Chapter 40
Pharmacogenomic Biomarkers in Neuropsychiatry: The Path to Personalized Medicine in Mental Disorders

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Abstract Neuropsychiatric disorders and dementia represent a major cause of disability and high cost in developed societies. Most disorders of the central nervous system (CNS) share some common features, such as a genomic background in which hundreds of genes might be involved, genome–environment interactions, complex pathogenic pathways, poor therapeutic outcomes, and chronic disability.

Recent advances in genomic medicine can contribute to accelerate our understanding on the pathogenesis of CNS disorders, improve diagnostic accuracy with the introduction of novel biomarkers, and personalize therapeutics with the incorporation of pharmacogenetic and pharmacogenomic procedures to drug development and clinical practice.

The pharmacological treatment of CNS disorders, in general, accounts for 10–20% of direct costs, and less than 30–40% of the patients are moderate responders to conventional drugs, some of which may cause important adverse drugs reactions (ADRs). Pharmacogenetic and pharmacogenomic factors may account for 60–90% of drug variability in drug disposition and pharmacodynamics. Approximately 60–80% of CNS drugs are metabolized via enzymes of the CYP gene superfamily; 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10–20% of Caucasians are carriers of defective CYP2D6 polymorphic variants that alter the metabolism of many psychotropic agents. Other 100 genes participate in the efficacy and safety of psychotropic drugs. The incorporation of pharmacogenetic/pharmacogenomic protocols to CNS research and clinical practice can foster therapeutics optimization by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety. To achieve this goal several measures have to be taken, including: (a) educate physicians and the public on the use of genetic/genomic screening in the daily clinical practice; (b) standardize genetic testing for major categories of drugs; (c) validate pharmacogenetic and pharmacogenomic procedures according to drug category and pathology; (d) regulate ethical, social, and economic issues; and (e) incorporate pharmacogenetic and pharmacogenomic procedures to both drugs in development and drugs in the market to optimize therapeutics.

Keywords CNS disorders • neuropsychiatric disease • schizophrenia • depression • dementia • Alzheimer's disease • APOE • CYPs • biomarkers • genomic medicine • pharmacogenetics • pharmacogenomics

Abbreviations ABCB1 ATP-binding cassette, subfamily b, member 1; ACE Angiotensin I converting enzyme; ACHE Acetylcholinesterase; AD Alzheimer's disease; ADRA1 Alpha-1-adrenergic receptor; ADRB1 Beta-1-adrenergic receptor; ADRB3 Beta-3-adrenergic receptor; APP Amyloid precursor protein; APOE Apolipoprotein E; CHRNA Cholinergic receptor, neuronal nicotinic, alpha polypeptide; CHRNB Cholinergic receptor, neuronal nicotinic, beta polypeptide; COMT Catechol-O-methyl transferase;

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CYP Cytochrome P450 family genes; DISC Disrupted in schizophrenia; DRD Dopamine Receptor; GABAR Gamma-aminobutyric acid receptors; G6PD Glucose-6-phosphate dehydrogenase; GNB3 G-protein beta-3 subunit; GNAS1 Gs protein alpha-subunit; GPIIIA Glycoprotein IIIa receptor; HLA-A1 Minor histocompatibility antigen HA-1; HRH Histamine receptor; 5HTR Serotonin receptor; INPP1 Inositol polyphosphate 1-phosphatase; KCNE2 Cardiac potassium ion channel; LTC4S Leukotriene C4 synthase; MAOA Monoamine oxidase A; MAOB Monoamine oxidase B; MAPT Microtubule-associated protein tau; PSEN1 Presenilin 1; PSEN2 Presenilin 2; RGS2 Regulator of G-protein signaling 2; SCN5A Cardiac sodium channel; SLC6A2 Solute carrier family 6 (neurotransmitter transporter, noradrenaline), Member 2; SLC6A3 Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3; SLC6A4 Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4; SCZ Schizophrenia; TNF-A Tumor necrosis factor-alpha; TPH2 Tryptophan hydroxylase.

Introduction

Central nervous system (CNS) disorders are the third problem of health in developed countries, representing 10–15% of deaths, after cardiovascular disorders (25–30%) and cancer (20–25%). Approximately, 127 million Europeans suffer brain disorders. The total annual cost of brain disorders in Europe is about €386 billion, with €135 billion of direct medical expenditures (€78 billion, inpatients; €45 billion, outpatients; €13 billion, pharmacological treatment), €179 billion of indirect costs (lost workdays, productivity loss, permanent disability), and €72 billion of direct non-medical costs. Mental disorders represent €240 billion (62% of the total cost, excluding dementia), followed by neurological diseases (€84 billion, 22%).[1]

Senile dementia is becoming a major problem of health in developed countries, and the primary cause of disability in the elderly. Alzheimer's disease (AD) is the most frequent form of dementia (50–70%), followed by vascular dementia (30–40%), and mixed dementia (15–20%). These prevalent forms of age-related neurodegeneration affect more than 25 million people at present, and probably more than 75 million people will be at risk in the next 20–25 years worldwide. The prevalence of dementia increases exponentially from approximately 1% at 60–65 years of age to more than 30–35% in people older than 80 years. It is very likely that in those patients older than 75–80 years of age most cases of dementia are mixed in nature (degenerative + vascular), whereas pure AD cases are very rare after 80 years of age. The average annual cost per person with dementia ranges from €10,000 to 40,000, depending upon disease stage and country, with a lifetime cost per patient of more than €150,000. In some countries, approximately 80% of the global costs of dementia (direct + indirect costs) are assumed by the patients and/or their families. About 10–20% of the costs in dementia are attributed to pharmacological treatment, including anti-dementia drugs, psychotropics (antidepressants, neuroleptics, anxiolytics), and other drugs currently prescribed in the elderly (antiparkinsonians, anticonvulsants, vasoactive compounds, anti-inflammatory drugs, etc). In addition, during the past 20 years more than 300 drugs have been partially or totally developed for AD, with the subsequent costs for the pharmaceutical industry, and only 5 drugs with moderate-to-poor efficacy and questionable cost-effectiveness have been approved in developed countries.[2–4]

The lack of accurate diagnostic markers for early prediction and an effective therapy of CNS disorders are the two most important problems to efficiently diagnose and halt disease progression. The pharmacological treatment of CNS disorders, in general, accounts for 10–20% of direct costs, and less than 30–40% of the patients are moderate responders to conventional drugs, some of which may cause important adverse drugs reactions (ADRs). In the case of dementia, less than 20% of the patients can benefit from current drugs (donepezil, rivastigmine, galantamine, memantine), with doubtful cost-effectiveness. The pathogenic mechanisms of most CNS disorders (e.g., psychosis, depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, etc) are poorly understood. This circumstance makes it difficult the implantation of a molecular intervention to neutralize causative factors. In fact, more than 80% of the 25,000 genes integrating the human genome are expressed in the CNS at different periods of the life span, and only a few neurotransmitters (e.g., noradrenaline, dopamine, acetylcholine, GABA, histamine, and less than ten neuropeptides) are the actual targets of

conventional psychopharmacology. Common features in CNS disorders include the following: (a) polygenic/complex disorders in which genomic and environmental factors are involved; (b) deterioration of higher activities of the CNS; (c) multifactorial dysfunctions in several brain circuits; and (d) accumulation of toxic proteins in the nervous tissue in cases of neurodegeneration. For instance, the neuropathological hallmark of Alzheimer's disease (AD) (amyloid deposition in senile plaques, neurofibrillary tangle formation, and neuronal loss) is but the phenotypic expression of a pathogenic process in which more than 200 genes and their products are potentially involved.

Drug metabolism, and the mechanisms underlying drug efficacy and safety, are also genetically regulated complex traits in which hundreds of genes cooperatively participate. Structural and functional genomics studies demonstrate that genomic factors, probably induced by environmental factors, cerebrovascular dysfunction, and epigenetic phenomena, might be responsible for pathogenic events leading to premature neuronal dysfunction and/or death.

Pharmacogenetic and pharmacogenomic factors may account for 60–90% of drug variability in drug disposition and pharmacodynamics. About 10–20% of Caucasians are carriers of defective CYP2D6 polymorphic variants that alter the metabolism of many psychotropic agents. The incorporation of pharmacogenetic/pharmacogenomic protocols to CNS research and clinical practice can foster therapeutics optimization by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety.[5–7]

Genomics of Neuropsychiatric Disorders

Extensive molecular genetics studies carried out in the past 2 decades have demonstrated that most CNS disorders are multifactorial, polygenic/complex disorders in which hundreds of genes distributed across the human genome might be involved (Tables 40.1–40.3).[8,9] For example, 255 genes have been associated with dementia (Table 40.1), 205 with schizophrenia (Table 40.2), 106 with depression (Table 40.3), 107 with anxiety, 103 with stroke, 385 with different types of ataxia, 155 with epilepsiy, 83 with meningioma, 105 with glioblastoma, 27 with astrocytoma, 73 with Parkinson's disease, and more than 30 genes with cerebrovascular disorders.[8,10] Many of these genetic associations could not be replicated in different settings and different populations due to many complex (methodological, technological) factors.[8,11,12] Furthermore, the same genomic defect can give rise to apparent diverse phenotypes, and different genomic defects can converge in an apparently common phenotype, this increasing the complexity of genomic studies (e.g., patient recruitment, pure controls, concomitant pathology, epigenetic factors, environmental factors). Several candidate genes for schizophrenia may also be associated with bipolar disorder, including G72, DISC1, NRG1, RGS4, NCAM1, DAO, GRM3, GRM4, GRIN2B, MLC1, SYNGR1, and SLC12A6. Genes associated with bipolar disorder include TRPM2 (21q22.3), GPR50 (Xq28), Citron (12q24), CHP1.5 (18p11.2), GCHI (14q22–24), MLC1 (22q13), GABRA5 (15q11–q13), BCR (22q11), CUX2, FLJ32356 (12q23–q24), and NAPG (18p11).[9]

Another paradigmatic example of heterogeneity and complexity is dementia, one of the most heterogeneous disorders of the CNS. The genetic defects identified in AD during the past 25 years can be classified into three main categories: (a) Mendelian or mutational defects in genes directly linked to AD, including (i) 32 mutations in the amyloid beta (Aβ)(ABP) precursor protein (APP) gene (21q21); (ii) 165 mutations in the presenilin 1 (PS1) gene (14q24.3); and (iii) 12 mutations in the presenilin 2 (PS2) gene (1q31–q42)[8,10,13] (Table 40.1). (b) Multiple polymorphic variants of risk characterized in more than 200 different genes distributed across the human genome can increase neuronal vulnerability to premature death[8] (Table 40.1). Among these genes of susceptibility, the apolipoprotein E (APOE) gene (19q13.2) is the most prevalent as a risk factor for AD, especially in those subjects harbouring the APOE-4 allele, whereas carriers of the APOE-2 allele might be protected against dementia.[8] APOE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD.[8] (c) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity.[8,14,15] It is also likely that defective functions of genes associated with longevity may influence premature neuronal survival, since neurons are potential pacemakers defining life span in mammals.[8] All these genetic factors may interact in still unknown genetic networks leading

Table 40.1 Selected human genes investigated as potential candidate genes associated with dementia and age-related neurodegenerative disorders

Locus	Symbol	Title/gene	OMIM
1p21.3–p13.1	SORT1	Sortilin	602458
1p31	BBP	Beta-amyloid binding protein precursor	
1p32	ZFYVE9	Zinc finger, FYVE domain containing 9	
	SARA	SMAD anchor for receptor activation	
	MADHIP	MADH-interacting protein	
1p34	LRP8	Low-density lipoprotein receptor-related protein 8	602600
	APOER2		
1p36	AD7CNTP	Alzheimer disease neuronal thread protein (ADNTP)	607413
1p36.3	MTHFR	Methylenetetrahydrofolate reductase	236253
			104300
1q21	S100A	S100 calcium-binding protein A1	176940
1q21–q23	APCS	Serum amyloid P component	104770
1q23	NCSTN	Nicastrin	605254
	APH2		
1q25	SOAT1	Acyl-CoA: Cholesterol acyltransferase	102642
	STAT	Csterol O-acyltransferase 1	
	ACAT		
1q31–q42	AD4	Presenilin-2	600759
	PSEN2		104300
	STM2		
Chr. 1	APH1A	C. elegans anterior pharynx defective homolog	607629
2p14–p13	RTN4 NOGO	Neurite outgrowth inhibitor (reticulon 4)	604475
2p25	ADAM17	A desintegrin and metalloproteinase domain 17	603639
	TACE	Tumor necrosis factor-alpha converting enzyme	
2q14	IL1A	Interleukin-1-alpha	147760
2q21.1	CSEN	Calsenilin	604662
	DREAM		
	KCNIP3		
2q21.2	LRP1B	Low density lipoprotein receptor-related protein 1B	608766
3q26.1–q26.2	BCHE	Butyrylcholinesterase	177400
3q32.3–q34	CREB1	cAMP response element-binding protein	123810
Chr. 4	APBB2	Amyloid beta-A4 precursor protein-binding, family B, member 2	602710
	FE65L1		
5q15–q21	CAST	Calpastatin	114090
5q31	APBB3	Amyloid beta A4 precursor protein-binding, family B, member 3	602711
	FE65L2		
5q35.3	DBN1	Drebrin E	12660
6p21.3	AGER	Advance glycosylation end product-specific receptor	600214
	RAGE		
6p21.3	TNFA	Tumor necrosis factor-α cachectin	191160
7p21	IL-6	Interleukin-6	147620
	IFNB2	beta-2 interferon	
7q36	NOS3	Nitric oxide synthase-3	163729
8p22	CTSB	Cathepsin B	116810
	CPSB	Amyloid precursor protein secretase	
9q13	APBA1	Amyloid beta-A4 precursor protein-binding, family A, member 1	602414
	X11		
	MINT1		
	LIN10		
10p13	AD7	Alzheimer disease-7	606187
10q23–q25	IDE	Insulin-degrading enzyme	146680
10q24	AD6	Alzheimer disease-6	605526
			104300

(continued)

Table 40.1 (continued)

Locus	Symbol	Title/gene	OMIM
10q24	PLAU	Plasminogen activator, urokinase	191840
	URK		
11p15	APBB1	Amyloid beta-A4 precursor protein-binding, family B, member 1	602709
	F65		
11p15.1	SAA1	Serum amyloid A1	104750
11q23.2–q24.2	SORL1	Sortilin-related receptor 1	602005
11q23.3	BACE1	Beta-site amyloid beta A4 precursor protein-cleaving enzyme	604252
	BACE	Beta-secretase	
		Memapsin-2	
11q24	APLP2	Amyloid beta-A4 precursor-like protein 2	104776
12p11.23–q13.12	AD5	Familial AD-5	602096
12p12.3–p12.1	IAPP	Islet amyloid polypeptide	147940
	IAP	Amylin	
	DAP	Diabetes-associated peptide	
12p13.3–p12.3	A2M	Alpha-2-macroglobulin	103950
12q13.1–q13.3	LRP1	Low density lipoprotein-related protein-1	107770
	A2MR	Alpha-2-macroglobulin receptor	
14q24.3	FOS	FBJ murine osteosarcoma viral (v-fos) oncogene homolog	164810
		Oncogene Fos	
14q24.3	AD3	Presenilin-1	104311
	PSEN1		
14q32.1	SERPINA3	Alpha-1-antichymotrypsin	107280
	AACT		
	ACT		
14q32.1	CYP46	Cytochrome P450	604087
	CYP46A1	family 46, subfamily A	
		polypeptide 1	
		Cholesterol 24-hydrolase	
Chr. 15	APH1B	Homolog of C. elegans anterior pharynx defective 1B	607630
15q11–q12	APBA2	Amyloid beta-A4 precursor protein-binding, family A, member 2	602712
	X11L		
16q22	APPBP1	Amyloid beta precursor protein-binding protein 1	603385
17q11.2	BLMH	Bleomycin hydrolase	602403
	BMH		
17q21	STH	Saitohin	607067
17q21.1	MAPT	Macrotubule-associated protein tau	157140
	MTBT1		600274
	DDPAC		168610
	MST		172700
			601104
17q21–q22	GPSC	Familial progressive subcortical gliosis	221820
17q22–q23	APPBP2	Amyloid beta precursor protein-binding protein 2	605324
	PAT1		
17q23	ACE	Angiotensin I converting enzyme	106180
	ACE1	Dipeptidyl carboxipeptidase-1	104300
	DCP1		
17q23.1	MPO	Myeloperoxidase	254600
17q24	FALZ	Fetal Alzheimer antigen	601819
	FAC1		
18q11.2–q12.2	TTR	Transthyretin	176300
	PALB	Prealbumin	
19p13.2	NOTCH3	Drosophila Notch 3 homolog	600276

(continued)

Table 40.1 (continued)

Locus	Symbol	Title/gene	OMIM
	CADASIL		
	CASIL		
19p13.2	AD8	Alzheimer disease 9	608907
19p13.3–p13.2	ICAM	Intercellular adhesion molecule 1	147840
	CD54		
	BB2		
19p13.3	APBA3	Amyloid beta-A4 precursor protein binding, family A, member 3	604262
	X11L2		
19q13.12	PEN2	Presenilin enhancer 2	607632
19q13.2	APOE	Apolipoprotein E	107741
19q13.2	APOC1	Apolipoprotein C-I	107710
19cen–q13.2	AD2	Alzheimer disease-2	104310
19cen–q13.2	APLP1	Amyloid beta-A4 precursor-like protein 1	104775
19q31–qter	APPL1	Amyloid beta-A4 precursor protein-like 1	104740
20p	AD8	Alzheimer disease-8	607116
			104300
20p11.2	CST3	Cystatin 3	604312
20p11.2	CST3	Cystatin C	604312
21q21	AD1	Amyloid beta (A4) precursor protein	104760
	APP	Amyloid of aging and Alzheimer disease	
	AAA	Cerebrovascular amyloid peptide	
	CVAP	Protease nexin II	
21q22.3	BACE2	Beta-site amyloid beta A4 precursor protein-cleaving enzyme 2	605668
	ALP56	Down syndrome-region aspartic protease	
	DRAP		
22q11	RTN4R, NOGOR	NOGO receptor (reticulon 4 receptor)	605566
	HN	Humanin	606120

Source: Adapted from Cacabelos et al.[8], and Cacabelos and Takeda.[19]

Table 40.2 Genes associated with schizophrenia and psychosis

Locus	Symbol	Title	OMIM	SCZ type
1p36.2	SCZD12	Schizophrenia 12	608543	Schizophrenia-12
1q21–q22	SCZD9	Schizophrenia susceptibility locus Chr. 1q-related	604906/181500	Schizophrenia-9
1q23.3	RGS4, SCZD9	Regulator of G protein signaling 4	602516	Schizophrenia-9; bipolar disorder
1q32.1	CHI3L1, GP39, YKL40, ASRT7	Chitinase 3-like 1 (cartilage glycoprotein-39)	601525	Schizophrenia, susceptibility to; asthma-related traits, susceptibility to
1q42.1	DISC1	Disrupted in schizophrenia 1	605210/181500	Schizophrenia-1
1q42.1	DISC2	Disrupted in schizophrenia 2	606271/181500	Schizophrenia-2
3p25	SYN2	Synapsin II	600755	Schizophrenia, susceptibility to
3q13.3	DRD3, ETM1, FET1	Dopamine receptor D3	126451	Schizophrenia, susceptibility to; essential tremor, susceptibility to
5q11.2–q13.3	SCZD1	Schizophrenia susceptibility locus/Chr. 5q-related	181510/181500	Schizophrenia-1
6p21.3	GRM4, MGLUR4	Glutamate receptor, metabotropic, 4	604100	Schizophrenia; bipolar disorder
6p22.3	DTNBP1, HPS7	Dystrobrevin-binding protein 1 (dysbindin)	607145	Schizophrenia; Hermansky-Pudlak syndrome 7
6p23	SCZD3	Schizophrenia susceptibility locus/Chr. 6p-related	600511/181500	Schizophrenia-3

(continued)

Table 13.2 (continued)

Locus	Symbol	Title	OMIM	SCZ type
6p22.3	DTNBP1	Dystrobrevin-binding protein 1	607145/181500	Schizophrenia
6q13–q26	SCZD5	Schizophrenia susceptibility locus/Chr. 6q-related	603175/181500	Schizophrenia-5
7q21.1–q21.2	GRM3	Glutamate receptor, metabotropic-3	601115	Schizophrenia; Bipolar disorder
8p21	SCZD6	Schizophrenia susceptibility locus/Chr. 8p-related	603013/181500	Schizophrenia-6
8p22—p11	NRG1, HGL, HRGA, ARIA	Neuregulin 1 (heregulin, alpha, 45kD; ERBB2 p185-activator)	142445	Schizophrenia; Bipolar disorder
10q22.3	SCZD11	Schizophrenia susceptibility locus, chromosome 10q-related	608078	Schizophrenia-11
11q14–q21	SCZD2	Schizophrenia susceptibility locus/Chr. 11-related	603342/181500	Schizophrenia-2
11q23.1	NCAM1	Neural cell adhesion molecule 1	116930	Schizophrenia; bipolar disorder
12p12	GRIN2B, NMDAR2B	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	138252	Schizophrenia; bipolar disorder
12q24	DAO, DAMOX	D-amino-acid oxidase	124050/181500	Schizophrenia
13q14–q21	HTR2A	5-Hydroxytryptamine receptor 2A	182135	Schizophrenia, susceptibility to; obsessive-compulsive disorder, susceptibility to; seasonal affective disorder, susceptibility to; alcohol dependence, susceptibility to; anorexia nervosa, susceptibility to; major depressive disorder, response to citalopram therapy in
13q32	SCZD7	Schizophrenia susceptibility locus/Chr. 13q-related	603176/181500	Schizophrenia-7
13q34	G72	G72 gene	607408/181500	Schizophrenia
14q32.3	AKT1	Murine thymoma viral (v-akt) oncogene homolog-1	164730	Breast cancer, somatic; colorectal cancer, somatic; ovarian cancer, somatic; schizophrenia, susceptibility to
15q13–q14	SLC12A6, KCC3A, KCC3B, KCC3, ACCPN	Solute carrier family 12 (potassium/chloride transporters), member 6	604878	Agenesis of the corpus callosum with peripheral neuropathy; schizophrenia; bipolar disorder
15q15	SCZD10	Schizophrenia susceptibility locus/Chr. 15q-related	605419/181500	Schizophrenia-10
18p	SCZD8	Schizophrenia susceptibility locus/Chr. 18-related	603206/181500	Schizophrenia-8
22q11	RTN4R, NOGOR	NOGO receptor (reticulon 4 receptor)	605566	Schizophrenia, susceptibility to
22q11–q13	SCZD4	Schizophrenia susceptibility locus/Chr. 22-related	600850/181500	Schizophrenia-4
22q11.2	COMT	Catechol-O-methyltransferase	116790/181500	Schizophrenia
22q11.2	PRODH, PRODH2	Proline dehydrogenase/Proline oxidase	606810/181500	Schizophrenia; hyperprolinemia type I
22q12.3	APOL1	Apolipoprotein L1	603743/181500	Schizophrenia
22q12.3	APOL2	Apolipoprotein L2	607252/181500	Schizophrenia
22q12.3	APOL4	Apolipoprotein L4	607254/181500	Schizophrenia
22q13	SYNGR1	Synaptogyrin 1	603925	Schizophrenia; bipolar disorder
22q13.33	MLC1, LVM, VL	MLC1 gene	605908	Megalencephalic leukoencephalopathy with subcortical cysts; schizophrenia; bipolar disorder

Source: www.ncbi.nlm.nih.gov[10]; Kato.[9]

