REVIEW

CNS Neuroscience & Therapeutics

Genomics and Pharmacogenomics of Schizophrenia

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SUMMARY

Schizophrenia (SCZ) is among the most disabling of mental disorders. Several neurobiological hypotheses have been postulated as responsible for SCZ pathogenesis: polygenic/multifactorial genomic defects, intrauterine and perinatal environment-genome interactions, neurodevelopmental defects, dopaminergic, cholinergic, serotonergic, gamma-aminobutiric acid (GABAergic), neuropeptidergic and glutamatergic/N-Methyl-D-Aspartate (NMDA) dysfunctions, seasonal infection, neuroimmune dysfunction, and epigenetic dysregulation. SCZ has a heritability estimated at 60–90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. 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. 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. About 10–20% of Western populations are defective in genes of the *CYP* superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the trigenic cluster integrated by the *CYP2D6+CYP2C19+CYP2C9* genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders.

Introduction

Central nervous system (CNS) disorders are the third health problem in developed countries, representing 10–15% of deaths, after cardiovascular disorders (25–30%) and cancer (20–25%). Among mental disorders, schizophrenia (SCZ) is the most disabling disease in individuals during their productive life. In addition, there is an alarming abuse of inappropriate psychotropic drug consumption worldwide. Clinicians use concomitant antipsychotic therapy for management of psychotic disorders despite a paucity of evidence for this practice. Overall, concomitant antipsychotic therapy was documented in 9% of the visits in US outpatient settings involving antipsychotic agents, and monotherapy in 91% of the visits. The use of atypical agents (risperidone, olanzapine, quetiapine) was common in both forms of therapy. Concomitant therapy is frequently used for psychoses and bipolar disorder (BD), especially in patients 40–64 years old [1]. From 1996/1997 to 2002/2003, visits involving atypical and combination antipsychotics increased by >150%, and visits involving typical antipsychotics decreased by 71% [2]. With the use of concomitant antipsychotic therapy as a quality of care measure, there is a need to optimize prescribing of these potent combinations [1].

It seems clear that abuse, misuse, self-prescription, and uncontrolled medical prescription of psychotropic drugs are becoming a major problem with unpredictable consequences for brain health in the future. In parallel a growing body of fresh knowledge on the pathogenesis of CNS disorders, together with data on neurogenomics and pharmacogenomics is emerging in recent times. The incorporation of this new armamentarium of molecular pathology and genomic medicine to the daily medical practice, together with educational programs for the correct use of medication, must help to optimize therapeutics [3,4].

Drug metabolism, and the mechanisms underlying drug efficacy and safety, are genetically regulated complex traits in which hundreds of genes cooperatively participate. Disease-associated genomics, transcriptomics, proteomics, and metabolomics are essential components of the therapeutic outcome [5]. 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, which alter the metabolism of many psychotropic agents. The incorporation of pharmacogenetic/pharmacogenomic protocols into CNS research and clinical practice can foster the optimization of therapeutics by helping to develop cost-effective pharmaceuticals and improving drug efficacy and safety [3–16].

Pathogenic Theories

SCZ and related disorders are highly heritable but cannot be explained by currently known genetic risk factors. SCZ has a heritability estimated at 60–90%. Several neurobiological hypotheses have been postulated as responsible for SCZ pathogenesis: polygenic/multifactorial genomic defects, intrauterine and perinatal environment-genome interactions, neurodevelopmental defects, dopaminergic, cholinergic, serotonergic, gamma-aminobutyric acid (GABA) ergic, neuropeptidergic and glutamatergic/N-methyl-D-aspartate (NMDA) dysfunctions, seasonal infection, neuroimmune dysfunction, and epigenetic dysregulation. The dopamine hypothesis of SCZ has been one of the most enduring ideas in psychiatry. Initially, the emphasis was on a role of hyperdopaminergia in the etiology of SCZ, but it was subsequently reconceptualized to specify subcortical hyperdopaminergia with prefrontal hypodopaminergia [17]. Carlsson's hypothesis postulates that the positive and negative symptoms of SCZ are due to failure of mesolimbic and mesocortical projections consequent on hypofunction of the glutamate NMDA receptor [18]. While multiple theories have been put forth regarding the origin of SCZ, by far the vast majority of evidence points to the neurodevelopmental model in which developmental insults as early as late first or early second trimester lead to the activation of pathologic neural circuits during adolescence or young adulthood leading to the emergence of positive or negative symptoms [19]. Another important issue is the role of gender in SCZ. Sex differences in SCZ can be caused by the disease process itself, by genetic and hormonal differences, by differences in the maturation and morphology of the brain, and in age- and gender-specific behavioral patterns [20].

