Review Article

Genomics of Dementia: APOE- and CYP2D6-Related Pharmacogenetics

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Received 16 June 2011; Accepted 12 November 2011

Dementia is a major problem of health in developed countries. Alzheimer’s disease (AD), vascular dementia, and mixed dementia account for over 90% of the most prevalent forms of dementia. Both genetic and environmental factors are determinant for the phenotypic expression of dementia. AD is a complex disorder in which many different gene clusters may be involved. Most genes screened to date belong to different proteomic and metabolomic pathways potentially affecting AD pathogenesis. The ε4 variant of the APOE gene seems to be a major risk factor for both degenerative and vascular dementia. Metabolic factors, cerebrovascular disorders, and epigenetic phenomena also contribute to neurodegeneration. Five categories of genes are mainly involved in pharmacogenomics: genes associated with disease pathogenesis, genes associated with the mechanism of action of a particular drug, genes associated with phase I and phase II metabolic reactions, genes associated with transporters, and pleiotropic genes and/or genes associated with concomitant pathologies. The APOE and CYP2D6 genes have been extensively studied in AD. The therapeutic response to conventional drugs in patients with AD is genotype specific, with CYP2D6-PMs, CYP2D6-UMs, and APOE-4/4 carriers acting as the worst responders. APOE and CYP2D6 may cooperate, as pleiotropic genes, in the metabolism of drugs and hepatic function. The introduction of pharmacogenetic procedures into AD pharmacological treatment may help to optimize therapeutics.

1. Introduction

Senile dementia is a major health problem 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 over €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, anti-inflammatory drugs, etc.). During the past 20 years over 300 drugs have been partially 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].

Dementia is a multifactorial/complex disorder where genetic, metabolic, vascular, and epigenetic factors interact along the lifespan leading to the premature death of neurons. With the advent of large-scale genomic studies, based on novel technology used for the mapping of the human genome, over 1,000 different genes have been screened over the past 20 years, but less than 100 genes have survived replication studies in different populations.

In recent times, significant advances have propelled the introduction of pharmacogenomic approaches in drug development and also in clinical practice to optimize therapeutics [4–8]. The vast majority of CNS drugs are metabolized via enzymes of the cytochrome P450 family (CYPs). The genes encoding CYP2D6, CYP2C19, CYP2C9, and CYR-P3A4/5 isoenzymes are highly polymorphic, with great allelic variation in different ethnic groups. In the Western population, only 25% of its members are extensive metabolizers (EM) for the trigenic cluster integrated by CYPs 2D6 + 2C19 + 2C9, the most relevant genes (and enzyme products) involved in drug metabolism, together with CYP3A4/5, which participates in the metabolism of over 80% of common drugs. The other 75% of the population is potentially at risk for developing adverse drug events (ADRs) due to defective variants encoding deficient enzymes which give rise to intermediate (IM), poor (PM), or ultrarapid metabolizers (UM). This population cluster of defective metabolizers requires dose adjustment to avoid side effects [5]. However, not only CYPs are important in terms of drug efficacy and safety. In fact, 5 categories of genes are mainly involved in pharmacogenomics: (i) genes associated with disease pathogenesis (e.g., APP, PSEN1, PSEN2, MAPT, and APOE) [4–6, 9, 10], (ii) genes associated with the mechanism of action of a particular drug (e.g., receptor genes) [11, 12], (iii) genes associated with phase I (CYPs) and phase II reactions (UGTs, SULTs, GSTs, and NATs) [10, 13–17], (iv) genes associated with transporters (ABCs, and OATs) [18–22], and (v) pleiotropic genes and/or genes associated with concomitant pathologies [23]. The APOE and CYP2D6 genes have been extensively studied in AD. Both genes may influence pathogenesis and the pharmacogenetic outcome in patients with dementia.

### 2. Structural Genomics of Alzheimer’s Disease

The genetic defects identified in AD can be classified into three main categories: (a) mendelian mutations in AD primary genes, (b) multiple susceptibility SNPs in many different genes distributed across the human genome, and (c) mitochondrial DNA (mtDNA) mutations.

(a) Mendelian or mutational defects in genes are directly linked to AD, including (i) >30 mutations in the amyloid beta (Aβ) precursor protein (APP) gene (21q21) (AD1), (ii) >160 mutations in the presenilin 1 (PSEN1) gene (14q24.3) (AD3), and (iii) >10 mutations in the presenilin 2 (PSEN2) gene (1q31–q42) (AD4) [9, 24, 25]. PSEN1 and PSEN2 are important determinants of β-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. Likewise, PSEN1, PSEN2, and microtubule-associated protein Tau (MAPT) (17q21.1) mutations are present in less than 2% of the cases. Mutations in these genes confer specific phenotypic profiles to patients with dementia: amyloidogenic pathology associated with APP, PSEN1, and PSEN2 mutations and tauopathy associated with MAPT mutations, representing the two major pathogenic hypotheses for AD [9, 26–28].

(b) Multiple polymorphic risk variants characterized in over 200 different genes can increase neuronal vulnerability to premature death [9]. Among 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 [9]. APOE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD.

In 1993 Allen Roses and coworkers found a clear association between APOE genotypes and AD, demonstrating that the frequency of the APOE-4 allele was significantly higher in LOAD [29–31]. Since then, many other studies have confirmed the early findings of Saunders et al. [30, 31] and Corder et al. [32], reporting an increased frequency of the APOE-4 allele in AD and the association of the APOE-4 allele with LOAD and sporadic forms of AD [29–34]. APOE-4 may influence AD pathology interacting with APP metabolism and Aβ accumulation, enhancing the 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 [9, 29–37]. Age-related changes in brain structure and function have been reported as potential indicators of premature neurodegeneration [38].

Other genes of this category are included in Table 1. One of the newest members of the AD gene family is SORL1, a gene that 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
| Locus             | Symbol     | Aliases                              | Title                                                                 |
|-------------------|------------|--------------------------------------|----------------------------------------------------------------------|
| 1p21.3-p13.1      | SORT1      | Gp95, NT3                            | Sortilin                                                              |
| 1p31.3            | TM2D1      | BBP                                  | TM2 domain containing 1                                              |
| 1p32              | ERI3       | PINT1; PRNPIP; MGC2683; FLJ22943      | ER1 exoribonuclease family member 3                                  |
| 1p32.3            | ZFYVE9     | MADHHP, NSP, SARA, SMADIP            | Zinc finger, FYVE domain containing 9                                |
| 1p33-p31.1        | DHRCR2     | KIAA0018, Nbla03646, SELADIN1, seladin-1 | 24-dehydrocholesterol reductase                                      |
| 1p34              | LRP8       | APOER2, HSZ75190, MCI1               | Low-density lipoprotein receptor-related protein 8, apolipoprotein E receptor |
| 1p36.1            | ECE1       | RP3-329E20.1, ECE                     | Endothelin-converting enzyme 1                                       |
| 1p36.13-q31.3     | APH1A      | RP4-790G17.3, 6530402N02Rik, APH-1, APH-1A, CGI-78 | Anterior pharynx defective 1 homolog A (C. elegans)                       |
| 1p36.22           | TARDBP     | RP4-635E18.2, ALS10, TDP-43          | TAR DNA-binding protein                                               |
| 1p36.3            | MTHFR      |                                       | 5,10-methylenetetrahydrofolate reductase (NADPH)                       |
| 1q21              | S100A1     | S100, S100-alpha, S100A              | S100 calcium-binding protein A                                        |
| 1q21.2-q21.3      | LMNA       | RP11-54H19.1, CDCD1, CDDG, CMD1A, CMT2B1, EMD2, FPL, FPLD, HGPS, IDC, LDP1, LFP, LGMD1B, LMN1, LMNC, PRO1 | Lamin A/C                                                                 |
| 1q21.3            | CHRNB2     | EFNL3, nACHRB2                       | Cholinergeric receptor, nicotinic, beta 2 (neuronal)                  |
| 1q21-q23          | APCS       | MGC88159, PTX2, SAP                  | Amyloid P component, serum                                            |
| 1q22-q23          | NCSTN      | RP11-517F10.1, APH2, KIAA0253        | Nicastrin                                                              |
| 1q25              | SOAT1      | RP11-215I23.1, ACACT, ACAT, ACAT1, RP11-215I23.2, SOAT, STAT | Sterol O-acyltransferase 1                                           |
| 1q25.2-q25.3      | PTGS2      | COX-2, COX2, GRIPGHS, PGG/HS, PGHS-2, PHS-2, hCox-2 | Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) |
| 1q31-q32          | IL10       | CSIF, IL-10, IL10A, MGC126450, MGC126451, TGF | Interleukin-10                                                        |
| 1q31-q42          | AD4        | AD3L, AD4, PS2, STM2                 | Presenilin 2 (Alzheimer’s disease 4)                                  |
| 1q32              | CR1        | C3BR, C4BR, CD35, KN                 | Complement component (3b/4b) receptor 1 (Knops blood group)           |
| 1q42-q43          | AGT        | ANHU, FLJ92595, FLJ97926, SERPINA8   | Angiotensinogen (serpin peptidase inhibitor, clade A, member 8)       |
| 2p16.3            | RTN4       | ASY, NI220/250, NOGO, NOGO-A, NOGOC, NSP, NSP-Cl, Nbla00271, Nbla10545, Nogo-B, Nogo-C, RTN-X, RTN-A, RTN4-B1, RTN4-B2, RTN4-C | Reticulon 4                                                             |
| 2p25              | ADAM17     | ADAM18, CD156B, CSP, MGC71942, TACE   | ADAM metalloproteinase domain 17                                      |
| 2q14              | BIN1       | AMPH, AMPHL, DKFZp547F068, MGC10367, SH3P9 | Bridging integrator 1                                                |
| 2q14              | IL1A       | IL-1A, IL1, IL1-ALPHA, IL1F1         | Interleukin-1-Alpha                                                   |
| 2q21.1            | KCNIP3     | CSEN, DREAM, KCHIP3, MGC18289        | Kv channel interacting protein 3, calsenil                          |
| 2q21.2            | LRP1B      | LRP-DIT, LRPDIT                      | Low-density lipoprotein-related protein 1B (deleted in tumors)       |
| 2q34              | CREB1      | CREB, MGC2984                        | cAMP responsive element binding protein 1                             |
| 3q25.1-q25.2      | CALLA      | CD10, MM EKFZp686O16152, MGC126681, MGC126707, NEP | Membrane metalloendopeptidase                                        |
| 3q26.1-q26.2      | BCHE       | CHEI, E1                             | Butyrylcholinesterase                                                |
| 3q26.2-pter       | APOD       | APOM                                  | Apolipoprotein D                                                      |
| 3q28              | SST        | SMST                                 | Somatostatin                                                          |
| 4p14-p13          | APBB2      | DKFZp434E033, FE65L, FE65L1, MGC35575 | Amyloid beta (A4) precursor-protein-Binding, family B, member 2     |
| 5q15              | CAST       | BS-17, MGC9402                       | Calpastatin                                                           |
| 5q31              | APBB3      | FE65L2, MGC15055, MGC87674, SRA       | Amyloid beta (A4) precursor-protein-binding, family B, member 3     |
| 5q35.3            | DBN1       | DOI117E, DKFZp434D064                 | Drebrin 1                                                             |
| 6p12              | VEGFA      | RP1-261G23.1, MGC70609, MVCD1, VEGF, VPF | Vascular endothelial growth factor A                                  |
| Locus     | Symbol | Aliases                                                                 | Title                                                                 |
|-----------|--------|--------------------------------------------------------------------------|----------------------------------------------------------------------|
| 6p21.3    | AGER   | DAMA-358M23.4, MGC22357, RAGE                                          | Advanced glycosylation end product-specific receptor                  |
| 6p21.3    | HFE    | HFEI, HH, HLA-H, MGC103790, MVCD7, dJ221C16.10.1                       | Hemochromatosis                                                      |
| 6p21.3    | HLA-A  | DAQB-90C11.16, Aw-68, Aw-69, FLJ26655, HLAA                              | Major histocompatibility complex, class I, A                         |
| 6p21.3    | TNF    | DADB-70P7.1, DIE, TNF-alpha, TNFA, TNFSF2                                | Tumor necrosis factor (TNF superfamily, member 2)                     |
| 6p22.1    | PGDB1  | HUCEP-4, SCAND4, dJ874C20.4                                            | PiggyBac transposable element derived 1                              |
| 6p23      | ATXN1  | ATX1, D6S504E, SCA1                                                     | Ataxin 1                                                             |
| 7p21      | IL6    | BSF2, HGF, HSF, IFNB2, IL-6                                             | Interleukin-6 (interferon, beta 2)                                   |
| 7q21.3    | PON1   | ESA, MVCD5, PON                                                        | Paraoxonase 1                                                        |
| 7q22      | RELN   | PRO1598, RL                                                            | Reelin                                                               |
| 7q36      | AD10   | ECNOS, eNOS                                                            | Alzheimer’s disease 10                                               |
| 7q36      | NOS3   |                                                                 | Nitric oxide synthase 3 (endothelial cell)                           |
| 7q36      | PAXIP1 | CAGF28, CAGF29, FLJ41049, PACIP1, PAXIP1L, PTIP, TNR2                  | PAX-interacting (with transcription-activation domain) protein 1     |
| 8p21-p12  | CLU    | AAG4, APOJ, CLI, KUB1, MGC24903, SGP-2, SGP2, SP-40, TRPM-2, TRPM2     | Clusters                                                             |
| 8p22      | CTSB   | APPS, CPSB                                                             | Cathepsin B                                                         |
| 9p24.1    | IL33   | C9orf26, DKFZp586H0523, DVS27, NF-HEV, NFEHEV, RP11-575C20.2           | Interleukin 33                                                       |
| 9q13-q21.1| APBA1  | D9S411E, MINT1, X11, X11A, X11ALPHA                                    | Amyloid beta (A4) precursor protein-binding, family A, member 1      |
| 9q31.1    | GRN3A  | FLJ45414, NMDAR-L, NR3A                                                 | Glutamate receptor, ionotropic, N-methyl-D-aspartate 3A             |
| 9q33-q34.1| HSPA5  | BIP, FLJ26106, GRP78, MIF2                                              | Heat shock 70 kDa protein 5 (glucose-regulated protein, 78 kDa)    |
| 9q34.1    | DAPK1  | DAPK, DKFZp781I035                                                     | Death-associated protein kinase 1                                   |
| 10p13     | AD7    |                                                                 | Alzheimer’s disease 7                                               |
| 10p15.2   | PITRM1 | RP11-298E9.1, KIAA1104, MGC138192, MGC141929, MP1, PreP, hMP1          | Pitrilysin metalloproteidase 1                                       |
| 10q       | AD6    |                                                                 | Alzheimer’s disease 6                                               |
| 10q11.2   | ALOX5  | RP11-67C2.3, 5-LO, 5-LOX, SLPG, LOG5, MGC163204                        | Arachidonate 5- lipoxgenase                                           |
| 10q21     | TFAM   | MtTf1, TCF6, TCF6L1, TCF6L2, TCF6L3, mtTFA                             | Transcription factor A, mitochondrial                               |
| 10q23     | CH25H  | C25H                                                                     | Cholesterol 25-hydroxylase                                            |
| 10q23-q25 | IDE    | RP11-366H13.1, FLJ35968, INSULYSIN                                       | Insulin-degrading enzyme                                             |
| 10q23-q25 | SORCS1 | RP11-446H13.1, FLJ41758, FLJ43475, FLJ44957                            | Sortilin-related VPS10 domain containing receptor 1                 |
| 10q23.32  | HECTD2 | FLJ16050                                                                | HECT domain containing 2                                             |
| 10q24     | COX15  |                                                                 | COX15 homolog, cytochrome c oxidase assembly protein (yeast)          |
| 10q24     | PLAU   | ATF, UPA, URK, u-PA                                                     | Plasminogen activator, urokinase                                     |
| 10q24.33  | CALHM1 | EAM26C, MGC39514, MGC39617                                             | Calcium homeostasis modulator 1                                      |
| 10q24.33  | SH3PXD2A| FISH, SH3MD1                                                            | SH3 and PX domains 2A                                                |
| 10q26.3   | ADAM12 | RP11-295J3.5, MCMC, MCMC Mltna, MLTN, Mltna                             | ADAM metallopeptidase domain 12                                      |
| 11p13     | BDNF   | MGC34632                                                                | Brain-derived neurotrophic factor                                    |
| 11p15     | APBB1  | FE65, MGC: 9072, RIR                                                    | Amyloid beta (A4) precursor protein-binding, family B, member 1 (Fe65) |
| 11p15.1   | SAA1   | MGC111216, PIQ4, SAA, TP5314                                            | Serum amyloid A1                                                     |
| 11p15.5   | CTSD   | CLN10, CPSD, MGC2311                                                  | Cathepsin D                                                         |
| 11q14     | PICALM | CALM, CLTH, LAP                                                        | Phosphatidylinositol binding clathrin assembly protein               |
| 11q14.1   | GAB2   | KIAA0571                                                               | GRB2-associated binding protein 2                                    |
| 11q23.2-q23.3 | BACE1 | ASP2, BACE, FLJ90568, HSPC104, KIAA1149 | Beta-site APP-cleaving enzyme 1                                      |
| Locus        | Symbol | Aliases                                                                 | Title                                                                 |
|-------------|--------|------------------------------------------------------------------------|----------------------------------------------------------------------|
| 11q23.2-q24.2 | SORL1  | C11orf32, FLJ21930, FLJ39258, LR11, LRP9, SORLA, SorLA-1, gp250         | Sortilin-related receptor, L(DLR class) A repeats-containing          |
| 11q24        | APLP2  | APPH, APL2, CDEBP                                                      | Amyloid beta (A4) precursor-like protein 2                            |
| 12p11.23-q13.12 | AD5    |                                                                        | Alzheimer’s disease 5                                                |
| 12p12.3-p12.1 | IAPP   | AMYLIN, DAP, IAP                                                       | Islet amyloid polypeptide                                             |
| 12p13.3-p12.3 | A2M    | CPAMD5, DKFZp779B086, FWP007, S863-7                                   | Alpha-2-macroglobulin                                                |
| 12q13-q14    | LRP1   | A2MR, APOER, APR, CD91, FLJ16451, IGBP3R, LRP, MGC8725, TGFB5         | Low-density lipoprotein-related protein 1 (alpha-2-macroglobulin receptor) |
| 13q34        | DAOA   | G72, LG72, SG72                                                       | D-amino acid oxidase activator                                        |
| 14q24.3      | FOS    | AP-1, C-FOS                                                           | FBJ murine osteosarcoma viral oncogene homolog                        |
| 14q24.3      | PSEN1  | AD3, FAD, PS1, S182                                                  | Presenilin-1                                                         |
| 14q32        | RAGE   | MOK, RAGE1                                                            | Renal tumor antigen                                                  |
| 14q32.1      | CYP46A1| CP46, CYP46                                                           | Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3 |
| 14q32.1      | SERPINA3| AACT, ACT, GIG24, GIG25, MGC88254                                    | Cytochrome P450, family 46, subfamily A, polypeptide 1              |
| 15q21.1      | CYP19A1| ARO, ARO1, CPV1, CYAR, CYP19, MGC104309, P-450AROM                   | Cytochrome P450, family 19, Subfamily A, polypeptide 1              |
| 15q22.2      | APH1B  | APH-1B, DKFZp564D0372, FLJ33115, PRO1328, PSFL, TAAV688              | Anterior pharynx defective 1 homolog B (C. elegans)                   |
| 15q11-q12    | APBA2  | D1S51518E, HsT16821, LIN-10, MGC99508, MGC: 14091, MINT2, X11L       | Amyloid beta (A4) precursor protein-binding, family A, member 2       |
| 16p13.3      | UBE2I  | C358B7.1, P18, UBC9                                                   | Ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)               |
| 16q21        | CETP   | HDLCQ10                                                              | Cholesterol ester transfer protein, plasma                            |
| 16q22        | NAE1   | A-116A10.1, APPBP1, HPP1, uda-1                                       | NEDD8 activating enzyme E1 subunit 1 COX10 homolog, cytochrome C oxidase assembly protein, heme A; farnesyltransferase (yeast) |
| 17p12-p11.2 | COX10  |                                                                        | Saitohin                                                             |
| 17q13        | MYH13  | MyHC-co                                                               | Myosin, heavy chain 13, skeletal muscle                               |
| 17p13.1      | TNK1   | MGC46193                                                              | Tyrosine kinase, nonreceptor, 1                                       |
| 17q11.2      | BLMH   | BH, BMH                                                               | Bleomycin hydrolase                                                  |
| 17q11.2      | MIR144 | MIRN144                                                               | MicroRNA 144                                                         |
| 17q21.1      | MAPT   | DPPAC, FLJ31424, FTDP-17, MAPT1, MGC138549, MSTD, MTBT1, MTBT2, PPND, TAU | Microtubule-associated protein tau                                   |
| 17q21.1      | STH    | MAPTIT, MGC163191, MGC163193                                         |                                        |
| 17q21.32     | GRN    | GEP, GP88, PCDG, PEPI, PGRN                                         |                                        |
| 17q21-q22    | GPSC   |                                                                        |                                        |
| 17q21-q23    | APPBP2 | HS.84084, KIAA0228, PAT1                                             |                                        |
| 17q23.1      | MPO    |                                                                        |                                        |
| 17q23.3      | ACE    | ACE1, CD143, DCP, DCP1, MGC26566, MVCD3                               |                                        |
| 17q24.3      | BPTF   | FAC1, FALZ, NURF301                                                  |                                        |
| 18q12.1      | TTR    | HsT2651, PALB, TBPA                                                  |                                        |
| 19p13        | PIN1   | DOD, UBL5                                                            |                                        |
| 19p13.2      | AD9    |                                                                        |                                        |
| 19p13.2-p13.1| NOTCH3 | Cadasil, Casil                                                        |                                        |
| 19p13.3      | APBA3  | MGC: 15815, X11L2, mint3                                             |                                        |
Table 1: Continued.

