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 pharmac genomic 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/pharmac genomic 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; CHRN B Cholinergic receptor, neuronal nicotinic, beta polypeptide; COMT Catechol-O-methyl transferase;
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; GPR1A 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%).

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.

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 epilepsy, 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, MLCl, SYNCR1, and SLC12A6. Genes associated with bipolar disorder include TRPM2 (21q22.3), GPR50 (Xq28), Citron (12q24), CHIPI.5 (18p11.2), GCH1 (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) (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 (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 heteroplasmatic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity.3,14,15 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  | Methylene tetrahydrofolate reductase           | 236253     |
| 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                      |            |
|              | ACAT   |                                                |            |
| 1q31–q42     | AD4    | Presenilin-2                                   | 600759     |
|              | PSEN2  |                                                | 104300     |
|              | STM2   |                                                |            |
| Chr. 1       | APH1A  | C. elegans anterior pharynx defective homolog  | 607629     |
| 2p14–p13     | RTN4   | Neurite outgrowth inhibitor (reticulin 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  |                                                |            |
|              | FE65L3 |                                                |            |
|              | KNCNIP3|                                                |            |
| 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)
| 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   |
|---------------|--------|--------------------------------------|--------|
| 19p13.2       | AD8    | Alzheimer disease 9                  | 608907 |
| 19p13.3–p13.2 | ICAM   | Intercellular adhesion molecule 1    | 147840 |
| 19p13.3       | APBA3  | Amyloid beta-A4 precursor protein binding, family A, member 3 | 604262 |
| 19q13.12      | PEN2   | Presenilin enhancer 2                | 607632 |
| 19q13.2       | APOE   | Apolipoprotein E                     | 107741 |
| 19cen–q13.2   | AD2    | Alzheimer disease-2                  | 104310 |
| 19cen–q13.2   | APPL1  | Amyloid beta-A4 precursor-like protein 1 | 104775 |
| 19q31–qter     | AD8    | Alzheimer disease-8                  | 104740 |
| 20p           | CST3   | Cystatin 3                           | 604312 |
| 20p11.2       | CST3   | Cystatin C                           | 604312 |
| 21q21         | AD1    | Amyloid (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 |
|              | ALPS6  | Down syndrome-region aspartic protease |        |
| 22q11         | RTN4R, NOGOR | NOGO receptor (reticulin 4 receptor) | 605566 |
|              | HN     | Humanin                              | 606120 |

Source: Adapted from Cacabelos et al., and Cacabelos and Takeda.

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 | 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 | Dystroblastin-binding protein 1 (dysbindin) | 607145     | Schizophrenia; Hermansky-Pudlak syndrome 7 |
| 6p23          | SCZD3  | Schizophrenia susceptibility locus/Chr. 6p-related | 600511/181500 | Schizophrenia-3                       |

(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 | APO1 | Apolipoprotein L1 | 603743/181500 | Schizophrenia |
| 22q12.3 | APO2 | Apolipoprotein L2 | 607252/181500 | Schizophrenia |
| 22q12.3 | APO4 | Apolipoprotein L4 | 607254/181500 | Schizophrenia |
| 22q13 | SYN1 | 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.\(^{9}\)
| Locus   | Symbol          | Description                                                                 | OMIM   | Disease                                                                                                    |
|---------|-----------------|------------------------------------------------------------------------------|--------|------------------------------------------------------------------------------------------------------------|
| 1q31–q32| IL10            | Interleukin 10                                                               | 124092 | Depression                                                                                                 |
| 1q42.11 | BPNT1           | 3′(2′),5′-biphosphate nucleotidase 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 | FKBPS, FKBPS1 | 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                      | 107920 | 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 | DPYS12          | Dihydrotryptamidase-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, ADCY9    | Major depressive disorder 2                      | 608691 | Major depressive disorder 2                                             |
| 16p13.3        | CHMP1A, PCOLN3, PRSM1 | CHMP family, member 1A                           | 164010 | Bipolar disorder                                                        |
| 17p13.1        | ALOX12         | Arachidonate 12-lipoxygenase                       | 152391 | 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 |
| 17q23          | ACE            | Angiotensin I converting enzyme                   | 106180 | Bipolar disorder                                                        |
| 18p            | MAFD1, BPAD, MD1 | Major affective disorder 1                      | 125480 | Major affective disorder 1; Bipolar depression                          |
| 18p11          | NAPG           | Soluble NSF-attachment protein, gamma            |        | 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*<sup>10</sup>; Kato.<sup>9</sup>

...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<sup>8,16–20</sup>(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).<sup>8,16–22</sup> The higher the number of genes involved in AD pathogenesis, the
earlier the onset of the disease, the faster its clinical course, and the poorer its therapeutic outcome.\(^8,16–20\)

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 possesses 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. Microarray technology has helped to elucidate gene expression profiles and potential pathogenic mechanisms in many other CNS disorders including schizophrenia and bipolar disorder, speech and language disorders, Parkinson’s disease, Huntington’s disease, prion disease, drug addiction, alcoholism, brain trauma, epilepsy, Cockayne syndrome, Rett syndrome, Friedreich ataxia, neuronal ceroid lipofuscinosis, multiple sclerosis, amyotrophic lateral sclerosis, acute pneumococcal meningitis, and the role of lipids in brain injury, psychiatric disorders, and neurodegenerative diseases.

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 oligodendrocytes 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. 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 non-preferring rats suggest the presence of powerful genomic influences on alcohol dependence. 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. Gene expression profiling of the nucleus accumbens of cocaine abusers suggests a dysregulation of myelin. 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.

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. 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.

**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, (xiv) nutrigenetics, (xv) nutrigenomics, (xvi) bioinformatics for data management, and (xvii) artificial intelligence procedures for...
diagnostic assignments and probabilistic therapeutic options (Table 40.4). 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

| 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                            |
| Neuropsychological assessment      | Neuropsychological tests                | Mood, behavior, cognition, functioning                       |
| Cardiovascular evaluation          | Electrocardiogram                       | Heart function                                              |
| Imaging                            | Conventional X-Ray                      | Chest, neck, other structures or organs                     |
| Structural neuroimaging            | Computerized Tomography (CT-Scan)       | Brain structure                                             |
| Functional neuroimaging            | Single Photon Emission                  | Brain function                                              |
|                                   | Computerized Tomography (SPECT)         | cerebrovascular function                                     |
|                                   | Positron Emission Tomography (PET)      | brain oxygenation                                           |
| Brain electrophysiology            | EEG, qEEG, EMG, EP                      | Brain mapping; neuromuscular transmission; evoked potentials |
| Cerebrovascular assessment         | SPECT                                   | Brain perfusion                                             |
|                                   | CT-Brain Perfusion                      | Brain oxygenation                                           |
| Structural genomics                | Gene mapping                            | Mutations                                                   |
|                                   | Linkage analysis                        | disease-associated genotypes                                 |
|                                   | 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 |
|                                   |                                         | efficacy issues                                             |
| (continued)                        |                                         |                                                             |
in the APP, PS1, PS2, and MAPT genes give rise to well-characterized differential neuropathological and clinical phenotypes of dementia. 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, \( \beta \)-amyloid deposition, ApoE secretion, lipid metabolism, brain bioelectrical activity, cognition, apoptosis, and treatment outcome. 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), \( \beta \)-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, \( \beta \)-amyloid, and histamine levels in blood. 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). 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. 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-\( \beta \) (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\textsuperscript{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\textsuperscript{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,
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. 40.2** APOE- and bigenic (APOE + PSEN1)-related blood histamine levels in Alzheimer’s disease (Adapted from R. Cacabelos\(^{8,61,62}\))

**Fig. 40.3** APOE- and bigenic (APOE + PSEN1)-related blood histamine levels in Alzheimer’s disease (Adapted from R. Cacabelos\(^ {8,61,62}\))

**Blood Histamine**

**APOE-Related Blood Histamine Levels**

**Alzheimer’s Disease**

| Blood Histamine (nmol/ml) |
|---------------------------|
| **sd**                    |
| **X**                     |

Blood Histamine (nmol/ml)

**Blood Histamine**

**Genotype-Related Blood Histamine Levels**

**Alzheimer’s Disease**

3311

3312

3322

3411

3412

3422

4411

4412

Blood Histamine (nmol/ml)
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. 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. It has been demonstrated that brain activity slowing correlates with progressive GDS staging in dementia (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 (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)
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. 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.

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. 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 and the identification and characterization of many genes associated with CNS disorders, 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) and drug metabolism.

Fig. 40.6  Efficacy and safety issues associated with pharmacogenetics and pharmacogenomics (Adapted from R. Cacabelos)
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 phenotype73; 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 involved8,16–22,74–77 (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)
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, thiopurinemethyltransferase, catechol-O-methyltransferase, glutathione-S-transferases, UDP-glucuronosyltransferases, glucosyltransferase, histamine methyltransferase; (c) Reductases: NADPH:quinone 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.\textsuperscript{19,20} Polymorphic variants in these genes can induce alterations in drug metabolism modifying the efficacy and safety of the prescribed drugs.\textsuperscript{85}

