The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes

THE HANDBOOK OF NEUROPSYCHIATRIC BIOMARKERS, ENDOPHENOTYPES AND GENES

Volume 1: Neuropsychological Endophenotypes and Biomarkers

Volume 2: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers

Volume 3: Metabolic and Peripheral Biomarkers

Volume 4: Molecular Genetic and Genomic Markers

Michael S. Ritsner
Editor

The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes

Volume 4

Molecular Genetic and Genomic Markers

Springer

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Foreword

Common genetically influenced neuropsychiatric disorders such as schizophrenia spectrum disorders, major depression, bipolar and anxiety disorders, epilepsy, neurodegenerative and demyelinating disorders, Parkinson and Alzheimer's diseases, alcoholism, substance abuse, and drug dependence are the most debilitating illnesses worldwide. They are characterized by their complexity of causes and by their lack of pathognomonic laboratory diagnostic tests. During the past decade many researchers around the world have explored the neuropsychiatric biomarkers and endophenotypes implicated, not only in order to understand the genetic basis of these disorders but also from diagnostic, prognostic, and pharmacological perspectives. These fields have therefore, witnessed enormous expansion in new findings obtained by neuropsychological, neurophysiological, neuroimaging, neuroanatomical, neurochemical, molecular genetic, genomic and proteomic analyses, which have generated a necessity for syntheses across the main neuropsychiatric disorders. The challenge now is to translate these findings into meaningful etiologic, diagnostic and therapeutic advances.

This four volume collection of Handbooks offers a broad synthesis of current knowledge about biomarker and endophenotype approaches in neuropsychiatry. Since many of the contributors are internationally known experts, they not only provide up-to-date state of the art overviews, but also clarify some of the ongoing controversies, future challenges and proposing new insights for future researches. The contents of the volumes have been carefully planned, organized, and edited in close collaboration with the chapter authors. Of course, despite all the assistance provided by contributors and others, I alone remain responsible for the content of these Handbooks including any errors or omissions, which may remain.

The Handbook is organized into four interconnected volumes covering five major sections.

Volume 1 "Neuropsychological Endophenotypes and Biomarkers" contains 17 chapters composed of two parts emphasizing schizophrenia as a prototype. The first section serves as an introduction and overview of methodological issues of the biomarker and endophenotype approaches in neuropsychiatry and some technological advances. Chapters review definitions, perspectives, and issues that provide a conceptual base for the rest of the collection. The second section comprises chapters in

which the authors present and discuss the neuropsychological, neurocognitive and neurophysiological candidate biomarkers and endophenotypes.

Volume 2 "Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers", focuses on neuroanatomical and neuroimaging findings obtained for wide spectra of neuropsychiatric disorders.

Volume 3 "Metabolic and Peripheral Biomarkers", explores several specific metabolic and peripheral biomarkers, such as neuroactive steroid biomarkers, cortisol to DHEA molar ratio, mitochondrial complex, biomarkers of excitotoxicity, melatonin, retinoic acid, abnormalities of inositol metabolism in lymphocytes, and others.

Volume 4 "Molecular Genetic and Genomic Markers" contains chapters devoted to searching for novel molecular genetic and genomic markers in less explored areas. This volume includes an Afterword written by Professor Robert H. Belmaker.

Similarly to other publications contributed to by diverse scholars from diverse orientations and academic backgrounds, differences in approaches and opinions, as well as some overlap, are unavoidable. I believe that this collection is probably the first of its kind to go beyond the neuropsychiatric disorders and delve into the neurobiological basis for diagnosis, treatment, and prevention. The take-home message is that principles of the biomarker-endophenotype approach may be applied no matter what kind of neuropsychiatric disorder afflicts our patients.

The Handbook is designed for use by a broad spectrum of readers including neuroscientists, psychiatrists, neurologists, endocrinologists, pharmacologists, psychologists, general practitioners, geriatricians, graduate students, health care providers in the fields of neurology and mental health, and others interested in trends that have crystallized in the last decade, and trends that can be expected to evolve in the coming years. It is hoped that this collection will also be a useful resource for the teaching of psychiatry, neurology, psychology and mental health.

With much gratitude, I would like to acknowledge the contributors from 16 countries for their excellent cooperation. In particular, I am most grateful to Professor Irving Gottesman for his support of this project. His unending drive and dedication to the field of psychiatric genetics never ceases to amaze me. I wish to acknowledge Professor Robert H. Belmaker, distinguished biological psychiatrist, who was very willing to write the afterword for these volumes. I also wish to take this opportunity to thank my close co-workers and colleagues Drs. Anatoly Gibel, Yael Ratner, Ehud Susser, Stella Lulinski, Rachel Mayan, Professor Vladimir Lerner and Professor Abraham Weizman for their support and cooperation. Finally, I am forever indebted to my wife Galina Ritsner, sons Edward and Yisrael for their understanding, endless patience and encouragement when it was most required.