| Locus     | Symbol | Aliases          | Title                                                                 |
|-----------|--------|------------------|----------------------------------------------------------------------|
| 19p13.3   | GRIN3B | NR3B             | Glutamate receptor, ionotropic, N-methyl-D-aspartate 3B               |
| 19p13.3-p13.2 | ICAM | BB2, CD54, P5.58 | Intercellular adhesion molecule 1                                    |
| 19q13     | TOMM40 | C19orf1, D19S1177E, PER-EC1, PEREC1, TOM40 | Translocase of outer mitochondrial membrane 40 homolog (yeast)         |
| 19q13.1   | APLP1  | APLP             | Amyloid beta (A4) precursor-like protein 1                           |
| 19q13.12  | PEN2   | MDS033, MSTP064, PEN-2, PEN2 | Presenilin enhancer 2 homolog (C. elegans)                        |
| 19q13.2   | APOE   | AD2, LDLQ5, LPG, MGC1571 | Apolipoprotein E                                                        |
| 19q13.2   | APOC1  |                  | Apolipoprotein C-1                                                    |
| 19q13.32  | BLOC1S3| BLOS3, FLJ26641, FLJ26676, HPS8, RP | Biogenesis of lysosomal organelles complex-1, subunit 3            |
| 19q13.32  | EXOC3L2| FLJ6147, MGC16332, XTP7 | Exocyst complex component 3-like 2                                   |
| 19q13.3   | MARK4  | FLJ90097, KIAA1860, MARK1, Nbl00650 | MAP/microtubule affinity-regulating kinase 4                           |
| 19q13.43  | GALP   |                  | Galanin-like peptide                                                  |
| 20p       | AD8    |                  | Alzheimer’s disease                                                   |
| 20p11.21  | CST3   | ARMD11, MGC117328 | Prion protein                                                         |
| 20p13     | PRNP   | ASCR, CD230, CJD, GSS, MGC26679, PRIP, PrP, PrP27-30, PrP33-35C, PrPc, prion | Phosphoenolpyruvate carboxykinase 1 (soluble)                        |
| 20q13.31  | PCK1   | MGC22652, PECK-C, PEPC1, PEPCKC | Amyloid beta (A4) precursor protein                                   |
| 21q21.3   | APP    | AAA, ABETA, ABP, AD1, APP1, CTFgamma, CVAP, PN2 | Beta-site APP-cleaving enzyme 2                                       |
| 21q22.3   | BACE2  | AEPIC, ALP56, ASP1, ASP21, BAE2, CDA13, CEAP1, DRAP | Reticulon 4 receptor                                                   |
| 22q11.21  | RTN4R  | NGR, NOGOR       | Catechol-O-methyltransferase                                           |
| 22q11.21  | COMT   |                  |                                                                      |

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 [39]. As with many other potential AD-related genes, the association of SORL1 with AD [39, 40] could not be replicated in other studies [41].

Sorting protein-related receptor with A-type repeats (SORLA) is a major risk factor in cellular processes leading to AD. It acts as a sorting receptor for the APP that regulates intracellular trafficking and processing into amyloidogenic-beta peptides (Aβ). Overexpression of SORLA in neurons reduces while inactivation of gene expression accelerates amyloidogenic processing and senile plaque formation. Brain-derived neurotrophic factor (BDNF) is a major inducer of SORLA that activates receptor gene transcription through the ERK (extracellular regulated kinase) pathway. Expression of the receptor is significantly impaired in mouse models with genetic (Bdnf−/−) or disease-related loss of BDNF activity in the brain (Huntington’s disease). Exogenous application of BDNF reduced Aβ production in primary neurons and in the brain of wild-type mice in vivo, but not in animals genetically deficient for Sorla. According to these findings reported by Rohe et al. [43], the beneficial effects ascribed to BDNF in APP metabolism act through induction of Sorla which encodes a negative regulator of neuronal APP processing. The presence of the BDNF Val allele in itself and in combination with the APOE-4 allele can be risk factors for AD, Lewy body dementia, and Pick’s disease [44].

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 [45, 46]. 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 [45].

Polymorphisms in the cholesteryl ester transfer protein (CETP) gene have been associated with exceptional longevity and lower cardiovascular risk, but associations with memory decline and dementia risk are unclear. Sanders et al. [47] tested the hypothesis that an SNP at CETP codon 405 (isoleucine to valine V405; SNP rs5882) is associated with a lower rate of memory decline and lower risk of incident dementia, including AD. Compared with isoleucine homozygotes, valine homozygotes had significantly slower memory decline and lower risk of dementia.

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 [48].

Promoter polymorphisms modulating HSPA5 expression might also increase susceptibility to AD. Endoplasmic reticulum chaperone heat shock 70 kDa protein 5 (HSP-A5/GRP78) is known to be involved in APP metabolism and neuronal death in AD. Of the three major polymorphisms (−415G/A, −370C/T, and −180-Del/G), 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 developing AD [49].

The rs952C and rs1568566T alleles of the APOD rs9527/C and rs1568566C/T variants increase the risk for AD, whereas the rs9522T-rs1568566C haplotype reduces it [50]. ApoD is a lipoprotein-associated glycoprotein which is increased in the hippocampus and CSF of AD patients [50].

CALHM1 encodes a multipass transmembrane glyco-protein that controls cytosolic Ca2+ concentrations and Aβ levels. The CALHM1 P86L polymorphism (rs2986017) has been associated with AD [51].

Harold et al. [52] 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. [53] found association with CLU and with the CR1 gene, encoding the complement component (3b/4b) receptor 1 on chromosome 1 (rs6656401). Jun et al. [54] determined whether genotypes at CLU, PICALM, and CR1 confer risk for AD and whether risk for AD associated with these genes is influenced by APOE genotypes in 7,070 cases with AD, 3,055 with autopsies, and 8,169 elderly cognitively normal controls, 1,092 with autopsies, from 12 different studies, including white, African American, Israeli-Arab, and Caribbean Hispanic individuals. They confirmed in a completely independent data set that CR1 (rs3818361), CLU (rs11136000), and PICALM (rs3851179) are AD susceptibility loci in European ancestry populations. Genotypes at PICALM confer risk predominantly in APOE-4-positive subjects. Thus, APOE and PICALM synergistically interact. Two new loci were identified to have genome-wide significance for the first time: rs744373 near BIN1 and rs597668 near EXOC3L2/BLOC13/3/MARK4 [55].

Kramer et al. [56] conducted a GWAS to identify genetic mechanisms that distinguish nondemented elderly with a heavy NFT burden from those with a low NFT burden. Both a genotype test, using logistic regression, and an allele test provided consistent evidence that variants in the RELN gene are associated with neuropathology in the context of cognitive health. Immunohistochemical data for reelin expression in AD-related brain regions added support for these findings. Reelin signaling pathways modulate phosphorylation of tau, the major component of NFTs, either directly or through beta-amyloid pathways that influence tau phosphorylation. Upregulation of reelin may be a compensatory response to tau-related or beta-amyloid stress associated with AD even prior to the onset of dementia [56]. Aβ induces synaptic dysfunction in part by altering the endocytosis and trafficking of AMPA and NMDA receptors. Reelin is a neuromodulator that increases glutamatergic neurotransmission by signaling through the postsynaptic ApoE receptors ApoER2 and VLDLR and thereby potently enhances synaptic plasticity. Reelin can prevent the suppression of long-term potentiation and NMDA receptors, which is induced by levels of Aβ comparable to those present in an AD-afflicted brain. This reversal is dependent upon the activation of Src family tyrosine kinases. Durakoglugil et al. [57] proposed that Aβ, Reelin, and ApoE receptors modulate neurotransmission and thus synaptic stability as opposing regulators of synaptic gain control.

A variable-length, deoxythymidine homopolymer (poly-T) within intron 6 of the TOMM40 gene was found to be associated with the age of onset of LOAD by Roses et al. [58]. This result was obtained with a phylogenetic study of the genetic polymorphisms that reside within the linkage disequilibrium (LD) block that contains the TOMM40, APOE, and PICALM genes from patients with LOAD and age-matched subjects without disease [59]. These new data explain the mean age at disease onset for patients with the APOE4/4 genotype and differentiate two forms of TOMM40 poly-T polymorphisms linked to APOE, with each form associated with a different age at disease onset distribution. When linked to APOE3 (encoding the e3 isoform of APOE), the longer TOMM40 poly-T repeats (19–39 nucleotides) at the rs10524523 (hereafter, 523) locus are associated with earlier age at onset and the shorter TOMM40 523 alleles (11–16 nucleotides) are associated with later age at onset. According to Roses [60], the data suggest that the poly-T alleles are codominant, with the age at onset phenotype determined by the two inherited 523 alleles, but with variable expressivity.