Drug metabolism includes phase I reactions (i.e., oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e., acetylation, glucuronidation, sulfation, methylation).\textsuperscript{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 (gluthathion S-transferase A), GST-P, GST-T, GST-M, NAT2 (N-acetyl transferase), NAT1, and others.\textsuperscript{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
| Drugs          | Pharmacological category | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|----------------|--------------------------|-----------------|-----------------|------------|----------|-------------|
| Acetaminophen  | Analgesic                | CYP1A2          | CYP2C19         | CYP3A4     | CYP2D6   | COMT        |
|                | Narcotic                 | CYP2C8/8        |                 |            |          | GPIIA       |
| Acetylsalicylic acid | Salicylate              |                 | CYP2C8/9        |            |          | LTC4S       |
|                |                          |                 |                 |            |          | COMT        |
| Alfentanil     | Analgesic                | CYP3A4          |                 |            |          |             |
|                | Narcotic                 |                 |                 |            |          |             |
| Almotriptan    | Antimigraine             |                 | CYP2D6          | CYP3A4     |          | HTR1B       |
|                | Serotonin 5HT-1B/1D      |                 |                 |            |          |             |
|                | receptor agonist         |                 |                 |            |          | HTR1D       |
| Alosetron      | Selective 5HT<sub>3</sub> receptor antagonist | CYP1A2 | CYP2C8/9 | CYP1A2 | CYP2E1 |
| Alprazolam     | Benzodiazepine           | CYP3A4          |                 |            |          |             |
| Amitriptyline  | Tricyclic antidepressant | CYP2D6          | CYP1A2          | CYP1A2     |          | ABCB1       |
|                | tertiary amine           |                 | CYP2B6          |            |          | ADRA1       |
|                | benzodiazepine           |                 | CYP2C8/9        |            |          | GNB3        |
|                |                          |                 | CYP2C19         |            |          | GNAS1       |
|                |                          |                 | CYP2D6          |            |          | KCNE2       |
|                |                          |                 | CYP3A4          |            |          | SCN5A       |
|                |                          |                 |                 |            |          | TNF-A       |
|                |                          |                 |                 |            |          | ADRA1       |
|                |                          |                 |                 |            |          | GnB3        |
|                |                          |                 |                 |            |          | GNAS1       |
| Amoxapine      | Tricyclic antidepressant | CYP2D6          |                 |            |          |             |
|                | secondary amine          |                 |                 |            |          |             |
| Amphetamine    | Stimulant                | CYP2D6          |                 |            |          |             |
| Aripiprazole   | Atypical antipsychotic   | CYP2D6          |                 | CYP3A4     |          | ADRA1       |
|                |                          |                 |                 |            |          | DRD2        |
|                |                          |                 |                 |            |          | DRD3        |
|                |                          |                 |                 |            |          | HTR1A       |
|                |                          |                 |                 |            |          | HTR2A       |
|                |                          |                 |                 |            |          | HTR2C       |
| Atomoxetine    | Selective norepinephrine | CYP2D6          |                 | CYP2C19    |          |             |
|                | reuptake inhibitor       |                 |                 |            |          |             |
| Azelastine     | Antihistamine            | CYP1A2          | CYP2B6          | CYP2C19    |          |             |
|                |                          | CYP2C19         |                 | CYP2C19    |          |             |
|                |                          | CYP2D6          |                 | CYP2D6     |          |             |
|                |                          | CYP3A4          |                 | CYP3A4     |          |             |
| Benzphetamine  | Anorexiant               | CYP3A4          | CYP2B6          |            |          |             |
| Benztropine    | Anticholinergic          | CYP3A4          | CYP2D6          |            |          |             |
|                | antiparkinsonian         |                 |                 |            |          |             |
| Bromazepam     | Benzodiazepine           | CYP3A4          |                 |            |          | COMT        |
| Bromocriptine  | Dopamine agonist         | CYP3A4          |                 |            |          |             |
|                | ergot derivative         |                 | CYP1A2          |            |          |             |
|                | antiparkinsonian         |                 | CYP3A4          |            |          |             |
| Buprenorphine  | Analgesic                | CYP3A4          | CYP1A2          |            |          | COMT        |
|                | narcotic                 |                 | CYP2A6          |            |          |             |
|                |                          |                 | CYP2C19         |            |          |             |
|                |                          |                 | CYP2D6          |            |          |             |
| Bupropion      | Antidepressant           | CYP2B6          | CYP1A2          |            |          |             |
|                | dopamine-reuptake inhibitor |           | CYP2A6          |            |          |             |

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

(continued)
| Drugs                  | Pharmacological category | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|------------------------|--------------------------|----------------|----------------|------------|----------|-------------|
| Clemastine             | Antihistamine            | CYP2D6         | CYP3A4         |            |          |             |
| Clozapine              | Tricyclic antidepressant tertiary amine | CYP1A2         | CYP3A4         | CYP2D6     |          | GNB3        |
| Clonazepam             | Benzodiazepine           | CYP3A4         |                |            |          |             |
| Clorazepate            | Benzodiazepine           | CYP3A4         |                |            |          |             |
| Clozapine              | Atypical antipsychotic   | CYP1A2         | CYP2A6         | CYP1A2     | ADRA1    |             |
|                        |                          |                | CYP2C8/9       | CYP2C8/9   | ADRB3    |             |
|                        |                          |                | CYP2C19        | CYP2C19    | DRD2     |             |
|                        |                          |                | CYP2D6         | CYP2D6     | DRD3     |             |
|                        |                          |                | CYP3A4         | CYP2E1     | DRD4     |             |
|                        |                          |                |                |            | GNB3     |             |
|                        |                          |                |                |            | GNAS1    |             |
|                        |                          |                |                |            | RGS2     |             |
|                        |                          |                |                |            | HLA-A1   |             |
|                        |                          |                |                |            | HRH1     |             |
|                        |                          |                |                |            | HRH2     |             |
|                        |                          |                |                |            | HTR1A    |             |
|                        |                          |                |                |            | HTR2A    |             |
|                        |                          |                |                |            | HTR2C    |             |
|                        |                          |                |                |            | HTR6     |             |
|                        |                          |                |                |            | SLC6A2   |             |
|                        |                          |                |                |            | SLC6A4   |             |
|                        |                          |                |                |            | TNF-A    |             |
| Cocaine                | Local anesthetic         | CYP3A4         |                | CYP2D6     |          | COMT        |
| Codeine                | Analgesic narcotic       | CYP2D6         | CYP3A4         | CYP2D6     |          |             |
| Cyclobenzaprine        | Skeletal muscle relaxant | CYP1A2         | CYP2D6         |            |          |             |
| Dantrolene             |                  | CYP3A4         |                |            |          |             |
| Desiramine             | Tricyclic antidepressant secondary amine | CYP2D6         | CYP1A2         | CYP2A6     |          |             |
|                        |                          |                | CYP2B6         |            | ADRA1    |             |
|                        |                          |                | CYP2D6         |            | ADRB3    |             |
|                        |                          |                | CYP2E1         |            | DRD2     |             |
|                        |                          |                |                |            | DRD3     |             |
|                        |                          |                |                |            | DRD4     |             |
|                        |                          |                |                |            | GNB3     |             |
|                        |                          |                |                |            | GNAS1    |             |
|                        |                          |                |                |            | RGS2     |             |
|                        |                          |                |                |            | HLA-A1   |             |
|                        |                          |                |                |            | HRH1     |             |
|                        |                          |                |                |            | HRH2     |             |
|                        |                          |                |                |            | HTR1A    |             |
|                        |                          |                |                |            | HTR2A    |             |
|                        |                          |                |                |            | HTR2C    |             |
|                        |                          |                |                |            | HTR6     |             |
|                        |                          |                |                |            | SLC6A2   |             |
|                        |                          |                |                |            | SLC6A4   |             |
|                        |                          |                |                |            | TNF-A    |             |
| Dextroamphetamine      | Stimulant                | CYP2D6         | CYP1A2         | CYP2A6     |          |             |
| Diazepam               | Benzodiazepine           | CYP2C19        | CYP1A2         | CYP2C19    |          |             |
|                        |                          |                | CYP2B6         | CYP2C19    |          |             |
|                        |                          |                | CYP2C8/9       | CYP3A4     |          |             |
|                        |                          |                |                |            | LTC4S    |             |
| Diclofenac             | Nonsteroidal anti-inflammatory drug | CYP2B6         | CYP1A2         | CYP1A2     |          |             |
|                        |                          |                | CYP2C8/9       |            |          |             |
|                        |                          |                | CYP2C8/9       |            |          |             |
|                        |                          |                | CYP2E1         |            |          |             |
| Drugs               | Pharmacological category        | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|---------------------|--------------------------------|-----------------|-----------------|------------|----------|-------------|
| Dihydrocodeine      | Analgesic narcotic             | CYP2D6          |                 | CYP3A4     |          | COMT        |
| Dihydroergotamine   | Ergot derivative               | CYP3A4          |                 | CYP3A4     |          | ABCB1       |
| Disulfiram          | Aldehyde dehydrogenase inhibitor |                 |                 | CYP1A2     | CYP1A2   |             |
|                     |                                |                 |                 | CYP2A6     | CYP2A6   |             |
|                     |                                |                 |                 | CYP2B2     | CYP2B6   |             |
|                     |                                |                 |                 | CYP2D6     | CYP2D6   |             |
|                     |                                |                 |                 | CYP2C8/9   | CYP2D6   |             |
|                     |                                |                 |                 | CYP2E1     | CYP2E1   |             |
|                     |                                |                 |                 | CYP3A4     | CYP3A4   |             |
| Domperidone         | Dopamine antagonist            |                 | CYP3A4          |            |          | ACHC        |
| Donepezil           | Acetylcholinesterase inhibitor | CYP2D6          |                 | CYP3A4     |          | ABCB1       |
| Doxepin             | Tricyclic antidepressant tertiary amine | CYP1A2 | CYP2D6 | CYP3A4 |            | APOE, GNB3  |
| Droperidol          | Antiemetic                     |                 |                 |            |          | ADRA1, KENE2, DRD2 |
|                     | Atypical antipsychotic         |                 |                 |            |          | SCN5A       |
| Duloxetine          | Antidepressant serotonin/norepinephrine reuptake inhibitor | CYP1A2 | CYP2D6 |            |          |             |
| Eletriptan          | Antimigraine serotonin 5HT-1B/1D receptor agonist |                 | CYP3A4          |            |          |             |
| Ergoloid Mesylates  | Ergot derivative               | CYP3A4          |                 |            |          | GNB3, GNAS1 |
| Ergonovine          | Ergot derivative               | CYP3A4          |                 |            |          |             |
| Ergotamine          | Ergot derivative               | CYP3A4          |                 | CYP3A4     |          |             |
| Escitalopram        | Antidepressant selective serotonin reuptake inhibitor | CYP2D6 | CYP3A4 |            |          |             |
| Estazolam           | Benzodiazepine                 | CYP3A4          |                 |            |          |             |
| Felbamate           | Anticonvulsant                 | CYP3A4          | CYP2E1          | CYP2C19    | CYP3A4   |             |
| Fentanyl            | Analgesic narcotic             |                 | CYP3A4          |            |          |             |
| Fexofenadine        | Antihistamine                  |                 | CYP3A4          | CYP2D6     |          | ABCB1       |
| Fluoxetine          | Antidepressant selective serotonin reuptake inhibitor | CYP2C8/9 | CYP1A2 | CYP2B2 | CYP2C8/9 |
|                     |                                |                 | CYP2B2          | CYP2C8/9   | CYP2D6   |             |
|                     |                                |                 | CYP2E1          | CYP2C8/9   | CYP2D6   |             |
|                     |                                |                 | CYP3A4          | CYP2D6     | CYP3A4   |             |
| Flupenthixol        | Atypical antipsychotic         |                 |                 |            |          | ADRA1, DRD2, SCN5A |
| Drugs      | Pharmacological category                        | Major substrate | Minor substrate | Inhibitors       | Inducers       | Other Genes |
|------------|-----------------------------------------------|-----------------|----------------|-----------------|---------------|-------------|
| Fluphenazine | Atypical antipsychotic phenothiazine           | CYP2D6          |                | CYP1A2          | ABCB1         | Adra1       |
|            |                                               |                 |                | CYP2C8/9        |               | Drd2        |
|            |                                               |                 |                | CYP2D6          |               |             |
|            |                                               |                 |                | CYP2E1          |               |             |
|            |                                               |                 |                | CYP2E1          |               |             |
| Flurazepam | Benzodiazepine                                 | CYP3A4          |                | CYP2C8/9        |               |             |
| Flurbiprofen | Nonsteroidal anti-inflammatory drug            | CYP2C8/9        |                |                 | LTC4S         |             |
|            |                                               |                 |                |                 |               |             |
| Fluvoxamine | Antidepressant selective serotonin reuptake inhibitor | CYP1A2          | CYP2D6         | CYP1A2          |               |             |
|            |                                               |                 |                | CYP2B6          |               |             |
|            |                                               |                 |                |                 |               |             |
|            |                                               |                 |                |                 |               |             |
| Fosphenytoin | Anticonvulsant hydantoin                       | CYP2C8/9        | CYP3A4         | CYP2B6          |               |             |
|            |                                               | CYP2C19         |                | CYP2C8/9        |               |             |
|            |                                               |                 |                | CYP2C8/9        |               |             |
|            |                                               |                 |                | CYP2C19         |               |             |
|            |                                               |                 |                | CYP3A4         |               |             |
|            |                                               |                 |                |                 |               |             |
| Frovatriptan | Antimigraine serotonin 5HT-1B/1D receptor agonist | CYP1A2          |                | CYP2D6          |               |             |
|            |                                               |                 |                | CYP3A4          |               |             |
| Galantamine | Acetylcholinesterase inhibitor                 | CYP2D6          | CYP3A4         |                |               | Adsre1a, Adr1a, Ddra1, Ddra2, Ddra3, Kcnd3, Scn5a |
| Haloperidol | Typical antipsychotic                          | CYP2D6          | CYP3A4         | CYP2D6          |               |             |
|            |                                               |                 |                | CYP3A4          |               |             |
| Halothane  | Anesthetic                                     | CYP2E1          |                | CYP2A6          |               |             |
|            |                                               |                 |                | CYP2B6          |               |             |
|            |                                               |                 |                | CYP2C8/9        |               |             |
|            |                                               |                 |                | CYP2D6          |               |             |
|            |                                               |                 |                | CYP3A4          |               |             |
| Hydrocodone | Analgesic                                      | CYP2D6          |                |                | Comt          |             |
| Hydromorphone | Analgesic narcotic                            |                 |                |                | Comt          |             |
| Ibuprofen  | Nonsteroidal anti-inflammatory drug            | CYP2C8/9        | CYP2C8/9       |                | LTC4S         |             |
|            |                                               |                 |                |                 |               |             |
| Imipramine | Tricyclic antidepressant tertiary amine        | CYP2C19         | CYP2D6         | CYP1A2          |               | Gnas1, Kcnd2, Scn5a |
|            |                                               |                 |                | CYP2B6          |               |             |
|            |                                               |                 |                | CYP2C19         |               |             |
|            |                                               |                 |                | CYP3A4          |               |             |
|            |                                               |                 |                | CYP2D6          |               |             |
|            |                                               |                 |                | CYP2E1          |               |             |