Table 40.3 Genes associated with depression and mood disorders

Locus	Symbol	Description	OMIM	Disease
1q31–q32	IL10	Interleukin 10	124092	Depression
1q42.11	BPNT1	3′(2′),5′-biphosphate nucleotidease 1	604053	Depression
2q32	INPP1	Inositol polyphosphate-1-phosphatase	147263	Bipolar disorder
5p15.3	SLC6A3, DAT1	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	126455	Attention-deficit hyperactivity disorder, susceptibility to; nicotine dependence, protection against; major affective disorder bipolar depression
5q11.2–q13	HTR1A	5-Hydroxytryptamine receptor 1A	109760	Depression
5q11.2–q13.3	CRHBP	Corticotropin releasing hormone binding protein	122559	Depression
6p21.3–p21.2	FKBP5, FKBP51	FK506-binding protein 5	602623	Major depressive disorder and accelerated response to antidepressant drug treatment
6q13	HTR1B	5-Hydroxytryptamine receptor 1B	182131	Depression bipolar disorder
7p11	DDC	Dopa decarboxylase Aromatic L-amino acid decarboxylase	107930	Bipolar disorder
7q21.1–q21.2	GRM3	Glutamate receptor, metabotropic 3	601115	Bipolar disorder
7q31–q35	CHRM2	Cholinergic receptor, muscarinic 2	118493	Depression
8p22–p21	DPYSL2	Dihydropyrimidinase-like 2	602463	Bipolar disorder
9q34.3	GRIN1	Glutamate receptor, ionotropic, N-methyl-D-aspartate 1	138249	Bipolar disorder
11p13	BDNF	Brain-derived neurotrophic factor	113505	Bipolar disorder
11p15.5	DRD4	Dopamine receptor D4	126452	Bipolar disorder; autonomic nervous system dysfunction; novelty seeking personality; attention deficit-hyperactivity disorder; Parkinson disease, protection against
11q13.1	GAL	Galanin	137035	Depression Anxiety
11q23	DIBD1	Disrupted in bipolar affective disorder 1	606941	Anxiety bipolar disorder congenital disorder of glycosylation, type II
12p13	GNB3	Guanine nucleotide binding protein (G protein), beta polypeptide 3	139130	Depression; hypertension
12q14	IFNG	Gamma interferon	147570	Depression interferon, immune, deficiency; TSC2 angiomyolipomas, renal, modifier of; tuberculosis, susceptibility to; aplastic anemia; AIDS, rapid progression to; Hepatitis C virus, resistance to
12q21.1	TPH2, NTPH	Tryptophan hydroxylase 2	607478	Unipolar depression, susceptibility to
12q22–q23.2	MDD1	Major depressive disorder	608520	Major depressive disorder 1
12q24.1–q24.3	STK21, CRIK, CIT	Serine/threonine protein kinase-21	605629	Bipolar disorder
13q14–q21	HTR2A	5-Hydroxytryptamine receptor 2A	182135	Schizophrenia, susceptibility to; obsessive-compulsive disorder, susceptibility to; seasonal affective disorder, susceptibility to; alcohol dependence, susceptibility to; anorexia nervosa, susceptibility to; major depressive disorder, response to citalopram therapy in

(continued)

Table 40.3 (continued)

Locus	Symbol	Description	OMIM	Disease
14q22.1–q22.2	GCH1, DYT5	GTP cyclohydrolase 1	600225	Phenylketonuria, atypical, due to GCH1 deficiency; Dystonia-5, DOPA-responsive; bipolar disorder
15q11.2–q12	GABRA5	Gamma-aminobutyric acid (GABA) A receptor, alpha-5	137142	Bipolar disorder
15q25.3–q26.2	MDD2	Major depressive disorder 2	608691	Major depressive disorder 2
16p13.3	ADCY9	Adenylate cyclase 9		Bipolar disorder
16q24.3	CHMP1A, PCOLN3, PRSM1	CHMP family, member 1A	164010	Bipolar disorder
17p13.1	ALOX12	Arachidonate 12-lipoxygenase	152391	Bipolar disorder
17q23	ACE	Angiotensin I converting enzyme	106180	Depression; Myocardial infarction, susceptibility to; Alzheimer disease, susceptibility to; diabetic nephropathy, susceptibility to; angiotensin I-converting enzyme, benign serum increase; SARS, progression of; renal tubular dysgenesis
18p	MAFD1, BPAD, MD1	Major affective disorder 1	125480	Major affective disorder 1; Bipolar depression
18p11	NAPG	Soluble NSF-attachment protein, gamma	*603216	Bipolar disorder
18p11.22–p11.21	GNAL	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide, olfactory type	139312	Depression
21q22.3	TRPM2, TRPC7, KNP3	Transient receptor potential cation channel, subfamily M, member 2	603749	Bipolar disorder
22q11.21	BCR, CML, PHL, ALL	Breakpoint cluster region	151410	Leukemia, chronic myeloid; leukemia, acute lymphocytic; bipolar disorder
22q12	XBP1, XBP2	X-box-binding protein-1	194355	Bipolar disorder
22q13.33	MLC1, LVM, VL	MLC1 gene	605908	Megalencephalic leukoencephalopathy with subcortical cysts; schizophrenia; bipolar disorder
Xq24	HTR2C	5-Hydroxytryptamine receptor 2C	312861	Bipolar disorder
Xq28	GPR50	G protein-coupled receptor 50	300207	Bipolar disorder

Source: www.ncbi.nlm.nih.gov[10]; Kato.[9]

to a cascade of pathogenic events characterized by abnormal protein processing and misfolding with subsequent accumulation of abnormal proteins (conformational changes), ubiquitin-proteasome system dysfunction, excitotoxic reactions, oxidative and nitrosative stress, mitochondrial injury, synaptic failure, altered metal homeostasis, dysfunction of axonal and dendritic transport, and chaperone misoperation[8,16–20](Fig. 40.1). These pathogenic events may exert an additive effect, converging in final pathways leading to premature neuronal death. Some of these mechanisms are common to several neurodegenerative disorders which differ depending upon the gene(s) affected and the involvement of specific genetic networks, together with cerebrovascular factors, epigenetic factors (DNA methylation) and environmental conditions (nutrition, toxicity, social factors, etc).[8,16–22] The higher the number of genes involved in AD pathogenesis, the

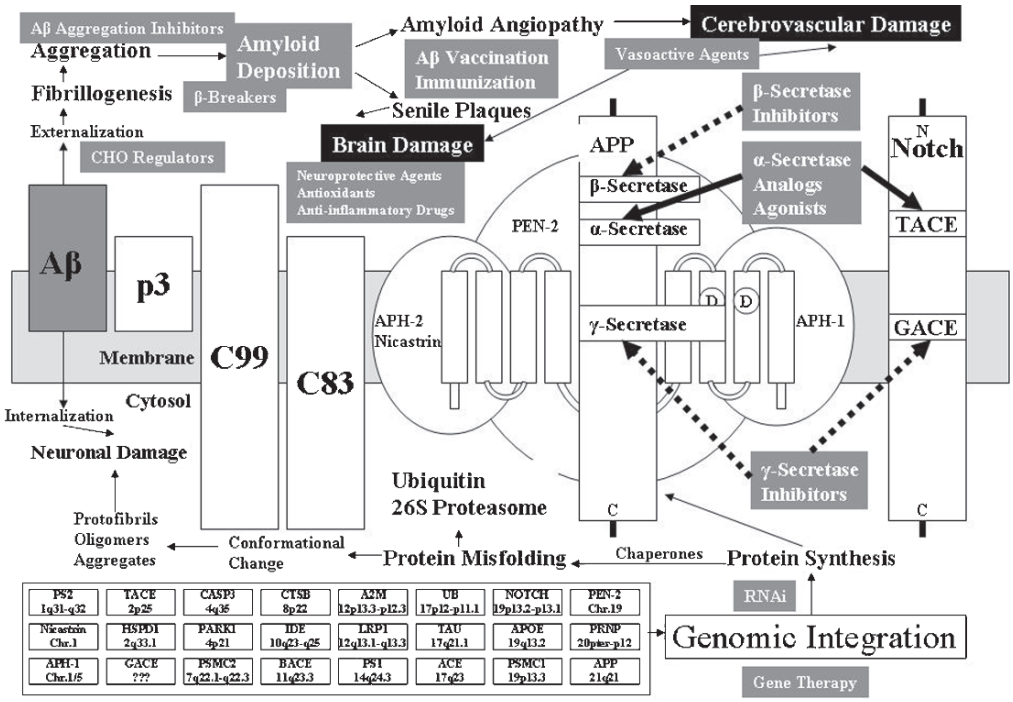

Fig. 40.1 Brain amyloidogenesis, pathogenic mechanisms of neurodegeneration, and potential therapeutic interventions in Alzheimer's disease (Adapted from R. Cacabelos[17–20])

earlier the onset of the disease, the faster its clinical course, and the poorer its therapeutic outcome.[8,16–20]

High throughput microarray gene expression profiling is an effective approach for the identification of candidate genes and associated molecular pathways implicated in a wide variety of biological processes or disease states. 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 the very early stages and is not devoid of technical obstacles and limitations.[23] Transcripts of 16,896 genes have been measured in different CNS regions. Each region possess its own unique transcriptome fingerprint that 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.[24]

With the advent of modern genomic technologies, new loci have been associated with different neuropsychiatric disorders, and novel pathogenic mechanisms have been postulated. Cryptic chromosome imbalances are increasingly acknowledged as a cause for mental retardation and learning disability. With subtelomeric screening, nine chromosomal anomalies and submicroscopic deletions of 1pter, 2qter, 4pter, 5qter and 9qter have been identified in patients with mental retardation.[25] Increased DNA fragmentation was observed in non-GABAergic neurons in bipolar disorder, suggesting that non-GABAergic cell may be selectively vulnerable to oxidative stress and apoptosis in patients with bipolar disorder.[26]

With laser microdissection, RNA amplification, and array hybridization, expression of more than 1,000 genes was detected in CA1 and CA3 hippocampal neurons under normoxic conditions. The comparison of each region under normoxic and ischemic conditions revealed more than 5,000 ischemia-regulated genes for each individual cell type.[27] Microarray technology has helped to elucidate gene expression profiles and potential pathogenic mechanisms in many other CNS disorders including schizophrenia and bipolar disorder,[28–30] speech and language disorders,[31] Parkinson's disease,[32,33] Huntington's disease,[34] prion disease,[35] drug addiction,[36,37] alcoholism,[38] brain trauma,[39] epilepsy,[40–42] Cockayne syndrome,[43] Rett syndrome,[44] Friedreich ataxia,[45] neuronal ceroid lipofuscinosis,[46] multiple sclerosis,[47] amyotrophic lateral esclerosis,[48] acute pneumococcal meningitis,[49] and the role of lipids in brain injury, psychiatric disorders, and neurodegenerative diseases.[50–52]

Interactions between genomic factors and environmental factors have been proposed as important contributors for brain neuropathology. In schizophrenia, neurodevelopmental disturbances, neurotoxins and perinatal infections, myelin- and olygodendrocytes abnormalities and synaptic dysfunctions have been suggested as pathophysiological factors. Individual genotoxicants can induce distinct gene expression signatures. Exposure of the brain to environmental agents during critical periods of neuronal development can alter neuronal viability and differentiation, global gene expression, stress and immune response, and signal transduction.[53] The binomial genome-neurotoxicants effect can be documented in cases of drug abuse or alcohol dependence. Functional gene expression differences between inbred alcohol-preferring and nonpreferring rats suggest the presence of powerful genomic influences on alcohol dependence.[54] Alcohol dependence and associated cognitive impairment may result from neuroadaptations to chronic alcohol consumption involving changes in expression of multiple genes. It has been suggested that cycles of alcohol intoxication/withdrawal, which may initially activate nuclear factor-kappa B (NF-κB), when repeated over years downregulate p65 (RELA) mRNA expression and NF-κB and p50 homodimer DNA-binding. Downregulation of the dominant p50 homodimer, a potent inhibitor of gene transcription apparently results in depression of κB regulated genes. Alterations in expression of p50 homodimer/NF-κB regulated genes may contribute to neuroplastic adaptation underlying alcoholism.[55] Gene expression profiling of the nucleus accumbens of cocaine abusers suggests a dysregulation of myelin.[56] Humans who abused cocaine, cannabis and/or phencyclidine share a decrease in transcription of calmodulin-related genes and increased transcription related to lipid/cholesterol and Golgi/ER function.[57]

Another important issue in the pathogenesis and therapeutics of CNS disorders is the role of microRNAs (miRNAs). miRNAs are small (22 nucleotide), endogenous noncoding RNA molecules that posttranscriptionally regulate expression of protein-coding genes. Computational predictions estimate that the vertebrate genomes may contain up to 1,000 miRNA genes. miRNAs are generated from long primary transcripts that are processed in multiple steps to cytoplasmic 22 nucleotide mature miRNAs. The mature miRNA is incorporated into the miRNA-induced silencing complex (miRISC), which guides it to target sequences located in 3′ UTRs where by incomplete base-pairing induce mRNA destabilization or translational repression of the target genes. An inventory of miRNA expression profiles from 13 regions of the mouse CNS has been reported.[58] This inventory of CNS miRNA profiles provides an important step toward further elucidation of miRNA function and miRNA-related gene regulatory networks in the mammalian CNS.[58]

Diagnostic Protocol in Neuropsychiatry

The introduction of novel procedures into an integral genomic medicine protocol for CNS disorders is an imperative requirement in drug development and in the clinical practice to improve diagnostic accuracy and to optimize therapeutics. This kind of protocol should integrate the following components: (i) clinical history, (ii) laboratory tests, (iii) neuropsychological assessment, (iv) cardiovascular evaluation, (v) conventional X-ray technology, (vi) structural neuroimaging, (vii) functional neuroimaging, (viii) computerized brain electrophysiology, (ix) cerebrovascular evaluation, (x) structural genomics, (xi) functional genomics, (xii) pharmacogenetics, (xiii) pharmacogenomics, (ix) nutrigenetics, (x) nutrigenomics, (xi) bioinformatics for data management, and (xii) artificial intelligence procedures for

diagnostic assignments and probabilistic therapeutic options (Table 40.4).[2,8,16–22,59,60] All these procedures, under personalized strategies adapted to the complexity of each case, are essential to depict a clinical profile based on specific biomarkers correlating with individual genomic profiles.

Genotype–Phenotype Correlations

Functional genomics studies have demonstrated the influence of many genes on CNS pathogenesis and phenotype expression (Tables 40.1–40.3). Taking AD as an example, it has been demonstrated that mutations

Table 40.4 The EuroEspes protocol for genomic medicine of CNS disorders

Procedure	Technology	Parametric data
Clinical history	Anamnesis. Pedigree. Physical, neurologic and psychiatric examination	Present conditions family history; personal history; physical, neurological and psychiatric information
Laboratory tests	Conventional	Blood, urine, cerebrospinal fluid
	Test-specific	
Neuropsychological assessment	Neuropsychological tests	Mood, behavior, cognition, functioning
	Batteries	
Cardiovascular evaluation	Electrocardiogram	Heart function
	Ecocardiogram	circulatory function
	Functional tests	
Imaging	Conventional X-Ray	Chest, neck, other structures or organs
Structural neuroimaging	Computerized Tomography (CT-Scan)	Brain structure
	Magnetic Resonance Imaging (MRI)	
Functional neuroimaging	Single Photon Emission	Brain function
	Computerized Tomography (SPECT)	cerebrovascular function
		brain oxygenation
	Positron Emission Tomography (PET)	
	CT-Brain Perfusion, Brain Digital Topography	
Brain electrophysiology	EEG, qEEG, EMG, EP	Brain mapping;
		neuromuscular
		transmission;
		evoked potentials
Cerebrovascular assessment	SPECT	Brain perfusion
	CT-Brain Perfusion	Brain oxygeneation
	Brain Digital Topography	Cerebrovascular
	Transcranial Doppler Ultrasonography	Hemodynamics
Structural genomics	Gene mapping	Mutations
	Linkage analysis	disease-associated
	Association studies	genotypes
	DNA microarrays	SNPs
Functional genomics	Microarray technology	Genotype-associated defects
	Genotype–phenotype correlations	
	Transcriptomics	
	Proteomics	
	Metabolomics	
Pharmacogenetics	Genotyping of genes associated with drug metabolism	Prediction of therapeutic response
		drug toxicity
		ADRs
		safety issues
Pharmacogenomics	Genotyping of genes associated with disease phenotype	Drug-induced gene(s) expression and disease phenotype modification
	High Throughput Screening	efficacy issues

(continued)

Table 40.4 (continued)

Procedure	Technology	Parametric data
Nutrigenetics	Genotyping of genes associated with nutrients metabolism	Nutrition-related effects nutrition benefits nutrition toxicity safety issues
Nutrigenomics	Genotyping of genes associated with disease induced by nutritional factors	Nutrition-related disease analysis nutrition-induced gene expression and disease phenotype modification
	High Throughput Screening	efficacy issues
Data integration	Bioinformatics	Data management correlation analysis
Intelligent assignments	Artificial intelligence	Probabilistic diagnosis; therapeutic optimization; nutritional optimization; predictive analysis; individual preventive options; risk evaluation; genetic counselling

in the APP, PS1, PS2, and MAPT genes give rise to well-characterized differential neuropathological and clinical phenotypes of dementia.[8] The analysis of genotype–phenotype correlations has also revealed that the presence of the APOE-4 allele in AD, in conjunction with other genes, influences disease onset, brain atrophy, cerebrovascular perfusion, blood pressure, β-amyloid deposition, ApoE secretion, lipid metabolism, brain bioelectrical activity, cognition, apoptosis, and treatment outcome.[8,16–22,61] The characterization of phenotypic profiles according to age, cognitive performance (MMSE and ADAS-Cog score), serum ApoE levels, serum lipid levels including cholesterol (CHO), HDL-CHO, LDL-CHO, VLDL-CHO, and triglyceride (TG) levels, as well as serum nitric oxide (NO), β-amyloid, and histamine levels, reveals sex-related differences in 25% of the biological parameters and almost no differences (0.24%) when patients are classified as APOE-4(−) and APOE-4(+) carriers, probably indicating that gender-related factors may influence these parametric variables more powerfully than the presence or absence of the APOE-4 allele; in contrast, when patients are classified according to their APOE genotype, dramatic differences emerge among APOE genotypes (>45%), with a clear biological disadvantage in APOE-4/4 carriers who exhibit (i) earlier age of onset, (ii) low ApoE levels, (iii) high CHO and LDL-CHO levels, and (iv) low NO, β-amyloid, and histamine levels in blood.[8,16–22,61] These phenotypic differences are less pronounced when AD patients are classified according to their PS1 (15.6%) or ACE genotypes (23.52%), reflecting a weak impact of PS1- and ACE-related genotypes on the phenotypic expression of biological markers in AD. PS1-related genotypes appear to influence age of onset, blood histamine levels and cerebrovascular hemodynamics, as reflected by significant changes in systolic (Sv), diastolic (Dv), and mean velocities (Mv) in the left middle cerebral arteries (MCA).[19] ACE-related phenotypes seem to be more influential than PS1 genotypes in defining biological phenotypes, such as age of onset, cognitive performance, HDL-CHO levels, ACE and NO levels, and brain blood flow Mv in MCA. However, when APOE and PS1 genotypes are integrated in bigenic clusters and the resulting bigenic genotypes are differentiated according to their corresponding phenotypes, an almost logarithmic increased expression of differential phenotypes is observed (61.46% variation), indicating the existence of a synergistic effect of the bigenic (APOE + PS1) cluster on the expression of biological markers, apparently unrelated to APP/PS1 mutations, since none of the patients included in the sample were carriers of either APP or PS1 mutations.[19,61,62] These examples illustrate the potential additive effects of AD-related genes on the phenotypic expression of biological markers. Furthermore, the analysis of genotype–phenotype correlations with a monogenic or bigenic approach documents a modest genotype-related variation in serum amyloid-β (ABP) levels, suggesting that peripheral levels of ABP are of relative value as predictors of disease-stage or as markers of disease progression and/

or treatment-related disease-modifying effects.[19,61,62] The peripheral levels of ABP in serum exhibit an APOE-dependent pattern according to which both APOE-4(+) and APOE-2(+) carriers tend to show higher ABP levels than APOE-4(−) or APOE-3 carriers[19,61–63](Fig. 40.2). This trend is even clearer when APOE, PS1, and PS2 genotypes are integrated in bigenic or trigenic clusters where the 3322, 3212,

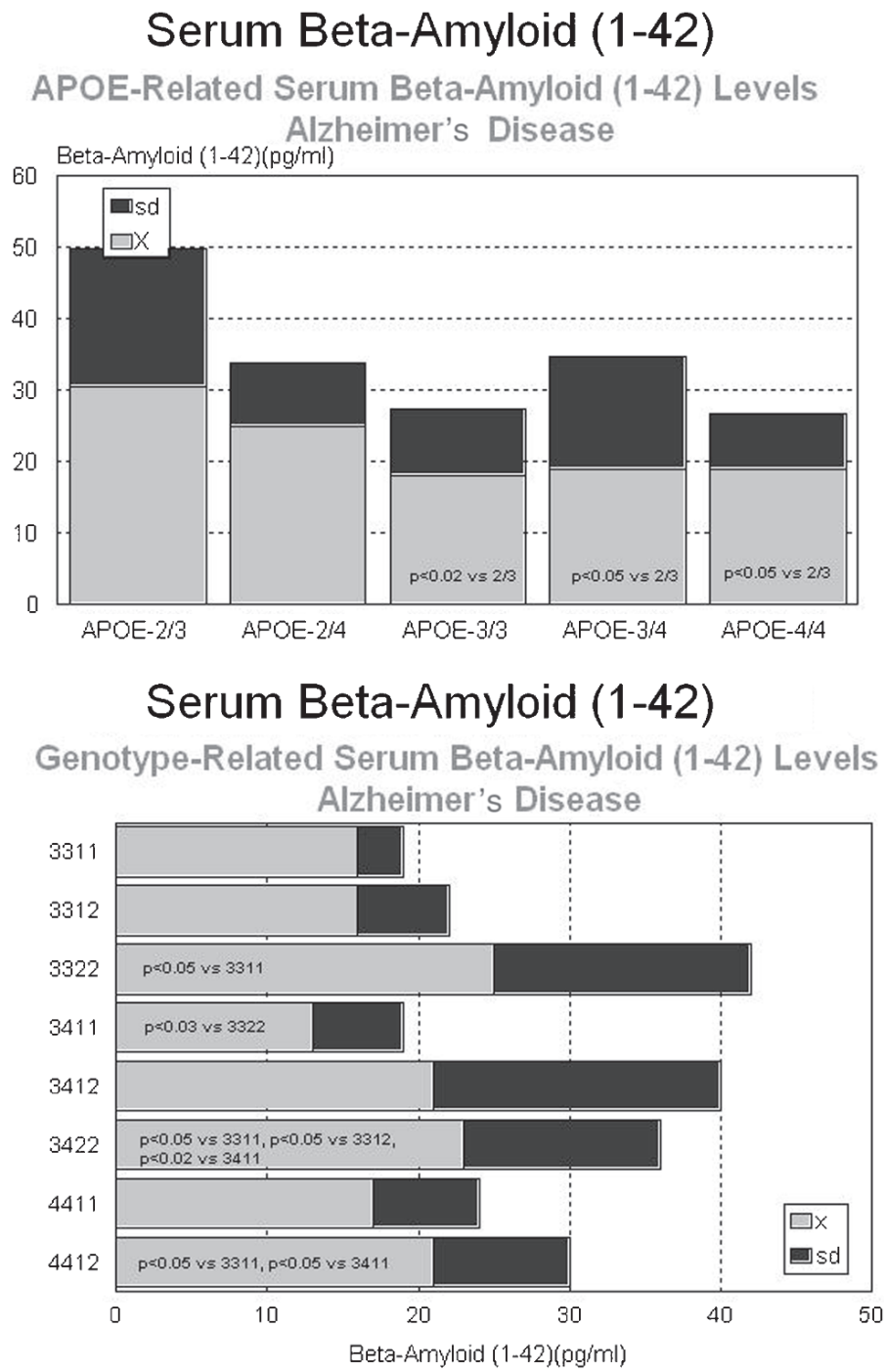

Fig. 40.2 APOE- and bigenic (APOE + PSEN1)-related serum amyloid-β peptide (1–42) levels in Alzheimer's disease (Adapted from R. Cacabelos[8,61,62])

and 4412 genotypes show the highest ABP levels as compared with other genotypes[19,61–63] (Fig. 40.2). In contrast to the inconsistent variability in ABP levels, genotype-related serum histamine changes exhibit an outstanding variation that can be modified by therapeutic intervention[64–66](Fig. 40.3). APOE-related serum histamine levels exhibit an opposite pattern to that observed in ABP levels (Figs. 40.2 and 40.3). The low-