Ohe and Mayeda [61] reported that overexpression of high-mobility group A protein 1a (HMGA1a) causes aberrant exon 5 skipping of the presenilin-2 (PSEN2) pre-mRNA, which is almost exclusively detected in patients with sporadic AD. An electrophoretic mobility shift assay confirmed aberrant U1 small-nuclear-ribonucleoprotein-particle- (snRNP-) HMGA1a complex formation (via the U1-70 K component), with RNA containing a specific HMGA1a-binding site and an adjacent 5′ splice site. The HMGA1a-induced aberrant exon skipping is caused by impaired dissociation of U1 snRNP from the 5′ splice site, leading to a defect in exon definition.

Kelley et al. [62] characterized a kindred with a familial neurodegenerative disorder associated with a mutation in progranulin (PGRN). PGRN analysis revealed a single base pair deletion in exon 2 (c.154delA), which caused a frameshift (p.Thr52HisfsX2) and, therefore, creation of a premature termination codon and a likely null allele. In this large kindred, most affected individuals had clinical presentations that resembled AD or amnestic mild...
cognitive impairment associated with a mutation in PGRN and underlying frontotemporal lobar degeneration with ubiquitin-positive neuronal cytoplasmic and intranuclear inclusions (FTLD-U). Mutation in the PGRN gene can cause frontotemporal dementia (FTD9). Yu et al. [63] identified 58 genetic variants that included 26 previously unknown changes. 24 variants appeared to be pathogenic, including eight novel mutations. The frequency of PGRN mutations was 6.9% of all FTD-spectrum cases, 21.4% of cases with a pathological diagnosis of FTLD-U, 16.0% of FTD-spectrum cases with a family history of a similar neurodegenerative disease, and 56.2% of cases of FTLD-U with a family history. Haploinsufficiency of PGRN is the predominant mechanism leading to FTD.

Polymorphisms within the promoter region of the vascular endothelial growth factor (VEGF) gene might elevate the risk for AD. In a Tunisian population, Smach et al. [64] found that the distribution of genotype and allele frequencies of the rs4988514 polymorphism (C/T) polymorphisms in the C allele of this polymorphism was elevated in the SAD cases compared to the control group in the Chinese population. In subjects with a family history of a similar neurodegenerative disease, and 56.2% of cases with a family history. Haploinsufficiency of PGRN is the predominant mechanism leading to FTD.

Endothelin-converting enzyme (ECT-1) is also a candidate AD susceptibility gene. Individuals homozygous for the C-338A polymorphism (AA) within the ECE1 gene promoter region are at reduced risk of developing late-onset AD (LOAD). A further polymorphism, T-839G, is present within the ECE1 promoter region but there is no significant association between T-839G and LOAD; however, the combined 839T/338A haplotype is associated with decreased risk of LOAD, suggesting that the ECE1 338A allele is protective against LOAD in a Chinese population [65].

Downregulation of somatostatin (SST) expression in the human brain during early stages of aging may lead to an elevation in the steady-state levels of Aβ and therefore may be involved in AD progression. Alterations in the SST gene might alter its expression or function and also play a role in the pathogenesis of sporadic AD (SAD). C/T polymorphisms (rs4988514) were screened in the 3′ untranslated region of the SST gene. The C allele of the rs4988514 polymorphism had an increased incidence in the SAD group compared to the control group in the Chinese population. In subjects with the APOE-4 allele, the presence of both the CC genotype and the C allele of this polymorphism was elevated in the SAD group compared to the control group. The C allele of the rs4988514 polymorphism may increase the risk for AD in the Chinese population and possibly have additive effect with the APOE-4 allele [66].

The receptor for advanced glycation end products (RAGE) is associated with several pathological states including AD pathology, while its soluble form (sRAGE) acts as a decoy receptor. Li et al. [67] studied an SNP in the RAGE gene (G82S; rs2070600) and an SNP associated with increased ligand affinity of RAGE. Analysis of a Chinese cohort showed a higher prevalence of the RAGE 82S allele and GS + SS genotype in EOAD patients. RAGE contributes to transport of Aβ from the cell surface to the intracellular space. Pretreatment of cultured neurons from wild-type mice with neutralizing antibody to RAGE and neurons from Rage knockout mice displayed decreased uptake of Aβ and protection from Aβ-mediated mitochondrial dysfunction [68].

The TAR-DNA-binding protein (TDP-43) has been postulated as the disease protein in amyotrophic lateral sclerosis and frontotemporal lobar dementia with ubiquitin-positive inclusions. TDP-43 may also play a role in the pathogenesis of AD. Shibata et al. [69] identified an association between a specific haplotype (G-A-A-G) of the TDP-43 gene and risk for AD.

Immune dysfunction and aberrant inflammatory reactions are present in AD neuropathology. Neurons express enzymes such as cyclooxygenases (COXs) and 5-lipoxygenase (5-LO), which are considered important in inflammatory cells. It has been suggested that COX-2 and 5-LO enzymes may play a role in the pathophysiology of AD. A significant difference was observed in the distribution of the −765G COX-2 and −1708A 5-LO alleles between AD cases and controls. COX-2 −765G and 5-LO −1708A alleles were over-represented in AD patients and underrepresented in controls [70]. The HLA-A*01 variant might also be associated with AD [71]. SNPs in the regulatory regions of the cytokine genes for tumor necrosis factor alpha (TNF-alpha), interleukin-6 (IL-6), and IL-10 have been suggested to influence the risk of AD with conflicting results. Heterozygotes (AG) or combined genotype (AA + AA) for IL-10 −1082 was associated with an approximately two-fold increase in the risk of AD. Carriers of A alleles of both TNF-alpha-308 and IL-10 −1082 had 6.5 times higher risk for AD in comparison with noncarriers. Concomitant presence of both mutant TNF-alpha-308 A and IL-6 −174 C alleles raised three-fold the AD risk, whereas there was no notable risk for AD afflicted by IL-6 −174 polymorphism alone [72, 73]. Interleukin-33 (IL-33), a newly described member of the IL-1 family, is located on chromosome 9p24, a chromosomal region of interest in AD. Three intronic rs1157505, rs11792633, and rs7044343 SNPs within IL-33 have been reported to be associated with risk of AD in Caucasian and Chinese populations [74].

Aromatase gene polymorphisms have also been associated with AD [75]. Polymorphisms in genes encoding amyloid-beta-peptide- (Aβ-) degrading enzymes neprilysin (NEP) and insulin-degrading enzyme (IDE) individually affect the susceptibility to AD among the Finnish population [76]. Nicastrin (NCSTN) is a type I transmembrane glycoprotein and an essential component of γ-secretase, a multi-protein complex required for the production of the mature form of Aβ. Overexpression of wild-type NCSTN increases Aβ production, indicating that the strict regulation of NCSTN expression may play a fundamental role in the pathogenesis of AD. Zhong et al. [77] investigated the effect of an SNP (rs10752637) located in the promoter region of the NCSTN gene, on NCSTN promoter activity. The distributions of the rs10752637 genotypes and allele frequencies were significantly different between the AD and control groups, with the −922T allele significantly associated with the occurrence of AD. Reporter assays indicated that the rs10752637 −922T allele had a significantly increased promoter activity relative to the −922G allele. The rs10752637 SNP can
probably influence the expression of NCSTN, and this may be an influencing factor during the pathogenesis of AD.

The FISH (five SH3 domains) adapter protein and ADAM12 (a disintegrin and metalloprotease) may mediate the neurotoxic effect of Aβ. Both genes are located on chromosome 10, within a region linked to AD (for \( 3p24.3\)) or nearby (for ADAM12). Two variants of these genes (rs3740473 for \( 3p24.3\)) and rs11244787 for ADAM12) have been associated with increased risk for developing AD, but these findings could not be confirmed in different populations [78].

Paraoxonase 1 (PON1) L55M and Q192R genetic variants might affect individual susceptibility to environmental events, such as exposure to cholinesterase inhibitors. The L55M Met allele exerts an AD risk-enhancing effect only in men, whereas both men and women carrying the M55M/Q192Q genotype exhibit increased survival and later age of onset. These genetic variants are also individually and significantly associated, sometimes in opposite directions for both genders, with beta-amyloid levels, senile plaque accumulation, and choline acetyltransferase activity in brain areas [79].

Liu et al. [80] studied the potential association of polymorphisms in NMDA receptor subunits NR3A and NR3B, encoded by the GRIN3A and GRIN3B genes, with AD, on the basis that memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may provide some clinical benefit in AD patients. Two SNPs, 3104G/A (rs10989563) and 3723G/A (rs3739722), in the GRIN3A gene, and two GRIN3B gene polymorphisms, 1210C/T (rs4807399) and 1730C/T (rs224-0158), were analyzed. Upon genotyping of the exonic polymorphism in the GRIN3A gene, the G allele was present at a higher rate than the A allele at position 3723 in AD patients compared with normal groups. Three haplotypes (designated Ht1-3) were identified from these two polymorphisms (3104G/A and 3723G/A), and the distribution of Ht2 (AG) differed between AD patients and controls. The two GRIN3B gene variants 1210C/T and 1730C/T did not show association with AD. These observations suggest that the genetic variation of the NR3A, but not NR3B, subunit of the NMDA receptor may be a risk factor for AD pathogenesis among the Taiwanese population. Di Maria et al. [81] reported that the occurrence of delusions and hallucinations in AD is associated with variations in the G72/DAOA gene (rs2153674), which is supposed to play a key role in the glutamate pathway regulated through the NMDA receptors. Martinez et al. [82] studied the influence of the catechol-O-methyltransferase (COMT) gene (polymorphism Val158 Met) as a risk factor for AD and mild cognitive impairment of the amnestic type (MCI) and its synergistic effect with APOE variants in the Basque Country. Neither COMT alleles nor genotypes were independent risk factors for AD or MCI; however, the high activity genotypes (GG and AG) showed a synergistic effect with the APOE-4 allele, increasing the risk of AD.

Peptidyl-prolyl isomerase NIMA-interacting 1 (PIN1) plays a significant role in the brain and is implicated in numerous cellular processes related to AD and other neurodegenerative conditions. Analysis of 18 PIN1 common polymorphisms and their haplotypes in EOAD, LOAD, and FTD individuals in comparison with the control group did not reveal their contribution to disease risk. In six unrelated familial AD patients four novel PIN1 sequence variants were detected. The c.58+64C>T substitution identified in three patients was located in an alternative exon. In silico analysis suggested that this variant highly increases a potential affinity for a splicing factor and introduces two intronic splicing enhancers. In the peripheral leukocytes of one living patient carrying the variant, a 2.82-fold decrease in PIN1 expression was observed [83].

Alzheimer’s and prion diseases are neurodegenerative disorders characterized by the abnormal processing of Aβ peptide and prion protein (PrPSC), respectively. PrPSc may play a critical role in the pathogenesis of AD. PrPSc interacts with and inhibits the β-secretase BACE1, the rate-limiting enzyme in the production of Aβ. PrPSc was also identified as a receptor for Aβ oligomers, and the expression of PrPSc appears to be controlled by the amyloid intracellular domain (AICD). PrPSc exerts an inhibitory effect on BACE1 to decrease both Aβ and AICD production, and the AICD upregulates PrPSc expression, thus maintaining the inhibitory effect of PrPSc on BACE1. According to Kellett and Hooper [84], this feedback loop is disrupted in AD, and the increased level of Aβ oligomers binds to PrPSc and prevents it from regulating BACE1 activity. It is also likely that PRNP gene mutations contribute to AD pathogenesis [9]. HECTD2 maps to 10q and has been implicated in susceptibility to human prion disease. A HECTD2 intronic tagging SNP, rs1249854 (A/T), has been studied in AD. The rs1249854 minor allele (A) frequency was higher (5.8%) in AD as compared to controls (3.9%). No significant difference was seen in minor allele frequency in the presence or absence of the APOE-4 allele. According to these results, it appears that the common haplotypes of HECTD2, tagged by rs1249854, are not associated with susceptibility to LOAD [85].

Ubiquitin-conjugating enzyme E21 (Ubc9) ligates small ubiquitin-related modifier (SUMO) to target proteins, resulting in changes of their localization, activity, or stability. Sumoylation of APP was reported to be associated with decreased levels of Aβ aggregates, suggesting that sumoylation may play a role in the pathogenesis of AD. Ahn et al. [86] investigated the association between genetic variations of Ubc9 gene (UBE21) and LOAD in Koreans. The genotype distribution of a polymorphism in intron 7 (rs761059) differed between AD cases and controls and one haplotype (ht2 CAGAG) was found in 14.0% of the AD patients and in 11.1% of the controls. Stratification by the APOE-4 allele gave no significant difference between the groups. When the samples were stratified by gender, the genotypes of two SNPs (rs8052688, rs8063) were significantly associated with the risk of MCI among women.

To gain insights into the evolution of the regulatory mechanisms of the aged brain, Persengiev et al. [87] compared age-related differences in microRNA (miRNA) expression levels in the cortex and cerebellum of humans, chimpanzees, and rhesus macaques on a genome-wide scale. In contrast to global miRNA downregulation, a small subset of miRNAs was found to be selectively upregulated in the aging
brain of all three species. miR-144 appeared to be associated with the aging progression. miR-144 plays a central role in regulating the expression of ataxin 1 (ATXN1), a gene which is associated with spinocerebellar ataxia type 1 (SCA1). miRNA activity, including miR-144, -101, and -130 processing, was increased in the cerebellum and cortex of SCA1 and Alzheimer’s patients relative to healthy aged brains. The activation of miRNA expression in the aging brain might serve to reduce the cytotoxic effect of polyglutamine expanded ATXN1 and the deregulation of miRNA expression might be a risk factor for neurodegeneration. Bettens et al. [88] also obtained evidence for association between rs179943, an intronic SNP in ATXN1 at 6p22.3, and AD.

The cholesterol transporter ATP-binding cassette transporter A1 (ABCA1) moves lipids onto apolipoproteins including ApoE. Donkin et al. [89] reported that in amyloid mouse models of AD, ABCA1 deficiency exacerbates amyloidogenesis, whereas ABCA1 overexpression ameliorates amyloid load, suggesting a role for ABCA1 in Aβ metabolism. Agonists of liver X receptors (LXRs), including GW3965, induce transcription of several genes including ABCA1 and ApoE, reduce Aβ levels, and improve cognition in AD mice. Treatment of APP/PS1 mice with GW3965 increased ABCA1 and ApoE protein levels. ABCA1 was observed to require significantly elevated ApoE levels in brain tissue and CSF upon GW3965 treatment. APP/PS1 mice treated with either 2.5 mg/kg/d or 33 mg/kg/d of GW3965 showed a clear trend toward reduced amyloid burden in hippocampus and whole brain, whereas treated APP/PS1 mice lacking ABCA1 failed to display reduced amyloid load in whole brain and showed trends toward increased hippocampal amyloid. Treatment of APP/PS1 mice with either dose of GW3965 completely restored novel object recognition (NOR) memory to wild-type levels, which required ABCA1. These results reported by Donkin and coworkers suggest that ABCA1 contributes to several beneficial effects of the LXR agonist GW3965 in APP/PS1 mice.