(continued)
| Drugs           | Pharmacological category | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|-----------------|--------------------------|-----------------|-----------------|------------|----------|-------------|
| Indomethacin    | Nonsteroidal anti-inflammatory drug |                | CYP2C8/9        | CYP2C8/9   | LTC4S    |             |
|                 |                          |                 | CYP2C19         |            |          |             |
| Ketamine        | Anesthetic               | CYP2B6          | CYP2C8/9        | CYP2C19    |          |             |
|                 |                          | CYP3A4          |                 |            |          |             |
| Levorphanol     | Analgesic narcotic       |                 |                 | COMT       |          |             |
| Lidocaine       | Analgesic Anesthetic     | CYP2D6          | CYP3A4          |            |          |             |
|                 |                          |                 | CYP1A2          |            |          |             |
|                 |                          |                 | CYP1A2          |            |          |             |
|                 |                          |                 | CYP2A6          |            |          |             |
|                 |                          |                 | CYP2B6          |            |          |             |
|                 |                          |                 | CYP3A4          |            |          |             |
|                 |                          |                 |                 | ABCB1      |          |             |
|                 |                          |                 |                 |            |          |             |
| Lithium         | Lithium                  |                 |                 |            |          | COMT        |
|                 |                          |                 |                 |            |          | DRD2        |
|                 |                          |                 |                 |            |          | DRD3        |
|                 |                          |                 |                 |            |          | DRD4        |
|                 |                          |                 |                 |            |          | GABA        |
|                 |                          |                 |                 |            |          | GNB3        |
|                 |                          |                 |                 |            |          | HTR2A       |
|                 |                          |                 |                 |            |          | HTR2C       |
|                 |                          |                 |                 |            |          | INPP1       |
|                 |                          |                 |                 |            |          | MAOA        |
|                 |                          |                 |                 |            |          | SLC6A4      |
|                 |                          |                 |                 |            |          | TPH2        |
| Loratidine      | Antihistamine            | CYP2D6          | CYP2C19         |            |          | ADR1A       |
|                 |                          | CYP3A4          | CYP2D6          |            |          |              |
| Loxapine        | Typical antipsychotic    |                 |                 |            |          | KCNE2       |
|                 |                          |                 |                 |            |          | SCN5A       |
|                 |                          |                 |                 |            |          | ABCB1       |
|                 |                          |                 |                 |            |          | LTC4S       |
| Maprotiline     | Tetracyclic antidepressant | CYP2D6        |                 |            |          |              |
| Mefenamic acid  | Nonsteroidal anti-inflammatory drug | CYP2C8/9 |                 |            |          |              |
| Meloxicam       | Nonsteroidal anti-inflammatory drug | CYP2C8/9 |                 |            |          | LTC4S       |
| Meperidine      | Analgesic narcotic       |                 | CYP3A4          |            |          | COMT        |
|                 |                          |                 | CYP2B6          |            |          |              |
|                 |                          |                 | CYP2C19         |            |          |              |
|                 |                          |                 | CYP3A4          |            |          |              |
|                 |                          |                 | CYP2B6          |            |          |              |
| Mephenytoin     | Anticonvulsant           | CYP2C8/9        | CYP2C19         |            |          | ADR1A       |
| Mephobarbital   | Barbiturate              | CYP2C19         | CYP2B6          | CYP2C19    | CYP2A6    |              |
| Mesoridazine    | Typical antipsychotic phenothiazine | CYP2C8/9 |                 |            |          |              |
| Methadone       | Analgesic narcotic       | CYP3A4          | CYP2C8/9        | CYP2D6     | CYP3A4    |              |
| Methamphetamine| Stimulant                | CYP2D6          |                 |            |          |              |
| Methamphetamine|                   | (continued)     |                 |            |          |              |
| Drugs                  | Pharmacological category                          | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|-----------------------|---------------------------------------------------|-----------------|-----------------|------------|----------|-------------|
| Methotrimeprazine     | Analgesic narcotic                                |                 |                 | CYP2C19    |          | COMT        |
| Methosuximide         | Anticonvulsant succinimide                         |                 |                 | CYP2C19    |          |             |
| Methylergonovine      | Ergot derivative                                  | CYP3A4          |                 | CYP2D6     |          |             |
| Metamphetamine       | Stimulant                                         |                 |                 | CYP1A2     | CYP2D6   | SLC6A3 DRD3 |
| Metoclopramide        | Antiemetic gastrointestinal prokinetic            |                 |                 | CYP2B6     | CYP2C8/9 | ABCB1       |
| Midazolam             | Benzodiazepine                                    | CYP3A4          |                 | CYP2B6     | CYP3A4   |             |
| Mirtazapine           | Antidepressant alpha-2 antagonist                  | CYP1A2          |                 | CYP2C8/9   | CYP1A2   | ADRA1       |
| Moclobemide           | Antidepressant reversible MAO inhibitor           |                 |                 | CYP2C19    | CYP2C19  | MAOA        |
| Modafinil             | Stimulant                                         | CYP3A4          |                 | CYP2A2     | CYP2C8/9 |             |
| Molindone             | Typical antipsychotic                             |                 |                 | CYP2A6     | CYP2E1   | ADRA1 DRD2  |
| Morphine sulfate      | Analgesic narcotic                                |                 |                 | CYP2D6     |          | COMT        |
| Naproxen              | Nonsteroidal anti-inflammatory drug               | CYP1A2          |                 | CYP2C8/9   |          | LTC4S       |
| Nefazodone            | Antidepressant serotonin reuptake inhibitor/      |                 |                 | CYP1A2     | CYP2A2   | ABCB1       |
|                       | antagonist                                        | CYP3A4          |                 | CYP2B6     |          | ADRA1       |
|                       |                                                   |                 |                 | CYP2D6     | CYP3A4   | GNB3 GNAS1  |
| Nicardipine           | Calcium channel blocker                           | CYP3A4          |                 | CYP2C8/9   | CYP2C19  | ABCB1       |
| Nicotine              | Cholinergic agonist stimulant                     |                 |                 | CYP2A6     | CYP2E1   | CHRNA2 CHRNA3 |
|                       |                                                   |                 |                 | CYP2A6     |          | CHRNA4 CHRNA5 CHRNA9 CHRNB2 |
|                       |                                                   |                 |                 | CYP2A6     |          | CHRNA3 CHRNA4 CHRNA5 CHRNA9 CHRNB2 |
|                       |                                                   |                 |                 | CYP2A6     |          | CHRNA4 CHRNA5 CHRNA9 CHRNB2 |
|                       |                                                   |                 |                 | CYP2A6     |          | CHRNA4 CHRNA5 CHRNA9 CHRNB2 |
| Nifedipine            | Calcium channel blocker                           | CYP3A4          |                 | CYP1A2     | CYP2C8/9 | ABCB1       |

(continued)
| Drugs       | Pharmacological category | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|------------|-------------------------|----------------|----------------|------------|----------|-------------|
| Nimodipine | Calcium channel blocker | CYP3A4         |                | CYP2D6     | CYP3A4   |             |
| Nisoldipine| Calcium channel blocker | CYP3A4         |                | CYP1A2     | CYP3A4   |             |
| Nitrendipine| Calcium channel blocker| CYP3A4         | CYP2D6         | CYP1A2     | CYP3A4   | ABCB1       |
| Nortriptyline| Tricyclic antidepressant secondary amine | CYP2D6 | CYP2C19 | CYP2E1 |     | ADRA1 GNB3 GNAS1 |
| Olanzapine | Atypical antipsychotic  | CYP1A2         | CYP2D6         | CYP1A2     | CYP2C8/9 | ADRA1 DRD2 DRD3 HRH1 HRH2 HTR2A HTR2C HTR6 RGS2 TNF-A |
| Ondansetron| Antiemetic              | CYP3A4         | CYP2C8/9       | CYP1A2     | CYP2C8/9 |             |
| Oxybutynin | Antispasmodic           | CYP3A4         | CYP2D6         | CYP1A2     | CYP2C8/9 |             |
| Oxycodeone | Analgesic narcotic      | CYP2D6         |                |            |          | COMT         |
| Oxymorphone| Analgesic narcotic      |                |                |            |          | COMT         |
| Paroxetine | Antidepressant selective serotonin reuptake inhibitor | CYP2D6 | CYP2C19 | CYP2D6 | CYP3A4 | GNB3 GNAS1 HTR2A MAOA SLC6A4 TNF-A TPH2 COMT |
| Pentazocine| Analgesic narcotic      |                |                |            |          |             |