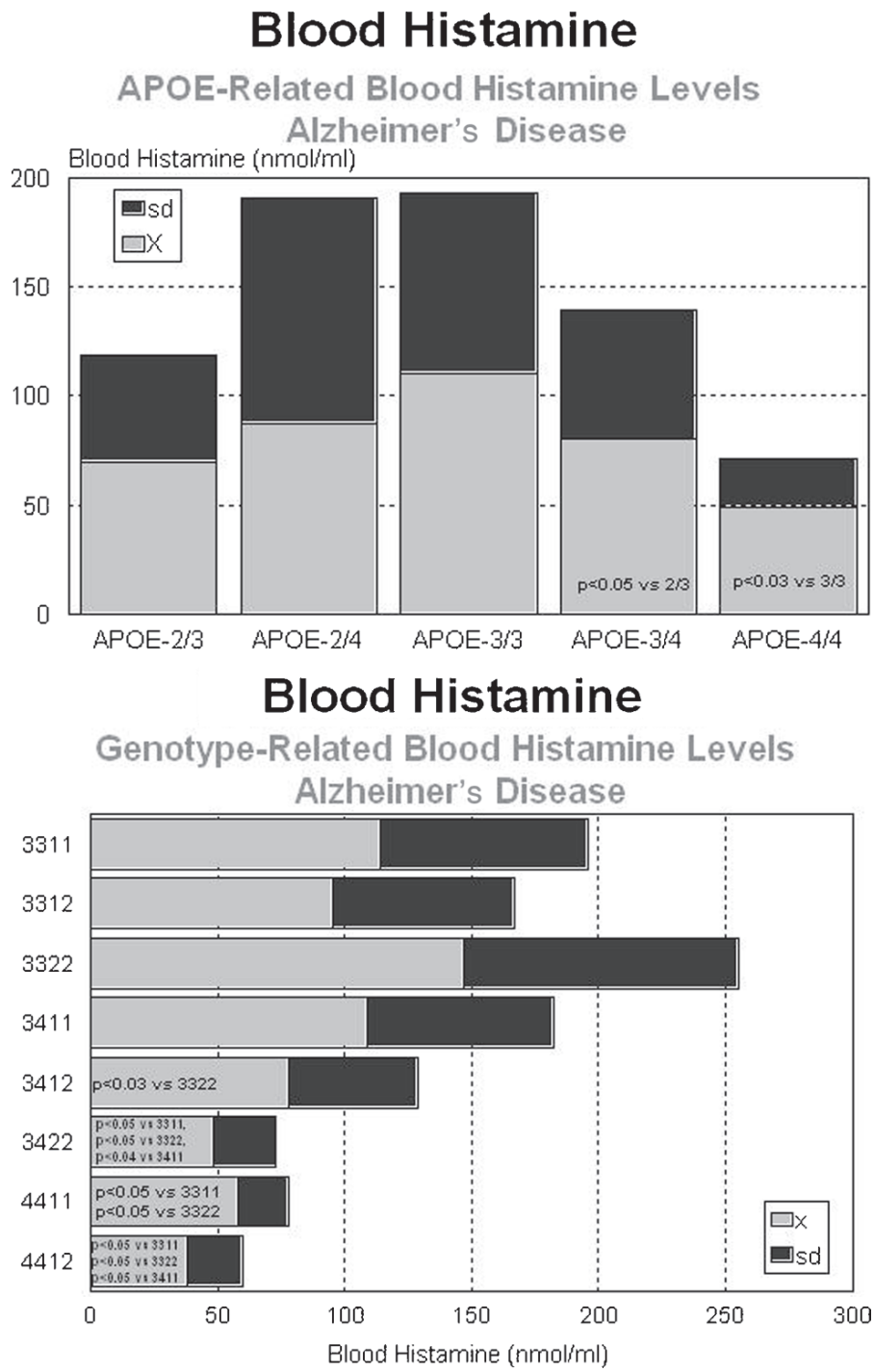

Fig. 40.3 APOE- and bigenic (APOE + PSEN1)-related blood histamine levels in Alzheimer's disease (Adapted from R. Cacabelos[8,61,62])

est concentration of serum histamine is systematically present in APOE-2(+) and APOE-4(+) carriers, and the highest levels of histamine are seen in APOE-3(+) carriers (Fig. 40.3). Central and peripheral histaminergic mechanisms may regulate cerebrovascular function in AD, which is significantly altered in APOE-4/4 carriers.[19,61–66] These observations can lead to the conclusion that the simple quantification of biochemical markers in fluids or tissues of AD patients with the aim of identifying pathogenic mechanisms and/or monitoring therapeutic effects, when they are not accompanied by differential genotyping for sample homogenization, are of very poor value.

Differential patterns of APOE-, PS1-, PS2-, and trigenic (APOE + PS1 + PS2) cluster-related lymphocyte apoptosis have been detected in AD. Fas receptor expression is significantly increased in AD, especially in APOE-4 carriers where lymphocyte apoptosis is more relevant.[19,67]

It has been demonstrated that brain activity slowing correlates with progressive GDS staging in dementia[8,16,18–20](Fig. 40.4). In the general population subjects harbouring the APOE-4/4 genotype exhibit a premature slowing in brain mapping activity represented by increased slow delta and theta activities as compared with other APOE genotypes. In patients with AD, slow activity predominates in APOE-4 carriers with similar GDS stage[8,16,18–20] (Fig. 40.4).

AD patients harbouring the APOE-4/4 genotype also exhibit a dramatically different brain optical topography map reflecting a genotype-specific differential pattern of neocortical oxygenation as well as a poorer activation of cortical neurons in response to somatosensory stimuli (Fig. 40.5).

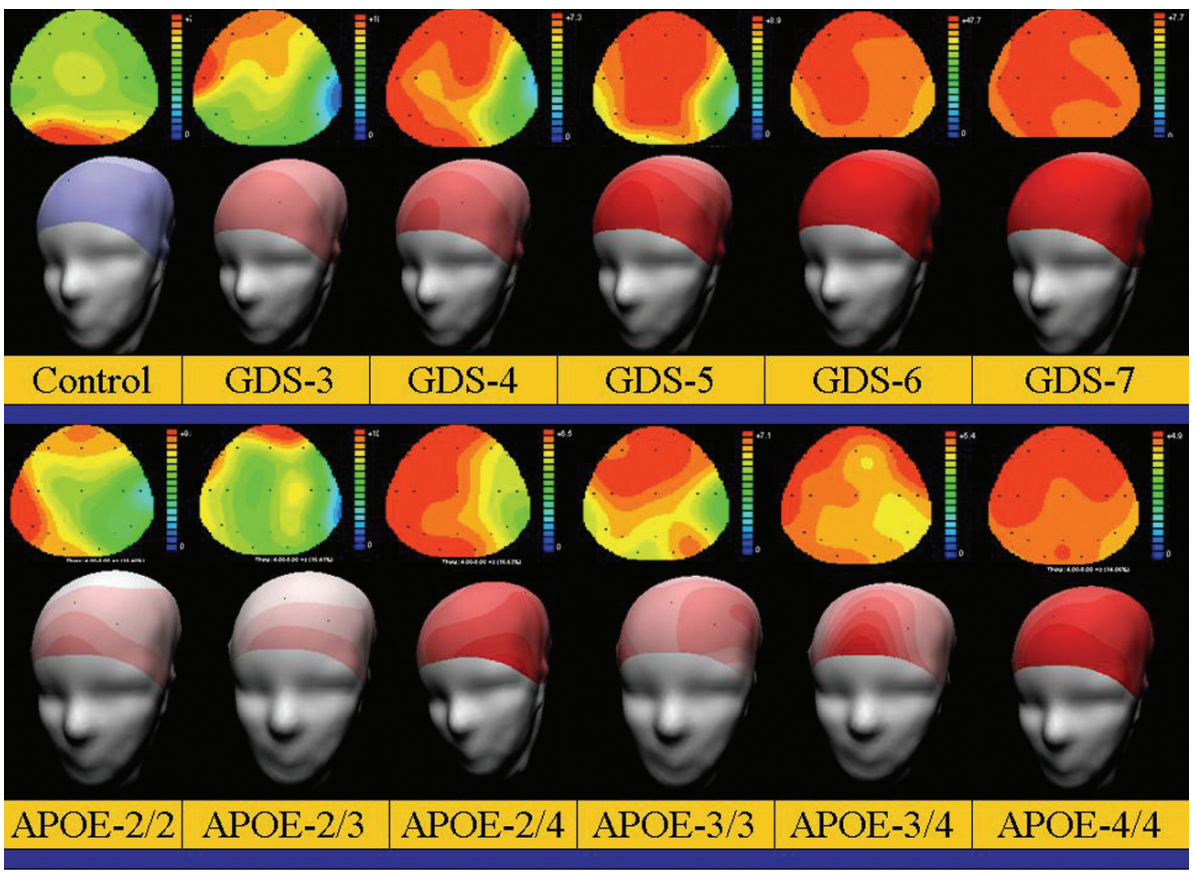

Fig. 40.4 Brain mapping activity (theta band) according to GDS staging (cognitive deterioration) and APOE genotype in Alzheimer's disease (From R. Cacabelos[19,20])

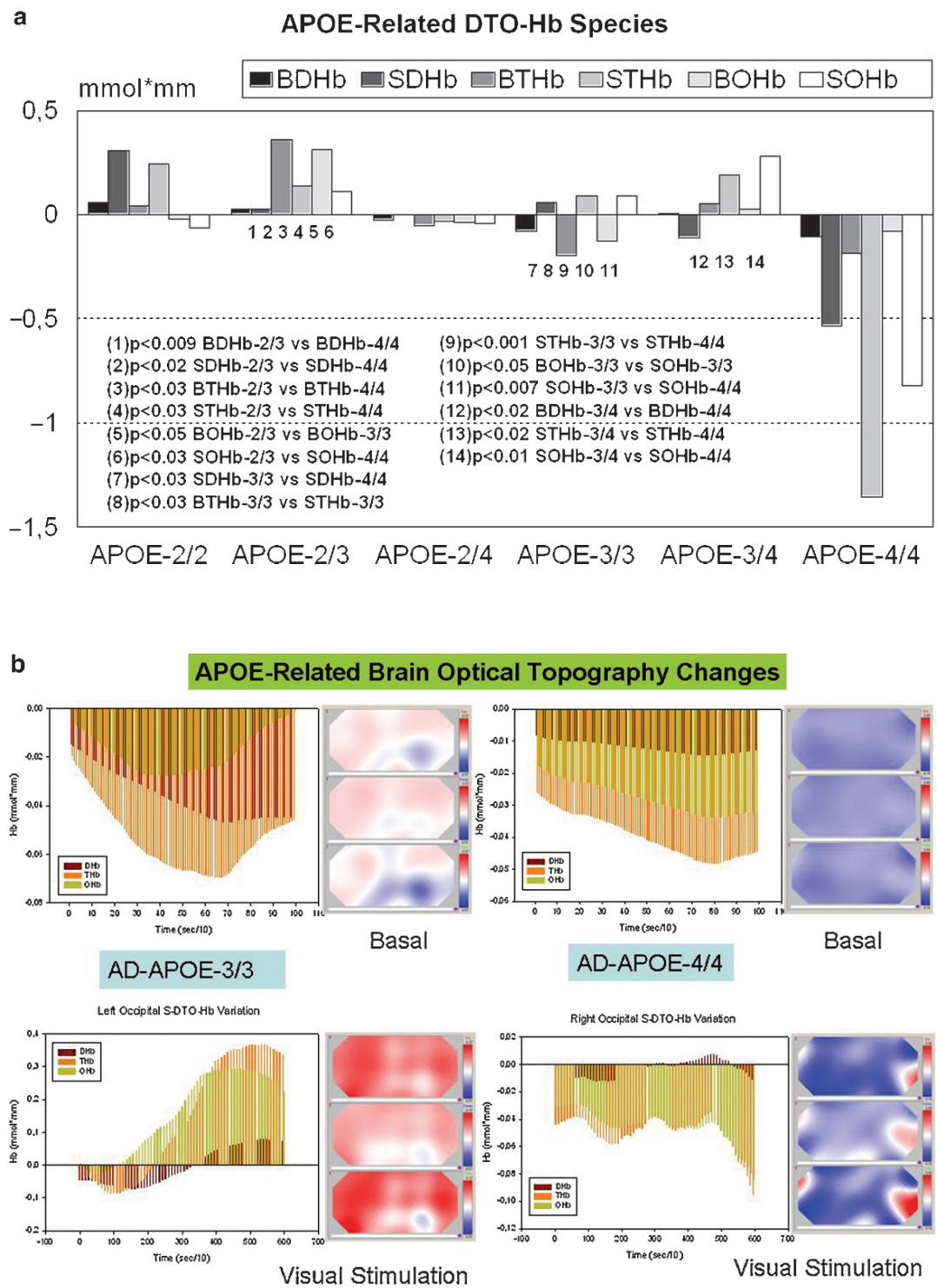

Fig. 40.5 APOE-related brain optical topography mapping in Alzheimer's disease (**a**) Basal and stimulated (light flash) oxy-, deoxy- and total haemoglobin in the occipital cortex of patients with Alzheimer's disease. (**b**) Differential pattern of basal and stimulated (light flash) brain optical topography mapping in the occipital cortex of patients with Alzheimer's disease harbouring APOE-3/3 and APOE-4/4 genotypes. BDHb: Basal deoxyhaemoglobin; SDHb: Stimulated deoxyhaemoglobin; BTHb: Basal total haemoglobin; STHb: Stimulated total haemoglobin; BOHb: Basal oxyhaemoglobin; SOHb: Stimulated oxyhaemoglobin.

All these examples of genotype–phenotype correlations, as a gross approach to functional genomics, illustrate the importance of genotype-related differences in AD and their impact on phenotype expression.[8,16–22,62,63] Similar protocols are applied to schizophrenia, depression, anxiety and other neuropsychiatric disorders. Most biological parameters, potentially modifiable by monogenic genotypes and/or polygenic cluster profiles, can be used in clinical trials for monitoring efficacy outcomes. These parametric variables also show a genotype-dependent profile in different types of dementia (e.g., AD vs. vascular dementia). For instance, striking differences have been found between AD and vascular dementia in structural and functional genomics studies.[8,16–22,62,63]

Pharmacogenetics and Pharmacogenomics

Our understanding of the pathophysiology of CNS disorders has advanced dramatically in the last 30 years, especially in terms of their molecular pathogenesis and genetics. Drug treatment of CNS disorders has also made remarkable strides, with the introduction of many new drugs for the treatment of schizophrenia, depression, anxiety, epilepsy, Parkinson's disease, and Alzheimer's disease, among many other quantitatively and qualitatively important neuropsychiatric disorders. Improvement in terms of clinical outcome, however, has fallen short of expectations, with up to one third of the patients continuing to experience clinical relapse or unacceptable medication-related side effects in spite of efforts to identify optimal treatment regimes with one or more drugs.[68] Potential reasons to explain this historical setback might be that: (a) the molecular pathology of most CNS disorders is still poorly understood; (b) drug targets are inappropriate, not fitting into the real etiology of the disease; (c) most treatments are symptomatic, but not anti-pathogenic; (d) the genetic component of most CNS disorders is poorly defined; and (e) the understanding of genome–drug interactions is very limited.

With the advent of recent knowledge on the human genome[69,70] and the identification and characterization of many genes associated with CNS disorders,[8,19] as well as novel data regarding CYP family genes and other genes whose enzymatic products are responsible for drug metabolism in the liver (e.g., NATs, ABCBs/MDRs, TPMT), it has been convincingly postulated that the incorporation of pharmacogenetic and pharmacogenomic procedures (Fig. 40.6) in drug development might bring about substantial benefits in terms of therapeutics optimization in CNS disorders and in many other complex disorders, assuming that genetic factors are determinant for both neuronal dysregulation (and/or neuronal death)[8,16–22] and drug metabolism.[71–73]

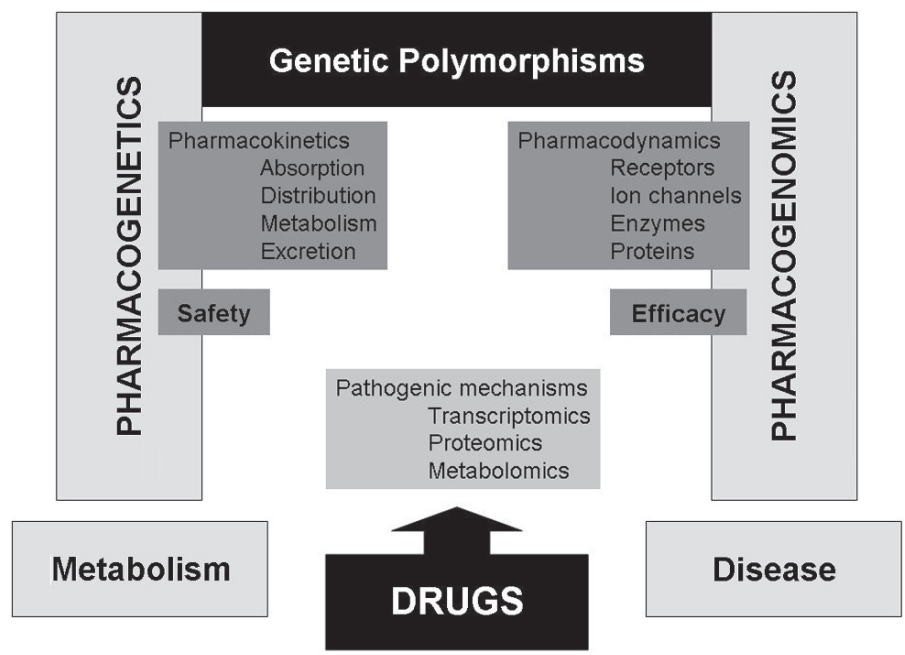

Fig. 40.6 Efficacy and safety issues associated with pharmacogenetics and pharmacogenomics (Adapted from R. Cacabelos[19,20])

However, this field is still in its infancy; and the incorporation of pharmacogenomic strategies to drug development and pharmacological screening in CNS disorders is not an easy task. The natural course of technical events to achieve efficient goals in pharmacogenetics and pharmacogenomics include the following steps: (a) genetic testing of mutant genes and/or polymorphic variants of risk; (b) genomic screening, and understanding of transcriptomic, proteomic, and metabolomic networks; (c) functional genomics studies and genotype–phenotype correlation analysis; and (d) pharmacogenetics and pharmacogenomics developments, addressing drug safety and efficacy, respectively.[8,16–22,74–77]

With pharmacogenetics we can understand how genomic factors associated with genes encoding enzymes responsible for drug metabolism regulate pharmacokinetics and pharmacodynamics (mostly safety issues).[78–80] With pharmacogenomics we can differentiate the specific disease-modifying effects of drugs (efficacy issues) acting on pathogenic mechanisms directly linked to genes whose mutations determine the disease phenotype.[16–22,74–77] The capacity of drugs to reverse the effects of the activation of pathogenic cascades (phenotype expression) regulated by networking genes basically deals with efficacy issues. At present, the terms pharmacogenetics and pharmacogenomics are often used interchangeably to refer to studies of the contribution of inheritance to variation in the drug response phenotype[73]; however, from historical and didactic reasons (until a more suitable and universal definition can be established) it would be preferable to maintain the term of pharmacogenetics for the discipline dealing with genetic factors associated with drug metabolism and safety issues, whereas pharmacogenomics would refer to the reciprocal influence of drugs and genomic factors on pathogenetic cascades and disease-associated gene expression (efficacy issues).[18–22,74–77]

The application of these procedures to CNS disorders is a very difficult task, since most neuropsychiatric diseases are complex disorders in which hundreds of genes might be involved[8,16–22,74–77] (Tables 40.1–40.3). In addition, it is very unlikely that a single drug be able to reverse the multifactorial mechanisms associated with neuronal dysfunction in most CNS processes with a complex phenotype affecting mood, personality, behaviour, cognition, and functioning. This heterogeneous clinical picture usually requires the utilization of different drugs administered simultaneously. This is particularly important in the elderly population. In fact, the average number of drugs taken by patients with dementia ranges from six to more than ten per day depending upon their physical and mental conditions. Nursing home residents receive, on average, seven to eight medications each month, and more than 30% of residents have monthly drug regimes of nine or more medications, including (in descending order) analgesics, antipyretics, gastrointestinal agents, electrolytic and caloric preparations, central nervous system (CNS) agents, anti-infective agents, and cardiovascular agents.[81] In population-based studies more than 35% of patients older than 85 years are moderate or chronic antidepressant users.[82] Polypharmacy, drug–drug interactions, adverse reactions, and non-compliance are substantial therapeutic problems in the pharmacological management of elderly patients,[83] adding further complications and costs to the patients and their caregivers. In 2000–2001, 23.0–36.5% of elderly individuals received at least 1 of 33 potentially inappropriate medications in ten health maintenance organizations (HMOs) of the USA.[84] Although drug effect is a complex phenotype that depends on many factors, it is estimated that genetics accounts for 20–95% of variability in drug disposition and pharmacodynamics.[79] Under these circumstances, therapeutics optimization is a major goal in neuropsychiatric disorders and in the elderly population, and novel pharmacogenetic and pharmacogenomic procedures may help in this endeavour.[16–22,74–77]

Determinant Factors for Sensitivity and Specificity of Pharmacogenomic Studies

The pharmacogenomic outcome depends upon many different determinant factors including (i) genomic profile (family history, ethnic background, disease-related genotype, pharmacogenetic genotype, pharmacogenomic genotype, nutrigenetic genotype, nutrigenomic genotype), (ii) disease phenotype (age at onset, disease severity, clinical symptoms), (iii) concomitant pathology, (iv) genotype–phenotype correlations, (v) nutritional conditions, (vi) age and gender, (vii) pharmacological profile of the drugs, (viii) drug–drug interactions, (ix) gene expression profile, (x) transcriptomic cascade, (xi) proteomic profile, and (xii) metabolomic networking (Fig. 40.7). The dissection and further integration of all these factors is of paramount importance for the assessment of the pharmacogenomic outcome in terms of safety and efficacy (Figs. 40.8 and 40.9).