The phospholipid transfer protein (PLTP) reduces phosphorylation of tau in human neuronal cells. Patients with AD have significantly higher levels of PLTP in brain tissue and significantly lower PLTP-mediated phospholipid transfer activity in cerebrospinal fluid. PLTP also affects ApoE secretion from glial cells. Kuerban et al. [90] investigated whether SNPs of the PLTP gene are associated with AD in the Japanese population and found no genetic association between PLTP and AD.

Genome-wide association studies (GWASs) in AD highlight over two dozen novel potential susceptibility loci beyond the well-established APOE association, including GAB2 (GRB2-associated binding protein 2), galanin-like peptide (GALP), piggyBac transposable element derived 1 (PGBD1), tyrosine kinase, non-receptor 1 (TNK1), and at least three replicated loci in hitherto uncharacterized genomic intervals on chromosomes 14q32.13, 14q31.2, and 6q24.1, probably implicating the existence of novel AD genes in these regions [91].

(c) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity [9, 92]. The human presequence protease (hPreP) was recently shown to be the major mitochondrial Aβ-degrading enzyme. Genetic variation in the hPreP gene PITRM1 has been investigated by Pinho et al. [93]. No genetic association was found between any of the SNPs and the risk for AD; however, functional analysis of four nonsynonymous SNPs in hPreP revealed a decreased activity compared to wild-type hPreP. Using Aβ, the presequence of ATP synthase F1β subunit and a fluorescent peptide as substrates, the lowest activity was observed for the hPreP(A525D) variant, corresponding to rs1224893, which displayed only 20–30% of wild-type activity. Genetic variation in the hPreP gene PITRM1 might contribute to mitochondrial dysfunction in AD.

Recent data suggest the possible contribution of heme deficiency to the progressive derangement of mitochondria in the AD brain; shortage of heme, and particularly of heme-a, actually leads to loss of mitochondrial cytochrome c oxidase (COX), abnormal production of reactive oxygen species, and altered amyloid precursor protein metabolism. Differences in the amount and/or functioning of COX assembly subunits 10 (COX10) and 15 (COX15), the key enzymes involved in heme-a biosynthesis, could be linked to variations of the individual risk to develop AD. Vitali et al. [94] analyzed mRNA expression in the hippocampus from AD patients and controls, as well as nucleotide variations in DNA sequences in AD. COX15 mRNA was significantly more abundant in the cerebral tissue of AD patients, and the IVS-178G>AN SNP in COX10 and the c+1120C>T SNP in COX15 were significantly less represented in AD, suggesting a possible protective role.

Japanese AD patients are associated with the haplogroups G2a, B4c1, and N9b1. Takasaki [95] compared mitochondrial haplogroups of AD patients with those of other classes of Japanese (centenarians, Parkinson’s disease (PD), type 2 diabetes mellitus (T2D), and nonobese young males). The four classes of people were associated with the following haplogroups: Japanese centenarians with M7b2, D4b2a, and B5b; PD patients with M7b2, B4e, and B5b; T2D patients with B5b, M8a1, G, D4, and F1; Japanese healthy nonobese young males with D4g and D4b1b. The haplogroups of the AD patients differed from those of the other four categories.

Santoro et al. [96] applied for the first time a high-resolution analysis to investigate the possible association between mtDNA-inherited sequence variation and AD in 936 AD patients and 776 cognitively assessed normal controls from central and northern Italy. Among over 40 mtDNA sub-haplogroups analyzed, they found that sub-haplogroup H5 is a risk factor for AD, particularly in females, independently of the APOE genotype. The H5a subgroup of molecules, harboring the 4336 transition in the tRNAAln gene, was about threefold more represented in AD patients than in controls (2.0% versus 0.8%), and it might account for the increased frequency of H5 in AD patients (4.2% versus 2.3%). The complete resequencing of the 56 mtDNAs belonging to H5 revealed that AD patients showed a trend towards a higher number of sporadic mutations in tRNA and rRNA genes when compared with controls.
Gene Interactions. Although APP and PSEN mutations are considered causative factors for AD, the total number of mutations identified in the 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, 9]. 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.

We have compared the distribution and frequency of major polymorphic variants of different genes potentially associated with AD (i.e., APOE, PSEN1, A2M-V1001, A2M-I/D, ACE, FOS, AGT-235, AGT-174, eNOS3-E298D, eNOS3-27bpTR, CETP, and MTHFR) in the general population, in adults (>45 years) with no family history of dementia, and in patients with dementia, and could not find any significant differences among the three groups except in the case of the APOE gene, which exhibits a clear accumulation of APOE-3/4 and APOE-4/4 genotypes (overload of the APOE-4 allele) in AD cases [5]. If we consider that a genetic variation higher than 2% could be of significant value, then several polymorphisms clearly differ in AD as compared with the other two population clusters, including the PSEN1-I/2, ACE-D/D, ACE-I/I, CEPT-B1/B1, and MTHFR-T/T polymorphisms [5].

Defective functions of genes associated with longevity may influence premature neuronal survival, since neurons are potential pacemakers defining lifespan in mammals [9, 97]. Hypothalamic expression of CREB-binding protein (CBP) and CBP-binding partner special AT-rich sequence binding protein 1 (SATB-1) is highly correlated with lifespan across five strains of mice, and expression of these genes decreases with age and diabetes in mice. In a transgenic Aβ42 model of AD, cbp-1 RNAi prevents protective effects of bacterial dilution (bDR) and accelerates Aβ42-related pathology. Consistent with the function of CBP as a histone acetyltransferase, drugs that enhance histone acetylation increase lifespan and reduce Aβ42-related pathology, protective effects completely blocked by cbp-1 RNAi. Other factors implicated in lifespan extension are also CBP-binding partners, suggesting that CBP constitutes a common factor in the modulation of lifespan and disease burden by DR and the insulin/IGF1 signaling pathway [98].

AD patients have been reported to have shorter telomeres in peripheral blood leukocytes (PBLs) than age-matched control subjects. However, it is unclear if PBL telomere length reflects brain telomere length, which might play a more direct role in AD pathogenesis. Lukens et al. [99] examined the correlation between PBL and cerebellum telomere length in AD patients. The PBL and cerebellum telomere lengths were directly correlated in individuals with AD. Nonetheless, cerebellum telomere lengths were not significantly different in AD patients and age-matched control subjects. Reduced PBL telomere length in AD might not reflect reduced telomere length in bulk brain tissue but may be a marker of changes in a subset of brain tissues or other tissues that affect the pathogenesis of AD. Zekry et al. [100] evaluated the usefulness of telomere length alone or combined with APOE polymorphism in diagnosing mild cognitive impairment (MCI) and in differentiating AD from vascular and mixed dementia. Although APOE-4 was associated with dementia, no significant differences in telomere length were found among patients with different types of dementia. The combination of telomere length and APOE-4 did not confer a significantly higher dementia risk [100].

3. Functional Genomics

Over 80% of the genes that conform the structural architecture of the human genome are expressed in the brain in a time-dependent manner along the lifespan. The cellular complexity of the CNS (with 10\(^3\) different cell types) and synapses (with each of the 10\(^11\) neurons in the brain having around 10\(^3\)-10\(^4\) synapses with a complex multiprotein structure integrated by 10\(^3\) different proteins) requires a very powerful technology for gene expression profiling, which is still in its very early stages and is not devoid of technical obstacles and limitations [101]. Transcripts of 16,896 genes have been measured in different CNS regions. Each region possesses its own unique transcriptome fingerprint which is independent of age, gender, and energy intake. Less than 10% of genes are affected by age, diet, or gender, with most of these changes occurring between middle and old age. Gender and energy restriction have robust influences on the hippocampal transcriptome of middle-aged animals. Prominent functional groups of age- and energy-sensitive genes are those encoding proteins involved in DNA damage responses, mitochondrial and proteasome functions, cell fate determination, and synaptic vesicle trafficking. The systematic transcriptome dataset provides a window into mechanisms of neuropathogenesis and CNS vulnerability [102].

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. Mutations in the APP, PSEN1, PSEN2, and MAPT genes give rise to well-characterized differential neuropathological and clinical phenotypes of dementia [9, 24, 25]. APP mutations are associated with AD1, early-onset progressive autosomal recessive dementia, early-onset AD with cerebral amyloid angiopathy, and hereditary amyloidosis with cerebral amyloid angiopathy Dutch type, Italian type, or Iowa type. PSEN1 mutations are associated with the phenotypes of familial AD3, familial AD3 with unusual plaques,
familial AD with spastic paraparesis and unusual plaques, familial AD with paraparesis and apraxia, frontotemporal dementia, Pick’s disease, and dilated cardiomyopathy. MAPT mutations are associated with frontotemporal dementia, frontotemporal dementia with parkinsonism, Pick’s disease, progressive supranuclear palsy, progressive atypical supranuclear palsy, tauopathy, and respiratory failure [9].

Transgenic animals also reproduce to some extent the neuropathological hallmarks of AD in a sequential manner. The triple transgenic mouse model of AD (3xTg-AD) harbors three AD-related loci: human PS1M146V, human APP-swe, and human MAPT P301L. 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, astroglisis, 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 [103]. 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 [104].

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 [4–9, 37, 97, 105–114], 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, and vitamin B12 deficiencies) accumulates more in APOE-4 carriers than in APOE-3 carriers; (xvi) some behavioral disturbances (bizarre behaviors and psychotic symptoms), alterations in circadian rhythm patterns (e.g., sleep disorders), and mood disorders (anxiety and 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; (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 [4–7, 9, 28, 37, 97, 105–118].

### 4. Dementia Phenotype and Biomarkers

The phenotypic features of the disease represent the biomarkers to be modified with an effective therapeutic intervention. Important differences have been found in the AD population as compared with healthy subjects in different biological parameters, including blood pressure, glucose, cholesterol, and triglyceride levels, transaminase activity, hematological parameters, metabolic factors, thyroid function, brain hemodynamic parameters, and brain mapping activity [4, 5, 9, 97, 105, 108–111]. Blood pressure values, glucose levels, and cholesterol levels are higher in AD than in healthy elderly subjects. Approximately 20% of AD patients are hypertensive, 25% are diabetics, 50% are hypercholesterolemic, and 23% are hypertriglyceridemic. Over 25% of the patients exhibit high GGT activity, 5–10% show anemic conditions, 30–50% show an abnormal cerebral vascular function characterized by poor brain perfusion, and over 60% have an abnormal electroencephalographic pattern, especially in frontal, temporal, and parietal regions, as revealed by quantitative EEG (qEEG) or computerized mapping [5, 9, 105]. Significant differences are currently seen between females and males, indicating the effect of gender on the phenotypic expression of the disease. In fact, the prevalence of dementia is 10–15% higher in females than in males from 65 to 85 years of age. All these parameters are highly relevant when treating AD patients because some of them reflect a concomitant pathology that also needs therapeutic consideration. They can also represent general biomarkers together with regional brain atrophy and perfusion and cognitive function, which may serve as therapeutic outcome measures. Other biomarkers of potential interest include cerebrospinal fluid (CSF) and peripheral levels of Aβ42, protein tau, histamine, interleukins, and some other candidate markers [5, 119, 120]. In proteomic studies, several candidate CSF protein biomarkers have been assessed.
in neuropathologically confirmed AD, nondemented (ND) elderly controls, and non-AD dementias (NADDs). Markers selected included apolipoprotein A-1 (ApoA1), hemopexin (HPX), transthyretin (TTR), pigment epithelium-derived factor (PEDF), Aβ1–40, Aβ1–42, total tau, phosphorylated tau, α-1 acid glycoprotein (A1GP), haptoglobin, zinc α-2 glycoprotein (Z2GP), and apolipoprotein E (ApoE). The concentrations of Aβ1–42, ApoA1, A1GP, ApoE, HPX, and Z2GP differed significantly among AD, ND, and NADD subjects. The CSF concentrations of these three markers distinguished AD from ND subjects with 84% sensitivity and 72% specificity, with 78% of subjects correctly classified. By comparison, using Aβ1–42 alone gave 79% sensitivity and 61% specificity, with 68% of subjects correctly classified. For the diagnostic discrimination of AD from NADD, only the concentration of Aβ1–42 was significantly related to diagnosis, with a sensitivity of 58% and a specificity of 86% [121].

5. 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, 5, 9, 37, 97, 105–112, 115]. Since the early 1980s, the neuropharmacology of AD was dominated by the acetylcholinesterase inhibitors, represented by tacrine, donepezil, rivastigmine, and galantamine [2, 3, 122]. Memantine, a partial NMDA antagonist, was introduced in the 2000s for the treatment of severe dementia [123], and the first clinical trials with immunotherapy, to reduce amyloid burden in senile plaques, were withdrawn due to severe ADRs [124, 125]. 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 [4, 126, 127]. However, assuming that the best treatment for AD is neuronal death prevention prior to the onset of the disease, novel therapeutic options and future candidate drugs for AD might be a new generation of anti-amyloid vaccines, such as DNA Aβ42 trimer immunization [128], heterocyclic indazole derivatives (inhibitors of the serum- and glucocorticoid-inducible-kinase 1 (SGK1)) [129], NSAID-like compounds [130], IgG single chain Fv fusion proteins [131], Hsp90 inhibitors and HSP inducers [132], inhibitors of class I histone deacetylases [133], some phenolic compounds [134], agonists of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) [135], microRNAs [136], and gene silencing (RNai) [137].

6. Pharmacogenetics of AD-Related Genes

Over 500 studies reported during the past two decades have postulated the potential involvement of APOE in dementia and other CNS disorders [9]. The distribution and frequency of APOE genotypes (Figure 1) have been investigated in 315 Spanish controls with no family history of neuropsychiatric disorders and in patients with anxiety, depression, psychosis, stroke, Alzheimer’s disease, Parkinson’s disease, attention-deficit hyperactivity disorder, migraine, epilepsy, vascular dementia, vascular encephalopathy (with hypertension, diabetes, or dyslipidemia), multiple sclerosis, cerebrovascular insufficiency, brain tumors (glioma, astrocytoma, glioblastoma, and meningioma), cranial nerve neuropathy (facial palsy and trigeminal neuralgia), mental retardation, and posttraumatic brain injury syndrome (Figure 1). The distribution of APOE genotypes in the Iberian peninsula is as follows: APOE-2/2 0.32%, APOE-2/3 7.3%, APOE-2/4 1.27%, APOE-3/3 71.11%, APOE-3/4 18.41%, and APOE-4/4 1.59% (Figure 1). There is a clear accumulation of APOE-4 carriers among patients with AD (APOE-3/4 30.30%; APOE-4/4 6.06%) (P < 0.001) and vascular dementia (APOE-3/4 35.85%, APOE-4/4 6.57%) (P < 0.001) as compared to controls. The distribution and frequencies of APOE genotypes in AD also differ from those of patients with anxiety (P < 0.001), depression (P < 0.001), psychosis (P < 0.005), migraine (P < 0.03), vascular encephalopathy (P < 0.001), and posttraumatic brain injury syndrome (P < 0.03). Significant differences are also present between vascular dementia and anxiety (P < 0.001), depression (P < 0.001), psychosis (P < 0.001), migraine (P < 0.002), vascular encephalopathy (P < 0.001), and posttraumatic brain injury syndrome (P < 0.008) (Figure 1).