Table 40.5 (continued)
| Drugs               | Pharmacological category | Major substrate | Minor substrate | Inhibitors          | Inducers | Other Genes |
|---------------------|--------------------------|-----------------|----------------|---------------------|----------|-------------|
| Pentobarbital       | Barbiturate              |                 |                |                     |          |             |
| Pergolide           | Antiparkinsonian         | CYP3A4          |                |                     |          |             |
|                     | dopamine agonist         |                 |                | CYP2D6              |          |             |
|                     | Ergot derivative         |                 |                |                     |          |             |
| Perphenazine        | Typical antipsychotic    | CYP2D6          | CYP1A2         |                     |          |             |
|                     | phenothiazine            |                 | CYP2C8/9       |                     |          |             |
|                     |                          |                 | CYP2C19        |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
| Phencyclidine       | Anesthetic               | CYP3A4          |                |                     |          |             |
| Phenobarbital       | Anticonvulsant barbiturate| CYP2D6         | CYP2C8/9       |                     |          |             |
|                     |                          |                 | CYP2E1         |                     |          |             |
| Phenytoin           | Anticonvulsant barbiturate| CYP2C8/9       | CYP3A4         |                     |          |             |
|                     |                          |                 | CYP2C19        |                     |          |             |
| Pimozide            | Typical antipsychotic    | CYP1A2          |                |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
| Pinazepam           | Benzodiazepine           |                 | CYP3A4         |                     |          |             |
| Pindolol            | Beta blocker             |                 | CYP2D6         |                     |          |             |
| Pizotiazine         | Typical antipsychotic    | CYP2D6          | CYP2D6         |                     |          |             |
|                     | phenothiazine piperidine |                 | CYP3A4         |                     |          |             |
| Piroxicam           | Nonsteroidal anti-inflammatory drug | | CYP2C8/9 | | CYP2C8/9 | LTC4S |
| Prazepam            | Benzodiazepine           |                 | CYP3A4         |                     |          |             |
| Proarrhythmicamide | Class Ia antiarrhythmic  |                 | CYP2D6         |                     |          |             |
| Prochlorperazine    | Typical antipsychotic    |                 |                |                     |          |             |
|                     | phenothiazine             |                 |                |                     |          |             |
| Promethazine        | Antihistamine            | CYP2B6          |                |                     |          |             |
|                     | phenothiazine             |                 | CYP2D6         |                     |          |             |
| Propafenone         | Class Ic antiarrhythmic  | CYP2D6          | CYP1A2         |                     |          |             |
|                     |                          |                 | CYP2C8/9       |                     |          |             |
|                     |                          |                 | CYP2C19        |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
| Propofol            | Anesthetic               | CYP2B6          | CYP1A2         |                     |          |             |
|                     |                          |                 | CYP2C8/9       |                     |          |             |
|                     |                          |                 | CYP2A6         |                     |          |             |
|                     |                          |                 | CYP2C19        |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
| Propranolol         | Class II antiarrhythmic  | CYP1A2          | CYP2C19        |                     |          |             |
|                     | nonselective beta-adrenergic blocker | | CYP2D6 | | CYP3A4 | ABCB1 |
|                     |                          |                 | CYP3A4         |                     |          |             |
| Propranolol         | Analgesic                | CYP1A2          | CYP2C19        |                     |          | COMT        |
|                     | narcotic                 |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP3A4         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
|                     |                          |                 | CYP2D6         |                     |          |             |
| (continued)         |                          |                 | CYP2D6         |                     |          |             |
| Drugs            | Pharmacological category               | Major substrate | Minor substrate | Inhibitors | Inducers | Other Genes |
|------------------|----------------------------------------|-----------------|----------------|------------|----------|-------------|
| Protriptyline    | Tricyclic antidepressant secondary amine | CYP2D6          |                |            |          |             |
| Quazepam         | Benzodiazepine                         | CYP3A4          | CYP2D6         |            |          | ADRA1, DRD2, KCN5A, SCN5A |
| Quetiapine       | Atypical antipsychotic                 | CYP3A4          | CYP2D6         |            |          | ADRA1, DRD2, KCN5A, SCN5A |
| Quinidine        | Class Ia antiarrhythmic                | CYP3A4          | CYP2C8/9, CYP2E1, CYP2D6, CYP3A4 |            |          | ABCB1, G6PD, KCN5A, SCN5A |
| Ranitidine       | Histamine H2 antagonist                | CYP1A2          | CYP1A2, CYP2D6, CYP2C19 |            |          | ABCB1, HRH2 |
| Remifentanil     |                                        |                 |                |            |          | COMT, ABCB1 |
| Reserpine        | Monoamine-depleting agent Rauwolfia alkaloid |                |                |            |          | ABCB1, HRH2 |
| Riluzole         | Glutamate inhibitor                    | CYP1A2          |                |            |          | ACH, APOE, ABCB1, ADRA1, DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C, KCN5A, RGS2, SLC6A2, SCN5A, HTR1 |
| Rivastigmine     | Acetylcholinesterase inhibitor         | CYP1A2          |                |            |          | ACH, APOE, ABCB1, ADRA1, DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C, KCN5A, RGS2, SLC6A2, SCN5A, HTR1 |
| Risperidone      | Atypical antipsychotic                 | CYP2D6          | CYP2A4, CYP2D6, CYP3A4 |            |          | ACH, APOE, ABCB1, ADRA1, DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C, KCN5A, RGS2, SLC6A2, SCN5A, HTR1 |
| Rizatriptan      | Antimigraine 5HT-1 receptor agonist    | CYP2D6          |                | CYP1A2     | CYP3A4   | LTC4S       |
| Rofecoxib        | Nonsteroidal anti-inflammatory drug COX-2 selective | CYP2D6          | CYP1A2, CYP2D6, CYP3A4 |            |          | LTC4S       |
| Ropinirole       | Antiparkinsonian dopamine agonist      | CYP1A2, CYP2D6, CYP2C8/9, CYP2C19, CYP2D6 |            |          |          |             |
| Rosiglitazone    | Antidiabetic thiazolidinedione         | CYP2C8/9        | CYP2C19, CYP2D6 |            |          |             |
| Secobarbital     | Barbirate                              | CYP2B6          | CYP1A2, CYP2A6, CYP2C8/9, CYP2D6, CYP3A4, CYP2C19 |            |          | CYP2A6, CYP2C8/9 |
| Selegiline       | Antiparkinsonian MAOB inhibitor        | CYP2C8/9        | CYP1A2, CYP2A6, CYP2C8/9, CYP2D6, CYP3A4, CYP2C19 |            |          | CYP2A6, CYP2C8/9 |

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

(continued)
Table 40.5 (continued)

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

**ABCBB1:** 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  
**CHRNB3:** Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 3  
**CHRNB4:** Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 4  
**CHRNB7:** Cholinergic Receptor, Neuronal Nicotinic, Beta Polypeptide 7  
**COMT:** Catechol-O-Methyl Transferase  
**CYP:** Cytochrome P450 Family Genes
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 al87 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 40.5 (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 |
| GN1A1: Gs Protein Alpha-Subunit |
| GPII: 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 |
| HTR3: Serotonin Receptor 3 |
| INP1: 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 |
| SC5NA: 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. Takeda19; L.M. Cavallari, V.L. Ellingrod, and J.M. Kolesar125; C.F. Lacy et al126; M.A. Fuller & M. Sajatovic127; www.pharmgkb.org206; www.ncbi.nlm.nih.gov10
| Gene      | Locus       | Name                                                                 | Alternate names                                                                                       | Related drugs                                                                                           | Related Diseases                                      | OMIM  | Alternate Symbols  |
|-----------|-------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------|-------------------|
| CYP1A2    | 15q22-pter  | 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 monoxygenase; microsomal monoxygenase; xenobiotic monoxygenase | Amiodarone, caffeine, citalopram, clozapine, cyclobenzaprine, dexamethasone, echinacea, estradiol, etoposide, fluvoxamine, haloperidol, imipramine, interferon alpha, lidocaine, mibefradil, midazolam, modafinil, naproxen, ondansetron, propranolol, ribavirin, rifazole, 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 monoxygenase; microsomal monoxygenase; xenobiotic monoxygenase | Estrogens                                                                                               | Breast neoplasms                                     | 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 monoxygenase; xenobiotic monoxygenase | 5-Fluorouracil, dexamethasone, etoposide, fadrozole, fluorouracil, midazolam, nicotine, rifampin, teniposide | Neoplasms, Coumarin resistance, protection from nicotine addiction | 122720 | CPA6; CYP2A3 |

(continued)
| Gene   | Locus      | Name                                                                 | Alternate names                                                                 | Related drugs                                                                 | Related Diseases                          | OMIM   | Alternate Symbols |
|--------|------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------|--------|-------------------|
| CYP2B6 | 19q13.2    | Cytochrome P450, family 2, subfamily IIIB (Phenobarbital-inducible), polypeptide 6 | Cytochrome P450, family 2, subfamily IIIB (Phenobarbital-inducible), polypeptide 6 | Aflatoxin B1, bupropion, cyclophosphamide, dexamethasone, etoposide, ifosfamide, midazolam, phenobarbital, propofol, rifampin, teniposide, thiopeta, vitamin D, xenobiotics | Nicotine addiction                         | 123930 | CPB6; CYP1IBB6; P450 |
| CYP2C19 | 10q24-24.3 | Cytochrome P450, family 2, subfamily C, polypeptide 19                | Cytochrome P450, family 2, subfamily C, polypeptide 19                            | Amitriptyline, carisoprodol, closephosphamide, diazepam, fluoxetine, fluvoxamine, glucorticoids, hexobarbital, lansoprazole, mephenytoin, modafinil, nelfinavir, nilotamide, omeprazole, pantoprazole, proguanil, rifampin, thiopeta, ticlopidine | Lupus nephritis, gastroesophageal reflux disease, peptic ulcer disease, visual disorders | 124020 | CPCJ; CYP2C; P450C2C; P450IC19 |
| CYP2C9  | 10q24      | Cytochrome P450, family 2, subfamily C, polypeptide 9                 | Cytochrome P450, family 2, subfamily C, polypeptide 9                            | Acenocoumarol, amiodarone, celecoxib, coumadin, dexamethasone, diclofenac, etoposide, fluconazole, fluoxetine, fluvastatin, fluvoxamine, glimepiride, glipizide, glyburide, ibuprofen, irbesartan, isoniazid, losartan, midazolam, phenylbutazone, phenytin, rifampin, teniposide, tenoxicam, thiopeta, 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; P450IC9 |
| Gene Symbol | Location | Gene Name | Protein Description | Drugs Metabolized | Phenotypes | Genotypes | Genes | Enzyme Name | Location | Functions |
|-------------|----------|-----------|---------------------|------------------|------------|-----------|-------|--------------|----------|-----------|
| CYP2D6      | 22q13.1  | Cytochrome P450, subfamily IID (debrisoquine, sparteine-like 1; debrisoquine 4-hydroxylase; flavoprotein-linked monooxygenase; microsomal monooxygenase; xenobiotic monooxygenase) | Amitriptyline, caffeine, cimetidine, clonazepam, cocaine, codeine, debrisoquine, desipramine, dextromethorphan, diltiazem, flecainide, fluoxetine, fluvoxamine, haloperidol, imipramine, interferon alpha, metoprolol, mexiletine, morphine, paroxetine, perhexilene, phenelzine, propanolol, ribavirin, risperidone, ritonavir, sparteine, tamoxifen, thioridazine, thiopeta, timolol, tramadol, venlafaxine, xenobiotics | Breast neoplasms, cystic fibrosis, depression, chronic hepatitis C, lung neoplasms, neoplasms, codeine dependence, pain, schizophrénia, codeine dependence, psychosis, Susceptibility to parkinsonism, debrisoquine sensitivity | 124030 | CPD6; CYP2D; CYP2DL1; P450-DB1; P450C2D |
| CYP2E1      | 10q24.3- qter | 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, thiopeta, xenobiotics | Alcoholic liver disease, lung neoplasms, nicotine dependency | 124040 | CPE1; CYP2E; CYP3A; P450-J; P450C2E |
| CYP3A        | 7q21.-q22.1 | Cytochrome P450, subfamily IIIA (nifedipine oxidase) | Dexmethasone, docetaxel, erythromycin, midazolam, rifampin, tamoxifen, thiopeta, xenobiotics | Anrhythmia, lung neoplasms | 124010 | CYP3 |
| CYP3A4       | 7q21.1 | Cytochrome P450, family 3, subfamily A, polypeptide 4 | P450-III, steroid inducible; cytochrome P450, subfamily II A (nifedipine oxidase), polypeptide 3; cytochrome P450, subfamily II A (nifedipine oxidase), polypeptide 4; glucocorticoid-inducible P450; nifedipine oxidase | Breast neoplasms, chronic hepatitis C, leukaemia, L1 acute lymphocytic leukaemia, myeloid leukaemia, neoplasms, prostatic neoplasms, helicobacter pylori gastric ulcers | 124010 | CP33; CP34; CYP3A; CYP3A3; CYP3A4; HLP; NF-25; P450C3; P450PCN1 |
| Gene   | Locus    | Name                                      | Alternate names                                                                 | Related drugs                        | Related Diseases                                                                 | OMIM   | Alternate Symbols |
|--------|----------|-------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------|----------------------------------------------------------------------------------|--------|------------------|
| CYP3A7 | 7q21-q22 | Cytochrome P450, family 3, subfamily A, polypeptide 7 | Aryl hydrocarbon hydrolase; cytochrome P450, subfamily IIA, 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\textsuperscript{[9]} )
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). 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. 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.