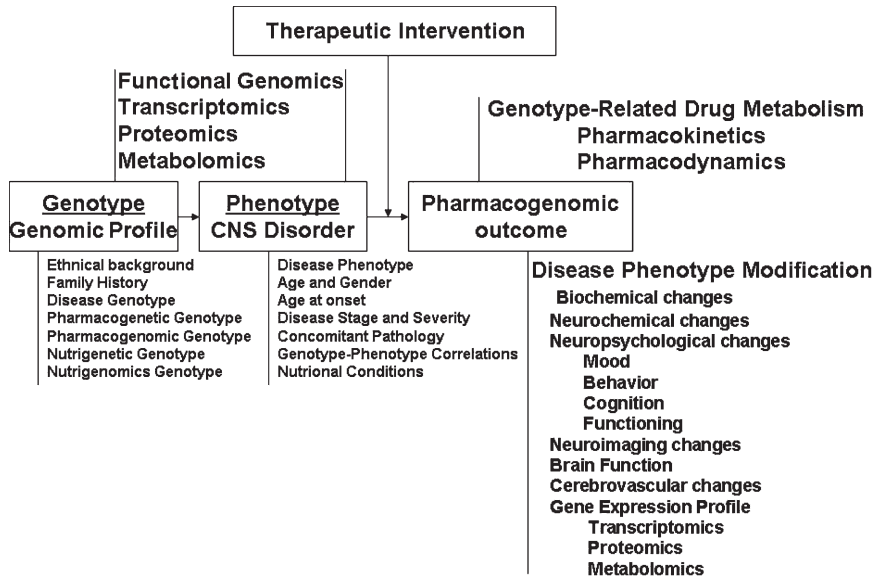

Fig. 40.7 Determinant factors for pharmacogenomic outcomes

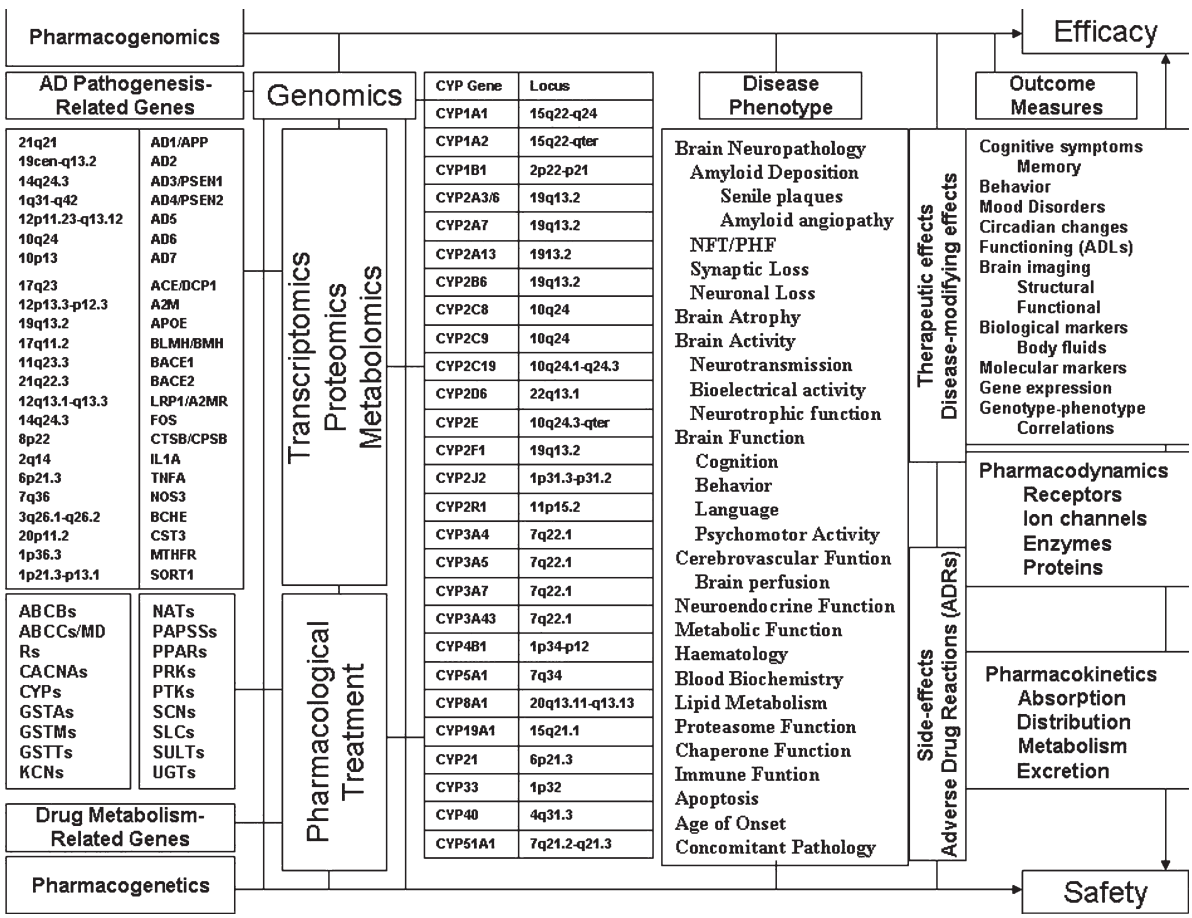

Fig. 40.8 Evaluation of efficacy and safety issues in Alzheimer's disease pharmacogenetics/pharmacogenomics (Adapted from R. Cacabelos[74])

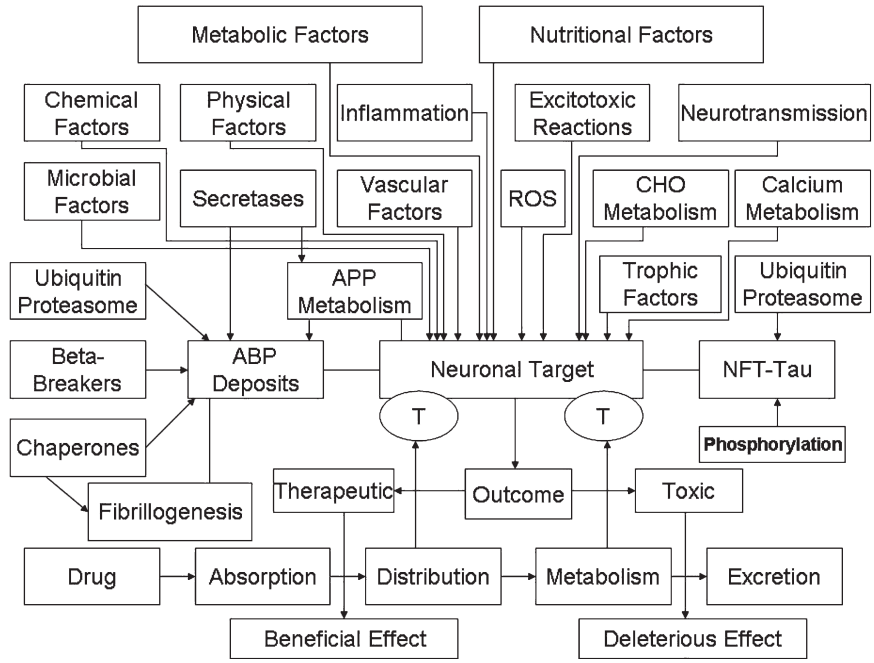

Fig. 40.9 Pathogenic events, therapeutic intervention, and potential pharmacological targets in the treatment of Alzheimer's disease (Adapted from R. Cacabelos[109])

Pharmacogenetics of Drug Metabolism

More than 80% of psychotropic drugs (Table 40.5) are metabolized by enzymes known to be genetically variable, including: (a) esterases: butyrylcholinesterase, paraoxonase/arylesterase; (b) transferases: N-acetyltransferase, sulfotransferase, thiol methyltransferase, thiopurine methyltransferase, catechol-O-methyltransferase, glutathione-S-transferases, UDP-glucuronosyltransferases, glucosyltransferase, histamine methyltransferase; (c) Reductases: NADPH: quinine oxidoreductase, glucose-6-phosphate dehydrogenase; (d) oxidases: alcohol dehydrogenase, aldehydehydrogenase, monoamine oxidase B, catalase, superoxide dismutase, trimethylamine N-oxidase, dihydropyrimidine dehydrogenase; and (e) cytochrome P450 enzymes, such as CYP1A1, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A5 (Table 40.6) and many others.[19,20] Polymorphic variants in these genes can induce alterations in drug metabolism modifying the efficacy and safety of the prescribed drugs.[85]

Drug metabolism includes phase I reactions (i.e., oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e., acetylation, glucuronidation, sulfation, methylation).[80] The principal enzymes with polymorphic variants involved in phase I reactions are the following: CYP3A4/5/7, CYP2E1, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2, epoxide hydrolase, esterases, NQO1 (NADPH-quinone oxidoreductase), DPD (dihydropyrimidine dehydrogenase), ADH (alcohol dehydrogenase), and ALDH (aldehyde dehydrogenase). Major enzymes involved in phase II reactions include the following: UGTs (uridine 5′-triphosphate glucuronosyl transferases), TPMT (thiopurine methyltransferase), COMT (catechol-O-methyltransferase), HMT (histamine methyl-transferase), STs (sulfotransferases), GST-A (glutathion S-transferase A), GST-P, GST-T, GST-M, NAT2 (N-acetyl transferase), NAT1, and others.[86] Polymorphisms in genes associated with phase II metabolism enzymes, such as GSTM1, GSTT1, NAT2 and TPMT are well understood, and information is also emerging on other GST polymorphisms and on polymorphisms in the UDP-glucuronosyltransferases and sulfotransferases.

The CYP Gene Family

The typical paradigm for the pharmacogenetics of phase I drug metabolism is represented by the cytochrome P-450 enzymes, a superfamily of microsomal

Table 40.5 Major and minor substrates, inhibitors and inducers of cytochrome P450 enzymes and other genes. Selected drugs with activity on the central nervous system

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Acetaminophen	Analgesic	CYP1A2	CYP2C19	CYP3A4		CYP2D6
	Narcotic	CYP2C8/8				COMT
Acetylsalicylic acid	Salicylate		CYP2C8/9			GPIIIA
						LTC4S
Alfentanil	Analgesic	CYP3A4				COMT
	Narcotic					
Almotriptan	Antimigraine		CYP2D6			HTR1B
	Serotonin 5HT-1B/1D receptor agonist		CYP3A4			HTR1D
Alosetron	Selective $5HT_3$ receptor antagonist	CYP1A2	CYP2C8/9	CYP1A2	CYP2E1	
			CYP3A4			
Alprazolam	Benzodiazepine	CYP3A4				
Amitriptyline	Tricyclic antidepressant	CYP2D6	CYP1A2	CYP1A2		ABCB1
	tertiary amine		CYP2B6	CYP2C8/9		ADRA1
	benzodiazepine		CYP2C8/9	CYP2C19		GNB3
			CYP2C19	CYP2D6		GNAS1
			CYP3A4	CYP2E1		KCNE2
						SCN5A
						TNF-A
Amoxapine	Tricyclic antidepressant	CYP2D6				ADRA1
	secondary amine					GnB3
						GNAS1
Amphetamine	Stimulant		CYP2D6			
Aripiprazole	Atypical antipsychotic	CYP2D6				ADRA1
		CYP3A4				DRD2
						DRD3
						HTR1A
						HTR2A
						HTR2C
Atomoxetin	Selective norepinephrine reuptake inhibitor	CYP2D6	CYP2C19			
Azelastine	Antihistamine		CYP1A2	CYP2B6		
			CYP2C19	CYP2C8/9		
			CYP2D6	CYP2C19		
			CYP3A4	CYP2D6		
				CYP3A4		
Benzphetamine	Anorexiant	CYP3A4	CYP2B6			
Benztropine	Anticholinergic antiparkinsonian		CYP2D6			
Bromazepam	Benzodiazepine	CYP3A4		CYP2E1		
Bromocriptine	Dopamine agonist	CYP3A4		CYP1A2		
	ergot derivative			CYP3A4		
	antiparkinsonian					
Buprenorphine	Analgesic	CYP3A4		CYP1A2		COMT
	narcotic			CYP2A6		
				CYP2C19		
				CYP2D6		
Bupropion	Antidepressant	CYP2B6	CYP1A2	CYP2D6		
	dopamine-reuptake inhibitor		CYP2A6			

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
			CYP2C8/9 CYP2D6 CYP2E1 CYP3A4			
Buspirone	Antianxiety	CYP3A4	CYP2D6			
Butorphanol	Analgesic narcotic					COMT
Caffeine	Stimulant	CYP1A2	CYP2C8/9 CYP2D6 CYP2E1 CYP3A4	CYP1A2 CYP3A4		
Carbamazepine	Anticonvulsant	CYP3A4	CYP2C8/9		CYP1A2 CYP2B6 CYP2C8/9 CYP2C19 CYP3A4	
Carisoprodol	Skeletal muscle relaxant	CYP2C19				
Celecoxib	Nonsteroidal anti-inflammatory drug COX-2 selective		CYP2C8/9 CYP3A4	CYP2D6		LTC4S
Cetirizine	Antihistamine		CYP3A4			
Cevimeline	Cholinergic agonist		CYP2D6 CYP3A4			
Chlordiazepoxide	Benzodiazepine	CYP3A4				
Chlorpheniramine	Antihistamine	CYP3A4	CYP2D6			
Chlorpromazine	Phenothiazine antipsychotic	CYP2D6	CYP1A2 CYP3A4	CYP2D6 CYP2E1		ABCB1 ADRA1 DRD2 KCNE2 SCN5A
Chlorzoxazone	Skeletal muscle relaxant	CYP2E1	CYP1A2 CYP2A6 CYP2D6 CYP3A4	CYP2E1 CYP3A4		
Cimetidine	Histamine H2 antagonist		CYP2D6	CYP1A2 CYP2C8/9 CYP2C19 CYP2E1 CYP3A4		ABCB1
Cisapride	Gastrointestinal prokinetic	CYP3A4	CYP1A2 CYP2A6 CYP2B6 CYP2C8/9 CYP2C19	CYP2D6 CYP3A4		KCNE2 SCN5A
Citalopram	Antidepressant selective serotonin reuptake inhibitor	CYP2C19 CYP3A4	CYP2D6	CYP1A2 CYP2B6 CYP2C19 CYP2D6		GNB3 GNAS1 HTR2A MAOA SLC6A4

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Clemastine	Antihistamine	CYP2D6				
Clobazam	Benzodiazepine	CYP2D6 CYP3A4				
Clomipramine	Tricyclic antidepressant tertiary amine	CYP1A2 CYP2C19 CYP2D6	CYP3A4	CYP2D6		GNB3 GNAS1
Clonazepam	Benzodiazepine	CYP3A4				
Clorazepate	Benzodiazepine	CYP3A4				
Clozapine	Atypical antipsychotic	CYP1A2	CYP2A6 CYP2C8/9 CYP2C19 CYP2D6 CYP3A4	CYP1A2 CYP2C8/9 CYP2C19 CYP2D6 CYP2E1 CYP3A4		ADRA1 ADRB3 DRD2 DRD3 DRD4 GNB3 GNAS1 RGS2 HLA-A1 HRH1 HRH2 HTR1A HTR2A HTR2C HTR6 SLC6A2 SLC6A4 TNF-A
Cocaine	Local anesthetic	CYP3A4		CYP2D6 CYP3A4		
Codeine	Analgesic narcotic	CYP2D6	CYP3A4	CYP2D6		COMT
Cyclobenzaprine	Skeletal muscle relaxant	CYP1A2	CYP2D6 CYP3A4			
Dantrolene	Skeletal muscle relaxant	CYP3A4				
Desipramine	Tricyclic antidepressant secondary amine	CYP2D6	CYP1A2	CYP2A6 CYP2B6 CYP2D6 CYP2E1 CYP3A4		
Dexmedetomidine	Alpha-2-adrenergic agonist sedative	CYP2A6	CYP1A2 CYP2C8/9 CYP2D6 CYP3A4			
Dextroamphetamine	Stimulant	CYP2D6				
Diazepam	Benzodiazepine	CYP2C19 CYP3A4	CYP1A2 CYP2B6 CYP2C8/9	CYP2C19 CYP3A4		
Diclofenac	Nonsteroidal anti-inflammatory drug		CYP1A2 CYP2B6 CYP2C8/9	CYP1A2 CYP2C8/9 CYP2E1		LTC4S

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
			CYP2C19	CYP3A4		
			CYP2D6			
			CYP3A4			
Dihydrocodeine	Analgesic	CYP2D6				COMT
	narcotic					
Dihydroergotamine	Ergot derivative	CYP3A4		CYP3A4		
Disulfiram	Aldehyde dehydrogenase inhibitor		CYP1A2	CYP1A2		ABCB1
			CYP2A6	CYP2A6		
			CYP2B2	CYP2B6		
			CYP2D6	CYP2C8/9		
			CYP2E1	CYP2D6		
			CYP3A4	CYP2E1		
				CYP3A4		
Domperidone	Dopamine antagonist		CYP3A4			
Donepezil	Acetylcholinesterase inhibitor	CYP2D6	CYP3A4			ACHE
						APOE
Doxepin	Tricyclic antidepressant	CYP1A2				ABCB1
	tertiary amine	CYP2D6				GNB3
		CYP3A4				GNAS1
Droperidol	Antiemetic					ADRA1
	Atypical antipsychotic					DRD2
						KCNE2
						SCN5A
Duloxetin	Antidepressant	CYP1A2		CYP2D6		
	serotonin/norepinephrine reuptake inhibitor	CYP2D6				
Eletriptan	Antimigraine	CYP3A4				
	serotonin 5HT-1B/1D receptor agonist					
Ergoloid Mesylates	Ergot derivative	CYP3A4				
Ergonovine	Ergot derivative	CYP3A4				
Ergotamine	Ergot derivative	CYP3A4		CYP3A4		
Escitalopram	Antidepressant	CYP2D6		CYP2D6		GNB3
	selective serotonin	CYP3A4				GNAS1
	reuptake inhibitor					HTR2A
						SLC6A4
Estazolam	Benzodiazepine		CYP3A4			
Felbamate	Anticonvulsant	CYP3A4	CYP2E1	CYP2C19	CYP3A4	
Fentanyl	Analgesic	CYP3A4		CYP3A4		
	narcotic					
Fexofenadine	Antihistamine		CYP3A4	CYP2D6		ABCB1
Fluoxetine	Antidepressant	CYP2C8/9	CYP1A2	CYP1A2		GNB3
	selective serotonin	CYP2D6	CYP2B2	CYP2B2		GNAS1
	reuptake inhibitor		CYP2C19	CYP2C8/9		HTR2A
			CYP2E1	CYP2C19		SLC6A4
			CYP3A4	CYP2D6		MAOA
				CYP3A4		
Flupenthixol	Atypical antipsychotic					ADRA1
						DRD2
						SCN5A

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Fluphenazine	Atypical antipsychotic phenothiazine	CYP2D6		CYP1A2 CYP2C8/9 CYP2D6 CYP2E1		ABCB1 ADRA1 DRD2
Flurazepam	Benzodiazepine	CYP3A4		CYP2E1		
Flurbiprofen	Nonsteroidal anti-inflammatory drug		CYP2C8/9	CYP2C8/9		LTC4S
Fluvoxamine	Antidepressant selective serotonin reuptake inhibitor	CYP1A2 CYP2D6		CYP1A2 CYP2B6 CYP2C8/9 CYP2C19 CYP2D6 CYP3A4		
Fosphenytoin	Anticonvulsant hydantoin	CYP2C8/9 CYP2C19	CYP3A4		CYP2B6 CYP2C8/9 CYP2C19 CYP3A4	
Frovatriptan	Antimigraine serotonin 5HT-1B/1D receptor agonist		CYP1A2			
Galantamine	Acetylcholinesterase inhibitor	CYP2D6	CYP3A4			ACHE APOE
Haloperidol	Typical antipsychotic	CYP2D6 CYP3A4	CYP1A2	CYP2D6 CYP3A4		ABCB1 ADR1A DRD2 DRD3 DRD4 KCNE2 SCN5A
Halothane	Anesthetic	CYP2E1	CYP2A6 CYP2B6 CYP2C8/9 CYP2D6 CYP3A4			
Hydrocodone	Analgesic	CYP2D6				COMT
Hydromorphone	Analgesic narcotic					COMT
Ibuprofen	Nonsteroidal anti-inflammatory drug		CYP2C8/9 CYP2C19	CYP2C8/9		LTC4S
Imipramine	Tricyclic antidepressant tertiary amine	CYP2C19 CYP2D6	CYP1A2 CYP2B6 CYP3A4	CYP1A2 CYP2C19 CYP2D6 CYP2E1		ABCB1 ADRA1 GNB3 GNAS1 KCNE2 SCN5A

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Indomethacin	Nonsteroidal anti-inflammatory drug		CYP2C8/9 CYP2C19	CYP2C8/9 CYP2C19		LTC4S
Ketamine	Anesthetic	CYP2B6 CYP2C8/9 CYP3A4				
Levorphanol	Analgesic narcotic					COMT
Lidocaine	Analgesic Anesthetic	CYP2D6 CYP3A4	CYP1A2 CYP2A6 CYP2B6 CYP2C8/9	CYP1A2 CYP2D6 CYP3A4		ABCB1
Lithium	Lithium					COMT DRD2 DRD3 DRD4 GABA GNB3 HTR2A HTR2C INPP1 MAOA SLC6A4 TPH2
Loratidine	Antihistamine		CYP2D6 CYP3A4	CYP2C19 CYP2D6		
Loxapine	Typical antipsychotic					ADR1A DRD2 KCNE2 SCN5A
Maprotiline	Tetracyclic antidepressant	CYP2D6				ABCB1
Mefenamic acid	Nonsteroidal anti-inflammatory drug		CYP2C8/9			LTC4S
Meloxicam	Nonsteroidal anti-inflammatory drug		CYP2C8/9 CYP3A4	CYP2C8/9		LTC4S
Meperidine	Analgesic narcotic		CYP2B6 CYP2C19 CYP3A4			COMT
Mephenytoin	Anticonvulsant	CYP2C8/9 CYP2C19	CYP2B6			
Mephobarbital	Barbiturate	CYP2C19	CYP2B6 CYP2C8/9	CYP2C19	CYP2A6	
Mesoridazine	Typical antipsychotic phenothiazine					ADR1A DRD2 KCNE2 SCN5A
Methadone	Analgesic narcotic	CYP3A4	CYP2C8/9 CYP2C19 CYP2D6	CYP2D6 CYP3A4		COMT
Methamphetamine	Stimulant	CYP2D6				

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Methotrimeprazine	Analgesic narcotic					COMT
Methosuximide	Anticonvulsant succinimide	CYP2C19		CYP2C19		
Methylergonovine	Ergot derivative	CYP3A4				
Methyphenidate	Stimulant	CYP2D6		CYP2D6		SLC6A3
Metoclopramide	Antiemetic gastrointestinal prokinetic		CYP1A2 CYP2D6			DRD2
Midazolam	Benzodiazepine	CYP3A4	CYP2B6	CYP2C8/9 CYP3A4		ABCB1
Mirtazapine	Antidepressant alpha-2 antagonist	CYP1A2 CYP2D6 CYP3A4	CYP2C8/9	CYP1A2 CYP3A4		ADRA1 GNB3 GNAS1
Moclobemide	Antidepressant reversible MAO inhibitor	CYP2C19 CYP2D6		CYP1A2 CYP2C19 CYP2D6		MAOA
Modafinil	Stimulant	CYP3A4		CYP1A2 CYP2A2 CYP2C8/9 CYP2C19 CYP2E1 CYP3A4		
Molindone	Typical antipsychotic					ADRA1 DRD2
Morphine sulfate	Analgesic narcotic		CYP2D6			COMT
Naproxen	Nonsteroidal anti-inflammatory drug		CYP1A2 CYP2C8/9			LTC4S
Nefazodone	Antidepressant serotonin reuptake inhibitor/ antagonist	CYP2C8/9 CYP3A4		CYP1A2 CYP2B6 CYP2D6 CYP3A4		ABCB1 ADRA1 GNB3 GNAS1
Nicardipine	Calcium channel blocker	CYP3A4	CYP1A2 CYP2C8/9 CYP2D6 CYP2E1	CYP2C8/9 CYP2C19 CYP2D6 CYOP3A4		ABCB1
Nicotine	Cholinergic agonist stimulant		CYP1A2 CYP2A6 CYP2B6 CYP2C8/9 CYP2C19 CYP2D6 CYP2E1 CYP3A4		CYP2A6 CYP2E1	CHRNA2 CHRNA3 CHRNA4 CHRNA5 CHRNA9 CHRNA10 CHRNB2 CHRNA3 CHRNA4 CHRNA7
Nifedipine	Calcium channel blocker	CYP3A4	CYP2D6	CYP1A2 CYP2C8/9		ABCB1