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 [5, 7, 9, 105, 112, 113, 138, 139]. 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, and rivastigmine), neuroprotective compounds (nootropics), endogenous nucleotides (CDP-choline), immunotrophins (anapsos), neurotrophic factors (cerebrolysin), rosiglitazone, or combination therapies [5–7, 9, 105, 112, 113, 138, 140]; however, controversial results are frequently found due to methodological problems, study design, and patient recruitment in clinical trials.

APOE-4 carriers show a less significant therapeutic response to tacrine (60%) than patients with no APOE-4 [141]. The frequency of APOE-4 alleles was higher in responders to a single oral dose of tacrine [142]. About 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 [141]. 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 \textit{APOE-4} inheritance is a negative predictor of treatment of tacrine in AD [143]. It has also been shown that the \textit{APOE} genotype may influence the biological effect of donepezil on APP metabolism in AD [144]. Prospective studies with galantamine in large samples of patients in Europe [145] and in USA [146] showed no effect of \textit{APOE} genotypes on drug efficacy, but a retrospective study with a small number of AD cases in Croatia showed the intriguing result of 71% responders to galantamine treatment among \textit{APOE-4} homozygotes [147]. MacGowan et al. [148] reported that gender is likely to be a more powerful determinant of outcome of anticholinesterase treatment than \textit{APOE} status in the short term. In contrast, other studies do not support the hypothesis that \textit{APOE} and gender are predictors of the therapeutic response of AD patients to tacrine or donepezil [149, 150]. Petersen et al. [151] showed that \textit{APOE-4} carriers exhibited a better response to donepezil. Similar results have been found by Bizzarro et al. [152]; however, Rigaud et al. [150] did not find any significant difference between \textit{APOE-4}-related responders and nonresponders to donepezil. An \textit{APOE}-related differential response has also been observed in patients treated with other compounds devoid of acetylcholinesterase inhibiting activity (CDP-choline, anapsos) [153, 154] suggesting that \textit{APOE}-associated factors may influence drug activity in the brain either directly acting on neural mechanisms or indirectly influencing diverse metabolic pathways [155].

In long-term open clinical trials with a multifactorial treatment, \textit{APOE-4/4} carriers are the worst responders [5–7, 9, 105, 112, 113]. With a similar therapeutic protocol, \textit{PSEN1-1/1} homozygotes are the worst responders and \textit{PSEN1-2/2} carriers are the best responders [5]. Significant \textit{ACE}-related therapeutic responses to multifactorial treatments have also been reported [5, 6]. Among \textit{ACE-I/D} variants, \textit{ACE-D/D} patients were the worst responders and \textit{ACE-I/D} carriers were the best responders, with \textit{ACE-I/I} showing an intermediate positive response [5, 6]. \textit{ACE}-related biochemical and hemodynamic phenotypes have been studied in patients with AD [4, 9, 97]. \textit{ACE-I/I} patients tend to be younger than \textit{ACE-I/D} or \textit{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 A6 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, 6, 9, 97]. Low triglyceride levels may facilitate cerebrovascular function. ACE-1/I patients with the highest cholesterol levels are the worst in mental performance. These data might suggest an association of poor cerebrovascular function with ACE-D/D and ACE-I/D and an association of alterations in lipid metabolism with ACE-I/I [4, 6].

Both APOE and ACE variants also affect behavior and the modification of behavioral changes (mood and anxiety) in dementia after nonpsychotropic pharmacological treatment [4, 6, 9, 105, 113]. 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 > APOE-2/3 > APOE-3/3 > APOE-3/4 carriers. 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 > APOE-2/3 > APOE-3/3 > APOE-3/4, and the worst responder was APOE-4/4 [4, 6]. Patients with each one of the 3 ACE-I/D indel variants were equally anxiogenic and depressive at baseline and all of them responded 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 > ACE-D/D > ACE-I/I. Depressive symptoms were also similarly improved in all ACE-I/D variants. The best responders were ACE-I/D > ACE-D/D > ACE-I/I. Comparatively, the worst responders among ACE-I/D variants were carriers of the ACE-1/I genotype, which were also the poorest responders in anxiety and cognition [4, 6, 115].

The combination of APOE and ACE polymorphic variants in bigenic clusters yielded different anxiety and depression patterns at baseline and after one year of treatment. The most anxiogenic patients at baseline were those with the 23DD, 44ID, and 34II genotypes, and the least anxiogenic patients were those harboring the 23II, 44DD, and 23ID genotypes. The most depressive clusters at baseline were 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 were those represented by carriers of the 23II, 44ID, and 23ID genotypes. All bigenic clusters showed a positive anxiolytic and antidepressive response to the multifactorial treatment, except 44DD carriers who exhibited the worst response [4, 6, 115].

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 [4, 6]. Both plasma TG levels and transaminase activity are significantly lower in AD patients harboring the APOE-4/4 genotype, probably indicating (i) that low TG levels protect against liver steatosis and (ii) 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 [4, 6, 115].

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 UM [5].

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 to 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 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
Figure 2: APOE-related therapeutic response to a multifactorial therapy in patients with dementia. Cognitive performance (MMSE Score). Tt: basal MMSE score prior to treatment; Tt: MMSE score after 3 months of treatment in the total sample. E2/3b: basal MMSE score in APOE-2/3 carriers; E2/3t: MMSE score after treatment in APOE-2/3 carriers; E2/4b: Basal MMSE score in APOE-2/4 carriers; E2/4t: MMSE score after treatment in APOE-2/4 carriers; E3/3b: basal MMSE score in APOE-3/3 carriers; E3/3t: MMSE score after treatment in APOE-3/3 carriers; E3/4b: basal MMSE score in APOE-3/4 carriers; E3/4t: MMSE score after treatment in APOE-3/4 carriers; E4/4b: basal MMSE score in APOE-4/4 carriers; E4/4t: MMSE score after treatment in APOE-4/4 carriers.

7. APOE-Related Therapeutic Response to a Multifactorial Therapy in Alzheimer’s Disease

Patients with dementia (N = 765, age: 69.44 ± 9.15 years, range: 50–96 years; 466 females, age: 69.18 ± 9.19 years, range: 50–96 years; 299 males, age: 69.85 ± 9.09 years, range: 50–91 years; P < 0.01) received for three months a multifactorial therapy integrated by CDP-choline (500 mg/day, p.o.), Nercogline (5 mg/day, p.o.), Sardilipin (E-SAR-94010) (LipoEsar) (250 mg, t.i.d.), and Animon Complex (2 capsules/day), a nutraceutical compound integrated by a purified extract of Chenopodium quinoa (250 mg), ferrous sulphate (38.1 mg equivalent to 14 mg of iron), folic acid (200 μg), and vitamin B12 (1 μg) per capsule (RGS: 26.06671/C). Patients with chronic deficiency of iron (<35 μg/mL), folic acid (<2.5 ng/mL), or vitamin B12 (<150 pg/mL) received an additional supplementation of iron (80 mg/day), folic acid (5 mg/day), and B complex vitamins (B1 15 mg/day; B2 15 mg/day; B6 10 mg/day; B12 10 μg/day; nicotinamide 50 mg/day), respectively, to maintain stable levels of serum iron (50–150 μg/mL), folic acid (5–20 ng/mL), and vitamin B12 levels (500–1,000 pg/mL) in order to avoid the negative influence of all these metabolic factors on cognition [6, 114]. Patients with hypertension (>150/85 mmHg) received Enalapril (20 mg/day). The frequency of APOE genotypes was APOE-2/3 7.97%; APOE-2/4 1.18%; APOE-3/3 58.95%; APOE-3/4 27.32%; and APOE-4/4 4.58% (Figure 2). Blood pressure, psychometric assessment (Mini-Mental State Examination (MMSE); ADAS; Hamilton Rating Scale-Depression (HAM-D); Hamilton Rating Scale-Anxiety (HAM-A)), and blood parameters (glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, iron, folate, vitamin B12, and TSH, T4) were evaluated at baseline and after 3 months of treatment [42].

Systolic (P < 0.0002) and diastolic blood pressure (P < 0.001), cognitive function (as assessed by MMSE, 20.51 ± 6.51 versus 21.45 ± 6.95, P < 0.000000001; ADAS-Cog, 22.94 ±
SBP (mm Hg)

N = 765; age: 69.44 ± 9.15 years
Females: 466; age: 69.18 ± 9.19 years
Males: 299; Age: 69.85 ± 9.39 years

Figure 3: APOE-related systolic blood pressure response to a multifactorial therapy in patients with dementia. Tb: basal systolic blood pressure (SBP) prior to treatment; Tt: SBP after 3 months of treatment in the total sample. E2/3b: basal SBP in APOE-2/3 carriers; E3/4t: SBP after treatment in APOE-2/3 carriers; E4/4b: basal SBP in APOE-3/4 carriers; E3/3b: basal SBP in APOE-3/3 carriers; E4/4t: basal SBP after treatment in APOE-3/4 carriers; E2/4t: SBP after treatment in APOE-2/4 carriers; E2/4b: SBP after treatment in APOE-2/4 carriers.

| Genotype   | RRs | NRs | SRs |
|------------|-----|-----|-----|
| E2/3 | 55.56% | 44.44% | 0.00% |
| E2/4 | 56.94% | 35.54% | 7.52% |
| E3/3 | 63.42% | 21.06% | 15.52% |
| E3/4 | 55.56% | 44.44% | 0.00% |
| E4/3 | 63.42% | 21.06% | 15.52% |
| E4/4 | 55.56% | 44.44% | 0.00% |

Glucose levels did not change.

8. APOE-Related Blood Lipid Response to Sardilipin (E-SAR-94010)

Basal cholesterol levels were significantly different in patients with the APOE-2/3 genotype versus APOE-3/3 (P <
Sardilipin. This was particularly significant in a clear reduction in cholesterol levels after treatment with 4/4 (APOE-4/4) versus 3/3 (APOE-3/3) (Figure 4) [42].

The highest cholesterol levels were seen in APOE-4/4 > APOE-3/4 > APOE-3/3. All patients showed a clear reduction in cholesterol levels after treatment with Sardilipin. This was particularly significant in APOE-3/3 (P < 0.000000001) > APOE-3/4 (P < 0.00000008) > APOE-4/4 (P < 0.002) > APOE-2/3 (P < 0.02) > APOE-2/4 carriers (P: 0.26) (Figure 4). The response rate by genotype was as follows: APOE-2/3: 63.93% RRs, 29.51% NRs, and 6.56% SRs; APOE-2/4: 44.44% RRs, 22.22% NRs, and 33.34% SRs; APOE-3/3: 54.32% RRs, 28.16% NRs, and 17.52% SRs; APOE-3/4: 53.59% RRs, 31.58% NRs, and 14.83% SRs; APOE-4/4: 65.71% RRs, 20.00% NRs, and 14.29% SRs [42].

HDL-cholesterol levels significantly decreased in APOE-3/3 (P < 0.001) > APOE-3/4 (P < 0.05), with no significant changes in patients with other genotypes. In contrast, LDL-cholesterol levels showed identical changes to those observed in total cholesterol, with similar differences among genotypes at baseline and almost identical decreased levels after treatment (APOE-3/3, P > 0.000000001; >APOE-3/4, P < 0.0001; >APOE-2/3, P < 0.0004; >APOE-4/4, P < 0.001; >APOE-2/4, P: 0.31) (Figure 5) [42].

Paradoxically, triglyceride levels tended to increase in all APOE genotypes (APOE-3/3, P < 0.01; >APOE-4/4, P < 0.03; >APOE-2/3, P: 0.12; >APOE-3/4, P: 0.17), except in APOE-2/4 carriers, who showed a tendency to decrease. Basal triglyceride levels were significantly lower in APOE-4/4 carriers than in APOE-2/3 (P < 0.03) and APOE-3/4 carriers (P < 0.04) [42].

Sardilipin (E-SAR-94010, LipoEsar, LipoSea) is a natural product extracted from the marine species Sardina pilchardus, by means of nondenaturing biotechnological procedures [156]. The main chemical compounds of LipoEsar are lipoproteins (60–80%) whose micelle structure probably mimics that of physiological lipoproteins involved in lipid metabolism. In preclinical studies, sardilipin has shown to be effective in (i) reducing blood cholesterol (CHO), triglyceride (TG), uric acid (UA), and glucose (Glu) levels, as well as liver alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, (ii) enhancing immunological function by regulating both lymphocyte and microglia activity, (iii) inducing antioxidant effects mediated by superoxide dismutase activity, and (iv) improving cognitive function [97, 156, 157].

According to these results, it appears that the therapeutic response of patients with dyslipidemia to sardilipin is APOE-related. The best responders were patients with APOE-3/3 > APOE-3/4 > APOE-4/4. Patients with the other APOE genotypes (2/2, 2/3, and 2/4) did not show any hypolipemic...
response to this novel compound [97, 157]. In patients with dementia, the effects of sardilipin were very similar to those observed in patients with chronic dyslipidemia, suggesting that the lipid-lowering properties of sardilipin are APOE-dependent.

Clinical studies have revealed that sardilipin reduces blood total cholesterol (T-CHO) (20–30%), Glu (5–10%), UA (10–15%), TG (30–50%), ALT, and AST, after 1–3 months of treatment at a daily dose of 250–500 mg (t.i.d). The effect on T-CHO is the result of decreasing LDL-CHO levels and increasing HDL-CHO levels in parallel with an improvement in hepatic protection reflected by reduction in ALT, AST, and GGT activity, as the result of reducing liver steatosis. Both LDL and HDL levels are modulated by dietary, behavioral, and genetic factors [97]. Most of these therapeutic effects on the regulation of lipid metabolism tend to show an age-dependent pattern and are also associated with specific genomic profiles in the population. In addition, sardilipin diminishes the size of xanthelasma plaques by 30–60% after 6–9 months of treatment and specifically protects against the hepatotoxicity induced by statins. Similar effects can be observed on atheromatous plaques on the aortic wall of patients with familial and sporadic dyslipidemia/hyperlipidemia. The daily administration of 1,000–1,500 mg/day of E-SAR p.o. for three months tends to reduce the average size of atherosclerotic plaques on the aortic wall by 10%. This effect is more significant in patients harboring the APOE-3/3 than in APOE-3/4 carriers in whom the size of the plaque is approximately 30–40% larger than in APOE-3/3 carriers [97, 158].