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 fulfill 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). 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.

Ethnic Differences

The most important enzymes of the P450 cytochrome family in drug metabolism by decreasing order are CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP2A6. 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. 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. 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, and CYP2C19*3 (Ile359Leu), with alterations in the specificity for the substrate in 6–9% of Caucasians and 2–3% of Asians. The most important mutations in the CYP2D6 gene are the following: CYP2D6*2xN, CYP2D6*4, CYP2D6*5, CYP2D6*10 and CYP2D6*17. The CYP2D6*2xN mutation gives rise to a gene duplication or multiplica-
tion 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 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. The most important mutations in the CYP2D6 gene are the following: CYP2D6*2xN, CYP2D6*4, CYP2D6*5, CYP2D6*10 and CYP2D6*17. The CYP2D6*2xN mutation gives rise to a gene duplication or multiplica-
tion 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.18–20,104–106

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, *1/*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%; *1/*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

| 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 |
| Poor metabolizers  |        |                 |
| *4/’10             |        | 127.80 ± 63.38(3) |
| 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
The 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

| Phenotype CYP2D6 | Cholesterol (mg/dl) | LDL-Cholesterol (mg/dl) | HDL-Cholesterol (mg/dl) | Triglycerides (mg/dl) |
|------------------|---------------------|------------------------|------------------------|----------------------|
| **Extensive metabolizers** |                   |                        |                        |                      |
| '1'/1            | 223.15 ± 41.58      | 147.20 ± 35.00         | 52.30 ± 9.98           | 128.24 ± 76.61       |
| '1'/10           | 275.57 ± 77.00      | 196.40 ± 62.70         | 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         | 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       |
| '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 ±             |
| Poor metabolizers |                   |                        |                        |                      |
| '4'/4            | 233.85 ± 62.50      | 148.72 ± 46.51         | 57.92 ± 17.76          | 144.76 ± 21.24       |
| **Ultra-rapid metabolizers** |             |                        |                        |                      |
| *1xN'/1          | 202.14 ± 52.23      | 129.71 ± 46.23         | 53.28 ± 10.25          | 150.16 ± 33.74       |
| *1xN'/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. '1xN'/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. '1xN'/1; (8) p < 0.05 vs. '1xN'/4; (9) p < 0.05 vs. '1xN'/1; (10) p < 0.05 vs. '1xN'/4; (11) p < 0.01 vs. '4'/10; (12) p < 0.05 vs. '4'/4; (13) p < 0.04 vs. '1xN'/1; (14) p < 0.008 vs. '4'/4; (15) p < 0.02 vs. '1xN'/1.

**Source**: Adapted from R. Cacabelos.109
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 activity20,77,109 (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 | 20.60 ± 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 | *1xN/*1 | 20.50 ± 3.01 | 18.00 ± 5.32 | 21.50 ± 9.22 |
|                      | *1xN/*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. *1xN/*4; (9) p < 0.05 vs. *1xN/*1; (10) p < 0.05 vs. *1xN/*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. *4/*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. *1xN/*1; (21) p < 0.05 vs. *1xN/*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 β-(5-bromonicotinoyl-oxymethyl)-10α-methoxerygoline (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, 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.

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%)
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 donepezil112 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 antidepressants, 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. 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 CHRN Bs (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 (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. 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; 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.

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.

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. 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 glial 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, acetooacetyl-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; farnesyl 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. Polyomorph 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, hydrolyase 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 antidepressants.158,159

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, 12kDa (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 coflin and collapsing response mediator protein, involved in neuronal survival and/or neurite outgrowth. Selective CDK5 inhibitors can also block mitochondrial translocation of pro-apoptotic coflin. Phosphoproteome and transcriptome analysis of neurons indicate that CDK5 inhibitors promote both neuronal survival and neurite outgrowth. 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. 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. Cumulative experiences throughout life history interact with genetic predispositions to shape the individual’s behaviour. 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. 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. This complexity requires a multifactorial approach to overcome the hurdles that CNS drug development faces at the present time.

**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. 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, and the accumulation of the APOE-4 allele has been reported as a risk factor for other forms of dementia and CNS disorders.

APOE-4 may influence AD pathology interacting with APP metabolism and Aβ 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.

**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, 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.

Fig. 40.11 APOE-related cognitive performance in patients with Alzheimer’s disease treated with a combination therapy for 1 year (Adapted from R. Cacabelos77,109). 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.

**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. 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. 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.

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.

**APOE-Related Anxiety and Depression in Dementia**

Behavioral disturbances and mood disorders are intrinsic components of dementia associated with
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 and panic disorder. 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. A positive association between APOE-4 and neuropsychiatric symptoms and depressive symptoms in AD has been reported, especially in women. 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. Some authors did not find association of APOE-4 with major depression in AD or in patients with major depression in a community of older adults, but an apparent protective effect of APOE-2 on depressive symptoms was detected. Others, in contrast, found that APOE-4 was associated with an earlier age-of-onset, but not cognitive functioning, in late-life depression. Apoe−/− mice without human ApoE or with APOE-4, but not APOE-3, show increased measures of anxiety. 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. 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.

In humans, APOE-4 carriers with deep white matter hyperintensities in MRI show association with depressive symptoms and vascular depression. Reduced caudate nucleus volumes and genetic determinants of
Homocysteine metabolism accumulate in patients with psychomotor slowing and cognitive deficits, and older depressed subjects have persisting cognitive impairments associated with hippocampal volume reduction. Depressive symptoms are also associated with stroke and atherogenic lipid profile.

Some multifactorial treatments addressing neuroprotection have shown to be effective in reducing anxiety progressively from the first month to the 12 month of treatment. 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 < 0.0000006) 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).

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.

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 (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). 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.
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.

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. 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.

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. 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.
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.18–20,74–77,109

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.18–20,74–77,109

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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References

1. Andlin-Sobocki P, Jönsson B, Wittchen H-U, Olesen J. Costs of disorders of the brain in Europe. Executive summary. Eur J Neurol 2005; 12(Suppl 1):x–xi.
2. Cacabelos R. Psychogeriatric research. A conceptual introduction to geriatric neuroscience. Psychogeriatrics 2001; 1:158–188.
3. Loveman E, Green C, Kirby J et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer’s disease. Health Technol Assess 2006; 10:1–176.
4. Cacabelos R, AlvarezXA, Lombardi V et al. Pharmacological treatment of Alzheimer disease: from phychotropics drugs and cholinesterase inhibitors to pharmacogenomics. Drugs Today 2000; 36:415–499.
5. Cacabelos R. Pharmacogenomics in Alzheimer’s disease. Min Rev Med Chem 2002; 2:59–84.
6. Cacabelos R. Pharmacogenomics for the treatment of dementia. Ann Med 2002; 34:357–379.
7. Roses AD. Pharmacogenetics and drug development: the path to safer and more effective drugs. Nat Rev Genet 2004; 5:645–656.
8. Cacabelos R. Molecular genetics of Alzheimer’s disease and aging. Meth Find Exper Clin Pharmacol 2005; 27 (Suppl. A):1–573.
9. Kato T. Molecular genetics of bipolar disorder and depression. Psychiatr Clin Neurosci 2007; 61:3–19.
10. www.ncbi.nlm.nih.gov/OMIM
11. Hu D, Ziv E. Confounding in genetic association studies and its solutions. Meth Mol Biol 2008; 448:31–39.
12. Berry N, Jobanputra V, Pal H. Molecular genetics of schizophrenia: a critical review. J Psychiatr Neurosci 2003; 28:415–429.
13. www.molgen.ua.ac.be/ADMutations/
14. Wright AF, Jaconson SG, Cideciyan AV et al. Lifespan and mitochondrial control of neurodegeneration. Nature Genet 2004; 36:1153–1158.
15. Lin MT, Simon DK, Ahn CH et al. High aggregate burden of somatic mtDNA point mutations in aging and Alzheimer’s disease brain. Hum Mol Genet 2002; 11:133–145.
16. Cacabelos R. The application of functional genomics to Alzheimer’s disease. Pharmacogenomics 2003; 4: 597–621.
17. Cacabelos R. Pharmacogenomics and therapeutic prospects in Alzheimer’s disease. Exp Opin Pharmacother 2005; 6:1967–1987.
18. Cacabelos R. Pharmacogenomics, nutrigenomics and therapeutic optimization in Alzheimer’s disease. Aging Health 2005; 1:303–348.
19. Cacabelos R, Takeda M. Pharmacogenomics, nutrigenomics and future therapeutics in Alzheimer’s disease. Drugs Future 2006; 31 (Suppl B):5–146.
20. Cacabelos R. Pharmacogenomics in Alzheimer’s disease. Meth Mol Biol 2008; 448:213–357.
21. Cacabelos R, Fernández-Novoa L, Lombardi V et al. Cerebrovascular risk factors in Alzheimer’s disease: brain hemodynamics and pharmacogenomic implications. Neurol Res 2003; 25:567–580.
22. Cacabelos R, Fernández-Novoa L, Corzo L et al. Phenotypic profiles and functional genomics in dementia with a vascular component. Neurol Res 2004; 26:459–480.
23. Anderson CNG, Grant SGN. High throughput protein expression screening in the nervous system – needs and limitations. J Physiol 2006; 575:2:367–372.
24. Xu X, Zhan M, Duan W et al. Gene expression atlas of the mouse central nervous system: impact and interactions of age, energy intake and gender. Genome Biol 2007; 8:R234. doi:10.1186/gb-2007-8-11-r234.
25. Sogaard M, Tümer Z, Hajlgrim H et al. Subtelomeric study of 132 patients with mental retardation reveals 9 chromosomal anomalies and contributes to the delineation of submicroscopic deletions of 1pter, 2qter, 4pter, 5qter and 9qter. BMC Med Genet 2005; 6:21. doi:10.1186/1471-2350-6-21.
26. Buttnner N, Bhattacharyya S, Walsh J, Benes FM. DNA fragmentation is increased in non-GABAergic neurons in bipolar disorder but not in schizophrenia. Schizophr Res 2007; 93:33–41.
27. Newrzella D, Pahlavan PS, Krüger C et al. The functional genome of CA1 and CA3 neurons under native conditions and in response to ischemia. BMC Genomics 2007; 8:370. doi:10.1186/1471-2164-8-370.
28. Matigian NA, McCurdy RD, Feron F et al. Fibroblast and lymphoblast gene expression profiles in schizophrenia: are non-neural cells informative? PLoS ONE 2008; 3:e2412. doi:10.1371/journal.pone.0002412.
29. Lencz T, Lambert C, DeRosse P et al. Runs of homozygosity reveal highly penetrant recessive loci in schizophrenia. Proc Natl Acad Sci USA 2007; 104:19942–19947.
30. Lehmann E, Hyde TM, Vawter MP et al. The use of microarrays to characterize neuropsychiatric disorders: post-mortem studies of substance abuse and schizophrenia. Curr Mol Med 2003; 3:437–446.
31. Vernes SC, Spiteri E, Nicod J et al. High-throughput analysis of promoter occupancy reveals direct neuronal targets of FOXP2, a gene mutated in speech and language disorders. Am J Hum Genet 2007; 81:1232–1250.
32. Anantharam V, Lehmann E, Kanthasamy A et al. Microarray analysis of oxidative stress regulated genes in mesencephalic dopaminergic neuronal cells: relevance to oxidative damage in Parkinson’s disease. Neurochem Int 2007; 50:834–847.
33. Moran LB, Graeber MB. Towards a pathway definition of Parkinson’s disease: a complex disorder with links to cancer, diabetes and inflammation. Neurogenetics 2008; 9:1–13.
34. Runne H, Kuhn A, Wild EJ et al. Analysis of potential transcriptomic biomarkers for Huntington’s disease in peripheral blood. Proc Natl Acad Sci USA 2007; 104:14424–14429.