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
				CYP2D6		
				CYP3A4		
Nimodipine	Calcium channel blocker	CYP3A4				
Nisoldipine	Calcium channel blocker	CYP3A4		CYP1A2		
				CYP3A4		
Nitrendipine	Calcium channel blocker	CYP3A4		CYP3A4		ABCB1
Nortriptyline	Tricyclic antidepressant	CYP2D6	CYP1A2	CYP2D6		ABCB1
	secondary amine		CYP2C19	CYP2E1		ADRA1
			CYP3A4			GNB3
						GNAS1
Olanzapine	Atypical antipsychotic		CYP1A2	CYP1A2		ADRA1
			CYP2D6	CYP2C8/9		DRD2
				CYP2C19		DRD3
				CYP2D6		HRH1
				CYP3A4		HRH2
						HTR2A
						HTR2C
						HTR6
						RGS2
						TNF-A
Ondansetron	Antiemetic	CYP3A4	CYP1A2	CYP1A2		
	Selective 5HT3 receptor		CYP2C8/9	CYP2C8/9		
	antagonist		CYP2D6	CYP2D6		
			CYP2E1			
Orphenadrine	Anticholinergic		CYP1A2	CYP1A2		
	antiparkinsonian		CYP2B6	CYP2A6		
	skeletal muscle relaxant		CYP2D6	CYP2B6		
			CYP3A4	CYP2C8/9		
				CYP2C19		
				CYP2D6		
				CYP2E1		
				CYP3A4		
Oxacepam	Benzodiazepine		CYP3A4			
Oxybutynin	Antispasmodic		CYP3A4	CYP2D6		
				CYP3A4		
Oxycodone	Analgesic	CYP2D6				COMT
	narcotic					
Oxymorphone	Analgesic					COMT
	narcotic					
Paroxetine	Antidepressant	CYP2D6		CYP1A2		DRD2
	selective serotonin reuptake inhibitor			CYP2B6		DRD4
				CYP2C8/9		GNB3
				CYP2C19		GNAS1
				CYP2D6		HTR2A
				CYP3A4		MAOA
						SLC6A4
						TNF-A
						TPH2
Pentazocine	Analgesic					COMT
	narcotic					

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Pentobarbital	Barbiturate				CYP2A6 CYP3A4	
Pergolide	Antiparkinsonian dopamine agonist Ergot derivative	CYP3A4		CYP2D6 CYP3A4		
Perphenazine	Typical antipsychotic phenothiazine	CYP2D6	CYP1A2 CYP2C8/9 CYP2C19 CYP3A4	CYP1A2 CYP2D6		ADRA1 DRD3
Phencyclidine	Anesthetic	CYP3A4		CYP3A4		
Phenobarbital	Anticonvulsant barbiturate	CYP2D6	CYP2C8/9 CYP2E1		CYP1A2 CYP2A6 CYP2B6 CYP2C8/9 CYP3A4	
Phenytoin	Anticonvulsant barbiturate	CYP2C8/9 CYP2C19	CYP3A4		CYP2B6 CYP2C8/9 CYP2C19 CYP3A4	ABCB1
Pimozide	Typical antipsychotic	CYP1A2 CYP3A4		CYP2C19 CYP2D6 CYP2E1 CYP3A4		ADRA1 DRD2 KCNE2 SCN5A
Pinazepam	Benzodiazepine		CYP3A4			
Pindolol	Beta blocker	CYP2D6		CYP2D6		
Pipotiazine	Typical antipsychotic phenothiazine piperidine	CYP2D6 CYP3A4				
Piroxicam	Nonsteroidal anti-inflammatory drug		CYP2C8/9	CYP2C8/9		LTC4S
Prazepam	Benzodiazepine		CYP3A4			
Procainamide	Class Ia antiarrhythmic	CYP2D6				
Prochlorperazine	Typical antipsychotic phenothiazine					ABCB1 ADRA1 DRD2
Promethazine	Antihistamine phenothiazine	CYP2B6 CYP2D6		CYP2D6		
Propafenone	Class Ic antiarrhythmic	CYP2D6	CYP1A2	CYP1A2 CYO2C8/9 CYP2D6		ABCB1
Propofol	Anesthetic	CYP2B6 CYP2C8/9	CYP1A2 CYP2A6 CYP2C19 CYP2D6 CYP2E1 CYP3A4	CYP1A2 CYP2C8/9 CYP2C19 CYP2D6 CYP2E1 CYP3A4		
Propoxyphene	Analgesic narcotic					COMT
Propranolol	Class II antiarrhythmic nonselective beta-adrenergic blocker	CYP1A2 CYP2D6	CYP2C19 CYP3A4	CYP1A2 CYP2D6		ABCB1 ADRB1 GNAS1

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
Protriptyline	Tricyclic antidepressant secondary amine	CYP2D6				
Quazepam	Benzodiazepine		CYP3A4			
Quetiapine	Atypical antipsychotic	CYP3A4	CYP2D6			ADRA1 DRD2 KCNE2 SCN5A
Quinidine	Class Ia antiarrhythmic	CYP3A4	CYP2C8/9 CYP2E1	CYP2C8/9 CYP2D6 CYP3A4		ABCB1 G6PD KCNE2 SCN5A
Ranitidine	Histamine H2 antagonist		CYP1A2 CYP2D6 CYP2C19	CYP1A2 CYP2D6		ABCB1 HRH2
Remifentanil						COMT
Reserpine	Monoamine-depleting agent Rauwolfia alkaloid					ABCB1
Riluzole	Glutamate inhibitor	CYP1A2				
Rivastigmine	Acetylcholinesterase inhibitor					ACHE APOE
Risperidone	Atypical antipsychotic	CYP2D6	CYP2A4	CYP2D6 CYP3A4		ABCB1 ADRA1 DRD2 DRD3 DRD4 HTR1A HTR2A HTR2C KCNE2 RGS2 SLC6A2 SCN5A
Rizatriptan	Antimigraine 5HT-1 receptor agonist					HTR1
Rofecoxib	Nonsteroidal anti-inflammatory drug COX-2 selective		CYP2D6	CYP1A2	CYP3A4	LTC4S
Ropinirole	Antiparkinsonian dopamine agonist			CYP1A2 CYP2D6		
Rosiglitazone	Antidiabetic thiazolidinedione	CYP2C8/9		CYP2C8/9 CYP2C19 CYP2D6		
Secobarbital	Barbiturate				CYP2A6 CYP2C8/9	
Selegiline	Antiparkinsonian MAOB inhibitor	CYP2B6 CYP2C8/9	CYP1A2 CYP2A6 CYP2D6	CYP1A2 CYP2A6 CYP2C8/9 CYP3A4 CYP2D6 CYP2E1	CYP2C19	

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
				CYP3A4		
Sertraline	Antidepressant	CYP2C19	CYP2B6	CYP1A2		
	selective serotonin	CYP2D6	CYP2C8/9	CYP2B6		
	reuptake inhibitor		CYP3A4	CYP2C8/9		
				CYP2C19		
				CYP2D6		
				CYP3A4		
Sildenafil	Phosphodiesterase-5 inhibitor	CYP3A4	CYP2C8/9	CYP1A2		
				CYP2C8/9		
				CYP2C19		
				CYP2D6		
				CYP2E1		
				CYP3A4		
Sufentanil	Analgesic	CYP3A4				
	anesthetic					
	narcotic					
Sumatriptan	Antimigraine					HTR1D
	serotonin 5HT-1D receptor agonist					
Tacrine	Tetrahydroaminoacridine	CYP1A2		CYP1A2		
	acetylcholinesterase inhibitor					
Temazepam	Benzodiazepine		CYP2B6			
			CYP2C8/9			
			CYP2D6			
			CYP3A4			
Thioridazine	Typical antipsychotic	CYP2D6	CYP2C19	CYP1A2		ADRA1
				CYP2C8/9		DRD2
	phenothiazine					
				CYP2D6		KCNE2
				CYP2E1		SCN5A
Thiothixene	Typical antipsychotic	CYP1A2		CYP2D6		ADRA1
						DRD2
						KCNE2
						SCN5A
Tiagabine	Anticonvulsant	CYP3A4				GABAR
Topiramate	Anticonvulsant			CYP2C19	CYP2E1	
Tramadol	Analgesic	CYP2D6	CYP3A4			COMT
Trazodone	Antidepressant	CYP3A4	CYP2D6	CYP2D6		ADRA1
	serotonin reuptake inhibitor/ antagonist					GNB3
						GNAS1
Triazolam	Benzodiazepine	CYP3A4		CYP2C8/9		
Trifluoperazine	Typical antipsychotic	CYP1A2				ADRA1
	phenothiazine					DRD2
Trimipramine	Tricyclic antidepressant	CYP2C19				ABCB1
	tertiary amine	CYP2D6				ADRA1
		CYP3A4				GNB3
						GNAS1
Valdecoxib	Nonsteroidal anti-inflammatory drug		CYP2C8/9			LTC4S
			CYP3A4			

(continued)

Table 40.5 (continued)

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Inducers	Other Genes
	COX-2 selective					
Valproic acid	Anticonvulsant		CYP2A6 CYP2B6 CYP2C8/9 CYP2C19 CYP2E1	CYP2C8/9 CYP2C19 CYP2D6 CYP3A4	CYP2A6	
Vardenafil	Phosphodiesterase-5 inhibitor	CYP3A4				
Venlafaxine	Antidepressant norepinephrine/serotonin reuptake inhibitor	CYP2D6 CYP3A4	CYP2C8/9 CYP2C19	CYP2B6 CYP2D6 CYP3A4		
Ziprasidone	Atypical antipsychotic		CYP1A2 CYP3A4	CYP2D6 CYP3A4		ADRA1 DRD2 DRD3 HTR1A HTR2A HTR2C KCNE2 SCN5A
Zolmitriptan	Antimigraine serotonin 5HT-1B/1D receptor agonist		CYP1A2			HTR1B HTR1D
Zolpidem	Hypnotic nonbenzodiazepine	CYP3A4	CYP1A2 CYP2C8/9 CYP2C19 CYP2D6			
Zonisamide	Anticonvulsant	CYP3A4				
Zopiclone	Hypnotic nonbenzodiazepine	CYP2C8/9 CYP3A4				
Zuclopenthixol	Typical antipsychotic	CYP2D6				ADRA1 DRD2 KCNE2 SCN5A

ABCB1: ATP-Binding Cassette, Subfamily B, Member 1
ACHE: Acetylcholinesterase
ADRA1: Alpha-1-Adrenergic Receptor
ADRB1: Beta-1-Adrenergic Receptor
ADRB3: Beta-3-Adrenergic Receptor
APOE: Apolipoprotein E
CHRNA2: Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 2
CHRNA3: Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 3
CHRNA4: Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 4
CHRNA5: Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 5
CHRNA9: Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 9
CHRNA10: Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 10
CHRNB2: Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 2
CHRNA3: Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 3
CHRNA4: Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 4
CHRNA7: Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 7
COMT: Catechol-O-Methyl Transferase
CYP: Cytochrome P450 Family Genes

Table 40.5 (continued)

DRD2: Dopamine Receptor D2
DRD3: Dopamine Receptor D3
DRD4: Dopamine Receptor D4
GABAR: Gamma-Aminobutyric Acid Receptors
G6PD: Glucose-6-Phosphate Dehydrogenase
GNB3: G-Protein Beta-3 Subunit
GNAS1: Gs Protein Alpha-Subunit
GPIIIA: Glycoprotein IIIa Receptor
HLA-A1: Minor Histocompatibility Antigen HA-1
HRH1: Histamine Receptor H1
HRH2: Histamine Receptor H2
HTR1A: Serotonin Receptor 1A
HTR1B: Serotonin Receptor 1B
HTR1D: Serotonin Receptor 1D
HTR2A: Serotonin Receptor 2A
HTR2C: Serotonin Receptor 2C
HTR6: Serotonin Receptor 6
INPP1: Inositol Polyphosphate 1-Phosphatase
KCNE2: Cardiac Potassium Ion Channel
LTC4S: Leukotriene C4 Synthase
MAOA: Monoamine Oxidase A
MAOB: Monoamine Oxidase B
RGS2: Regulator of G-Protein Signaling 2
SCN5A: Cardiac Sodium Channel
SLC6A2: Solute Carrier Family 6 (Neurotransmitter Transporter, Noradrenaline), Member 2
SLC6A3: Solute Carrier Family 6 (Neurotransmitter Transporter, Dopamine), Member 3
SLC6A4: Solute Carrier Family 6 (Neurotransmitter Transporter, Serotonin), Member 4
TNF-A: Tumor Necrosis Factor-Alpha
TPH2: Tryptophan Hydroxylase
Source: R. Cacabelos. CIBE Database (2008); R. Cacabelos and M. Takeda[19]; L.M. Cavallari, V.L. Ellingrod, and J.M. Kolesar[125]; C.F. Lacy et al[126]; M.A. Fuller & M. Sajatovic[127]; www.pharmgkb.org[206]; www.ncbi.nlm.nih.gov[10]

drug-metabolizing enzymes. P450 enzymes comprise a superfamily of heme-thiolate proteins widely distributed in bacteria, fungi, plants and animals. The P450 enzymes are encoded in genes of the CYP superfamily (Table 40.6) and act as terminal oxidases in multicomponent electron transfer chains which are called P450-containing monooxigenase systems. Some of the enzymatic products of the CYP gene superfamily can share substrates, inhibitors and inducers whereas others are quite specific for their substrates and interacting drugs.[18–20,71–73,78–80]

There are more than 200 P450 genes identified in different species. Saito et al[87] provided a catalogue of 680 variants among eight CYP450 genes, nine esterase genes, and two other genes in the Japanese population.

The microsomal, membrane-associated, P450 isoforms CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2E1, and CYP1A2 are responsible for the oxidative metabolism of more than 90% of marketed drugs. About 60–80% of the psychotropic agents currently used for the treatment of neuropsychiatric disorders are metabolized via enzymes of the CYP family, especially CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6 and CYP3A4 (Table 40.5). CYP3A4 metabolizes more drug molecules than all other isoforms together. Most of these polymorphisms exhibit geographic and ethnic differences.[88–94] These differences influence drug metabolism in different ethnic groups in which drug dosage should be adjusted according to their enzymatic capacity, differentiating normal or extensive metabolizers (EMs), poor metabolizers (PMs) and ultrarapid metabolizers (UMs). Most drugs act as substrates, inhibitors or inducers of CYP enzymes. Enzyme induction enables some xenobiotics to

Table 40.6 CYP genes encoding Cytochrome P450-related enzymes involved in human pharmacogenetic activities

Gene	Locus	Name	Alternate names	Related drugs	Related Diseases	OMIM	Alternate Symbols
CYP1A2	15q22-qter	Cytochrome P450, subfamily (aromatic compound-inducible), polypeptide 2	P450 form 4; aryl hydrocarbon hydroxylase; cytochrome P450, subfamily 1 (aromatic compound-inducible), polypeptide 2; dioxin-inducible P3–450; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Amiodarone, caffeine, citalopram, clozapine, cyclobenzaprine, dexamethasone, echinacea, estradiol, etoposide, fluovoxamine, haloperidol, imipramine, interferon alpha, lidocaine, mibefradil, midazolam, modafinil, naproxen, ondansetron, propranolol, ribavirin, riluzole, ropivacaine, tacrine, teniposide, theophylline, thiotepa, ticlopidine, verapamil, zolmitriptan, zoxazolamine	Chronic hepatitis C, schizophrenia, psychosis	124060	CP12; P3–450; P450(PA)
CYP1B1	2p21	Cytochrome P450, subfamily 1 (dioxin-inducible), polypeptide 1 (glaucoma 3, primary infantile)	Aryl hydrocarbon hydroxylase; cytochrome P450, subfamily 1 (dioxin-inducible), polypeptide 1 (glaucoma 3, primary infantile); flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Estrogens	Breast neoplasms Primary congenital glaucoma 3A; early-onset digenic glaucoma; Peters anomaly	601771	CP1B; GLC3A
CYP2A6	19q13.2	Cytochrome P450, family 2, subfamily A, polypeptide 6	Coumarin 7-hydroxylase; cytochrome P450, subfamily IIA (Phenobarbital-inducible), polypeptide 3; cytochrome P450, subfamily IIA (Phenobarbital-inducible), polypeptide 6; flavoprotein-linked monooxygenase; xenobiotic monooxygenase	5-Fluorouracil, dexamethasone, etoposide, fadrozole, fluorouracil, midazolam, nicotine, rifampin, teniposide	Neoplasms, Coumarin resistance, protection from nicotine addiction	122720	CPA6; CYP2A3

(continued)

Table 40.6 CYP genes encoding Cytochrome P450-related enzymes involved in human pharmacogenetic activities

Gene	Locus	Name	Alternate names	Related drugs	Related Diseases	OMIM	Alternate Symbols
CYP2B6	19q13.2	Cytochrome P450, family 2, subfamily B, polypeptide 6	Cytochrome P450, subfamily IIB (Phenobarbital-inducible), polypeptide 6	Aflatoxin B1, bupropion, cyclophosphamide, dexamethasone, etoposide, ifosfamide, midazolam, phenobarbital, propofol, rifampin, teniposide, thiotepa, vitamin D, xenobiotics	Nicotine addiction	123930	CPB6; CYPIIB6; P450
CYP2C19	10q24.-q24.3	Cytochrome P450, family 2, subfamily C, polypeptide 19	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 19; flavoprotein-linked monooxygenase; mephenytoin 4′-hydroxylase; microsomal monooxygenase; xenobiotic monooxygenase	Amitriptyline, carisoprodol, citalopram, cyclophosphamide, diazepam, fluoxetine, fluvoxamine, glucorticoids, hexobarbital, lansoprazole, mephenytoin, modafinil, nelfinavir, nilutamide, omeprazole, pantoprazole, proguanil, rifampin, thiotepa, ticlopidine	Lupus nephritis, gastroesophageal reflux disease, peptic ulcer disease, visual disorders Mephenytoin poor metabolizer	124020	CPCJ; CYP2C; P450C2C; P450IIC19
CYP2C9	10q24	Cytochrome P450, family 2, subfamily C, polypeptide 9	Cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 10; cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase), polypeptide 9; flavoprotein-linked monooxygenase; mephenytoin 4-hydroxylase; microsomal monooxygenase; xenobiotic monooxygenase	Acenocoumarol, amiodarone, celecoxib, coumadin, dexamethasone, diclofenac, etoposide, fluconazole, fluoxetine, fluvastatin, fluvoxamine, glimepiride, glipizide, glyburide, ibuprofen, irbesartan, isoniazid, losartan, midazolam, phenylbutazone, phenytoin, rifampin, teniposide, tenoxicam, thiotepa, tolbutamide, torsemide, vitamin D, warfarin	Arthritis, blood coagulation disorders, diabetes mellitus, epilepsy, hypertension, thrombolytic disease, Tolbutamide poor metabolizer, warfarin sensitivity	601130	CPC9; CYP2C10; P450 MP-4; P450 PB-1; P450IIC9

CYP2D6	22q13.1	Cytochrome P450, family 2, subfamily D, polypeptide 6	Cytochrome P450, subfamily IID (debrisoquine, sparteine), polypeptide 6; cytochrome P450, subfamily IID (debrisoquine, sparteine)-like 1; debrisoquine 4-hydroxylase; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Amitriptyline, caffeine, cimetidine, citalopram, clomipramine, clozapine, cocaine, codeine, debrisoquine, desipramine, dextromethorphan, diltizem, flecainide, fluoxetine, fluvoxamine, haloperidol, imipramine, interferon alpha, metoprolol, mexiletine, morphine, paroxetine, perhexiline, perphenazine, propafenone, propranolol, ribavirin, risperidone, ritonavir, sparteine, tamoxifen, thioridazine, thiotepa, timolol, tramadol, venlafaxine, xenobiotics, yohimbine, zuclopenthixol	Breast neoplasms, cystic fibrosis, depression, chronic hepatitis C, lung neoplasms, neoplasms, codeine dependence pain, schizophrenia, codeine dependence, psychosis, Susceptibility to parkinsonism, debrisoquine sensitivity	124030	CPD6; CYP2D; CYP2D6; CYP2DL1; P450-DB1; P450C2D
CYP2E1	10q24.3-qter	Cytochrome P450, subfamily IIE (ethanol-inducible)	Cytochrome P450, subfamily IIE (ethanol-inducible); cytochrome P450, subfamily IIE (ethanol-inducible), polypeptide 1; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Dexamethasone, ethanol, etoposide, midazolam, nicotine, teniposide, thiotepa, xenobiotics	Alcoholic liver disease, lung neoplasms, nicotine dependency	124040	CPE1; CYP2E; CYP2E1; P450-J; P450C2E
CYP3A	7q21.--q22.1	Cytochrome P450, family 3, subfamily A	Cytochrome P450, subfamily IIIA (niphedipine oxidase)	Dexamethasone, docetaxel, erythromycin, midazolam, rifampin, tamoxifen, thiotepa, xenobiotics	Arrhythmia, lung neoplasms	124010	CYP3
CYP3A4	7q21.1	Cytochrome P450, family 3, subfamily A, polypeptide 4	P450-III, steroid inducible; cytochrome P450, subfamily IIIA (nifedipine oxidase), polypeptide 3; cytochrome P450, subfamily IIIA (nifedipine oxidase), polypeptide 4; glucocorticoid-inducible P450; nifedipine oxidase	Alprazolam, anthracycline, cisapride, citalopram, dexamethasone, docetaxel, epipodophyllotoxin, etoposide, glucocorticoids, interferon alpha, irinotecan, losartan, midazolam, nifedipine, omeprazole, ribavirin, rifampin, tamoxifen, teniposide, testosterone, topotecan, vitamin D, xenobiotics	Breast neoplasms, chronic hepatitis C, leukaemia, L1 acute lymphocytic leukaemia, myeloid leukaemia, neoplasms, prostatic neoplasms, helycobarcter pylori gastric ulcers	124010	CP33; CP34; CYP3A; CYP3A3; CYP3A4; HLP; NF-25; P450C3; P450PCN1

(continued)

Table 40.6 (continued)

Gene	Locus	Name	Alternate names	Related drugs	Related Diseases	OMIM	Alternate Symbols
CYP3A7	7q21-q22.1	Cytochrome P450, family 3, subfamily A, polypeptide 7	Aryl hydrocarbon hydrolase; cytochrome P450, subfamily IIIA, polypeptide 7; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase	Cisapride, midazolam, vitamin D, xenobiotics		605340	CP37; P450-HFLA
CYP4B1	1p34-p12	Cytochrome P450, subfamily IVB, polypeptide 1	Cytochrome P450, subfamily IVB, member 1; cytochrome P450, subfamily IVB, polypeptide 1; microsomal monooxygenase	Xenobiotics		124075	P-450HP
CYP11B2	8q21-q22	Cytochrome P450, family 11, subfamily B, polypeptide 2	Steroid 11-beta/18-hydrolase; aldosterone synthase; cytochrome P450, subfamily XIB (steroid 11-beta-hydrolase), polypeptide 2; steroid 11-beta-monooxygenase; steroid 11-beta/18-hydrolase	Candesartan	Aldosterone to rennin ratio raised, congenital hypoaldosteronism due to CMO I deficit, congenital hypoaldosteronism due to CMO II deficit, low rennin hypertension	124080	ALDOS; CPN2; CYP11B; CYP11BL; P-450C-18; P450aldo

(Adapted from R. Cacabelos and M. Takeda[19])

accelerate their own biotransformation (auto-induction) or the biotransformation and elimination of other drugs. A number of P450 enzymes in human liver are inducible. Induction of the majority of P450 enzymes occurs by increase in the rate of gene transcription and involves ligand-activated transcription factors, aryl hydrocarbon receptor, constitutive androstane receptor (CAR), and pregnane X receptor (PXR).[93,95] In general, binding of the appropriate ligand to the receptor initiates the induction process that cascades through a dimerization of the receptors, their translocation to the nucleus and binding to specific regions in the promoters of CYPs.[95] CYPs are also expressed in the CNS, and a complete characterization of constitutive and induced CYPs in brain is essential for understanding the role of these enzymes in neurobiological functions and in age-related and xenobiotic-induced neurotoxicity.[96]