9. New Insights into APOE-Related Pathogenesis and Therapeutics in Alzheimer's Disease

APOE is a pleiotropic gene with many polymorphic activities, most of them influencing AD pathogenesis. In this regard, the influence of APOE variants on AD therapeutics cannot be neglected, especially taking into account that (a) APOE polymorphic variants by themselves are enough to modify the therapeutic response to conventional antide mentia drugs, (b) ApoE interacts with many receptors and participates in a large number of metabolic cascades and signaling pathways, and (c) the presence of the APOE-4 allele can alter the phenotypic profile of CYP2D6 genotype-related drug metabolizers and probably also of other cytochrome P450 enzymes, such as those encoded by the CYP3A5 gene, which affect more than 50% of the drugs currently prescribed in the clinical setting. Moreover, many metabolic pathways in which APOE participates (e.g., lipid metabolism, APP/Aβ processing, cardiovascular and cerebrovascular function,
etc.) are involved in pathogenic processes that represent major risk factors of dementia (e.g., atherosclerosis, hypercholesterolemia, hypertension, and brain hypoperfusion), which can be potentially predictable and preventable with therapeutic intervention.

ApoE is a ligand for the 7 identified mammalian members of the evolutionarily conserved low-density lipoprotein (LDL) receptor family: the low-density lipoprotein receptor (LDLR), ApoE receptor 2 (ApoER2), the very-low-density lipoprotein receptor (VLDLR), multiple epidermal growth factor (EGF) repeat-containing protein (MEGF7), megalin, LDL-related-protein-1 (LRP1) and LDL-related protein-1b (LRP1b) [159]. The LDLR family consists of over 10 receptors that function in receptor-mediated endocytosis and cellular signaling. Together with LDLR itself, the family includes LRP/LRP1, megalin/LRP2, VLDLR, ApoER2/LRP8, SORLA-1/LR11, LRP4, LRP5, LRP6, and LRP1B. Most of the ApoE receptors have been found in the CNS where they participate in endocytosis, intracellular signaling, synaptic plasticity, and Aβ metabolism [159]. ApoE receptors have been suggested to act as clearance mechanisms for Aβ and have also been implicated in the production of Aβ. LRP interacts with APP through the intracellular adaptor protein FE65 or via direct binding to the KPI domain, and its endocytosis facilitates APP endocytic trafficking and Aβ production [160–162]. SORLA/LR11 alters APP trafficking and APP processing by β- and γ-secretases [163–165]. It has also been suggested that soluble ApoE receptors could play roles as dominant negative regulators of ApoE, and thus understanding their generation and actions might be important for understanding normal and pathological functions of ApoE in the CNS and in AD [159].

It might be possible that normalization of biological parameters associated with ApoE-related pathogenic pathways contributing to brain dysfunction and neurodegeneration could be beneficial in terms of prevention and/or slowing the clinical course of dementia. In this strategic category we can include the following: (i) lipid metabolism dyshomeostasis, (ii) ApoE-related APP/Aβ processing, (iii) blood pressure control, (iv) atherogenesis, (v) cerebrovascular hemodynamics, and (vi) neuroprotection.

Cardiovascular and cerebrovascular disorders associated with lipid metabolism disturbance and atherosclerosis represent major risk factors for dementia [119, 120, 166]. Atherosclerosis is the primary cause of heart disease and stroke in which genetic and environmental factors converge [167]. More than 90% of patients with dementia older than 70–80 years of age show signs of atherosclerosis in their arteries and a clear cerebrovascular component in their dementia process. It is very likely that pure AD is practically absent in octogenarians in whom the prevalent diagnosis is vascular or mixed-dementia [119, 120, 166] in which the ApoE-4 allele also accumulates [97, 110, 111, 168].

ApoE genotypes directly influence lipid metabolism and atherosclerosis. The presence of the ApoE-4 allele contributes to the phenotypic manifestation of atherosclerosis, brain amyloid angiopathy, and cerebral white matter damage [169]. The size of atheroma plaques in the abdominal and thoracic aorta of patients with dementia and/or dyslipidemia is significantly larger in ApoE-4 carriers than in ApoE-3 carriers [97, 110, 111]. In addition, the effect of lipid-lowering agents on atheroma plaques is ApoE related with a more effective response in ApoE-4 carriers [97, 110, 111].

Evidence from epidemiological, in vitro, and in vivo studies suggests that brain cholesterol may play a role in AD. The exact nature and magnitude of this role is unknown, but a number of possibilities have emerged, including modulation of APP cleavage pathways and Aβ production and clearance, ApoE-mediated cholesterol transport, and cholesterol efflux from the brain [170–172].

Cholesterol is implicated in the production of Aβ, the primary constituent of senile plaques in the AD brain [173–177]. In APP transgenic mice, hypercholesterolemia correlates with increased Aβ levels and more severe amyloid plaque load [178, 179]. Some retrospective epidemiological studies indicate that statin therapy might decrease AD risk [180], but statins do not alter serum Aβ levels [181, 182] and in some cases may worsen cognitive function, increase brain Aβ load, and/or activate inflammatory responses involving microglia [120, 166, 183]. Some studies have reported an association between high cholesterol levels and AD risk [184] and increased brain Aβ1–42 levels [185]. Defective binding of ApoE to heparan sulfate proteoglycans (HSPGs) is associated with increased risk of atherosclerosis and AD probably due to the inefficient clearance of lipoprotein remnants from the liver with negative consequences for neuronal repair [186]. CYP46α (cholesterol 24-hydroxylase) along with ApoE-4 was found associated with higher cognitive decline in AD and both variants synergistically increase the risk of AD [187–189] as well as brain and CSF Aβ load [190]. Deficiency of the cholesterol transporter ABCA1 produced by glial cells impairs ApoE metabolism in the CNS [191]. Some studies also indicate that genetic variants of ABCA1 modify AD risk and tau- and Aβ-related pathogenesis [192]; however, other studies have demonstrated that several SNPs in the multi-drug resistance (ABCB1) gene (MRD1) (C1236T in exon 12, G2677T/A in exon 21, and C3435T in exon 26) do not show association with AD [193]; in contrast, ABCA2 has been reported to be a strong genetic risk factor for early-onset AD [194, 195]. The ATP-binding cassette (ABC) superfamily consists of membrane proteins that transport a wide variety of substrates across membranes [196]. ABCA1 and ABCG1 play a pivotal role in the regulation of neuronal cholesterol to ApoE disc and in suppression of APP processing to generate Aβ. ABCA1 is required for normal brain ApoE levels and for lipidation of astrocyte-secreted ApoE [197], and the absence of ABCA1 decreases soluble ApoE levels but does not diminish Aβ deposition in AD murine models [198], whereas others have reported increased Aβ deposition in APP23 and PDAPP mice in the absence of ABCA1, suggesting that despite substantially lower ApoE levels, poorly lipidated ApoE produced in the absence of ABCA1 is strongly amyloidogenic [199, 200]. ABCA1 protein expression is induced by ligands of the nuclear hormone receptors of the retinoid X receptor and liver X receptor family. Treatment of neuroblastoma cells with retinoic acid and 22(R)-hydroxycholesterol
causes significant increases in secreted Aβ40 and Aβ42, and treatment with a nonsteroidal liver X receptor ligand, TO-901317, similarly increases Aβ40 and Aβ42 levels, which can be reduced by RNAi blocking of ABCA1 expression [201]. Maintenance of an adequate supply of cholesterol is important for neuronal function whereas excess cholesterol promotes APP cleavage and generation of toxic Aβ isoforms [202]. Impaired recycling of APOE-4 is associated with intracellular cholesterol accumulation [203]. Cholesterol- and sphingolipid-rich membrane microdomains are involved in regulating trafficking and processing of APP. In this metabolic pathway, the amyloidogenic processing of APP depends on lipid rafts since access of α- and β-secretase to APP may be determined by dynamic interactions of APP with membrane lipid microdomains [204]. γ-Secretase is also located in lipid raft microdomains of post-Golgi and endosomes that are implicated in APP processing [205]. Methyl-β-cyclodextrin and leptin reduce β-secretase activity in neuronal cells possibly by altering the lipid composition of membrane lipid rafts. This phenotype contrasts treatments with cholesterol and etomoxir, an inhibitor of carnitine-palmitoyl-transferase-1. Conversely, inhibitors of acetyl CoA carboxylase and fatty acid synthase mimic the action of leptin. Leptin is also able to increase ApoE-dependent Aβ uptake in vitro; thus, leptin can modulate bidirectional Aβ kinesis, reducing its levels extracellularly. The chronic administration of leptin to AD-transgenic animals notably reduces the brain Aβ load [206].

APOE-4 may affect AD risk by conferring high cholesterol levels and thereby increasing Aβ production [207]. APOE-4 carriers with AD have increased levels of brain and cerebrospinal fluid Aβ and have more extensive plaque pathology [208, 209]; however, with a genomic-based approach, by using an APOE knock-in mouse, which expresses each human allele under the endogenous regulatory elements, on a defined C57BL/6J background, Mann et al. [207] were able to demonstrate that the presence of APOE significantly increases brain Aβ levels, irrespective of genotype, this indicating an independent role for APOE in cholesterol metabolism in the periphery relative to the CNS. In humans, probably thousands of genes may regulate lipid metabolism. Some relevant genes, such as APOE (50%), CETP (28%), LIPC (9%), APOB (8%), and LDLR (5%) may influence variation in LDL, and LIPC (53%), CETP (25%), ABCA1 (10%), LPL (6%), and LDLR (6%) may influence the HDL variance [210]. The APOE-2 allele is associated with the lower and the APOE-4 allele with the higher total plasma cholesterol and LDL-cholesterol levels compared with the APOE-3 allele [211]. Individuals with APOE-2 and APOE-3 reduce plasma cholesterol and LDL-cholesterol levels more than APOE-4 individuals treated with hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins), gemfibrozil and cholestyramine. In contrast, APOE-4 carriers might respond better than carriers of other genotypes to probucol. Perimenopausal women with APOE-2 or APOE-3 genotypes appear to improve plasma lipoprotein-lipid profiles more than APOE-4 women under protocols with hormone replacement therapy. Likewise, APOE-2 and APOE-3 individuals tend to improve plasma lipid profiles with exercise training more than APOE-4 individuals [212]. In an attempt to reverse the ApoE deficit in AD, Poirier [213] has reported the identification and characterization of several ApoE inducer agents using a throughput screening assay. The old cholesterol-lowering drug, probucol, led to significant increases in CSF ApoE levels and a decrease of CSF Aβ1-42 with effect on CSF tau or lipid peroxide levels [213]. In a prospective, dose-finding, 36-week treatment trial with statins (simvastatin or atorvastatin) conducted in 39 patients with hypercholesterolemia, Aβ levels remained unchanged [214]. The Heart Protection Study Collaborative Group [215] and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [216] have both reported that neither simvastatin nor pravastatin appeared to slow cognitive decline in the elderly during 5 years of treatment in the Heart Protection Study and 3.2 years in the PROSPER.

Since ApoE can protect against cardiovascular disease (e.g., coronary artery disease) via hepatic removal of atherogenic remnant proteins, sequestration of cholesterol from vessel walls, and local antioxidant, antiplatelet, and anti-inflammatory actions, it has been postulated that APOE gene transfer might ameliorate a hyperlipidemic profile and exert a beneficial effect at lesion sites to prevent or regress atherosclerosis [217]. Using plasmid vectors expressing allelic human ApoE-2 or ApoE-3 isoforms, Athanasopoulos et al. [217] demonstrated that skeletal muscle was an effective secretory platform for ApoE gene augmentation and that muscle-based expression of ApoE-2 after intramuscular plasmid injection in ApoE−/− mice was able to reduce atherosclerotic lesions in proximal aorta by 20–30%, with total abolishment of gross dorsal xanthoma (>5 mm diameter) up to 9 months following a single ApoE-2 plasmid administration. The same group of George Dickson [218], 2 years later, with an improved technology, observed an acute regression of advanced and retardation of early aortic atheroma in immunocompetent ApoE-deficient mice by administration of a second-generation (E1-, E3-, polymerase-) adenovirus vector expressing human ApoE. Intramuscular injections resulted in low expression of ApoE and afforded no sustainable protection against atherogenesis; in contrast, intravenous (liver-directed) injections into ApoE−/− mice resulted in increased plasma ApoE levels accompanied by reductions in plasma cholesterol and normalization of lipoprotein profiles. Liver-directed ApoE gene transfer to these mice retarded progression of atherosclerosis by 38% during the 70-day study period, with a progressive decline in ApoE levels and no evoked humoral immune response [218].

10. CYP2D6-Related Pharmacogenetics

CYP2D6 is a 4.38 kb gene with 9 exons mapped on 22q13.2. Four RNA transcripts of 1190–1684 bp are expressed in the brain, liver, spleen, and reproductive systems where 4 major proteins are identified: CYP2D6-001, 55.73 kDa, 497 aa; CYP2D6-002, 50.02 kDa, 446 aa; CYP2D6-004, 55.19 kDa, 494 aa; CYP2D6-201, 48.92 kDa, 493 aa; CYP2D6-202,
phenotype, characterized by a decreased ability to metabolize population; certain alleles result in the poor metabolizer phenotype. This gene is highly polymorphic in the human population; approximately 25% of commonly prescribed drugs and over 60% of current psychotropics. Its substrates include many as 25% of commonly prescribed drugs and over 371 drugs are substrates, over 375 drugs are inhibitors, and 18 drugs are CYP2D6 inducers [220]. In a study to investigate the elimination routes for the 200 drugs most often sold by prescription count in the United States, the majority (78%) of the hepatically cleared drugs were found to be subject to oxidative metabolism via cytochromes P450 of the families 1, 2, and 3, with major contributions from CYP3A4/5 (37% of drugs) followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), CYP2C8 (6%), and CYP2B6 (4%). Clinically well-established polymorphic CYPs (i.e., CYP2C9, CYP2C19, and CYP2D6) were involved in the metabolism of approximately half of those drugs, including (in particular) NSAIDs metabolized mainly by CYP2C9, proton-pump inhibitors metabolized by CYP2C19, and β-blockers and several antipsychotics and antidepressants metabolized by CYP2D6 [221].

CYP2D6 is one of the most important enzymes catalyzing biotransformation of xenobiotics in the human liver. This enzyme activity shows a high degree of interindividual variability caused in part by its genetic polymorphism, the so-called debrisoquine/sparteine polymorphism. There are 141 CYP2D6 allelic variants of which –100C>T, −1023C>T, −1659G>A, −1707delIT, −1846G>A, −2549delA, −2613–2615delAGA, −2850C>T, −2988G>A, and −3183G>A represent the 10 most important variants [24, 220, 222, 223].

The genetic component influencing CYP2D6 activity can be determined by genotyping. However, genotyping alone is not sufficient to accurately predict an individual actual CYP2D6 activity, as this is also influenced by other factors. To determine the exact actual enzymatic activity (phenotyping), adequate probe drugs have to be administered prior to measurements of these compounds and/or their metabolites in body fluids. The enzymatic activity is reflected by various pharmacokinetic metrics such as the partial clearance of a parent compound to the respective CYP2D6-mediated metabolite or metabolic ratios [224].

The relative catalytic activities (enzyme kinetics) of three functionally active human CYP2D6 allelic variants, CYP2D6.1, CYP2D6.10, and CYP2D6.17, were systematically investigated for their ability to metabolize a structurally diverse set of clinically important CYP2D6-metabolized drugs (atomoxetine, buspironal, codeine, debrisoquine, dextromethorphan, S-fluoxetine, nortriptyline, and tramadol) and the effects of various CYP2D6 inhibitors (cocaine, S-fluoxetine, S-norfluoxetine, imipramine, quinidine, and thioridazine) on these three variants. The most significant difference observed was a consistent but substrate-dependent decrease in the catalytic efficiencies of cDNA-expressed CYP2D6.10 and CYP2D6.17 compared with CYP2D6.1, yielding 1.32 to 27.9 and 7.33 to 80.4% of the efficiency of CYP2D6.1, respectively [225].