35. Sorensen G, Medina S, Parchiali D, Phillipson C, Robertson C, Booth SA. Comprehensive transcriptional profiling of prion infection in mouse models reveals networks of responsive genes. BMC Genomics 2008; 9:114. doi:10.1186/1471-2164-9-114.

36. Lehrmann E, Oyler J, Vawter M et al. Transcriptional profiling in the human prefrontal cortex: evidence for two activation states with cocaine use. Pharmacogenomics J 2003; 3:27–40.

37. Bannon MJ, Kapatos G, Albertson DN. Gene expression profiling in the brains of human cocaine abusers. Addict Biol 2005; 10:119–126.

38. Harper C, Matsumoto I. Ethanol and brain damage. Curr Opin Pharmacol 2005; 5:73–78.

39. Von Gertsen C, Flores Morales A et al. Genomic responses in rat cerebral cortex after traumatic injury. BMC Neurosci 2005; 6:69. doi:10.1186/1471-2202-6-69.

40. Becker AJ, Chen J, Paus S et al. Transcriptional profiling in human epilepsy: expression array and single cell real-time qRT-PCR analysis reveal distinct cellular gene regulation. Neuroreport 2002; 13:1327–1333.

41. Majores M, Eils J, Wiestler OD, Becker AJ. Molecular profiling of temporal lobe epilepsy: comparison of data from human tissue and animal models. Epilepsy Res 2004; 60:173–178.

42. Gu J, Lynch BA, Anderson D et al. The antiepileptic drug levetiracetam selectively modifies kindling-induced alterations in gene expression in the temporal lobe of rats. Eur J Neurosci 2004; 19:334–345.

43. Laposa RR, Huang EJ, Cleaver JE. Increased apoptosis, p53 up-regulation, and cerebellar neuronal degeneration in repair-deficient Cockayne syndrome mice. Proc Natl Acad Sci USA 2007; 104:1389–1394.

44. Peddada S, Yasui DH, LaSalle JM. Inhibitors of differentiation (ID1, ID2, ID3 and ID4) genes are neuronal targets of MeCP2 that are elevated in Rett syndrome. Hum Mol Genet 2006; 15:2003–2014.

45. Rai M, Doragni E, Jenssen K et al. HDAC inhibitors correct praxatonia deficiency in a Friedreich ataxia mouse model. PLoS ONE 2008; 3:e1958. doi:10.1371/journal.pone.0001958.

46. Qiao X, Lu J-Y, Hofmann SL. Gene expression profiling in a Mouse model of infantile neuronal lipofuscinosis reveals upregulation of immediate early genes and mediators of the inflammatory response. BMC Neurosci 2007; 8:95. doi:10.1186/1471-2202-8-95.

47. Lindberg RL, De Groot CJ, Certa U et al. Multiple sclerosis as a generalized CNS disease – comparative microarray analysis of normal appearing white matter and lesions in secondary progressive MS. J Neuroimmunol 2004; 152:154–167.

48. Lederer CW, Torrisi A, Pantelidou M et al. Pathways and genes differentially expressed in the motor cortex of patients with sporadic amyotrophic lateral sclerosis. BMC Genomics 2007; 8:26. doi:10.1186/1471-2164-8-26.

49. Coimbra RS, Voinis V, de Saizieu AB et al. Gene expression in cortex and hippocampus during acute pneumococcal meningo- tis. BMC Biology 2006; 4:15. doi:10.1186/1741-7007-4-15.

50. Adibhatla RM, Hatcher JF. Role of lipids in brain injury and diseases. Future Lipidol 2007; 2:403–422.

51. Glanzer JG, Haydon PG, Eberwine JH. Expression profile analysis of neurodegenerative disease: advances in specificity and resolution. Neurochem Res 2004; 29:1161–1168.

52. Davis JE, Eberwine JH, Hinkle DA, Marciano PG, Meaney DF, McIntosh TK. Methodological considerations regarding single-cell gene expression profiling for brain injury. Neurochem Res 2004; 29:1113–1121.

53. Kishy GE, Olivas A, Standlee M et al. Genotoxicants target distinct molecular networks in neonatal neurons. Environ Health Perspect 2006; 114:1703–1712.

54. Kimpel MW, Brotherton WN, McClintick JN et al. Functional gene expression differences between inbred alcohol-prefering and – non-prerats in five brain regions. Alcohol 2007; 41:95–132.

55. Ökvist A, Johansson S, Kuzmin A et al. Neuroadaptations in human chronic alcoholics: tion of the NF-xB system. PLoS ONE 2007; 2(9):e930. doi:10.1371/journal.pone.0000930.

56. Albertson DN, Pruetz B, Schmidt CJ et al. Gene expression profile of the nucleus accumbens of human cocaine abusers: evidence for dysregulation of myelin. J Neurochem 2004; 88:1211–1219.

57. Lehrmann E, Colantuoni C, Deep-Soboslav A et al. Transcriptional changes common to human cocaine, cannabis and phencyclidine abuse. PLoS ONE 2006; 1:e114. doi:10.1371/journal.pone.0000114.

58. Bak M, Silhataroglu A, Moller M et al. MicroRNA expression in the adult mouse central nervous system. RNA 2008; 14:432–444.

59. Capabos R, Alvarez A, Fernández-Novoa L, Lombardi VRM. A pharmacogenomic approach to Alzheimer’s disease. Acta Neurol Scand 2000; 176(Suppl.):12–19.

60. Capabos R. Dementia. In: Clinical Psychiatry. Jobe TH, Gaviria M, Kovilparambil A (Eds). Blackwell Science, Massachusetts 1997; 73–122.

61. Capabos R, Fernández-Novoa L, Corzo L, Pichel V, Lombardi V, Kubota Y. Genomics and phenotypic profiles in dementia: implications for pharmacological treatment. Meth Find Exp Clin Pharmacol 2004; 26:421–444.

62. Capabos R, Lombardi V, Fernández-Novoa L et al. A functional genomics approach to the analysis of biological markers in Alzheimer disease. In: Molecular Neurobiology of Alzheimer Disease and Related Disorders. Takeda M, Tanaka T, Capabos R (Eds). Karger, Basel, 2004; 236–285.

63. Capabos R. Genomic characterization of Alzheimer’s disease and genotype-related phenotypic analysis of biological markers in dementia. Pharmacogenomics 2004; 5:1049–1105.

64. Capabos R. The histamine-cytokine network in Alzheimer disease: etiopathogenic and pharmacogenomic implications. In: Mapping Progress of Alzheimer’s and Parkinson’s diseases. Advances in Behavioral Biology. Vol. 51. Mizuno Y, In: Mapping Progress of Alzheimer’s and Parkinson’s diseases. Advances in Behavioral Biology. Vol. 51. Mizuno Y, Cacabelos R (Eds). Karger, Basel, 2004; 236–285.

65. Cacabelos R. Histamine function in Alzheimer’s disease: etiopathogenic and pharmacogenomic implications. In: Mapping Progress of Alzheimer’s and Parkinson’s diseases. Advances in Behavioral Biology. Vol. 51. Mizuno Y, Cacabelos R (Eds). Karger, Basel, 2004; 236–285.

66. Cacabelos R, Alvarez A, Fernández-Novoa L, Lombardi VRM. A pharmacogenomic approach to Alzheimer’s disease. Acta Neurol Scand 2000; 176(Suppl.):12–19.

67. Lombardi VR, García M, Rey L, Capabos R. Characterization of cytokine production, screening of
lymphocyte subset patterns and in vitro apoptosis in healthy and Alzheimer’s disease individuals. J Neuroimmunol 1999; 97:163–171.

68. Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. Neurotherapeutics 2007; 4:18–61.

69. International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. Nature 2004; 431:931–945.

70. Subramanian G, Adams MD, Venter JC, Broder S. Implications of the human genome for understanding human biology and medicine. JAMA 2001; 286:2296–2307.

71. Nebert DW, Jorge-Nebert LF. Pharmacogenetics and pharmacogenomics. In: Emery and Rimoin’s Principles and Practice of Medical Genetics. 4th Edn. Rimoin DL, Connor JM, Pyeritz R, Korf BR (Eds). Churchill-Livingstone, Edinburgh, 2002; 590–631.

72. Evans WE, Johnson JA. Pharmacogenomics: the inherited basis for interindividual differences in drug response. Ann Rev Genomics Genet 2001; 2:9–39.

73. Weinshilboum RM, Wang L. Pharmacogenetics and pharmacogenomics: development, science, and translation. Annu Rev Genomics Hum Genet 2006; 7:223–245.

74. Cacabelos R. Pharmacogenomics and therapeutic prospect in Alzheimer’s disease. Mol Diag Ther 2007; 11:385–405.

75. Cacabelos R. Influence of pharmacogenetic factors on Alzheimer’s disease therapeutics. Neurodegener Dis 2008; 5:176–178.

76. Cacabelos R, Llovo R, Fraile C, Fernández-Novoa L. Pharmacogenetic aspects of therapy with cholinesterase inhibitors: the role of CYP2D6 in Alzheimer’s disease pharmacogenetics. Curr Alzheimer Res 2007; 4:479–500.

