP (6.23%) than in AD (5.90%); (iv) there are differences between females and males in the distribution and frequency of *CYP2D6* genotypes which might be of relevance in therapeutic terms and risk of ADRs; (v) there is an accumulation of AD-related genes of risk in PMs and UMs; (vi) PMs and UMs tend to show higher transaminase activities than EMs and IMs; (vii) 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 (viii) 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 [4,9,22,24,25,36–39].

CYP Clustering in Alzheimer's disease

Since over half of the available drugs are metabolized via different CYP enzymes and other metabolic pathways, it is convenient to understand the networking activity of *CYP* genes and the genomic profiles of these genes in particular groups of risk. In the case of dementia, 73.71% of AD patients are *CYP2C19*-EMs, 25.12% IMs, and 1.16% PMs. The distribution and frequency of *CYP2C9* genotypes is as follows: *1/*1-EM 60.87%, *1/*2-IM 23.98%, *1/*3-IM 10.17%, *2/*2-PM 2.54%, *2/*3-PM 2.16%, and *3/*3-PM 0.25%, globally representing 60.87% *CYP2C9*-EMs, 34.16% IMs, and 4.97% PMs [23]. This is especially important because the *CYP2C9*-Ile359Leu (*CYP2C9*3* allele) and *CYP2C9*-Arg144Cys (*CYP2C9*2* allele) variants are associated with warfarin sensitivity. Clustering together *CYP2C9* and *VKORC1* variants, we can estimate that approximately 30% of the elderly population is sensitive to warfarin anticoagulants.

Concerning *CYP3A4/5* polymorphisms, 82.75% of AD cases are EMs (*CYP3A5*3/*3*), 15.88% are IMs (*CYP3A5*1/*3*), and 1.37% are UMs (*CYP3A5*1/*1*) [25].

The human *CYP3A* subfamily plays a dominant role in the metabolic elimination of more drugs than any other biotransformation enzyme. CYP3A enzyme is localized in the liver and small intestine and thus contributes to first-pass and systemic metabolism. CYP3A expression varies as much as 40-fold in liver and small intestine donor tissues. Unlike other human P450s (*CYP2D6*, *CYP2C19*) there is no evidence of a 'null' allele for *CYP3A4*. Over 50 SNPs have been identified in the *CYP3A4* gene. The most common variant, *CYP3A4*1B*, is an A-392G transition in the 5'-flanking region with an allele frequency ranging from 0% (Chinese and Japanese) to 45% (African-Americans). *CYP3A5* is polymorphically expressed in adults with readily detectable expression in about 10–20% in Caucasians, 33% in Japanese and 55% in African-Americans. The primary causal mutation for its polymorphic expression (*CYP3A5*3*) confers low CYP3A5 protein expression as a result of improper mRNA splicing and reduced translation of a functional protein. The *CYP3A5*3* allele frequency varies from approximately 50% in African-Americans to 90% in Caucasians. Functionally, microsomes from a *CYP3A5*3/*3* liver contain very low CYP3A5 protein and display on average reduced catalytic activity towards midazolam. Additional intronic or exonic mutations (*CYP3A5*5*, **6*, and **7*) may alter splicing and result in premature stop codons or exon deletion. As CYP3A5 is the primary extrahepatic CYP3A isoform, its polymorphic expression may be implicated in disease risk and the metabolism of endogenous steroids or xenobiotics [55].

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*1-*1*1 (10.45%), *1*4-*1*1-*1*1 (8.09%), *1*4-*1*2-*1*1 (4.91%), *1*4-*1*1-*1*2 (4.65%), and *1*1-*1*3-*1*3 (4.33%). These 82 trigenic genotypes represent 36 different pharmacogenetic phenotypes. According to these trigenic clusters, only 26.51% of the patients show a pure 3EM phenotype, 15.29% are 2EM1IM, 2.04% are pure 3IM, 0% are pure 3PM, and 0% are 1UM2PM (the worst possible phenotype) [25].

Pharmacogenomics of AD-Related Genes

APOE- and *ACE*-related pharmacogenomics

The pharmacogenomics of AD is still in a very primitive stage. In over 100 clinical trials for dementia, *APOE* has been used as the only gene of reference for the pharmacogenomics of AD [4,24,25,36–38,56,57]. Several studies indicate that the presence of the *APOE-4* allele differentially affects the quality and extent of drug responsiveness in AD patients treated with cholinergic enhancers (tacrine, donepezil, galantamine, rivastigmine), neuroprotective compounds (nootropics), endogenous nucleotides (CDP-choline), immunotrophins (anapsos), neurotrophic factors (cerebrolysin), rosiglitazone, or combination therapies [4,24,25,36–39,56–58]; however, controversial results are frequently found due to methodological problems, study design, and patient recruitment in clinical trials.