11. Selected Variants with Clinical Relevance

The CYP2D6 locus is highly polymorphic, with different CYP2D6 alleles identified in the general population showing deficient (PM), normal (EM), intermediate (IM), or
increased enzymatic activity (UM) [222, 223]. 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 [97, 226, 227]. 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% [228].

The most important SNPs with clinical relevance include the following.

rs1135840: CYP2D6-S486T. This SNP is found in the reduced function of the CYP2D6*10, *17, and *41 haplotypes with an allelic frequency of C: 0.635 and G: 0.365.

rs59421388: CYP2D6-3183G>A and 3271G>A. This variant is part of the reduced functioning haplotype CYP2D6*29, which is found at an estimated allele frequency of 20% in African Tanzanians.

rs28371725: CYP2D6*41 and CYP2D6-2988G>A. CYP2D6 2988G>A is an intronic polymorphism that has been shown to be associated with aberrant splicing of CYP2D6. This splicing defect leads to the omission of exon 6 from some of the transcribed RNA and leads to a reduction in activity. CYP2D6 2988G>A is diagnostic of the haplotype CYP2D6*41, which is believed to be responsible for the IM phenotype in the majority of Caucasians.

rs16947: CYP2D6-2850C>T (also named 2938C>T). This is a common SNP in CYP2D6 and is found in the CYP2D6*2 haplotype among others. CYP2A6*2 activity is slightly reduced but is considered to be in the same extensive metabolizer (EM) category as CYP2D6*1. The presence of CYP2D6 2850C>T and the absence of several others is diagnostic of the CYP2D6*2 haplotype.

rs28371720: CYP2D6*9-CYP2D6: 2613–2615delAGA (2701–2703delAGA). Causes deletion of amino acid K281.

rs4986774: CYP2D6*3 and CYP2D6-2549delA (also known as 2637delA in the literature). This causes a frameshift mutation that results in a truncated, nonfunctional protein with an Arg/Gly translation.

rs3892097: CYP2D6*4 and CYP2D6-1846G>A. CYP2D6 1846G>A (1934G>A) is part of the nonfunctional CYP2D6*4 haplotype. This causes a splicing defect that results in a nonfunctional protein. This variant is responsible for the majority of the PMs found in Caucasian populations, and is also found at much lower frequencies in other populations such as Koreans.

rs5030655: CYP2D6*6 and CYP2D6-1707delT. This variant (CYP2D6-1707delT or 1795delT) causes a frame-shift mutation (Trp/Gly) that results in a truncated, nonfunctional version of CYP2D6. This is the defining SNP for CYP2D6*6. Individuals with CYP2D6*6/4, *5/4, or *6/*6 genotypes are poor metabolizers of venlafaxine and are more prone to drug-induced side effects such as nausea, vomiting, and diarrhea. However, CYP2D6 genotype does not seem to influence venlafaxine efficacy.

rs61736512: CYP2D6-1659G>A and 1747G>A. This variant (CYP2D6 1659G>A or 1747G>A) is rare in Caucasians and is part of the reduced functioning haplotype CYP2D6*29, which is found at an estimated allele frequency of 20% in African Tanzanians.

rs28371706: CYP2D6-1023C>T. CYP2D6-1023C>T (1111C>T) was first identified when screening for reduced function alleles in a Zimbabwean population. It was identified as being part of the reduced function haplotype CYP2D6*17 in the African Bantu populations. The presence of CYP2D6 1023C>T (1111C>T) and 2850C>T (2938C>T) is diagnostic for CYP2D6*17. CYP2D6 1023C>T single mutation exhibited normal function in transfected COS-1 cells, but when made in combination with another mutation led to an increased Km (decreased affinity) for bufuralol; when the substrate was codeine, CYP2D6 1023C>T alone was sufficient to cause an increase in the Km of CYP2D6 for codeine, suggesting that this mutation exhibits substrate-specific effects and may contribute to the reduction in function of CYP2D6*17.

rs1065852: CYP2D6-100C>T. CYP2D6 100C>T (188C>T) is part of both the nonfunctional CYP2D6*4 haplotype and the reduced function CYP2D6*10 haplotype. Since CYP2D6 100C>T is present in both a nonfunctional and a reduced function haplotype, it is not likely to be the causative SNP for the lack of function observed with CYP2D6*4. The presence of CYP2D6 100C>T (188C>T) and the absence of CYP2D6 1846G>A (1934G>A) is diagnostic of CYP2D6*10. Cells transfected with CYP2D6 100C>T alone exhibit reduced function, suggesting that this mutation contributes to the reduced function of the CYP2D6*10 allele. Association studies have examined the role of this variant in contributing to generalized tonic-clonic seizures (GTCS) seen in epilepsy and tardive dyskinesia in Chinese schizophrenic patients [24, 220, 223].

12. Major Haplotypes

CYP2D6-related major haplotypes include the following.

CYP2D6*1. CYP2D6*1 is the reference haplotype for CYP2D6. Together with CYP2D6*2, this haplotype forms the group of individuals known as extensive metabolizers or EMs. CYP2D6*1 is usually the majority allele for populations of European and African descent. EMs are considered the norm, and all the other haplotypes are defined as deviations
from CYP2D6*1. Population frequencies of this haplotype are African-American: 29–35%; Amerindian: 66%; Central/South Asia: 31%; Chinese: 23%; Colombian: 39%; East Asian: 31%; European: 34%; European Caucasian: 33–36%; Gabonese: 32%; Ghanaian: 44%; Iberian: 56–72%; Japanese: 42–43%; Malay: 36%; Mexican: 57%; Middle Eastern: 35%; Native American: 60%; North African: 12%; Oceanian: 72%; Subsaharan African: 24%; Tanzanian: 28–59%; US Caucasian: 36–40% [220].

CYP2D6*2. CYP2D6*2 (CYP2D6-2850C>T) has slightly reduced function when compared with CYP2D6*1. CYP2D6*1 and CYP2D6*2 represent typical EMs. Population frequencies are African-American: 18–27%; Amerindian: 19%; Central/South Asian: 29%; Chinese: 2%; Colombian: 37%; East Asian: 16%; European: 29%; European Caucasian: 22–33%; Gabonese: 44%; Ghanaian: 11%; Iberian: 2%; Japanese: 9–12%; Mexican: 23%; Middle Eastern: 25%; Native American: 30%; North African: 28%; Oceanian: 0%; Subsaharan African: 33%; Tanzanian: 2%; US Caucasian: 26–37% [220].

CYP2D6*3. CYP2D6*3 (CYP2D6-2549delA) is a completely nonfunctional allele caused by a frameshift mutation that causes a premature truncation of the CYP2D6 protein. CYP2D6*3 is one of several CYP2D6 haplotypes that can contribute to the phenotypic expression of a poor metabolizer (PM). CYP2D6*3 makes a minor contribution to the poor metabolizer phenotype in Caucasian populations and is virtually nonexistent in non-Caucasian populations. Population frequencies are African-American: 0%; Amerindian: 0%; Central/South Asian: 0%; Chinese: 1%; Colombian: 1.2%; East Asian: 0%; Ethiopian: 0%; European: 0%; European Caucasian: 1–4%; Ghanaian: 0%; Iberian: 2%; Inuit: 0%; Mexican: 1%; Middle Eastern: 0%; Native American: 0%; North African: 0%; Oceanian: 0%; Subsaharan African: 0%; Tanzanian: 0%; US Caucasian: 1–2%; Zimbabwean: 0% [220].

CYP2D6*4. CYP2D6*4 (CYP2D6-100C>T and 1846G>A) is a nonfunctional haplotype that contributes to the majority of PMs in Caucasian populations. CYP2D6*4 carriers are at increased risk when compared to their EM counterparts for toxicities or lack of efficacy due to CYP2D6 inactivity. Population frequencies are African-American: 6–8%; Amerindian: 4–17%; Central/South Asian: 8%; Chinese: 1%; Colombian: 19.4%; East Asian: 3%; Ethiopian: 1%; European: 17%; European Caucasian: 12–21%; Ghanaian: 7%; Iberian: 13%; Inuit: 8%; Japanese: 1%; Malay: 3%; Mexican: 10%; Middle Eastern: 7%; Native American: 3%; North African: 12%; Oceanian: 0%; Subsaharan African: 3%; Tanzanian: 1%; US Caucasian: 18–23%; Zimbabwean: 2–3% [220].

CYP2D6*5. CYP2D6*5 results in a nonfunctional haplotype due to a whole gene deletion. This allele contributes to the PM phenotype pool with a frequency of 1–7% in most populations. Population frequencies are African-American: 6–7%; Amerindian: 4%; Central/South Asian: 4%; Chinese: 6%; Colombian: 0.8%; East Asian: 6%; Ethiopian: 3%; European: 3%; European Caucasian: 2–7%; Gabonese: 1%; Ghanaian: 1%; Iberian: 3%; Japanese: 5–6%; Malay: 5%; Mexican: 2%; Middle Eastern: 4%; Native American: 1%; North African: 3%; Oceanian: 1%; Subsaharan African: 6%; Tanzanian: 6%; US Caucasian: 2–5%; Zimbabwean: 4% [220].

CYP2D6*6. CYP2D6*6 (CYP2D6-1707delT) is a nonfunctional haplotype of CYP2D6. CYP2D6*6 is caused by a frameshift mutation that results in a truncated and nonfunctional CYP2D6 protein. CYP2D6*6 is found primarily in Caucasian populations. Population frequencies are African-American: 0%; Amerindian: 1%; Central/South Asian: 0%; Colombian: 0%; East Asian: 0%; European: 1%; European Caucasian: 1%; Ghanaian: 0%; Iberian: 3%; Inuit: 8%; Middle Eastern: 1%; Native American: 0%; North African: 0%; Oceanian: 0%; Subsaharan African: 0%; Tanzanian: 0%; US Caucasian: 1% [220].

CYP2D6*9. CYP2D6*9 (CYP2D6-2613–2615delAGA) is a reduced function haplotype caused by the deletion of a single amino acid; its mRNA lacks a single codon resulting in deletion of Lys281. This variant probably represents less than 1.5% of all CYP2D6 alleles. The highest frequency is present among Caucasians of Europe and North America. Population frequencies are African-American: 0%; Amerindian: 0%; Central/South Asian: 0%; East Asian: 0%; European: 3%; European Caucasian: 0–2%; Ghanaian: 0%; Malay: 3%; Middle Eastern: 0%; Native American: 0%; North African: 0%; Oceanian: 0%; Subsaharan African: 0%; Tanzanian: 0%; US Caucasian: 2–3%; Zimbabwean: 0% [220].

CYP2D6*10. CYP2D6*10 (CYP2D6-100C>T) is a reduced function haplotype very common in populations of Asian ancestry, especially among Japanese and Malay. Homozygotes of this allele are common and result in the IM genotype. IMs are also at risk for adverse events and lack of efficacy similar to those seen in PMs, although not as severe, due to the residual activity of CYP2D6*10. Population frequencies are African-American: 3–8%; Amerindian: 2–18%; Central/South Asian: 4%; Chinese: 5–7%; East Asian: 4%; Ethiopian: 9%; European: 3%; European Caucasian: 1–2%; Ghanaian: 3%; Iberian: 2–5%; Inuit: 2%; Japanese: 38–41%; Malay: 50%; Mexican: 7%; Middle Eastern: 1%; Native American: 0%; North African: 0%; Oceanian: 3%; Subsaharan African: 4%; Tanzanian: 4%; US Caucasian: 2–8%; Zimbabwean: 0% [220].

CYP2D6*17. CYP2D6*17 (CYP2D6-2850C>T and 1023C>T) is a reduced function allele of CYP2D6. CYP2D6*17 was frequently misdiagnosed as CYP2D6*2 in the early studies of CYP2D6 genotyping, particularly in populations of African origin. CYP2D6*17 carriers show an IM phenotype. The highest frequency of this haplotype appears in Africans. Population frequencies are African-American: 15–23%; Central/South Asian: 0%; Colombian: 1.7%; East Asian: 0%; Ethiopian: 1%; European: 0%; European Caucasian: 0%;
Gabonese: 24%; Ghanaian: 28%; Malay: 1%; Mexican: 1%; Middle Eastern: 2%; Native American: 1%; North African: 8%; Oceanian: 0%; Subsaharan African: 12%; Tanzanian: 17%; US Caucasian: 0%; Zimbabwean: 34% [220].

CYP2D6* 29. CYP2D6* 29 (CYP2D6 2850C>T and CYP2D6 1659G>A and CYP2D6 3183G>A) is a reduced functioning haplotype of CYP2D6. This haplotype was originally discovered in African populations and contributes towards the IM phenotype of CYP2D6. Population frequencies are Central/South Asian: 0%; East Asian: 0%; European: 0%; Middle Eastern: 0%; Native American: 0%; North African: 0%; Oceanian: 0%; Subsaharan African: 7% [220].

CYP2D6* 11. CYP2D6* 11 (CYP2D6 4860A>G and 4860G>A) is also a reduced functioning haplotype of CYP2D6 that contributes towards the IM phenotype. Population frequencies are Central/South Asian: 11%; East Asian: 2%; European: 7%; Middle Eastern: 17%; Native American: 0%; North African: 8%; Oceanian: 0%; Subsaharan African: 1% [220].

CYP2D6-UM. CYP2D6 UM is a generic term used to indicate multiple CYP2D6 copies (2–13) that cause the ultrarapid metabolizer (UM) phenotype. Gene duplications are present in many different CYP2D6 haplotypes, including CYP2D6* 4, CYP2D6* 4, CYP2D6* 10, and CYP2D6* 41. These gene copies can cause a lack of efficacy by quickly metabolizing a parent drug. UMs can suffer from similar problems as PMs, despite having opposite phenotypes. For instance, both can experience a lack of efficacy, but in the case of UMs it would be from quickly metabolizing a parent drug, whereas in the case of PMs it would be the inability to form an active metabolite. Toxicity can occur in both haplotypes. UMs would experience toxicities resulting from a high level of metabolite, whereas the PMs would experience toxicities resulting from a high level of parent drug. Population frequencies of combined CYP2D6* 1 and CYP2D6* 2 haplotypes are African-American: 1–5%; Amerindian: 3%; Central/South Asian: 1%; Chinese: 1%; Colombian: 1.2%; East Asian: 12%; European: 1%; European Caucasian: 2%; Gabonese: 3%; Iberian: 7%; Middle Eastern: 2%; Native American: 5%; North African: 7%; Oceanian: 5%; Subsaharan African: 28%; Tanzanian: 14%; US Caucasian: 1% [220, 223].

13. Phenotypes

The classification of CYP2D6 phenotypes according to major haplotypes is as follows.

Extensive Metabolizers (EMs): normal enzyme activity: CYP2D6* 1, CYP2D6* 2, CYP2D6* 27, CYP2D6* 33, CYP2D6* 35, CYP2D6* 39, and CYP2D6* 48.