77. Motulski AG. From pharmacogenetics and ecogenetics to pharmacogenomics. Med Sci Monit 2002; 8:269–281.

78. Weinshilboum R. Inheritance and drug response. N Engl J Med 2002; 346:529–537.

79. Evans WE, McLeod HL. Pharmacogenetics and functional characterization of a new CYP2C9 variant (CYP2C9*5) expressed among African Americans. Mol Pharmacol 2001; 60:382–387.

80. Tribut O, Lessard Y, Reymann JM, Allain H, Bentue-Ferrer D. Pharmacogenomics. Med Sci Monit 2002; 8:152–163.

81. Saito S, Ishida A, Sekine A et al. Catalog of 680 variants among eight cytochrome P450 (CYP) genes: nine esterase genes, and two other genes in the Japanese population. J Hum Genet 2003; 48:249–270.

82. Wooding SP, Watkins WS, Bamshad MJ et al. DNA sequence variations in a 3.7-kb noncoding sequence 5-prime of the CYP1A2 gene: implications for human population history and natural selection. Am J Hum Genet 2002; 71:528–542.

83. Xie HG, Prasad HG, Kim RB, Stein CM. CYP2C9 allelic variants: ethnic distribution and functional significance. Adv Drug Deliv Rev 2002; 54:1257–1270.

84. Madan A, Graham RA, Carroll KM et al. Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos 2003; 31:421–431.

85. Tribut O, Lessard Y, Reymann JM, Allain H, Bentue-Ferrer D. Pharmacogenomics. Med Sci Monit 2002; 8:152–163.

86. Madan A, Graham RA, Carroll KM et al. Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos 2003; 31:421–431.

87. Wooding SP, Watkins WS, Bamshad MJ et al. DNA sequence variations in a 3.7-kb noncoding sequence 5-prime of the CYP1A2 gene: implications for human population history and natural selection. Am J Hum Genet 2002; 71:528–542.

88. Wooding SP, Watkins WS, Bamshad MJ et al. DNA sequence variations in a 3.7-kb noncoding sequence 5-prime of the CYP1A2 gene: implications for human population history and natural selection. Am J Hum Genet 2002; 71:528–542.

89. Madan A, Graham RA, Carroll KM et al. Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos 2003; 31:421–431.
function of CYP2D6 in a German population. Pharmacogenetics 1998; 8:15–26.

106. Bernal ML, Sinues B, Johansson I et al. Ten percent of North Spanish individuals carry duplicated or triplicated CYP2D6 genes associated with ultrarapid metabolism of debrisoquine. Pharmacogenetics 1999; 9:657–660.

107. Farlow MR. Clinical pharmacokinetics of galantamine. Clin Pharmacokinet 2003; 42: 1383–1392.

108. Varsaldi F, Miglio G, Scordo MG et al. Impact of the CYP2D6 polymorphism on steady-state plasma concentrations and clinical outcome of donepezil in Alzheimer’s disease patients. Eur J Clin Pharmacol 2006; 62:721–726.

109. Cacabelos R. Molecular pathology and pharmacogenomics in Alzheimer’s disease: polygenic-related effects of multifactorial treatments on cognition, anxiety, and depression. Meth Find Exp Clin Pharmacol 2007; 29(Suppl B):1–91.

110. Cacabelos R, Fernández-Novoa L, Pichel V, Lombardi V, Kubota Y, Takeda M. Pharmacogenomic studies with a combination therapy in Alzheimer’s disease. In: Molecular Neurobiology of Alzheimer Disease and Related Disorders. Takeda M, Tanaka T, Cacabelos R (Eds). Karger, Basel, 2004; 94–107.

111. Bernard S, Neville KA, Nguyen AT, Flockhart DA. Interethic differences in genetic polymorphisms of CYP2D6 in the U.S. population: clinical implications. Oncologist 2006; 11:126–135.

112. Barner EL, Gray SL. Donepezil use in Alzheimer disease. Ann Pharmacother 1998; 32:70–77.

113. Haugh KH, Bogen IL, Osmundsen H et al. Effects of cholinergic markers in rat brain and blood after short and prolonged administration of donepezil. Neurochem Res 2005; 30:1511–1520.

114. Bachus R, Bickel U, Thomsen T, Roots I, Kewitz H. The O-demethylation of the antidementia drug galantamine is catalyzed by cytochrome P450 2D6. Pharmacogenetics 1999; 9:661–669.

115. Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer’s disease: a comparison of tolerability and pharmacology. Drug Saf 1998; 19:465–480.

116. Zhao Q, Brett M, van Osselaer N et al. Oat-like cholinesterase inhibition and interindividual variation as a predictor of sustained response to anticholinergic medication in first-episode schizophrenic patients. Am J Psychiatr 2006; 163:529–531.

117. Crismon ML. Pharmacokinetics and drug interactions of cholinesterase inhibitors administered in Alzheimer’s disease. Pharmacotherapy 1998; 18:47–54.

118. Mannens GS, Snel CA, Hendrickx J et al. The metabolism and excretion of galantamine in rats, dogs, and humans. Drug Metab Dispos 2002; 30:553–563.

119. Egger SS, Bachmann A, Hubmann N, Schlienger RG, Krüenbühl S. Prevalence of potentially inappropriate medication use in elderly patients. Comparison between general medicine and geriatric wards. Drugs Aging 2006; 24:1002–1010.

120. Schuetz EG, Rellinger MV, Kishi S et al. PharGKB update: II. CYP3A5, cytochrome P450, family 3, subfamily A, polypeptide 5. Pharmacol Rev 2004; 56:159.

121. Malhorta AK, Lencz T, Correll CU, Kane JM. Genomics and the future of pharmacotherapy in psychiatry. Int Rev Psychiatr 2007; 19:523–530.

122. Dorado P, Peñas-Lledó EM, Llerena A. CYP2D6 polymorphism: implications for antipsychotic drug response, schizophrenia and personality traits. Pharmacogenomics 2007; 8:1597–1608.

123. Scordo MG, Spina E. Cytochrome P450 polymorphisms and response to antipsychotic therapy. Pharmacogenomics 2002; 3:201–218.

124. Ingelman-Sundberg M, Sim SC, Gomez A, Rodríguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoeigenetic and clinical aspects. Pharmacol Ther 2007; 116:496–526.

125. Cavallari LM, Ellingrod VL, Kolesar JM. Pharmacogenomics Handbook. 2nd Edn. Lexi-Comp. Hudson, Ohio, 2005.

126. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug Information Handbook with International Trade Names Index. 17th Edn. Lexi-Comp. Hudson, Ohio, 2008.

127. Fuller MA, Sajatovic M. Drug Information Handbook for Psychiatry. 6th Edn. Lexi-Comp. Hudson, Ohio, 2007.

128. Basile VS, Masellis M, Potkin SG, Kennedy JL. Pharmacogenomics in schizophrenia: the quest for individualized therapy. Hum Mol Genet 2002; 11:2517–2530.

129. Reynolds GP, Templeman LA, Zhang ZJ. The role of 5-HT2C receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. Prog Neuropsychopharmacol Biol Psychiatr 2005; 29:1021–1028.

130. Zhao AL, Zhao JP, Zhang YH, Xue ZM, Chen JD, Chen XG. Dopamine D4 receptor gene exon III polymorphism and individual variation in response to clozapine. Int J Neurosci 2005; 115:1539–1547.

131. Yasui-Furukori N, Saito M, Nakagami T, Kaneda A, Tateishi T, Kaneko S. Association between multilocus resistance 1 (MDR1) gene polymorphism and therapeutic response to bripemidol in schizophrenic patients: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatr 2006; 30:286–291.

132. Srivastava V, Varma PG, Prasad S et al. Genetic susceptibility to tardive dyskinesia among schizophrenia subjects: IV. Role of dopaminergic pathway gene polymorphisms. Pharmacogenet Genomics 2006; 16:111–117.

133. Lenz T, Robinson DG, Xu K et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenic patients. Am J Psychiatr 2006; 163:529–531.

134. Reynolds GP, Templeman LA, Godewska BR. Phachizophrenia. Expert Opin Pharmacother 2006; 7:1429–1440.

135. Lin YC, Ellingrod VL, Bishop JR, Miller D. The relationship between P-glycoprotein (PGP) polymorphisms and response to olanzapine treatment in schizophrenia. Ther Drug Monit 2006; 28:668–672.

136. Xing Q, Gao R, Li H et al. Polymorphisms of the ABCB1 (MDR1) gene polymorphism and therapeutic response to broaperidol in schizophrenic patients: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatr 2006; 30:286–291.

137. Fuller MA, Sajatovic M. Drug Information Handbook for Psychiatry. 6th Edn. Lexi-Comp. Hudson, Ohio, 2007.

138. Basile VS, Masellis M, Potkin SG, Kennedy JL. Pharmacogenomics in schizophrenia: the quest for individualized therapy. Hum Mol Genet 2002; 11:2517–2530.

139. Reynolds GP, Templeman LA, Zhang ZJ. The role of 5-HT2C receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. Prog Neuropsychopharmacol Biol Psychiatr 2005; 29:1021–1028.

140. Foster A, Miller D, Buckley PF. Pharmacogenetics and schizophrenia. Psychiatr Clin North Am 2007; 30:417–435.
141. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Mol Psychiatr 2007; 12:707–743.

142. Wong M-L, Whelan F, Deloukas P et al. Phosphodiesterase genes are associated with susceptibility to major depression and antidepressant treatment response. Proc Natl Acad Sci USA 2006; 103:15124–15129.

143. Hansen T, Jakobsen KD, Fenger M et al. Variation in the CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene in schizophrenia. Eur Neuropsychopharmacol 2008; 18:34–40.

144. Hamdani N, Tabeze JP, Ramoz N et al. The CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene in schizophrenia. Eur Neuropsychopharmacol 2008; 18:34–40.

145. Greenbaum L, Smith RC, Rigbi A et al. Further evidence for association of the RGS2 gene with antipsychotic-induced parkinsonism: protective role of a functional polymorphism in the 3’-untranslated region. Pharmacogenomics 2008 (Epub ahead of print).

146. Greenbaum L, Smith RC, Rigbi A et al. Further evidence for association of the RGS2 gene with antipsychotic-induced parkinsonism: protective role of a functional polymorphism in the 3’-untranslated region. Pharmacogenomics 2008 (Epub ahead of print).

147. Campbell DB, Ebert PJ, Skelly T et al. Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in schizophrenia. Biol Psychiatr 2008; 63:32–41.

148. Ozdemir V, Basile VS, Masellis M, Kennedy JL. Pharmacogenetic assessment of antipsychotic-induced movement disorders: contribution of the dopamine D3 receptor and cytochrome P450 1A2 genes. J Biochem Biophys Methods 2001; 47:151–157.

149. Nikoloff D, Shim JC, Fairchild M et al. Association between CYP2D6 genotype and tardive dyskinesia in Korean schizophrenics. Pharmacogenomics J 2002; 2:400–407.

150. Liou YJ, Lai IC, Lin MW et al. Haplotype analysis of the 5-HT1A receptor gene is associated with negative symptoms and tardive dyskinesia in patients with schizophrenia. Pharmacogenet Genomics 2006; 16:151–157.