In long-term open clinical trials with a multifactorial treatment, *APOE-4/4* carriers are the worst responders [4,24,25,36–39]. With a similar therapeutic protocol, *PSEN1-1/1* homozygotes are the worst responders and *PSEN1-2/2* carriers are the best responders [25]. Significant *ACE*-related therapeutic responses to multifactorial treatments have also been reported [22,39]. Among *ACE-I/D* variants, *ACE-D/D* patients were the worst responders ($r = -0.58$), and *ACE-I/D* carriers were the best responders ($r = +0.26$), with *ACE-I/I* showing an intermediate positive response ($r = +0.01$) [22,39]. *ACE*-related biochemical and hemodynamic phenotypes have been studied in patients with AD [4,22,23]. *ACE-I/I* patients tend to be younger than *ACE-I/D* or *ACE-D/D* patients at the time of diagnosis and also to show a more severe cognitive deterioration. Serum ApoE, total cholesterol, LDL-cholesterol, HDL-cholesterol, nitric oxide, histamine, and ACE levels are higher in *ACE-I/I* carriers than in patients with the other genotypes; in contrast, serum triglyceride and VLDL levels are notably lower in *ACE-I/I* patients compared to patients harboring the *ACE-I/D* or *ACE-D/D* genotypes, whereas Aβ levels do not show any clear difference among *ACE*-related genotypes. Cerebrovascular function tends to be worse in *ACE-D/D*, with lower brain blood flow velocities and higher pulsatility and resistance indices, than in *ACE-I/D* (intermediate cerebrovascular hemodynamics) or *ACE-I/I*

(almost normal cerebrovascular function) [4,22,23,39]. The correlation between lipid levels and brain hemodynamics is very similar in this study to data observed in that of *CYP2D6*-related metabolizer profiles in which EM patients with moderate cholesterol and lipoprotein levels (as well as relatively high nitric oxide, histamine, ACE, and ApoE levels) tend to show a better cerebrovascular hemodynamic profile than AD patients with lower cholesterol and lipoprotein levels [39]. This apparently paradoxical correlation appears to indicate that major influences in cerebrovascular homeostasis and hemodynamic brain blood flow are cholesterol, lipoproteins, nitric oxide, ACE, and histamine, among many other factors, in AD, and that peripheral levels of Aβ are indifferent in this concern. On the other hand, it seems likely that low triglyceride levels may facilitate cerebrovascular function. It is also worth mentioning that *ACE-I/I* patients with the highest cholesterol levels are the worst in mental performance. Other interpretation of these data might suggest an association between poor cerebrovascular function with *ACE-D/D* and *ACE-I/D*, and an association between alterations in lipid metabolism in *ACE-I/I* [22,39].

Both *APOE* and *ACE* variants also affect behavior and the modification of behavioral changes (mood, anxiety) in dementia after nonpsychotropic pharmacological treatment [4,22,24,37,40]. At baseline, all *APOE* variants show similar anxiety and depression rates, except the *APOE-4/4* carriers who differed from the rest in significantly lower rates of anxiety and depression. Remarkable changes in anxiety were found among different *APOE* genotypes. Practically, all *APOE* variants responded with a significant diminution of anxiogenic symptoms, except patients with the *APOE-4/4* genotype who only showed a slight improvement. The best responders were *APOE-2/4* ($r = -0.87$) > *APOE-2/3* ($r = -0.77$) > *APOE-3/3* ($r = -0.69$) > *APOE-3/4* carriers ($r = -0.45$). The potential influence of *APOE* variants on anxiety and cognition in AD does not show a clear parallelism, suggesting that other more complex mechanisms are involved in the onset of anxiety in dementia. Concerning depression, all *APOE* genotypes improved their depressive symptoms with treatment except those with the *APOE-4/4* genotype, which worsen along the treatment period. The best responders were *APOE-2/4* ($r = -0.85$) > *APOE-2/3* ($r = -0.77$) > *APOE-3/3* ($r = -0.73$) > *APOE-3/4* ($r = -0.16$), and the worst responder was *APOE-4/4* ($r = +0.31$) [22,39]. Patients with each one of the 3 *ACE-I/D* indel variants are equally anxiogenic and depressive at baseline and all of them respond favorably to the multifactorial protocol by gradually reducing anxiety and depressive symptoms over the 12-month treatment period. The best responders were *ACE-I/D* ($r = -0.89$) > *ACE-D/D* ($r = -0.68$) > *ACE-I/I* ($r = -0.08$). Depressive symptoms were also similarly improved in all *ACE-I/D* variants. The best responders were *ACE-I/D* ($r = -0.88$) > *ACE-D/D* ($r = -0.55$) > *ACE-I/I* ($r = -0.13$). Comparatively, the worst responders among *ACE-I/D* variants were carriers of the *ACE-I/I* genotype which were also the poorest responders in anxiety and cognition [22,39,41].

The combination of *APOE* and *ACE* polymorphic variants in bigenic clusters yields different anxiety and depression patterns at baseline and after one year of treatment. The most anxiogenic patients at baseline are those with the *23DD*, *44ID*, and *34II* genotypes, and the least anxiogenic patients are those harboring the *23II*, *44DD*, and *23ID* genotypes. The most depressive clusters at baseline are those harboring the *23DD*, *33ID*, and *33II* genotypes, with a clear accumulation of *APOE-3/3* carriers in these groups, and the least depressive clusters are those represented by carriers of the *23II*, *44ID*, and *23ID* genotypes. All bigenic clusters show a positive anxiolytic and anti-depressive response to the multifactorial treatment, except *44DD* carriers who exhibited the worst response [22,39,41].