I sincerely hope that these four interconnected volumes of the Handbook will further knowledge in the complex field of neuropsychiatric disorders.

February, 2009

Michael S. Ritsner
Editor

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Part IV
Molecular Genetic and Genomic Markers

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

Ramón Cacabelos

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

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

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

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

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

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

Introduction

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

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

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

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

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

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

Genomics of Neuropsychiatric Disorders

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

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

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

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

(continued)

Table 40.1 (continued)

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

(continued)

Table 40.1 (continued)

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

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

Table 40.2 Genes associated with schizophrenia and psychosis

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

(continued)

Table 13.2 (continued)

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

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

Table 40.3 Genes associated with depression and mood disorders

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

(continued)

Table 40.3 (continued)

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

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

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

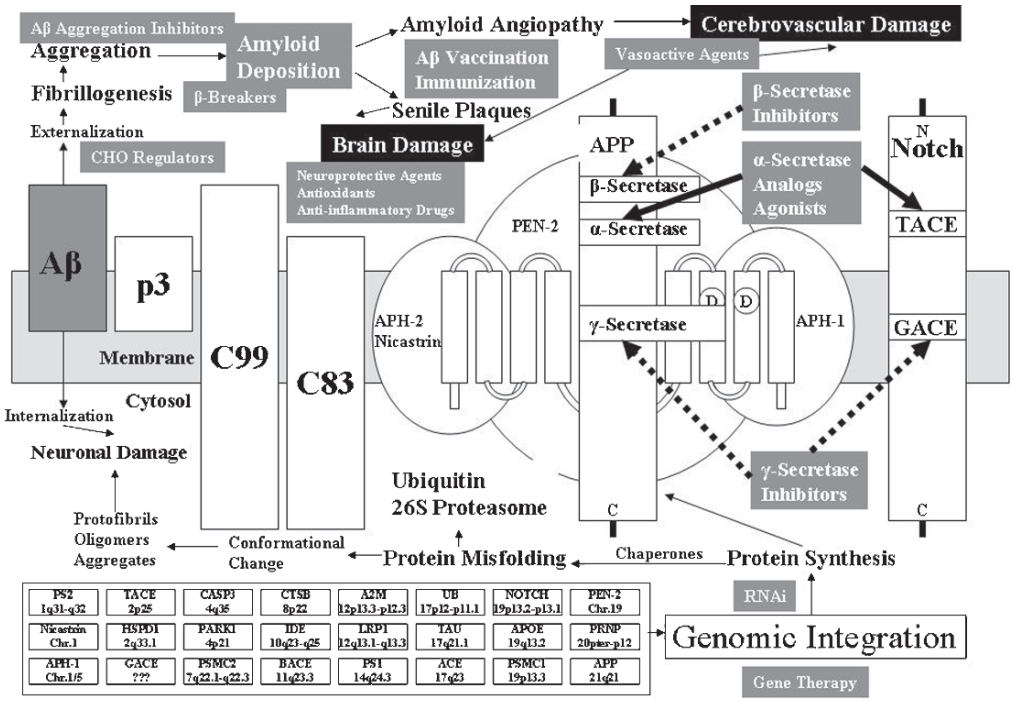

Fig. 40.1 Brain amyloidogenesis, pathogenic mechanisms of neurodegeneration, and potential therapeutic interventions in Alzheimer's disease (Adapted from R. Cacabelos[17–20])

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

High throughput microarray gene expression profiling is an effective approach for the identification of candidate genes and associated molecular pathways implicated in a wide variety of biological processes or disease states. The cellular complexity of the CNS (with 10^3 different cell types) and synapses (with each of the 10^{11} neurons in the brain having around 10^3–10^4 synapses with a complex multiprotein structure integrated by 10^3 different proteins) requires a very powerful technology for gene expression profiling, which is still in the very early stages and is not devoid of technical obstacles and limitations.[23] Transcripts of 16,896 genes have been measured in different CNS regions. Each region possess its own unique transcriptome fingerprint that is independent of age, gender and energy intake. Less than 10% of genes are affected by age, diet or gender, with most of these changes occurring between middle and old age. Gender and energy restriction have robust influences on the hippocampal transcriptome of middle-aged animals. Prominent functional groups of age- and energy-sensitive genes are those encoding proteins involved in DNA damage responses, mitochondrial and proteasome functions, cell fate determination and synaptic vesicle trafficking. The systematic transcriptome dataset provides a window into mechanisms of neuropathogenesis and CNS vulnerability.[24]

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

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

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

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

Diagnostic Protocol in Neuropsychiatry

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

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

Genotype–Phenotype Correlations

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

Table 40.4 The EuroEspes protocol for genomic medicine of CNS disorders

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

(continued)