Intermediate Metabolizers (IMs): decreased enzyme activity: CYP2D6* 9, CYP2D6* 10, CYP2D6* 17, CYP2D6* 29, CYP2-

D6* 41, CYP2D6* 49, CYP2D6* 50, CYP2D6* 51, CYP2D6* 55, CYP2D6* 59, and CYP2D6* 72.

Poor Metabolizers (PMs): no or negligible enzyme activity: CYP2D6* 3, CYP2D6* 4, CYP2D6* 5, CYP2D6* 6, CYP2D6* 11, CYP2D6* 12, CYP2D6* 13, CYP2D6* 14, CYP2D6* 15, CYP2D6* 16, CYP2D6* 18, CYP2D6* 19, CYP2D6* 20, CYP2D6* 21, CYP2D6* 36, CYP2D6* 38, CYP2D6* 40, CYP2D6* 42, CYP2D6* 44, CYP2D6* 47, CYP2D6* 51, CYP2D6* 56, CYP2D6* 57, and CYP2D6* 62.

Ultrarapid Metabolizers (UMs): increased enzyme activity: CYP2D6* 1×N, CYP2D6* 2×N, CYP2D6* 35×2, and CYP2D6* 53 [24, 220, 222, 223].

14. CYP2D6 Genophenotypes in CNS Disorders

Members of most CYP families have been identified in animal and human brains. There is extensive information available on the regional and cellular distribution of most CYP families in rodent brains, but very little is known about the human brain; only CYP2D6 has been mapped throughout the human brain. An important role ascribed to brain CYPs is the metabolism of endogenous neurally derived or acting compounds, such as neurotransmitters and neurosteroids. Although CYP2D6 does not have a primary role in the synthesis of dopamine, it may have a modulatory effect on dopamine metabolism in the brain. CYP2D6 was found in close association with the dopamine transporter, CYP2D enzymes have been found in dopaminergic cells in the rat substantia nigra, and CYP2D6 and rat brain-specific CYP2D18 have been implicated in dopamine metabolism [229]. Genetic polymorphisms in CYP2D6 have been suggested to be associated with smoking behavior, and this modification may occur through the involvement of CYP2D6 in the dopaminergic pathway. Genetic defects in CYP2D6 have been associated with Parkinson’s disease, which may be linked to the role of CYP2D6 in dopamine metabolism in the brain [229]. Not only may CYPs contribute to the metabolism of neurotransmitters, but neurotransmitters, their precursors, and their metabolites may have a modulatory effect on the catalytic activity of CYPs in the brain. Tryptamine inhibits CYP2D6-mediated dextrimethorphan O-demethylation, serotonin and tryptamine inhibit CYP1A2 phenacetin O-deethylase activity, and 5-hydroxytryptamine and adrenaline inhibit diclofenac 4-hydroxylation by CYP2C9 in vitro. The effect of these indoleamines and catecholamines on CYP activity suggests that in the brain local drug metabolism by CYPs may be modulated or regulated by endogenous neurotransmitters, their precursors, or metabolites, and this may play a role in the observed interindividual variability in drug response [229].

CYP2D6 is involved in the biotransformation of many drugs, which predominantly act in the CNS, including opioids, many psychotropic drugs, and neurotoxins. Until now, however, only controversial information is available

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regarding the presence of CYP2D6 in the CNS. The regional and cellular expression of CYP2D6 transcripts and proteins in postmortem brain tissues of three individuals was analyzed [230]. Neuronal cells, as well as glial cells, showed labeling for mRNA in brain regions such as the neocortex, caudate nucleus, putamen, globus pallidus, hippocampus, hypothalamus, thalamus, substantia nigra, and cerebellum. In contrast, CYP2D6 protein was primarily localized in large principal neurons such as pyramidal cells of the cortex, pyramidal cells of the hippocampus, and Purkinje cells of the cerebellum. In glial cells, CYP2D6 protein was absent. These results provide clear evidence of CYP2D6 expression in certain regions of the CNS and may indicate the role CYP2D6 plays in a number of drug interactions that are of potential clinical importance for neurological diseases [230].

The distribution and frequency of CYP2D6 genotypes (Figure 6) and phenotypes (Figure 7) were investigated in 315 Spanish controls with no family history of neuropsychiatric disorders and in patients with anxiety (N = 285), depression (N = 419), psychosis (N = 162), stroke (N = 67), Alzheimer’s disease (N = 231), Parkinson’s disease (N = 73), attention-deficit hyperactivity disorder (N = 42), migraine (N = 217), epilepsy (N = 71), vascular dementia (N = 198), vascular encephalopathy (with hypertension, diabetes, or dyslipidemia) (N = 380), multiple sclerosis (N = 21), cerebrovascular insufficiency (N = 138), brain tumors (glioma, astrocytoma, glioblastoma, and meningioma) (N = 11), cranial nerve neuropathy (facial palsy, and trigeminal neuralgia) (N = 25), mental retardation (N = 115), and posttraumatic brain injury syndrome (N = 59) (Figures 6 and 7). In healthy subjects, EMs accounted for 55.71% of the population, whereas IMs were 34.7%, PMs 2.28%, and UMs 7.31% (Figure 7). Patients with depression showed significant differences in the genotypic and phenotypic profiles as compared to controls (P < 0.02) and also with respect to patients with psychosis (P < 0.05), Parkinson’s disease (P < 0.05), or brain tumors (P < 0.05). Patients with stroke showed differences as compared to patients with brain tumors (P < 0.05), and both patients with brain tumors or with cranial nerve neuropathies differed in their CYP2D6 phenotype with regard to controls (P < 0.05). These genotypic and phenotypic profiles might be important in the pathogenesis of some CNS disorders and in the therapeutic response to conventional psychotropic drugs as well (Figures 6 and 7).

15. CYP2D6 in Alzheimer’s Disease

In the Iberian population (Spain + Portugal), where the mixture of ancestral cultures has occurred for centuries, the distribution of the CYP2D6 genotypes differentiates 4 major categories of CYP2D6-related metabolizer types: (i) extensive metabolizers (EMs) (*1/*1, *1/*2, *1/*10), (ii) intermediate metabolizers (IMs) (*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10), (iii) poor metabolizers (PMs) (*4/*4, *5/*5), and (iv) ultrarapid metabolizers (UMs) (*1×N/*I, *1×N/*4, Dupl). In our sample we found 51.61% EMs, 32.26% IMs, 9.03% PMs, and 7.10% UMs [4, 6, 7, 9, 28, 112, 113, 115]. In a more recent study with 1,637 subjects and 644 patients with AD we did not find any significant difference between AD cases and the general population (GP) [5]. A variation rate higher than 2% was found only in the EM-×1/*1 genotype, which is more frequent in the GP than in AD. The proportion of EMs was 59.51% in GP and 57.76% in AD; IMs were 29% in GP and 31% in AD; PMs were 4.46% in GP and 5.27% in AD; UMs were 6.23% in GP and 5.9% in AD [5]. No major differences between females and males were found in the GP group; however, in AD, EMs are more frequent in females than in males, and PMs are more frequent in males than in females, indicating that males might be at higher risk for developing ADRs [5].

16. Association of CYP2D6 Variants with Alzheimer’s Disease-Related Genes

We have also investigated the association of CYP2D6 genotypes with AD-related genes, such as APP, MAPT, APOE, PSEN1, PSEN2, A2M, ACE, AGT, FOS, and PRNP variants [4–7, 112, 113]. Homozygous APOE-2/2 (12.56%) and APOE-4/4 (12.50%) accumulate in UMs, and APOE-4/4 cases were also more frequent in PMs (6.66%) than in EMs (3.95%) or IMs (0%). PSEN1-1/1 genotypes were more frequent in EMs (45%), whereas PSEN1-2/2 genotypes were overrepresented in IMs (63.16%) and UMs (60%). The presence of the PSEN1-2/2 genotype was especially high in PMs (38.46%) and UMs (20%). A mutation in the PSEN2 gene exon 5 (PS2E5+) was markedly present in UMs (66.67%). About 100% of UMs were A2M-V100I-A/A, and the A2M-V100I-G/G genotype was absent in PMs and UMs. The A2M-1/I genotype was absent in UMs, and 100% of UMs were A2M-1/D and ACE-D/D. Homozygous mutations in the FOS gene (B/B) were also only present in UMs. AGT-T235T cases were absent in PMs, and the AGT-M174M genotype appeared in 100% of PMs. Likewise, the PRNP-M129M variant was present in 100% of PMs and UMs. These association studies clearly show that in PMs and UMs there is an accumulation of AD-related polymorphic variants of risk which might be responsible for the defective therapeutic responses currently seen in these AD clusters [4, 6, 7, 112–115].

17. CYP2D6-Related Biochemical and Hemodynamic Phenotypes in Alzheimer’s Disease

It appears that different CYP2D6 variants, expressing EMs, IMs, PMs, and UMs, influence to some extent several biochemical parameters, liver function, and vascular hemodynamic parameters, which might affect drug efficacy and safety. Blood glucose levels are found to be elevated in EMs (*1/*1 versus *4/*10) and in some IMs (*4/*10 versus *1×N/*4), whereas other IMs (*1/*5 versus *4/*4) tend to show lower levels of glucose compared with PMs (*4/*4) or UMs (*1×N/*4). The highest levels of total cholesterol are detected in the EMs with the CYP2D6-×1/*10 genotype (versus *1/*1, *1/*4, and *1×N/*1). The same pattern has
Figure 6: Distribution and frequency of CYP2D6 variants in patients with CNS disorders. C: controls; ANX: anxiety; DEP: depression; PSY: psychotic disorders; STR: stroke; AD: Alzheimer’s disease; PAR: Parkinson’s disease; DHD: attention-deficit hyperactivity disorder; MIG: migraine; EPI: epilepsy; VD: vascular dementia; VE: vascular encephalopathy; MS: multiple sclerosis; CVI: cerebrovascular insufficiency; BT: brain tumors; CNN: cranial nerve neuropathies; MR: mental retardation; PTBS: posttraumatic brain injury syndrome. Source: R. Cacabelos. CIBE Database. EuroEspes Biomedical Research Center, Institute for CNS Disorders, Coruña, Spain.

been observed with regard to LDL-cholesterol levels, which are significantly higher in the EM-∗1/*10. In general, both total cholesterol levels and LDL-cholesterol levels are higher in EMs (with a significant difference between ∗1/*1 and ∗1/*10), intermediate levels are seen in IMs, and much lower levels in PMs and UMs; and the opposite occurs with HDL-cholesterol levels, which on average appear much lower in EMs than in IMs, PMs, and UMs, with the highest levels detected in ∗4/*8 and ∗1/*N/*8. The levels of triglycerides are highly variable among different CYP2D6 polymorphisms, with the highest levels present in IMs (∗4/*10 versus ∗4/*5 and ∗1/*N/*1) [4, 6, 115]. These data clearly indicate that lipid metabolism can be influenced by CYP2D6 variants or that specific phenotypes determined by multiple lipid-related genomic clusters are necessary to confer the character of EMs and IMs. Another possibility might be that some lipid metabolism genotypes interact with CYP2D6-related enzyme products, leading to the definition of the pheno-genotype of PMs and UMs. No significant changes in blood pressure values have been found among CYP2D6 genotypes; however, important differences became apparent in brain cerebrovascular hemodynamics. The best cerebrovascular hemodynamic pattern is observed in EMs and PMs, with higher brain blood flow velocities and lower resistance and pulsatility indices, but differential phenotypic profiles are detectable among CYP2D6 genotypes. Systolic
blood flow velocities (Sv) in the left middle cerebral arteries (LMCA) of AD patients are significantly lower in $^{*}1/10$ EMs, with high total cholesterol and LDL-cholesterol levels, than in IMs ($^{*}4/10$); diastolic velocities (Dv) also tend to be much lower in $^{*}1/10$ EMs, with high total cholesterol and LDL-cholesterol levels, than in IMs ($^{*}4/10$) and especially in PMs ($^{*}4/10$) and UMs ($^{*}1/10$). More striking are the results of both the pulsatility index (PI = (Sv − Dv)/Mv) and resistance index (RI = (Sv − Dv)/Sv), which are worse in IMs and PMs than in EMs and UMs. These data taken together seem to indicate that CYP2D6-related AD PMs exhibit a poorer cerebrovascular function which might affect drug penetration into the brain, with the consequent therapeutic implications [4, 6, 7, 112–115].

UMs and PMs tend to show the highest GOT activity and IMs the lowest. Significant differences appear among different IM-related genotypes. The $^{*}10/10$ genotype exhibited the lowest GOT activity with marked differences as compared to PMs. GPT activity was significantly higher in PMs ($^{*}4/4$) than in EMs ($^{*}1/10$) or IMs ($^{*}4/4$ and $^{*}1/5$). The lowest GPT activity was found in EMs and IMs. Striking differences have been found in GGT activity between PMs ($^{*}4/4$), which showed the highest levels, and EMs ($^{*}1/1$ and $^{*}1/10$), IMs ($^{*}1/5$), or UMs ($^{*}1/5$) [6]. Interesting enough, the $^{*}10/10$ genotype, with the lowest values of GOT and GPT, exhibited the second highest levels of GGT after $^{*}4/4$, probably indicating that CYP2D6-related enzymes differentially regulate drug metabolism and transaminase activity in the liver. These results are also clear in demonstrating the direct effect of CYP2D6 variants on transaminase activity [4, 6, 7].

With a multifactorial therapeutic intervention in patients with dementia who received (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, 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 (r = +0.96), whereas PMs and UMs deteriorated 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*/X*/1 genotypes, respectively [4–7, 9, 28, 112, 113]. In a recent study, Pitollo et al. [231] have confirmed the influence of CYP2D6 variants (rs1080985) on the efficacy of donepezil in AD.

From all these data in patients with dementia 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*/X*/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, 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%); 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; (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 [4–7, 9, 28, 105, 112, 113].

20. CYP Clustering

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 [5]. This is especially important because the CYP2C9-Ilc359Leu (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 PMs (CYP3A5*1/*1) [5].

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*/1-1*/1-1*/1 (8.09%), *1*/1-1*/1-1*/2 (4.91%), *1*/1-1*/1-1*/2 (4.65%), and *1*/1-1*/1-1*/1/*1-1*/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 EM phenotype, 15.29% are 2EM1IM, 2.04% are pure 3IM, 0% are pure 3PM, and 0% are 1UM2PM (the worst possible phenotype) [5].

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 [7, 9, 105, 112, 113].

21. Conclusions

Major conclusions to be drawn from studies on AD genomics and pharmacogenomics would be the following: (i) AD is a complex disorder in which many different gene clusters may be involved; (ii) most genes screened to date belong to different proteomic and metabolic pathways potentially affecting AD pathogenesis; (iii) the APOE gene seems to be a major risk factor for both degenerative and vascular dementia; (iv) the therapeutic response to conventional drugs in patients with AD is genotype-specific, with CYP2D6-PMs, CYP2D6-UMs, and APOE-4/4 carriers acting as the
worst responders; (v) APOE and CYP2D6 may cooperate, as pleiotropic genes, in the metabolism of drugs and hepatic function; (vi) the introduction of pharmacogenetic procedures into AD pharmacological treatment may help to optimize therapeutics.

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