Influence of *APOE-CYP2D6* interaction on AD pharmacogenomics

APOE influences liver function and CYP2D6-related enzyme activity probably via regulation of hepatic lipid metabolism. It has been observed that APOE may influence liver function and drug metabolism by modifying hepatic steatosis and transaminase activity. There is a clear correlation between APOE-related TG levels and GOT, GPT, and GGT activities in AD [22,39]. Both plasma TG levels and transaminase activity are significantly lower in AD patients harboring the *APOE-4/4* genotype, probably indicating (a) that low TG levels protect against liver steatosis, and (b) that 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 [22,39,41].

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* 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. In addition, a clear accumulation of *APOE-4/4* genotypes is observed among *CYP2D6* PMs and UMs [25].

Conclusions

From these studies we can conclude the following: (i) Most studies with acetylcholinesterase inhibitors indicate that the presence or absence of the *APOE-4* allele influences the therapeutic outcome in patients with AD. (ii) Multifactorial treatments combining neuroprotectants, endogenous nucleotides, nootropic agents, vasoactive substances, cholinesterase inhibitors, and NMDA antagonists associated with metabolic supplementation on an individual basis adapted to the phenotype of the patient may be useful to improve cognition and slow-down disease progression in AD. (iii) The therapeutic response in AD seems to be genotype-specific under different pharmacogenomic conditions. (iv) In monogenic-related studies, patients harboring the *APOE-4/4* genotype are the worst responders. (v) *APP*, *PSEN1* and *PSEN2* mutations influence the therapeutic response in AD. (vi) In trigenic-related studies (*APOE*+*PSEN1*+*PSEN2*) the best responders are those patients carrying the *331222*–, *341122*–, *341222*–, and *441112*– genomic clusters. (vii) The worst responders in all genomic clusters are patients with the *441122*+ genotype. (viii) The interaction of several AD-related genes seems to be determinant for drug efficacy and safety.

(ix) *APOE-CYP2D6* interactions might influence the therapeutic response in AD via changes in lipid metabolism and liver function. (x) *APOE* may also interact with PSEN1, ACE, A2M, and other genes (e.g., *CETP*, *AGT*, and *NOS3*) to regulate the effect of drugs on cognition and behavioral changes in dementia. (xi) The *APOE-4/4* genotype seems to accelerate neurodegeneration anticipating the onset of the disease by 5–10 years; and in general, *APOE-4/4* carriers show a faster disease progression and a poorer therapeutic response to all available treatments than any other polymorphic variant. (xii) Pharmacogenomic studies using monogenic, bigenic, trigenic, tetragenic or polygenic clusters as a harmonization procedure to reduce genomic heterogeneity in clinical trials are very useful in order to widen the therapeutic scope of limited pharmacological resources [4,22–31,36–41].

Taking into consideration the data available, it might be inferred that at least 10–15% 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 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 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 [4,24,25,36–38]. 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. Although most studies predict the safety of donepezil and galantamine, as the two principal cholinesterase inhibitors metabolized by CYP2D6-related enzymes few pharmacogenetic studies have been performed so far on an individual basis to personalize the treatment, and most studies reporting safety issues are the result of pooling together pharmacological and clinical information obtained with routine procedures. In certain cases, genetic polymorphism in the expression of *CYP2D6* is not expected to affect the pharmacodynamics of some cholinesterase inhibitors because major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization. However, excretion rates are substantially different in EMs and PMs. For instance, in EMs, urinary metabolites resulting from O-demethylation of galantamine represent 33.2% of the dose compared with 5.2% in PMs, which show correspondingly higher urinary excretion of unchanged galantamine and its N-oxide [59]. Therefore, there are still many unanswered questions regarding the metabolism of cholinesterase inhibitors and their interaction with other drugs (potentially leading to ADRs) which require pharmacogenetic elucidation. It is also worth mentioning that dose titration (a common practice in AD patients treated with cholinesterase inhibitors, e.g., tacrine, donepezil) is an unwise strategy, since 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. As a general rule, it is recommended to avoid AChEIs (donepezil, galantamine) and major psychotropic drugs (neuroleptics, antidepressants) in *APOE-4/4* carriers and *CYP2D6*-PMs. In these particular cases (> 15%), alternative treatments should be administered.

To achieve a mature discipline of pharmacogenetics and pharmacogenomics in CNS disorders and dementia it would be convenient to accelerate the following processes: (a) to educate physicians and the public on the use of genetic/genomic screening in the daily clinical practice; (b) to standardize genetic testing for major categories of drugs; (c) to validate pharmacogenetic and pharmacogenomic procedures according to drug category and pathology; (d) to regulate ethical, social, and economic issues; and (e) to incorporate pharmacogenetic and pharmacogenomic procedures to both drugs in development and drugs on the market in order to optimize therapeutics [4,22–31,37–39,41].

Conflict of Interest

No potential conflict of interest relevant to this article is declared.

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