Structural Genomics

Genetic studies in SCZ have revealed the presence of cytogenetic changes, chromosome anomalies, copy-number variants (CNV), multiple single nucleotide polymorphisms (SNPs) of susceptibility (Table 1), aberrant SNPs in microRNA (miRNA) genes, mitochondrial DNA (mtDNA) mutations, and epigenetic phenomena [21]. First-degree relatives of probands with SCZ or BD are at increased risk of these disorders. Heritability for SCZ and BD is 64 and 59, respectively. Shared environmental effects are small but substantial for both disorders (SCZ: 4.5%; BD: 3.4%). SCZ and BD partly share common genetic determinants [22].

Polymorphic variants in top 30 genes associated with SCZ at SZGene are listed in Table 2 [3,15,23]. A selective number of genes (or pathological pathways) with potential effect in SCZ pathogenesis include the following (in alphabetical order)(Table 1):

ABCA13 (ATP-Binding Cassette, Subfamily A [ABC1], Member 13)

The lipid transporter gene *ABCA13* is a susceptibility factor for both SCZ and BD. Multiple rare coding variants were identified including one nonsense and nine missense mutations and compound heterozygosity/homozygosity in 6% of cases. The population attributable risk of these mutations was 2.2% for SCZ and 4.0% for BD [24].

Abelson Helper Integration Site 1 (*AHI1*)

The *AHI1* gene locus on chromosome 6q23 is among a group of candidate loci for SCZ susceptibility. The region contains two genes, *AHI1* and *C6orf217*. Both genes and the neighboring phosphodiesterase 7B (*PDE7B*) may be considered candidates for involvement in the genetic etiology of SCZ [25]. Of 14 SNPs tested (*ATP2B2*, *HS3ST2*, *UNC5C*, *BAG3*, *PDE7B*, *PAICS*, *PTGFRN*, *NR3C2*, *ZBTB20*, *ST6GAL2*, *PIP5K1B*, *EPHA6*, *KCNH5*, and *AJAP1*), only one (rs9389370) in *PDE7B* showed significant evidence for association with SCZ [26].

Adenylosuccinate Synthase (*ADSS*) and Ataxia Telangiectasia (*ATM*) Genes

The blood-derived RNA levels of the *ADSS* and *ATM* genes were found to be down- and up-regulated, respectively, in schizophrenics compared with controls. ADSS catalyzes the first committed step of adenosine monophosphate (AMP) synthesis, while ATM kinase serves as a key signal transducer in the DNA double-strand breaks response pathway. Studies with 6 SNPs in the *ADSS* gene and 3 SNPs in the *ATM* gene did not show significant difference in the genotype, allele, or haplotype distributions in a Chinese population of SCZ patients. Interactions among rs3102460 in the *ADSS* gene and rs227061 and rs664143 in the *ATM* gene revealed a significant association with SCZ with a maximum testing accuracy of 60.4% [27].