Assuming that the human genome contains about 20,000–30,000 genes, at the present time only 0.31% of commercial drugs have been assigned to corresponding genes whose gene products might be involved in pharmacokinetic and pharmacodynamic activities of a given drug; and only 4% of the human genes have been assigned to a particular drug metabolic pathway. Supposing a theoretical number of 100,000 chemicals in current use worldwide, and assuming that practically all human genes can interact with drugs taken by human beings, each gene in the human genome should be involved in the metabolism and/or biopharmacological effect of 30–40 drugs; however, assuming that most xenobiotic substances in contact with our organism can influence genomic function, it might be possible that for 1,000,000 xenobiotics in daily contact with humans, an average of 350–500 xenobiotics have to be assigned to each one of the genes potentially involved in drug metabolism and/or xenobiotics processing. To fulfil this task a single gene has to possess the capacity of metabolizing many different xenobiotic substances and at the same time many different genes have to cooperate in orchestrated networks to metabolize a particular drug or xenobiotic under sequential biotransformation steps (Figs. 40.7 and 40.8). Numerous chemicals increase the metabolic capability of organisms by their ability to activate genes encoding various xenochemical-metabolizing enzymes, such as CYPs, transferases and transporters. Many natural and artificial substances induce the hepatic CYP subfamilies in humans, and these inductions might lead to clinically important drug–drug interactions. Some of the key cellular receptors that mediate such inductions have been recently identified, including nuclear receptors, such as the constitutive androstane receptor (CAR, NR1I3), the retinoid X receptor (RXR, NR2B1), the pregnane X receptor (PXR, NR1I3), and the vitamin D receptor (VDR, NR1I1) and steroid receptors such as the glucocorticoid receptor (GR, NR3C1).[97] There is a wide promiscuity of these receptors in the induction of CYPs in response to xenobiotics. Indeed, this adaptive system acts as an effective network where receptors share partners, ligands, DNA response elements and target genes, influencing their mutual relative expression.[97,98]

Ethnic Differences

The most important enzymes of the P450 cytochrome family in drug metabolism by decreasing order are CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP2A6.[85–87,94,99,100] The predominant allelic variants in the CYP2A6 gene are CYP2A6*2 (Leu160His) and CYP2A6del. The CYP2A6*2 mutation inactivates the enzyme and is present in 1–3% of Caucasians. The CYP2A6del mutation results in no enzyme activity and is present in 1% of Caucasians and 15% of Asians.[18–20,86] The most frequent mutations in the CYP2C9 gene are CYP2C9*2 (Arg144Cys), with reduced affinity for P450 in 8–13% of Caucasians, and CYP2C9*3 (Ile359Leu), with alterations in the specificity for the substrate in 6–9% of Caucasians and 2–3% of Asians.[18–20,86] The most prevalent polymorphic variants in the CYP2C19 gene are CYP2C19*2, with an aberrant splicing site resulting in enzyme inactivation in 13% of Caucasians, 23–32% of Asians, 13% of Africans, and 14–15% of Ethiopians and Saoudians, and CYP2C19*3, a premature stop codon resulting in an inactive enzyme present in 6–10% of Asians, and almost absent in Caucasians.[18–20,86,101] The most important mutations in the CYP2D6 gene are the following: CYP2D6*2xN, CYP2D6*4, CYP2D6*5, CYP2D6*10 and CYP2D6*17.[18–20,96,102] The CYP2D6*2xN mutation gives rise to a gene duplication or multiplication resulting in an increased enzyme activity which appears in 1–5% of the Caucasian population, 0–2% of Asians, 2% of Africans, and 10–16% of Ethiopians. The defective splicing caused by the CYP2D6*4 mutation inactivates the enzyme and is present in 12–21% of Caucasians. The deletion in CYP2D6*5 abolishes enzyme activity and shows a frequency of 2–7% in

Caucasians, 1% in Asians, 2% in Africans, and 1–3% in Ethiopians. The polymorphism CYP2D6*10 causes Pro34Ser and Ser486Thr mutations with unstable enzyme activity in 1–2% of Caucasians, 6% of Asians, 4% of Africans, and 1–3% of Ethiopians. The CYP2D6*17 variant causes Thr107Ile and Arg296Cys substitutions which produce a reduced affinity for substrates in 51% of Asians, 6% of Africans, and 3–9% of Ethiopians, and is practically absent in Caucasians.[18–20,86,96,102]

CYP2D6 in Dementia

The CYP2D6 enzyme, encoded by a gene that maps on 22q13.1–13.2, catalyses the oxidative metabolism of more than 100 clinically important and commonly prescribed drugs such as cholinesterase inhibitors, antidepressants, neuroleptics, opioids, some β-blockers, class I antiarrhythmics, analgesics and many other drug categories, acting as substrates, inhibitors or inducers with which most psychotropics may potentially interact (Table 40.5), this leading to the outcome of ADRs.[18–20,86,96,103] The CYP2D6 locus is highly polymorphic, with more than 100 different CYP2D6 alleles identified in the general population showing deficient (poor metabolizers, PM), normal (extensive metabolizers, EM) or increased enzymatic activity (ultra-rapid metabolizers, UM).[100,104] 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.[18–20,89,91–94,102] On the average, approximately 6.28% of the world population belongs to the PM category. Europeans (7.86%), Polynesians (7.27%), and Africans (6.73%) exhibit the highest rate of PMs, whereas Orientals (0.94%) show the lowest rate. The frequency of PMs among Middle Eastern populations, Asians, and Americans is in the range of 2–3%.[16–20,94] 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%.[73]

The most frequent CYP2D6 alleles in the European population are the following: CYP2D6*1 (wild-type) (normal), CYP2D6*2 (2850C > T)(normal), CYP2D6*3 (2549A > del)(inactive), CYP2D6*4 (1846G > A)(inactive), CYP2D6*5 (gene deletion)(inactive), CYP2D6*6 (1707T > del)(inactive), CYP2D6*7 (2935A > C)(inactive), CYP2D6*8 (1758G > T)(inactive), CYP2D6*9 (2613–2615 delAGA)(partially active), CYP2D6*10 (100C > T)(partially active), CYP2D6*11 (883G > C) (inactive), CYP2D6*12 (124G>A)(inactive), CYP2D6*17 (1023C > T)(partially active), and CYP2D6 gene duplications (with increased or decreased enzymatic activity depending upon the alleles involved).[16–20,104–106]

In the Spanish population, 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 (EM)(*1/*1, *1/*10); (ii) Intermediate Metabolizers (IM)(*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10); (iii) Poor Metabolizers (PM)(*4/*4, *5/*5); and (iv) Ultra-rapid Metabolizers (UM)(*1xN/*1, *1xN/*4, Dupl). In this sample we have found 51.61% EMs, 32.26% IMs, 9.03% PMs, and 7.10% UMs.[20,74–77] The distribution of all major genotypes is the following: *1/*1, 47.10%; *1/*10, 4.52%; *1/*3, 1.95%; *1/*4, 17.42%; *1/*5, 3.87%; *1/*6, 2.58%; *1/*7, 0.65%; *10/*10, 1.30%; *4/*10, 3.23%; *6/*10, 0.65%; *7/*10, 0.65%; *4/*4, 8.37%; *5/*5, 0.65%; *1xN/*1, 4.52%; *1xN/*4, 1.95%; and Dupl, 0.65%.[20,74–77]

In some instances, there is association of CYP2D6 variants of risk with genes potentially involved in the pathogenesis of specific CNS disorders. When comparing AD cases with controls, we observed that EMs are more prevalent in AD (*1/*1, 49.42%; *1/*10, 8.04%)(total AD-EMs: 57.47%) than in controls (*1/*1, 44.12%; *1/*10, 0%)(total C-EMs: 44.12%). In contrast, IMs are more frequent in controls (41.18%) than in AD (25.29%), especially the *1/*4 (C: 23.53%; AD: 12.64%) and *4/*10 genotypes (C: 5.88%; AD: 1.15%). The frequency of PMs was similar in AD (9.20%) and controls (8.82%), and UMs were more frequent among AD cases (8.04%) than in controls (5.88%).[20,74,75,77]

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, PS1, PS2, A2M, ACE, AGT, FOS, and PRNP variants.[20,74,75,77] No APP or MAPT mutations have been found in AD cases. 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%). PS1–1/1 genotypes were more frequent in EMs (45%), whereas PS-1/2 genotypes were over-represented in IMs (63.16%) and UMs (60%). The presence of the PS1–2/2 genotype was especially high in PMs (38.46%) and UMs (20%). A mutation in the PS2 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-I/I genotype was absent in UMs, and 100% of UMs were A2M-I/D and ACE-D/D. Homozygous mutations in the FOS gene (B/B) were only present in UMs, as well. 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.[20,74,75,77] 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.[20,74–77]

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 elevated in EMs ($^{*}1/^{*}1$ vs. $^{*}4/^{*}10$, $p < 0.05$) and in some IMs ($^{*}4/^{*}10$ vs. $^{*}1xN/^{*}4$, $p < 0.05$), whereas other IMs ($^{*}1/^{*}5$ vs. $^{*}4/^{*}4$, $p < 0.05$) tend to show lower levels of glucose compared with PMs ($^{*}4/^{*}4$) or UMs ($^{*}1xN/^{*}4$) (Table 40.7). The highest levels of total-cholesterol are detected in the EMs with the CYP2D6$^{*}1/^{*}10$ genotype (vs. $^{*}1/^{*}1$, $^{*}1/^{*}4$ and $^{*}1xN/^{*}1$, $p < 0.05$). The same pattern has 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 $^{*}1/^{*}3$ and $^{*}1xN/^{*}4$ (Table 40.8). The levels of triglycerides are very variable among different CYP2D6 polymorphisms, with the highest levels present in IMs ($^{*}4/^{*}10$ vs. $^{*}4/^{*}5$ and $^{*}1xN/^{*}1$, $p < 0.02$). 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. Other possibility might be that some lipid metabolism genotypes interact with CYP2D6-related enzyme products leading to define 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 (Table 40.9). In general terms, the best

Table 40.7 CYP2D6-related blood glucose levels in Alzheimer's disease

Phenotype	CYP2D6	Glucose (mg/dl)
Extensive metabolizers	**$^{*}1/^{*}1$**	101.01 ± 30.90(1)
	$^{*}1/^{*}10$	104.85 ± 26.35
Intermediate metabolizers	**$^{*}1/^{*}3$**	94.66 ± 13.31
	$^{*}1/^{*}4$	101.56 ± 36.12
	$^{*}1/^{*}5$	91.83 ± 5.84(2)
	$^{*}1/^{*}6$	99.66 ± 15.27
	$^{*}10/^{*}10$	99.33 ± 18.14
	$^{*}4/^{*}10$	127.80 ± 63.38(3)
Poor metabolizers	**$^{*}4/^{*}4$**	96.76 ± 13.37
Ultra-rapid metabolizers	**$^{*}1xN/^{*}1$**	105.57 ± 23.77
	$^{*}1xN/^{*}4$	82.61 ± 6.65

Values: mean ± SD

(1) $p < 0.05$ vs. $^{*}4/^{*}10$; (2) $p < 0.05$ vs. $^{*}1xN/^{*}4$; (3) $p < 0.05$ vs. $^{*}4/^{*}4$

Source: Adapted from R. Cacabelos.[109]

Table 40.8 CYP2D6-related blood lipid levels in Alzheimer's disease

Phenotype	CYP2D6	Cholesterol (mg/dl)	LDL-Cholesterol (mg/dl)	HDL-Cholesterol (mg/dl)	Triglycerides (mg/dl)
Extensive metabolizers	***1/*1**	223.15 ± 41.58(1)	147.20 ± 35.00(4)	52.30 ± 9.98(10)	128.24 ± 76.61(11)
	***1/*10**	275.57 ± 77.00(2,3)	196.40 ± 62.70(5–8)	53.28 ± 12.67	129.85 ± 71.58
Intermediate metabolizers	***1/*3**	235.33 ± 47.07	134.86 ± 21.06	64.66 ± 22.12	179.00 ± 149.22
	***1/*4**	235.39 ± 49.64	158.44 ± 36.33(9,10)	54.37 ± 11.64	121.76 ± 93.76
	***1/*5**	222.00 ± 41.45	148.08 ± 35.72	50.40 ± 8.96	154.00 ± 59.33(12,13)
	***1/*6**	234.61 ± 32.53	162.75 ± 31.43	57.75 ± 13.81	106.5 ± 47.59
	***10/*10**	239.00 ± 22.62	152.30 ± 27.01	52.50 ± 3.50	171.00 ± 40.24
	***4/*10**	255.20 ± 52.71	170.15 ± 59.87	45.25 ± 5.43	226.75 ± 124.84(14,15)
Poor metabolizers	***4/*4**	233.85 ± 62.50	148.72 ± 46.51	57.92 ± 17.76	144.76 ± 21.24
Ultra-rapid metabolizers	***1×N/*1**	202.14 ± 52.23	129.71 ± 46.23	53.28 ± 10.25	150.16 ± 33.74
	***1×N/*4**	203.66 ± 19.50	113.21 ± 28.30	63.01 ± 9.20	145.66 ± 31.65

Values: mean ± SD.

(1) $p < 0.004$ vs. *1/*10; (2) $p < 0.05$ vs. *1/*4; (3) $p < 0.05$ vs. *1×N/*1; (4) $p < 0.001$ vs. *1/*10; (5) $p < 0.05$ vs. *1/*4; (6) $p < 0.05$ vs. *4/*4; (7) $p < 0.04$ vs. *1×N/*1; (8) $p < 0.05$ vs. *1×N/*4; (9) $p < 0.05$ vs. *1×N/*1; (10) $p < 0.05$ vs. *1×N/*4; (11) $p < 0.01$ vs. *4/*10; (12) $p < 0.05$ vs. *4/*4; (13) $p < 0.04$ vs. *1×N/*1; (14) $p < 0.008$ vs. *4/*4; (15) $p < 0.02$ vs. *1×N/*1.

Source: Adapted from R. Cacabelos.[109]

Table 40.9 CYP2D6-related brain hemodynamics in Alzheimer's disease

Phenotype	CYP2D6	LMCA-Mv (IU/L)	LMCA-Sv (IU/L)	LMCA-Dv (IU/L)	LMCA-PI (units)	LMCA-RI (units)
Extensive metabolizers	***1/*1**	44.97 ± 13.62	71.27 ± 20.40	28.29 ± 10.06	0.98 ± 0.22(4)	0.60 ± 0.07(10,11)
	***1/*10**	38.22 ± 8.85	61.42 ± 12.07(1)	24.32 ± 7.39	0.99 ± 0.37	0.59 ± 0.11
Intermediate metabolizers	***1/*3**	62.30 ± 15.23	87.20 ± 20.12	30.21 ± 10.80	0.67 ± 0.46	0.47 ± 0.12
	***1/*4**	47.73 ± 15.56	76.62 ± 22.91	29.74 ± 11.29	1.03 ± 0.24(5)	0.61 ± 0.05(12,13)
	***1/*5**	52.16 ± 13.76	81.16 ± 19.30	35.46 ± 10.45(2)	0.88 ± 0.07(6)	0.56 ± 0.02(14)
	***1/*6**	42.00 ± 15.24	67.00 ± 20.30	24.80 ± 5.30	0.98 ± 0.20	0.61 ± 0.17
	***10/*10**	42.75 ± 6.57	78.85 ± 7.70	22.60 ± 3.67	1.47 ± 0.32(7–9)	0.75 ± 0.07(15–17)
	***4/*10**	47.50 ± 10.84	76.84 ± 11.90	28.00 ± 9.47	1.07 ± 0.31	0.62 ± 0.08
Poor metabolizers	***4/*4**	42.04 ± 12.24	68.85 ± 18.90	23.68 ± 7.42(3)	1.06 ± 0.14	0.64 ± 0.07(18)
Ultra-rapid metabolizers	***1×N/*1**	46.32 ± 11.31	71.42 ± 15.41	31.87 ± 9.24	0.86 ± 0.21	0.55 ± 0.10
	***1×N/*4**	39.00 ± 11.26	60.66 ± 16.19	24.00 ± 7.03	0.95 ± 0.07	0.60 ± 0.02

Values: mean ± SD.

LMCA: Left Middle Cerebral Artery; Mv: Mean velocity; Sv: Systolic velocity; Dv: Diastolic velocity; PI: Pulsatility Index; RI: Resistance Index.

(1) $p < 0.05$ vs. *4/*10; (2) $p < 0.03$ vs. *4/*4; (3) $p < 0.05$ vs. *1×N/*1; (4) $p < 0.003$ vs. *10/*10; (5) $p < 0.02$ vs. *10/*10; (6) $p < 0.04$ vs. *10/*10; (7) $p < 0.006$ vs. *4/*4; (8) $p < 0.05$ vs. *1×N/*1; (9) $p < 0.05$ vs. *1×N/*4; (10) $p < 0.05$ vs. *4/*4; (11) $p < 0.01$ vs. *10/*10; (12) $p < 0.003$ vs. *10/*10; (13) $p < 0.05$ vs. *1×N/*1; (14) $p < 0.02$ vs. *10/*10; (15) $p < 0.05$ vs. *4/*4; (16) $p < 0.05$ vs. *1×N/*1; (17) $p < 0.03$ vs. *1×N/*4; (18) $p < 0.05$ vs. *1×N/*1.

Source: Adapted from R. Cacabelos.[109]

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 (Table 40.9). For instance, 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, $p < 0.05$); and diastolic velocities (Dv) also tend to be much lower in *1/*10 and especially in PMs (*4/*4) and UMs (*1xN/*4), whereas the best Dv is measured in *1/*5 IMs. 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 (Table 40.9). These data taken together seem to indicate that CYP2D6-related AD PMs exhibit a poorer cerebrovascular function which might affect drug penetration in the brain with the consequent therapeutic implications.[16–20,74–77]

Influence of CYP2D6 Genotypes on Liver Transaminase Activity

Some conventional anti-dementia drugs (tacrine, donepezil, galantamine) are metabolized via CYP-related enzymes, especially CYP2D6, CYP3A4, and CYP1A2, and polymorphic variants of the CYP2D6 gene can affect the liver metabolism, safety and efficacy of some cholinesterase inhibitors.[107,108] In order to elucidate whether or not CYP2D6-related variants may influence transaminase activity, we have studied the association of GOT, GPT, and GGT activity with the most prevalent CYP2D6 genotypes in AD (Table 40.10). Globally, 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 UMs ($p < 0.05$ vs. *1xN/*1; $p < 0.05$ vs. *1xN/*4). GPT activity was significantly higher in PMs (*4/*4) than in EMs (*1/*10, $p < 0.05$) or IMs (*1/*4, *1/*5, $p < 0.05$). 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, $p < 0.05$; *1/*10, $p < 0.05$), IMs (*1/*5, $p < 0.05$), or UMs (*1xN/*1, $p < 0.01$)) (Table 40.10). 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[20,77,109] (Table 40.10).

Table 40.10 CYP2D6-related liver transaminase activity in Alzheimer's disease

Phenotype	CYP2D6	GOT (IU/L)	GPT (IU/L)	GGT (IU/L)
Extensive metabolizers	***1/*1**	23.49 ± 8.70(1)	23.77 ± 16.04	31.16 ± 31.26(14–16)
	***1/*10**	17.57 ± 6.29(2)	16.28 ± 7.40(11)	18.14 ± 6.79(17)
Intermediate metabolizers	***1/*3**	22.33 ± 1.52(3,4)	24.66 ± 10.59	22.00 ± 8.71
	***1/*4**	21.76 ± 3.57(5,6)	21.88 ± 8.40	32.23 ± 25.53
	***1/*5**	18.33 ± 2.33(7,8)	16.16 ± 5.60(12,13)	18.50 ± 6.47(18,19)
	***1/*6**	23.00 ± 4.83	23.25 ± 5.31	33.50 ± 26.41
	***10/*10**	16.00 ± 1.41(9,10)	16.50 ± 3.53	39.00 ± 11.31(20)
	***4/*10**	20.00 ± 3.87	20.60 ± 4.03	34.20 ± 16.20
Poor metabolizers	***4/*4**	21.78 ± 6.48	17.64 ± 15.05	59.71 ± 113.58(21)
Ultra-rapid metabolizers	***1×N/*1**	20.50 ± 3.01	18.00 ± 5.32	21.50 ± 9.22
	***1×N/*4**	23.33 ± 4.04	23.00 ± 5.01	25.66 ± 6.02

Values: mean ± SD.

GGT: Gamma-Glutamyl Transpeptidase; GOT: Glutamic-Oxalacetic Transaminase; GGT: Glutamic-Pyruvic Transaminase.

(1) $p < 0.05$ vs. *1/*10; (2) $p < 0.05$ vs. *1/*4; (3) $p < 0.03$ vs. *1/*5; (4) $p < 0.001$ vs. *1/*10; (5) $p < 0.03$ vs. *1/*5; (6) $p < 0.03$ vs. *10/*10; (7) $p < 0.05$ vs. *1/*6; (8) $p < 0.04$ vs. *1×N/*4; (9) $p < 0.05$ vs. *1×N/*1; (10) $p < 0.05$ vs. *1×N/*4; (11) $p < 0.05$ vs. *4/*4; (12) $p < 0.05$ vs. *1/*6; (13) $p < 0.05$ vs. *4/*4; (14) $p < 0.05$ vs. *4/*4; (15) $p < 0.01$ vs. *10/*10; (16) $p < 0.01$ vs. *4/*10; (17) $p < 0.05$ vs. *4/*4; (18) $p < 0.01$ vs. *10/*10; (19) $p < 0.05$ vs. *4/*10; (20) $p < 0.05$ vs. *1×N/*1; (21) $p < 0.05$ vs. *1×N/*1.