151. Kim B, Choi CY, Song K, Joo YH. Could HTR2A T102C and DRD3 Ser9Gly predict clinical improvement in patients with acutely exacerbated schizophrenia? Results from treatment responses to risperidone in a naturalistic setting. Hum Psychopharmacol 2008; 23:61–67.

152. Wang L, Fang C, Zhang A et al. The -1019 C/G polymorphism of the 5-HT1A receptor gene is associated with negative symptom response to risperidone treatment in schizophrenia patients. J Psychopharmacol 2008 (Epub ahead of print).

153. Anttila S, Ilii A, Kampman O, Mattila KM, Lehtimaki T. Interaction between NOTCH4 and catechol-O-methyltransferase genotypes in schizophrenia patients with poor response to typical neuroleptics. Pharmacogenetics 2004; 14:303–307.

154. Lavedan C, Volpi S, Polymeropoulos MH, Wolfgang CD. Effect of a ciliary neurotrophic factor polymorphism on schizophrenia symptom improvement in an iloperidone clinical trial. Pharmacogenomics 2008; 9:289–301.

155. Strous RD, Greenbaum L, Kanyas K et al. Association of the dopamine receptor interacting protein gene, NEF3, with early response to antipsychotic medication. Int J Neuropsychopharmacol 2007; 10:321–333.

156. Méary A, Brousse G, Jamain S et al. Pharmacogenetic study of atypical antipsychotic drug response: involvement of the norepinephrine transporter gene. Am J Med Genet B Neuropsychiatr Genet 2008; 147B:491–494.

157. Zhang XY, Tan YL, Zhou DF et al. Association of clozapine-induced weight gain with a polymorphism in the leptin promoter region in patients with chronic schizophrenia in a Chinese population. J Clin Psychopharmacol 2007; 27:246–251.

158. Ellingrod VL, Bishop JR, Moline J, Lin YC, Miller D. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. Psychopharmacol Bull 2007; 40:57–62.

159. Templeman LA, Reynolds GP, Arranz B, SanL. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. Pharmacogenet Genomics 2005; 15:195–200.

160. Gass JT, Olive MF. Transcriptional profiling of the rat frontal cortex following administration of the mGlur5 antagonists MPEP and MTEP. Eur J Pharmacol 2008; 584:253–262.

161. Padock S, Laje G, Charney D et al. Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. Am J Psychiatr 2007; 164:1181–1188.

162. Tsai SJ, Liou YJ, Hong CJ, Yu YY, Chen TJ. Glycogen synthase kinase-3beta gene is associated with antidepressant treatment response in Chinese major depressive disorder. Pharmacogenomics J 2008 (Epub ahead of print).

163. Mamdani F, Alda M, Grof P, Young LT, Rouleau G, Turecki G. Lithium response and genetic variation in the CREB family of genes. Am J Med Genet B Neuropsychiatr Genet 2008; 147B:500–504.

164. Duke DC, Moran LB, Pearce RK, Graeber MB. The medial and lateral substantia nigra in Parkinson’s disease: mRNA profiles associated with higher brain tissue vulnerability. Neurogenetics 2007; 8:83–94.

165. Gillardon F, Steinlein P, Bürger E, Hildebrandt T, Gerner C. Epigenetic alterations of the dopaminergic system in major psychiatric disorders. Meth Mol Biol 2008; 29:344–357.

166. Chavez-Blanco A, Pérez-Plascencia C, Pérez-Cárdenas E et al. Antineoplastic effects of the DNA methylation inhibitor 5-azacytidine and the histone deacetylase inhibitor valproic acid in cancer cell lines. Cancer Cell Intern 2006; 5:1299–1307.

167. Pinsonneault JK, Papp AC, Sadée W. Allelic mRNA expression of X-linked monoamine oxidase A (MAOA) in human brain: dissection of epigenetic and genetic factors. Hum Mol Genet 2006; 15:2636–2649.

168. Crews D. Epigenetics and its implications for behavioural neuroendocrinology. Neuroendocrinol 2008; 29:344–357.

169. Abdolmaleky HM, Smith CL, Zhou JR, Thiagalingam S. Antineoplastic effects of the DNA methylation inhibitor 5-azacytidine and the histone deacetylase inhibitor valproic acid in cancer cell lines. Cancer Cell Intern 2006; 5:1299–1307.

170. Gómez-Mancilla B, Marrer E, Keheen J et al. Central nervous system drug development: an integrative biomarker approach toward individualized medicine. NeuroRx 2005; 2:683–695.

171. Cacabelos R. Pleiotropic effects of APOE in dementia: influence on functional genomics and pharmacogenetics. In: Advances in Alzheimer’s and Parkinson’s disease. Insights,
Pharmacogenomic Biomarkers in Neuropsychiatry

Progress, and Perspectives. Fisher A, Memo M, Stocchi F, Hanin I (Eds). Springer, New York, 2008; 355–367.

172. Cacabelos R, Rodríguez B, Carrera C et al. APOE-Related dementia symptoms: frequency and progression. Ann Psychiatria 1996; 6:189–205.

173. Cacabelos R, Rodríguez B, Carrera C, Caamaño J, Beyer K, Lao JI, Sellers MA. APOE-Related frequency of cognitive and noncognitive symptoms in dementia. Meth Find Exp Clin Pharmacol 1996; 18:693–706.

174. Cacabelos R, Rodríguez B, Carrera C et al. Behavioral changes associated with different apolipoprotein E genotypes in dementia. Alzheimer’s Dis Assoc Dis 1997; 11(Suppl. 4): S27–S37.

175. Baghai TC, Binder EB, Schule C et al. Polymorphisms in the angiotensin-converting enzyme gene are associated with unipolar depression, ACE activity and hypercortisolism. Mol Psychiatr 2006; 11:1003–1015.

176. Bellivier F, Laplanche JL, Schurhoff F et al. Apolipoprotein E gene polymorphism in early and late onset bipolar patients. Neurosci Lett 1997; 233:45–48.

177. Olsson M, Annerbrink K, Westberg L et al. Angiotensin-related genes in patients with panic disorder. Am J Med Genet B Neuropsychiatr Genet 2004; 127:81–84.

178. Steinberg M, Corcoran C, Tschanz JT et al. Risk factors for neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatri 2006; 21:824–830.

179. van der Flier Wm, Staekenborg S, Pijnenburg Y A et al. Apolipoprotein E gene polymorphism and noncognitive symptoms in dementia. Meth Find Exp Clin Pharmacol 1996; 18:693–706.

180. Flicker L, Martins RN, Thomas J et al. Apolipoprotein E genotype influences presence and severity of delusions and aggressive behavior in Alzheimer disease. Dement Geriatr Cogn Disord 2006; 23:42–46.

181. Flicker L, Martins RN, Thomas J et al. Homocysteine, Alzheimer genes and proteins, and measures of cognition and depression in older men. J Alzheimer Dis 2004; 6:329–336.

182. Muller-Thomsen T, Arlt S, Ganzer S et al. Depression in Alzheimer’s disease might be associated with apolipoprotein E epsilon 4 allele frequency in women but not in men. Dement Geriatr Cogn Disord 2002; 14:59–63.

183. Hollingsworth P, Hamshire ML, Moskvina V et al. Four components describe behavioral symptoms in 1,120 individuals with late-onset Alzheimer’s disease. J Am Geriatr Soc 2006; 54:1348–1354.

184. Gabryelewicz T, Religa D, Styczynska M et al. Behavioural pathology in Alzheimer’s disease with special reference to apolipoprotein E genotype. Dement Geriatr Cogn Disord 2005; 19:154–157.

185. Steffens DC, Norton MC, Hart AD et al. Apolipoprotein E genotype and major depression in a community of older adults. The Cache County Study. Psychol Med 2003; 33:541–547.

186. Fan PL, Chen CD, Kao WT et al. Protective effect of the ApoE2 allele in major depressive disorder in Taiwanese. Acta Psychiatr Scand 2006; 113:48–53.

187. Butters MA, Sweet RA, Mulсанt BH et al. APOE is associated with age-of-onset, but not cognitive functioning, in late-life depression. Int J Geriatr Psychiatr 2003; 18:1075–1081.

188. Robertson J, Curley J, Kaye J, Quinn J, Pfankuch T, Raber J. ApoE isoforms and measures of anxiety in probable AD patients and Apoe-/- mice. Neurobiol Aging 2005; 26:637–643.

189. McLachlan CS, Yi Xing Soh C. Differences in anxiety-related behaviour between apolipoprotein E-deficient C57BL/6 and wild type C57BL/6 mice. Physiol Rev 2005; 54:701–704.

190. Bongers G, Leurs R, Robertson J, Raber J. Role of H3-receptor-mediated signaling in anxiety and cognition in wild-type and ApoE-/- mice. Neuropsychopharmacology 2004; 29:441–449.

191. Nebes RD, Vora JJ, Meltzer CC et al. Relationship of deep white matter hyperintensities and apolipoprotein E genotype to depressive symptoms in older adults without clinical depression. Am J Psychiatr 2001; 158:878–884.

192. Naismith S, Hickie I, Ward PB et al. Caudate nucleus volumes and genetic determinants of homocysteine metabolism in the prediction of psychomotor speed in older persons with depression. Am J Psychiatr 2002; 159:2096–2098.

193. O’Brien JT, Lloyd A, McKieith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am J Psychiatr 2004; 161:2081–2090.

194. Hickie I, Naismith S, Ward PB et al. Reduced hippocapal volumes and memory loss in patients with early- and late-onset depression. Br J Psychiatr 2005; 186:197–202.

195. Kim JM, Stewart R, Shin IS, Yoon JS. Vascular/risk and late-life depression in a Korean community population. Br J Psychiatr 2004; 185:102–107.

196. Philips KA, Van Bebber SL. Measuring the value of pharmacogenomics. Nature Rev Drug Discovery 2005; 4:500–509.

197. Veenstra DL, Higashi MK. Assessing the cost-effectiveness of pharmacogenomics. AAPs Pharm Sci 2000; 2(3) Artic 29:1–11. http://www.pharsci.org/.

198. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia. A review of the evidence. JAMA 2005; 293: 596–608.

199. Reisberg B, Doody R, Stoffler A et al. Memantine in moderate-to-severe Alzheimer’s disease. N Engl J Med 2003; 348:1333–1341.

200. Winblad B, Kilander L, Eriksson S et al. Donepezil in patients with severe Alzheimer’s disease: double-blind, parallel-group, placebo-controlled study. Lancet 2006; 367:1057–1065.

201. Hogan DB. Donepezil for severe Alzheimer’s disease. Lancet 2006; 367:1031–1032.

202. Need AC, Motulsy AG, Goldstein DB. Priorities and standards in pharmacogenetic research. Nature Genet 2005; 37:671–681.

203. Van Steen K, McQueen MB, Herbert A et al. Genetic linkage of variability in the efficacy and adverse effect profile of donepezil to a single nucleotide polymorphism in the CYP3A4 gene. Pharmacogenet J 2006; 6(2):77–83.

204. Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmogenomics and individualized drug therapy. Annu Rev Med 2006; 57:119–137.

205. Barlow-Stewart K, Burnett L. Ethical considerations in the use of DNA for the diagnosis of disease. Clin Biochem Rev 2006; 27:53–61.

206. www.pharmgkb.org/