Source: Adapted from R. Cacabelos.[109]

CYP2D6-Related Therapeutic Response to a Multifactorial Treatment in Dementia

No clinical trials have been performed to date to elucidate the influence of CYP2D6 variants on the therapeutic outcome in AD in response to cholinesterase inhibitors or other anti-dementia drugs. To overcome this lack of pharmacogenetic information, we have performed the first prospective study in AD patients who received a combination therapy with (a) an endogenous nucleotide and choline donor, CDP-choline (500 mg/day), (b) a nootropic substance, piracetam (1,600 mg/day), (c) a vasoactive compound, 1,6 dimethyl 8β-(5-bromonicotinoyl-oxymethyl)-10α-methoxyergoline (nicergoline)(5 mg/day), and (d) a cholinesterase inhibitor, donepezil (5 mg/day), for 1 year. With this multifactorial therapeutic intervention, EMs improved their cognitive function (MMSE score) from 21.58 ± 9.02 at baseline to 23.78 ± 5.81 after 1-year treatment (r = + 0.82; a Coef. = + 20.68; b Coef.: +0.4). IMs also improved from 21.40 ± 6.28 to 22.50 ± 5.07 (r = +0.96; a Coef. =+21.2; b Coef. = +0.25), whereas PMs and UMs deteriorate from 20.74 ± 6.72 to 18.07 ± 5.52 (r = –0.97; a Coef. = +21.63; b Coef. = –0.59), and from 22.65 ± 6.76 to 21.28 ± 7.75 (r = –0.92; a Coef. = +23.35; b Coef. = –0.36), respectively. According to these results, PMs and UMs were the worst responders, showing a progressive cognitive decline with no therapeutic effect, and EMs and IMs were the best responders, with a clear improvement in cognition after 1 year of treatment (Fig. 40.10). Among EMs, AD patients harbouring 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 *1xN/*1 genotypes, respectively.[20,77,109]

From all these data we can conclude the following: (i) The most frequent CYP2D6 variants in the Spanish population are the *1/*1 (47.10%), *1/*4 (17.42%), *4/*4 (8.37%), *1/*10 (4.52%) and *1xN/*1 (4.52%), accounting for more than 80% of the population; (ii) the frequency of EMs, IMs, PMs, and UMs is about 51.61%, 32.26%, 9.03%, and 7.10%, respectively; (iii) EMs are more prevalent in AD (57.47%) than in controls (44.12%); IMs are more frequent in controls (41.18%)

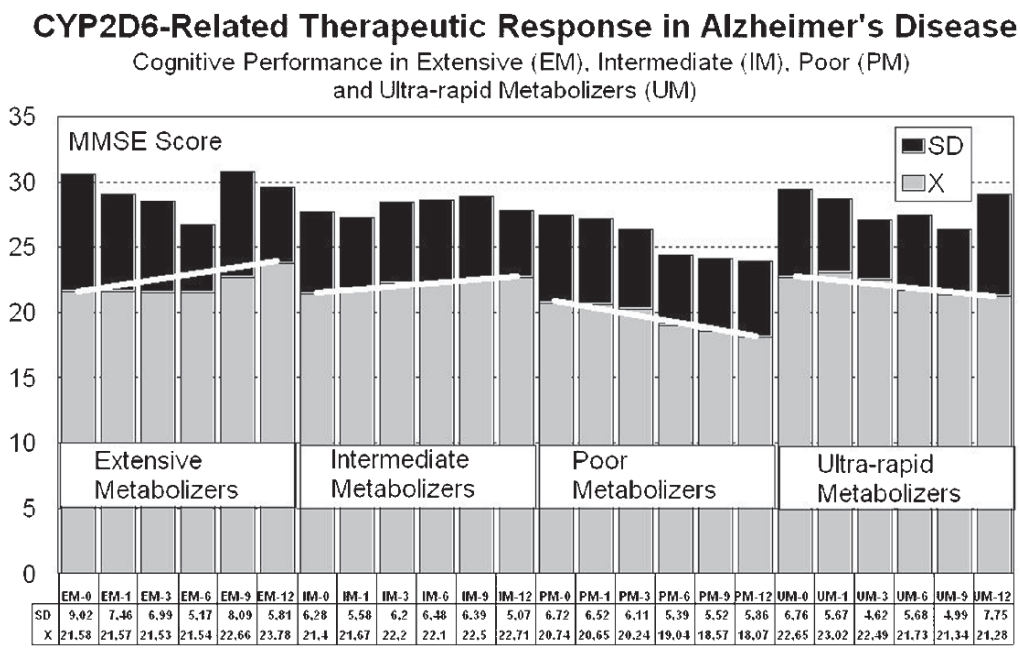

Fig. 40.10 CYP2D6-related therapeutic response to a multifactorial treatment in Alzheimer's disease over a 1-year period (Adapted from R. Cacabelos[77,109]).Patients received a combination therapy for 1 year, and cognitive function (MMSE score) was assessed at baseline (B) and after 1, 3, 6, 9, and 12 months of treatment.

than in AD (25.29%), especially the *1/*4 (C: 23.53%; AD: 12.64%) and *4/*10 genotypes (C: 5.88%; AD: 1.15%); the frequency of PMs is similar in AD (9.20%) and controls (8.82%); and UMs are more frequent among AD cases (8.04%) than in controls (5.88%); (iv) there is an accumulation of AD-related genes of risk in PMs and UMs; (v) PMs and UMs tend to show higher transaminase activities than EMs and IMs; (vi) EMs and IMs are the best responders, and PMs and UMs are the worst responders to a combination therapy with cholinesterase inhibitors, neuroprotectants, and vasoactive substances; and (vii) 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.[16–20,74–77,109,110]

Taking into consideration the available data, it might be inferred that at least 15% of the AD population may exhibit an abnormal metabolism of cholinesterase inhibitors and/or other drugs which undergo oxidation via CYP2D6-related enzymes. Approximately 50% of this population cluster would show an ultrarapid metabolism, requiring higher doses of cholinesterase inhibitors to reach a therapeutic threshold, whereas the other 50% of the cluster would exhibit a poor metabolism, displaying potential adverse events at low doses. If we take into account that approximately 60–70% of therapeutic outcomes depend upon pharmacogenomic criteria (e.g., pathogenic mechanisms associated with AD-related genes), it can be postulated that pharmacogenetic and pharmacogenomic factors are responsible for 75–85% of the therapeutic response (efficacy) in AD patients treated with conventional drugs.[16–20,74–77,109,110] Of particular interest are the potential interactions of cholinesterase inhibitors with other drugs of current use in patients with AD, such as antidepressants, neuroleptics, antiarrhythmics, analgesics, and antiemetics which are metabolized by the cytochrome P450 CYP2D6 enzyme.[111] Although most studies predict the safety of donepezil[112] and galantamine,[107] as the two principal cholinesterase inhibitors metabolized by CYP2D6-related enzymes,[113,114] no pharmacogenetic studies have been performed so far on an individual basis to personalize the treatment, and most studies reporting safety issues are the result of pooling together pharmacological and clinical information obtained with routine procedures.[103,115–117] In certain cases, genetic polymorphism in the expression of CYP2D6 is not expected to affect the pharmacodynamics of some cholinesterase inhibitors because major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization. However, excretion rates are substantially different in EMs and PMs. For instance, in EMs, urinary metabolites resulting from O-demethylation of galantamine represent 33.2% of the dose compared with 5.2% in PMs, which show correspondingly higher urinary excretion of unchanged galantamine and its N-oxide.[118] Therefore, still there are many unanswered questions regarding the metabolism of cholinesterase inhibitors and their interaction with other drugs (potentially leading to ADRs) which require pharmacogenetic elucidation. It is also worth to mention that dose titration (a common practice in AD patients treated with cholinesterase inhibitors; e.g., tacrine, donepezil) is an unwise strategy, since approximately 30–60% of drug failure or lack of therapeutic efficacy (and/or ADR manifestation) is not a matter of drug dosage but a problem of poor metabolizing capacity in PMs. Additionally, inappropriate drug use is one of the risk factors for adverse drug reactions (ADRs) in the elderly. The prevalence of use of potentially inappropriate medications in patients older than 65 years of age admitted to a general medical or geriatric ward ranges from 16% to 20%,[119] and these numbers may double in ambulatory patients. Overall, the most prevalent inappropriate drugs currently prescribed to the elderly are amiodarone, long-acting benzodiazepines and anticholinergic antispasmodics; however, the list of drugs with potential risk also include antidepressant, antihistaminics, NSAIDs, amphetamines, laxatives, clonidine, indomethacin, and several neuroleptics,[119] most of which are processed via CYP2D6 and CYP3A5 enzymes.[120] Therefore, pre-treatment CYP screening might be of great help to rationalize and optimize therapeutics in the elderly, by avoiding medications of risk in PMs and UMs.

Novel Targets in the Pharmacogenomics of CNS Disorders

There are substantial differences between individuals in the effects of psychotropic drugs in the treatment of neuropsychiatric disorders. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment.[121] More than 200 different genes are

potentially involved in the metabolism of psychotropic drugs influencing pharmacokinetics and pharmacodynamics. Of all genes affecting drug metabolism, efficacy and safety, the CYP gene family is the most relevant since more than 60% of CNS drugs are metabolized by cytochrome P450 enzymes.[122–124] Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4 (Table 40.5). Approximately, 80% of patients with resistant depression, 60% of patients non-responsive to neuroleptics, and 50–70% of patients with paradoxical responses to benzodiazepines are carriers of mutant variants of the CYP2D6, CYP2C9 and CYP3A4 genes, falling within the categories of poor or ultra-rapid metabolizers.

Other genes influencing psychotropic drug activity include the following: ABCB1 (ATP-Binding Cassette, Subfamily B, Member 1), ACHE (Acetylcholinesterase), ADRA1 (Alpha-1-Adrenergic Receptor), ADRB1 (Beta-1-Adrenergic Receptor), ADRB3 (Beta-3-Adrenergic Receptor), APOE (Apolipoprotein E), different CHRNAs (Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptides) and CHRNBs (Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptides), COMT (Catechol-O-Methyl Transferase), several DRDs (Dopamine Receptors), GABARs (Gamma-Aminobutyric Acid Receptors), G6PD (Glucose-6-Phosphate Dehydrogenase), GNB3 (G-Protein Beta-3 Subunit), GNAS1 (Gs Protein Alpha-Subunit), GPIIIA (Glycoprotein IIIa Receptor), HLA-A1 (Minor Histocompatibility Antigen HA-1), HRHs (Histamine Receptors), different classes of HTRs (Serotonin Receptors), INPP1 (Inositol Polyphosphate 1-Phosphatase), KCNE2 (Cardiac Potassium Ion Channel), LTC4S (Leukotriene C4 Synthase), MAOA (Monoamine Oxidase A), MAOB (Monoamine Oxidase B), RGS2 (Regulator of G-Protein Signaling 2), SCN5A (Cardiac Sodium Channel), SLC6A2 (Solute Carrier Family 6 (Neurotransmitter Transporter, Noradrenaline), Member 2), SLC6A3 (Solute Carrier Family 6 (Neurotransmitter Transporter, Dopamine), Member 3), SLC6A4 (Solute Carrier Family 6 (Neurotransmitter Transporter, Serotonin), Member 4), TNF-A (Tumor Necrosis Factor-Alpha), TRFRs (TNF receptors), and TPH2 (Tryptophan Hydroxylase), among many other still poorly investigated genes[128–138] (Table 40.5).

Historically, the vast majority of pharmacogenetic studies of CNS disorders have been addressed to evaluate the impact of cytochrome P450 enzymes on drug metabolism.[125–127] Furthermore, conventional targets for psychotropic drugs were the neurotransmitters dopamine, serotonin, noradrenaline, GABA, ion channels, acetylcholine and their respective biosynthetic and catalyzing enzymes, receptors and transporters[121]; however, in the past few years many different genes have been associated with both pathogenesis and pharmacogenomics of neuropsychiatric disorders. Some of these genes and their products constitute potential targets for future treatments. New developments in genomics, including whole genome genotyping approaches and comprehensive information on genomic variation across populations, coupled with large-scale clinical trials in which DNA collection is routine, now provide the impetus for a next generation of pharmacogenetic studies and identification of novel candidate drugs.[139–141]

Cyclic nucleotide phosphodiesterases (PDEs) are a family of enzymes that degrade cAMP and cGMP. Intracellular cyclic nucleotide levels increase in response to neurotransmitters and are down-regulated through hydrolysis catalyzed by PDEs, which are therefore candidate therapeutic targets. cAMP is a second messenger involved in learning, memory, and mood, and cGMP modulates brain processes that are controlled by the nitric oxide (NO)/cGMP pathway. The analysis of SNPs in 21 genes of this superfamily revealed that polymorphisms in PDE9A and PDE11A are associated with major depressive disorder. In addition, remission on antidepressants was associated with polymorphisms in PDE1A and PDE11A. According to these results, it has been postulated that PDE11A (haplotype GAACC) has a role in the pathogenesis of major depression.[142]

Another example is the purinergic receptor gene P2RX(7), located in a major linkage hotspot for schizophrenia and bipolar disorder (12q21–33), which has been associated with bipolar disorder, but nine functionally characterized variants of P2RX(7) did not show association with schizophrenia.[143]

The possible role of a tag SNP (the 1359G/A polymorphism) of the gene encoding the cannabinoid receptor type 1 (CNR1) has been investigated in schizophrenics treated with atypical antipsychotics. No difference in 1359G/A polymorphism was observed between patients and control subjects, and no relation-

ships were noted between this polymorphism and any clinical parameter considered as potential intermediate factor; however, the G allele was significantly higher among non-responders vs. responsive patients, suggesting that the G allele of the CNR1 gene could be a pharmacogenetic rather than a vulnerability factor for schizophrenics.[144]

Synaptic dysfunction is a potential pathogenic factor in schizophrenia. Cholesterol is an essential component of myelin and has proved important for synapse formation and lipid raft function. It has been demonstrated that the antipsychotic drugs clozapine and haloperidol stimulate lipogenic gene expression in glioma cells in culture through activation of the sterol regulatory element-binding protein (SREBP) transcription factors. Recently, the action of chlorpromazine, haloperidol, clozapine, olanzapine, risperidone and ziprasidone on SREBP and SREBP-controlled gene expression (acetyl-CoA acetyltransferase 2, acetoacetyl-CoA thiolase, ACAT2; 3-hydroxy-3-methylglutaryl-CoA reductase, HMGCR; 3-hydroxy-3-methylglutaryl-CoA synthase 1, HMGCS1; FDPS; sterol-C5-desaturase like, SC5DL; 7-dehydrocholesterol reductase, DHCR7; low density lipoprotein receptor, LDLR; fatty acid synthase; farsenyl diphosphate synthase, FASN; stearoyl-CoA desaturase, delta-9-desaturase, SCD1) has been investigated in different CNS human cell lines, demonstrating that antipsychotic-induced activation of lipogenesis is most prominent in glial cells and that this mechanism could be relevant for the therapeutic efficacy of some antipsychotic drugs.[145]

RGS2 (regulator of G-protein signaling 2) modulates dopamine receptor signal transduction. Functional variants of this gene (RGS2-rs 4606 C/G) may influence susceptibility to extrapyramidal symptoms induced by antipsychotic drugs. This SNP is located in the 3′-regulatory region of the gene, and is known to influence RGS2 mRNA levels and protein expression.[146] Furthermore, RGS4 (regulator of G protein signaling 4) genotypes predict both the severity at baseline symptoms and relative responsiveness to antipsychotic medication.[147]

Tardive dyskinesia is characterized by involuntary movements predominantly in the orofacial region and develops in approximately 20% of patients during long-term treatment with typical antipsychotics. Polymorphic variants of CYP1A2, CYP2D6, and DRD3 genes have been associated with tardive dyskinesia in schizophrenics.[148,149] In contrast, the haplotype T-4b-Glu of the endothelial nitric oxide synthase (NOS3) gene (-786T > C in the promoter region, 27-bp variable number of tandem repeats (27-bp VNTR) in intron 4, Glu298Asp in exon 7) might represent a protective haplotype against tardive dyskinesia after long-term antipsychotic treatment.[150]

The T102C variant in the serotonin 2A receptor (HTR2A) and the Ser9Gly variant in the dopamine D3 receptor (DRD3) were associated with a risperidone response to exacerbated schizophrenia. The patients with T/T in the HTR2A gene show less clinical improvement than do those with T/C or C/C. The C allele is more frequent in responders. When combinations of both polymorphisms are considered, patients who have T/T in the HTR2A gene and encode Ser/Ser or Ser/Gly from DRD3 gene have a higher propensity to non-responsiveness compared to other subjects, suggesting that the HTR2A T102C variant could be a potential indicator of clinical improvement after risperidone treatment.[151]

There is a significant relationship between a promoter region polymorphism in the serotonin transporter gene and antidepressant response, as well as for associations between candidate neurotransmitter receptor genes and second generation antipsychotic drug response.[121] Polymorphic variants of several serotonin receptor subtypes seem to be involved in the efficacy and symptomatic response of schizophrenic patients to atypical antipsychotics. For instance, the −1019 C/G polymorphism of the HTR1A receptor gene is associated with negative symptom response to risperidone in schizophrenics.[152] Interaction between COMT and NOTCH4 genotypes may also predict the treatment response to typical neuroleptics in patients with schizophrenia.[153] The efficacy of iloperidone in patients with schizophrenia has been associated with the homozygous condition for the rs1800169 G/G genotype of the ciliary neurotrophic factor (CNTF) gene.[154] Dopamine receptor interacting proteins (DRIPs) are pivotally involved in regulating dopamine receptor signal transduction. Two SNPs in the dopamine receptor interacting protein gene, NEF3, which encodes the DRIP, neurofilament-medium (NF-M), were associated with early response (rs1457266, rs1379357). A 5 SNP haplotype spanning NEF3 was over-represented in early responders. Since NEF3 is primarily associated with dopamine D1 receptor function, it is likely that both genes cooperate in eliciting genotype-specific antipsychotic response.[155]

The improvement in the Positive and Negative Syndrome Scale (PANSS) positive subscore was found significantly greater in patients homozygous for the A1287 allele of the SLC6A2 (Solute Carrier Family 6 (Noradrenaline Transporter), Member 2) gene, and smaller in patients homozygous for the C-182 allele of the SLC6A2 gene, suggesting that these polymorphisms of the noradrenaline transporter gene are specifically involved in the variation of positive symptoms in schizophrenia.[156]

Weight gain is a problem commonly found in patients treated with neuroleptics, tricyclic antidepressants, and some antiepileptics (e.g., valproic acid). The adipocyte-derived hormone, leptin, has been associated with body weight and energy homeostasis, and abnormal regulation of leptin could play a role in weight gain induced by antipsychotics. The leptin gene promoter variant G2548A was associated with clozapine-induced weight in Chinese patients with chronic schizophrenia.[157] Likewise, studies in Caucasians suggest that genetic vulnerability in the leptin gene (–1548G/A) and leptin receptor (Q223R) may predispose some individuals to excessive weight gain from increased exposure to olanzapine.[158,159]

The development of selective type 5 metabotropic glutamate receptor (mGlu5) antagonists, such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP), has demonstrated the potential involvement of these receptors in several CNS disorders including depression, anxiety, epilepsy, Parkinson's disease, drug addiction, and alcoholism. Treatment with MPEP and MTEP can induce gene expression related to ATP synthesis, hydrolase activity, and signaling pathways associated with mitogen-activated protein kinase (MAPK) in the frontal cortex, this constituting another potential therapeutic target in some neuropsychiatric disorders.[160] A new marker (rs1954787) in the GRIK4 gene, which codes for the kainic acid-type glutamate receptor KA1, has been associated with response to the antidepressant citalopram, suggesting that the glutamate system plays a role in modulating response to selective serotonin reuptake inhibitors (SSRIs).[161]

Glycogen synthase kinase-3β (GSK3B) activity is increased in the brain of patients with major depressive disorders. Inhibition of GSK3B is thought to be a key feature in the therapeutic mechanism of antidepressants. Four polymorphisms of the GSK3B gene [rs334555 (–50 T > C); rs13321783 (IVS7 + 9227 A > G); rs2319398 (IVS + 11660 G > T); rs6808874 (IVS + 4251 T > A)] have been genotyped in Chinese patients with major depression. GSK3B TAGT carriers showed poorer response to antidepressants.[162]

Lithium has been used for over 40 years as an effective prophylactic agent in bipolar disorder. Response to lithium treatment seems to be, at least in part, genetically determined. It has been suggested that lithium exerts an effect on signal transduction pathways, such as the cyclic adenosine monophosphate (cAMP) pathway. Association studies in patients with bipolar disorders revealed that CREB1–1H SNP (G/A change at 2q32.3-q34) and CREB1–7H (T/C change) may be associated with bipolar disorder and lithium response.[163]

DNA oligonucleotide microarrays have been used to evaluate gene expression in the substantia nigra of patients with Parkinson's disease (PD). Sporadic PD is characterized by progressive death of dopaminergic neurons within the substantia nigra, where cell death is not uniform. The lateral tier of the substantia nigra (SNL) degenerates earlier and more severely than the more medial nigral component (SNM). Genes expressed more highly in the PD SNL included the cell death gene, p53 effector related to PMP22, the TNFR gene, TNFR superfamily, member 21, and the mitochondrial complex I gene, NADH dehydrogenase (ubiquinone) 1-beta subcomplex, 3, 12 kDa (NDUFβ3). Genes that were more highly expressed in PD SNM included the dopamine cell signaling gene, cyclic adenosine monophosphate-regulated phosphoprotein, 21 kDa, the activated macrophage gene, stabilin 1, and two glutathione peroxidase (GPX) genes, GPX1 and GPX3. This gene expression profile reveals that there is increased expression of genes encoding pro-inflammatory cytokines and subunits of the mitochondrial electron transport chain in glial cells, and that there is a decreased expression of several glutathione-related genes in the GNL, suggesting a molecular basis for pathoclisis.[164] These findings may contribute to open new therapeutic avenues in PD, where glial cells might represent potential targets to halt disease progression.

Pharmacological inhibition of cyclic-dependent kinase 5 (CDK5) protects neurons under distinct stressful conditions. In AD and amyotrophic lateral sclerosis deregulation of CDK5 causes hyperphosphorylation of tau and neurofilament proteins, respectively, leading to neuronal cell death. By two-dimensional gel electrophoresis and matrix assisted laser desorption/ionisation-time of flight (MALDI-TOF)-mass spectrometry,

several phosphoproteins that are modulated by CDK5 inhibitors have been identified. These phosphoproteins include syndapin I which is involved in vesicle recycling, and dynein light intermediate chain 2 which represents a regulatory subunit of the dynein protein complex, confirming the role of CDK5 in synaptic signaling and axonal transport. Other phosphoproteins detected are cofilin and collapsing response mediator protein, involved in neuronal survival and/or neurite outgrowth. Selective CDK5 inhibitors can also block mitochondrial translocation of pro-apoptotic cofilin. Phosphoproteome and transcriptome analysis of neurons indicate that CDK5 inhibitors promote both neuronal survival and neurite outgrowth.[165] These compounds might represent novel therapeutic alternatives in neurodegenerative disorders.

Despite the promising results obtained with structural and functional genomic procedures to identify associations with disease pathogenesis and potential drug targets in CNS disorders, it must be kept in mind that allelic mRNA expression is affected by genetic and epigenetic events, both with the potential to modulate neurotransmitter tone in the CNS.[166] Epigenetics is the study of how the environment can affect the genome of the individual during its development as well as the development of its descendants, all without changing the DNA sequence, but inducing modifications in gene expression through DNA methylation–demethylation or through modification of histones by processes of methylation, deacetylation, and phosphorylation.[167] Cumulative experiences throughout life history interact with genetic predispositions to shape the individual's behaviour.[167] Epigenetic phenomena can not be neglected in the pathogenesis and pharmacogenomics of CNS disorders. Studies in cancer research have demonstrated the antineoplastic effects of the DNA methylation inhibitor hydralazine and the histone deacetylase inhibitor valproic acid, of current use in epilepsy.[168] Novel effects of some pleiotropic drugs with activity on the CNS have to be explored to understand in full their mechanisms of action and adjust their dosages for new indications. Both hyper- and hypo-DNA methylation changes of the regulatory regions play critical roles in defining the altered functionality of genes (MB-COMT, MAOA, DAT1, TH, DRD1, DRD2, RELN, BDNF) in major psychiatric disorders, such as schizophrenia and bipolar disorder.[169] This complexity requires a multifactorial approach to overcome the hurdles that CNS drug development faces at the present time.[170]

APOE in Alzheimer's Disease Therapeutics

Polymorphic variants in the APOE gene (19q13.2) are associated with risk (APOE-4 allele) or protection (APOE-2 allele) for AD.[8,18–20] For many years, alterations in ApoE and defects in the APOE gene have been associated with dysfunctions in lipid metabolism, cardiovascular disease, and atherosclerosis. During the past 25 years an enormous amount of studies clearly documented the role of APOE-4 as a risk factor for AD, an the accumulation of the APOE-4 allele has been reported as a risk factor for other forms of dementia and CNS disorders.[8,18–20]

APOE-4 may influence AD pathology interacting with APP metabolism and ABP accumulation, enhancing hyperphosphorylation of tau protein and NFT formation, reducing choline acetyltransferase activity, increasing oxidative processes, modifying inflammation-related neuroimmunotrophic activity and glial activation, altering lipid metabolism, lipid transport and membrane biosynthesis in sprouting and synaptic remodelling, and inducing neuronal apoptosis.[8,18–20]

APOE-Related Phenotypic Profiles in Alzheimer's Disease

Different APOE genotypes 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,[8,16–22,62,63,74–77,109,110] several confirmed conclusions can be drawn: (i) the age-at-onset is 5–10 years earlier in approximately 80% of AD cases harbouring the APOE-4/4 genotype; (ii) the serum levels of ApoE are the 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 ABP 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 (Fig. 40.4); (xii) brain hemodynamics, as reflected by reduced brain blood flow velocity and increase pulsatility and resistance indices, is significantly worst in APOE-4/4 (and in APOE-4 carriers, in general, as compared with APOE-3 carriers); (xiii) lymphocyte apoptosis is markedly enhanced in APOE-4 carriers; (xiv) cognitive deterioration is faster in APOE-4/4 patients than in carriers of any other APOE genotype; (xv) occasionally, in approximately 3–8% of the AD cases, the presence of some dementia-related metabolic dysfunctions (e.g., iron, folic acid, vitamin B12 deficiencies) accumulate in APOE-4 carriers more than in APOE-3 carriers; (xvi) some behavioral disturbances (bizarre behaviors, psychotic symptoms), alterations in circadian rhythm patterns (e.g., sleep disorders), and mood disorders (anxiety, depression) are slightly more frequent in APOE-4 carriers; (xvii) aortic and systemic atherosclerosis is also more frequent in APOE-4 carriers; (xviii) liver metabolism and transaminase activity also differ in APOE-4/4 with respect to other genotypes; (xix) blood pressure (hypertension) and other cardiovascular risk factors also accumulate in APOE-4; and (xx) APOE-4/4 are the poorest responders to conventional drugs (Fig. 40.11). 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.[2,4,8,16–22,62,63,74–77,109,110]

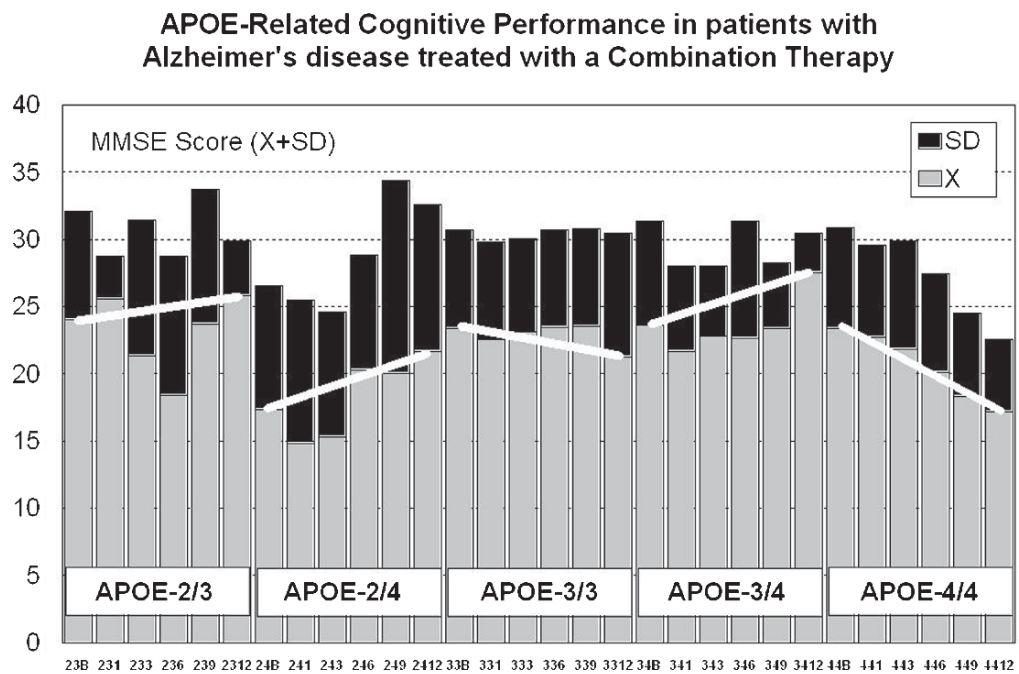

Fig. 40.11 APOE-related cognitive performance in patients with Alzheimer's disease treated with a combination therapy for 1 year (Adapted from R. Cacabelos[77,109]). Patients received a combination therapy for 1 year, and cognitive function (MMSE score) was assessed at baseline (B) and after 1, 3, 6, 9, and 12 months of treatment.

APOE-Related Therapeutic Response to Cholinesterase Inhibitors and Multifactorial Treatments

Several studies indicate that the presence of the APOE-4 allele differentially affects the quality and size of drug responsiveness in AD patients treated with cholinergic enhancers, neuroprotective compounds or combination therapies; however, controversial results are frequently found due to methodological problems, study design, and patients recruitment in clinical trials. From these studies we can conclude the following: (i) Multifactorial treatments combining neuroprotectants, endogenous nucleotides, nootropic agents, vasoactive substances, cholinesterase inhibitors, and NMDA antagonists associated with metabolic supplementation on an individual basis adapted to the phenotype of the patient may be useful to improve cognition and slow-down disease progression in AD. (ii) In our personal experience the best results have been obtained combining (a) CDP-choline with piracetam and metabolic supplementation, (b) CDP-choline with piracetam and anapsos, (c) CDP-choline with piracetam and cholinesterase inhibitors (donepezil, rivastigmine), (d) CDP-choline with memantine, and (e) CDP-choline, piracetam and nicergoline. (iii) Some of these combination therapies have proven to be effective, improving cognition during the first 9 months of treatment, and not showing apparent side-effects. (iv) The therapeutic response in AD seems to be genotype-specific under different pharmacogenomic conditions. (v) In monogenic-related studies, patients with the APOE-2/3 and APOE-3/4 genotypes are the best responders, and APOE-4/4 carriers are the worst responders (Fig. 40.11). (vi) PS1- and PS2-related genotypes do not appear to influence the therapeutic response in AD as independent genomic entities; however, APP, PS1, and PS2 mutations may drastically modify the therapeutic response to conventional drugs. (vii) In trigenic-related studies the best responders are those patients carrying the 331222-, 341122-, 341222-, and 441112-genomic clusters. (viii) A genetic defect in the exon 5 of the PS2 gene seems to exert a negative effect on cognition conferring PS2+ carriers in trigenic clusters the condition of poor responders to combination therapy. (ix) The worst responders in all genomic clusters are patients with the 441122+ genotype. (x) The APOE-4/4 genotype seems to accelerate neurodegeneration anticipating the onset of the disease by 5–10 years; and, in general, APOE-4/4 carriers show a faster disease progression and a poorer therapeutic response to all available treatments than any other polymorphic variant. (xi) Pharmacogenomic studies using trigenic, tetragenic or polygenic clusters as a harmonization procedure to reduce genomic heterogeneity are very useful to widen the therapeutic scope of limited pharmacological resources.[4–6,16–22,62,63,74–77,109,110]

Influence of APOE-CYP2D6 Interactions on Alzheimer's Disease Therapeutics

APOE influences liver function and CYP2D6-related enzymes probably via regulation of hepatic lipid metabolism.[20,42,74–77] 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.[20,74–77,171] Both plasma TG levels and transaminase activity are significantly lower in AD patients harbouring the APOE-4/4 genotype, probably indicating (a) that low TG levels protect against liver steatosis, and (b) that the presence of the APOE-4 allele influences TG levels, liver steatosis, and transaminase activity. Consequently, it is very likely that APOE influences drug metabolism in the liver through different mechanisms, including interactions with enzymes such as transaminases and/or cytochrome P450-related enzymes encoded in genes of the CYP Superfamily.[20,74–77,109,171]

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 after 1 year of treatment, it becomes clear that the presence of the APOE-4/4 genotype is able to convert pure CYP2D6*1/*1 EMs into full PMs (Fig. 40.12), indicating the existence of a powerful influence of the APOE-4 homozygous genotype on the drug metabolizing capacity of pure CYP2D6-EMs.[20,74,75,109]

APOE-Related Anxiety and Depression in Dementia

Behavioral disturbances and mood disorders are intrinsic components of dementia associated with

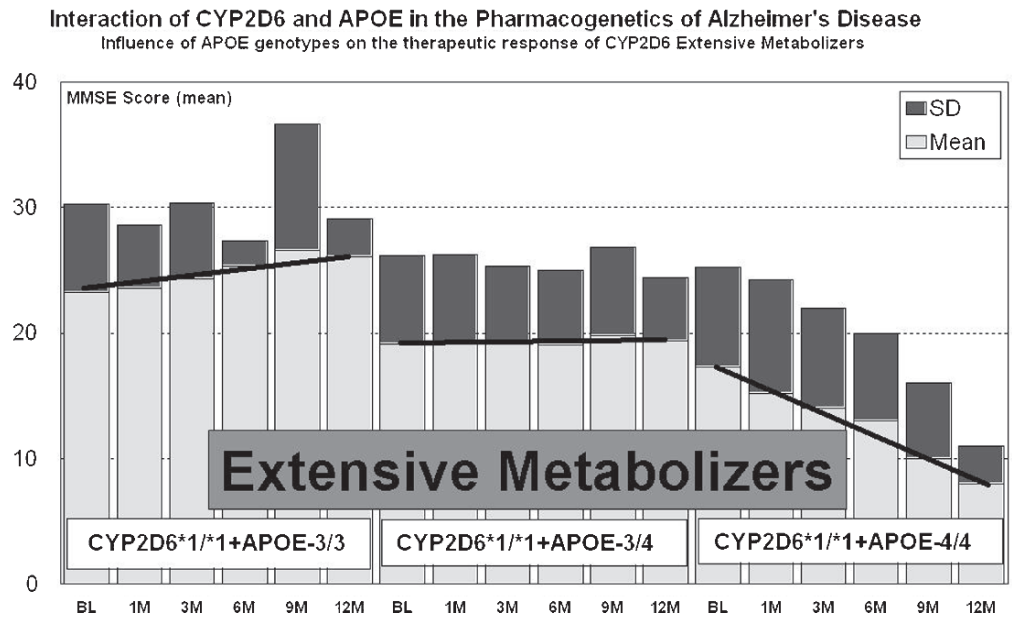

Fig. 40.12 Interaction of CYP2D6 and APOE in the pharmacogenetics of Alzheimer's disease (Adapted from R. Cacabelos[109]). CYP2D6 Extensive Metabolizers (EM) are converted into Poor Metabolizers (PM) with a very deficient therapeutic response to a multifactorial treatment in the presence of the APOE-4/4 genotype, reflecting (**a**) an interaction of CYP2D6 and APOE genes, and (**b**) a deleterious effect of APOE-4/4 in EMs in terms of therapeutic outcome. Patients received a combination therapy for 1 year, and cognitive function (MMSE score) was assessed at baseline (B) and after 1, 3, 6, 9, and 12 months of treatment.

memory disorders.[60,172–174] The appearance of anxiety, depression, psychotic symptoms, verbal and physical aggressiveness, agitation, wandering and sleep disorders complicate the clinical picture of dementia and add important problems to the therapeutics of AD and the daily management of patients as well. Under these conditions, psychotropic drugs (antidepressants, anxyolitics, hypnotics, and neuroleptics) are required, and most of these substances contribute to deteriorate cognition and psychomotor functions. APOE-related polymorphic variants have been associated with mood disorders[175,176] and panic disorder.[177] Gender, age, dementia severity, APOE-4, and general medical health appear to influence the occurrence of individual neuropsychiatric symptoms in dementia, and medical comorbidity increases the risk of agitation, irritability, disinhibition, and aberrant motor behavior.[178] A positive association between APOE-4 and neuropsychiatric symptoms[179] and depressive symptoms in AD has been reported,[180] especially in women.[181] In other studies, no association of APOE-4 with behavioral dyscontrol (euphoria, disinhibition, aberrant motor behavior, and sleep and appetite disturbances), psychosis (delusions and hallucinations), mood (depression, anxiety, and apathy), and agitation (aggression and irritability) could be found.[182] Some authors did not find association of APOE-4 with major depression in AD[183,184] or in patients with major depression in a community of older adults,[185] but an apparent protective effect of APOE-2 on depressive symptoms was detected.[186] Others, in contrast, found that APOE-4 was associated with an earlier age-of-onset, but not cognitive functioning, in late-life depression.[187] Apoe−/− mice without human ApoE or with APOE-4, but not APOE-3, show increased measures of anxiety.[188] Differences in anxiety-related behavior have been observed between APOE-deficient C57BL/6 and wild type C57BL/6 mice, suggesting that APOE variants may affect emotional state.[189] Histamine H3 autoreceptor antagonists increase anxiety measures in wild-type, but not ApoE−/−, mice, and ApoE deficient mice show higher sensitivity to the anxiety-reducing effects of the H1 receptor antagonist mepyramine than wild-type mice, suggesting a role of H3-autoreceptor-mediated signaling in anxiety-like symptoms in this AD-related animal model.[190]

In humans, APOE-4 carriers with deep white matter hyperintensities in MRI show association with depressive symptoms and vascular depression.[191]. Reduced caudate nucleus volumes and genetic determinants of

homocysteine metabolism accumulate in patients with psychomotor slowing and cognitive deficits,[192] and older depressed subjects have persisting cognitive impairments associated with hippocampal volume reduction.[193,194] Depressive symptoms are also associated with stroke and atherogenic lipid profile.[195]

Some multifactorial treatments addressing neuroprotection have shown to be effective in reducing anxiety progressively from the first month to the 12 month of treatment.[109] The anxiety rate was declining from a baseline HRS-A score of 10.90 ± 5.69 to 9.07 ± 4.03 ($p < 0.0000000001$) at 1 month, 9.01 ± 4.38 ($p < 0.000006$) at 3 months, 8.90 ± 4.47 ($p < 0.005$) at 6 months, 7.98 ± 3.72 ($p < 0.00002$) at 9 months, and 8.56 ± 4.72 ($p < 0.01$) at 12 months of treatment ($r = -0.82$, a coef.: 10.57, b coef.: –0.43).[109]

Similar striking results were found in depression, suggesting that improvement in mood conditions can contribute to stabilize cognitive function or that neuroprotection (with the consequent stabilization or improvement in mental performance) can enhance emotional equilibrium.[20,74,75,109]

At baseline, all APOE variants showed similar anxiety and depression rates, except the APOE-4/4 carriers who differed from the rest in a significantly lower rates of anxiety and depression (Figs. 40.13 and 40.14). Remarkable changes in anxiety were found among different APOE genotypes (Fig. 40.13). 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 (Fig. 40.13). The modest anxiolytic effect seen in APOE-4/4 patients might be due to the very low anxiety rate observed at baseline. 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, especially after 9 months (Fig. 40.14). The best responders were patients with APOE-2/4 > APOE-2/3 > APOE-3/3 > APOE-3/4, and the worst responders were patients harbouring the APOE-4/4 genotype[20,74,75,109] (Fig. 40.14).

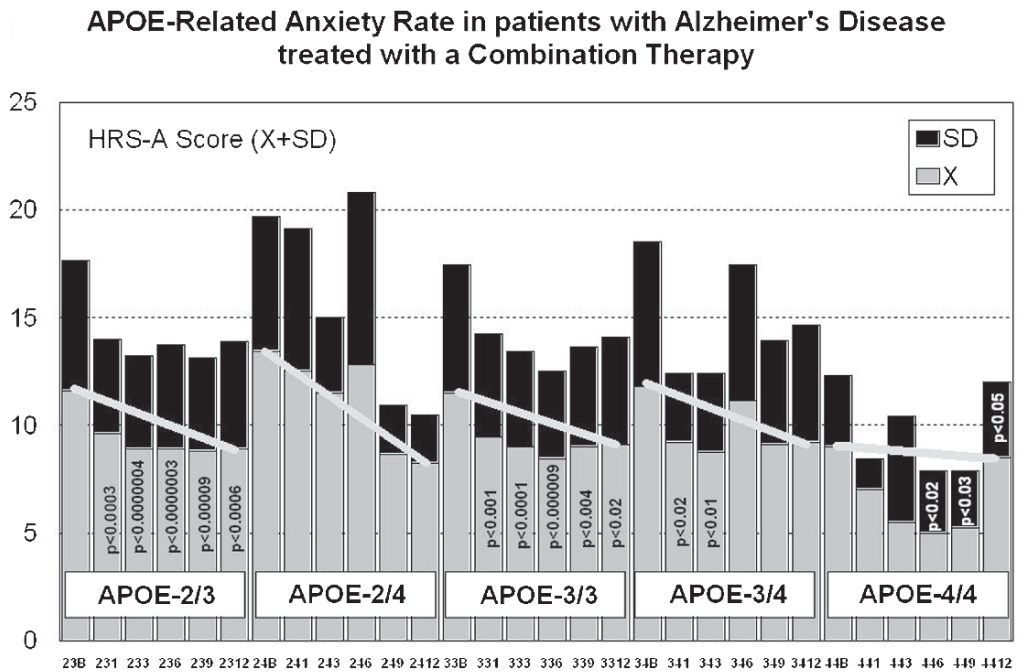

Fig. 40.13 APOE-related anxiety rate in patients with Alzheimer's disease treated with a combination therapy (Adapted from R. Cacabelos[109]). Patients received a combination therapy for 1 year, and anxiety symptoms (Hamilton Rating Scale for Anxiety, HAM-A) was assessed at baseline (B) and after 1, 3, 6, 9, and 12 months of treatment.

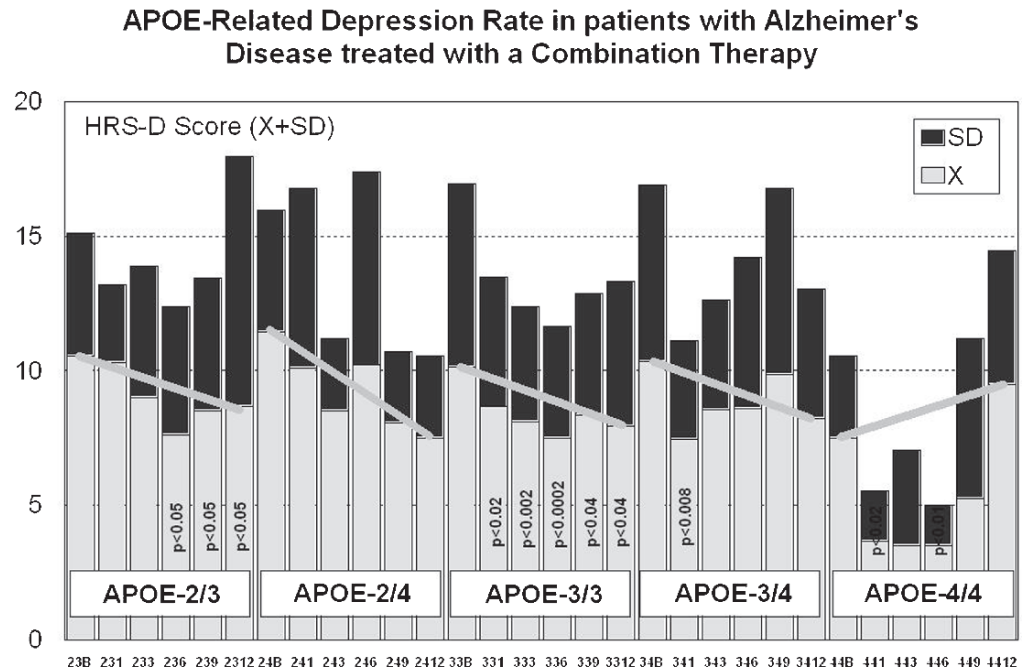

Fig. 40.14 APOE-related depression rate in patients with Alzheimer's disease treated with a combination therapy (Adapted from R. Cacabelos[109]). Patients received a combination therapy for 1 year, and depressive symptoms (Hamilton Rating Scale for Depression, HAM-D) was assessed at baseline (B) and after 1, 3, 6, 9, and 12 months of treatment.

Conclusions and Future Directions

The optimization of CNS therapeutics requires the establishment of new postulates regarding (a) the costs of medicines, (b) the assessment of protocols for multifactorial treatment in chronic disorders, (c) the implementation of novel therapeutics addressing causative factors, and (d) the setting-up of pharmacogenetic/pharmacogenomic strategies for drug development.[20,74–77,109]

The cost of medicines is a very important issue in many countries because of (i) the growing of the aging population (>5% disability), (ii) neuropsychiatric and demented patients (>5% of the population) belong to an unproductive sector with low income, and (iii) the high cost of health care systems and new health technologies in developed countries. Despite the effort of the pharmaceutical industry to demonstrate the benefits and cost-effectiveness of available drugs, the general impression in the medical community and in some governments is that some psychotropics and most anti-dementia drugs present in the market are not cost-effective.[20,74–77,109] Conventional drugs for neuropsychiatric disorders are relatively simple compounds with unreasonable prices. Some new products are not superior to conventional antidepressants, neuroleptics, and anxiolytics. There is an urgent need to assess the costs of new trials with pharmacogenetics and pharmacogenomics strategies, and to implement pharmacogenetic procedures to predict drug-related adverse events.[20,74,75,109]

Cost-effectiveness analysis has been the most commonly applied framework for evaluating pharmacogenetics. Pharmacogenetic testing is potentially relevant to large populations that incur in high costs. For instance, the most commonly drugs metabolized by CYP2D6 account for 189 million prescriptions and US$12.8 billion annually in expenditures in the US, which represent 5–10% of total utilization and expenditures for outpatient prescription drugs.[196] Pharmacogenomics offer great potential to improve patients' health in a cost-effective manner; however, pharmacogenetics/pharmacogenomics will not be applied to all drugs available in the market, and careful evaluations should be done on a case-by-case basis prior to investing resources in R&D of pharmacogenomic-based therapeutics and making reimbursement decisions.[197]

In performing pharmacogenomic studies in CNS disorders, it is necessary to rethink the therapeutic expectations of novel drugs, redesign the protocols for drug clinical trials, and incorporate biological markers as assessable parameters of efficacy and prevention. In addition to the characterization of genomic profiles, phenotypic profiling of responders and non-responders to conventional drugs is also important (and currently neglected). Brain imaging techniques, computerized electrophysiology, and optical topography in combination with genotyping of polygenic clusters can help in the differentiation of responders and non-responders. The early identification of predictive risks requires genomic screening and molecular diagnosis, and individualized preventive programs will only be achieved when pharmacogenomic/pharmacogenetic protocols are incorporated to the clinical armamentarium with powerful bioinformatics support.[18–20,74,75.109]

An important issue in AD therapeutics is that antidementia drugs should be effective in covering the clinical spectrum of dementia symptoms represented by memory deficits, behavioural changes, and functional decline. It is difficult (or impossible) that a single drug be able to fulfil this criteria. A potential solution to this problem is the implementation of cost-effective, multifactorial (combination) treatments integrating several drugs, taking into consideration that traditional neuroleptics and novel antipsychotics (and many other psychotropics) deteriorate both cognitive and psychomotor functions in the elderly and may also increase the risk of stroke.[198] Few studies with combination treatments have been reported and most of them are poorly designed. We have also to realize that the vast majority of dementia cases in people older than 75–80% are of a mixed type, in which the cerebrovascular component associated with neurodegeneration can not be therapeutically neglected. In most cases of dementia, the multifactorial (combination) therapy appears to be the most effective strategy.[18–20,74–77,109] The combination of several drugs (neuroprotectants, vasoactive substances, AChEIs, metabolic supplementation) increases the direct costs (e.g., medication) by 5–10%, but in turn, annual global costs are reduced by approximately 18–20% and the average survival rate increases about 30% (from 8 to 12 years post-diagnosis).

There are major concerns regarding the validity of clinical trials in patients with severe dementia. Despite the questionable experience with memantine,[199] similar strategies have been used to demonstrate the utility of donepezil in severe AD.[200] This kind of studies bears some important pitfalls, including (a) short duration (<1 year), (b) institutionalized patients, (c) patients receiving many different types of drugs, (d) non-evaluated drug–drug interactions, (e) side-effects (e.g., hallucinations, gastrointestinal disorders) that may require the administration of additional medication, (f) lack of biological parameters demonstrating actual benefits, and (e) no cost-effectiveness assessment, among many other possibilities of technical criticism.[18–20,109,201] Some of these methodological (and costly) problems might be overcome with the introduction of pharmacogenetic/pharmacogenomic strategies to identify good responders who might obtain some benefit by taking expensive medications.

Major impact factors associated with drug efficacy and safety include the following: (i) the mechanisms of action of drugs, (ii) drug-specific adverse reactions, (iii) drug–drug interactions, (iv) nutritional factors, (v) vascular factors, (vi) social factors, and (vii) genomic factors (nutrigenetics, nutrigenomics, pharmacogenetics, pharmacogenomics). Among genomic factors, nutrigenetics/nutrigenomics and pharmacogenetics/pharmacogenomics account for more than 80% of efficacy–safety outcomes in current therapeutics.[18–20,74,75,77,109]

Some authors consider that priority areas for pharmacogenetic research are to predict serious adverse reactions (ADRs) and to establish variation in efficacy.[202] Both requirements are necessary in CNS disorders to cope with efficacy and safety issues associated with either current CNS drugs and new drugs.[121,138] Since drug response is a complex trait, genome-wide approaches (oligonucleotide microarrays, proteomic profiling) may provide new insights into drug metabolism and drug response. Genome-wide family-based association studies, using single SNPs or haplotypes, can identify associations with genome-wide significance.[203,204]

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

and pharmacogenomic procedures to both drugs in development and drugs in the market to optimize therapeutics.[18–22,74–77,109,205]

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