Cholesterol Transport Genes

Several studies suggest an accumulation of *APOE-4* allele in SCZ [6]. Disturbances in lipid homeostasis and myelination have been proposed in the pathophysiology of SCZ and BD. Several antipsychotic and antidepressant drugs increase lipid biosynthesis through activation of the Sterol Regulatory Element-Binding Protein (SREBP) transcription factors, which control the expression of numerous genes involved in fatty acid and cholesterol biosynthesis. Significant transcriptional changes of cholesterol transport genes (*APOE*, *ABCA1*, *NPC1*, *NPC2*, *NPC1L1*), which are

Table 1. Genes associated with schizophrenia and psychosis [15,159,160]

Locus	Symbol	Aliases	Title	OMIM
1cen-q12	*ADSS*	*ADEH, MGC20404*	Adenylosuccinate synthase	103060
1p	*SCZD12*		schizophrenia 12	608543
1p13.3	*GSTM1*	*GST1, GSTM1-1, GSTM1a-1a, GSTM1b-1b, GTH4, GTM1, H-B, MGC26563, MU, MU-1*	Glutathione S-transferase mu 1	138350
1q23-q25	*FMO3*	*FMOII, MGC34400, TMAU, dJ127D3.1*	Flavin containing monooxygenase 3	136132
1p31	*LEPR*	*CD295, OBR*	Leptin receptor	601007
1p31	*PDE4B*	*RP5–876C12.1, DKFZp686F2182, DPDE4, MGC126529, PDE4B5, PDEIVB*	Phosphodiesterase 4B, camp-specific (phosphodiesterase E4 dunce homolog, drosophila)	600127
1p33	*SLC6A9*	*DKFZp547A1118, GLYT1*	Solute carrier family 6 (neurotransmitter transporter, glycine), member 9	601019
1p34-p33	*GRIK3*	*EAA5, GLR7, GLUR7, GluR7a*	Glutamate receptor, ionotropic, kainate 3	138243
1p36.3	*MTHFR*		5,10-methylenetetrahydrofolate reductase (nadph)	607093
1p36.11	*CNR2*	*RP11–4M23.1, CB2, CX5*	Cannabinoid receptor 2 (macrophage)	605051
1q21	*CTSK*	*RP11–363I22.4, CTS02, CTSO, CTSO1, CTSO2, MGC23107, PKND, PYCD*	Cathepsin K	601105
1q21-q22	*SELENBP1*	*RP11–126K1.7, FLJ13813, LPSB, SP56, hSBP, hSP56*	Selenium binding protein 1	604188
1q21-q23	*CRP*	*MGC149895, MGC88244, PTX1*	c-Reactive protein, pentraxin-related	123260
1q23.3	*RGS4*	*RP11–430G6.1, DKFZp761F1924, MGC2124, MGC60244, RGP4, SCZD9*	Regulator of G-protein signaling 4	602516
1q25.1	*PRDX6*	*1-Cys, AOP2, KIAA0106, MGC46173, NSGPx, PRX, aiPLA2, p29*	Peroxiredoxin 6	602316
1q31-q42	*PSEN2*	*AD3L, AD4, PS2, STM2*	Presenilin 2 (alzheimer disease 4)	600759
1q31-q32	*IL10*	*CSIF, IL-10, IL10A, MGC126450, MGC126451, TGIF*	Interleukin 10	124092
1q32	*AVPR1B*	*AVPR3*	Arginine vasopressin receptor 1B	600264
1q32.1	*CHI3L1*	*ASRT7, DKFZp686N19119, FLJ38139, GP39, HC-gp39, HCGP-3P, YKL40, YYL-40*	Chitinase 3-like 1 (cartilage glycoprotein-39)	601525
1q32.2	*PLXNA2*	*RP11–328D5.3, FLJ11751, FLJ30634, KIAA0463, OCT, PLXN2*	Plexin A2	601054
1q42.1	*DISC1*	*RP4–730B13.1, C1orf136, FLJ13381, FLJ21640, FLJ25311, FLJ41105, KIAA0457, SCZD9*	Disrupted in schizophrenia 1	605210/181500
1q42.1	*DISC2*	*DISC1OS; NCRNA00015*	Disrupted in schizophrenia 2	606271/181500
1q42.1	*TSNAX*	*DISC1, TRAX*	Translin-associated factor x	602964
2p16.3	*NRXN1*	*DKFZp313P2036, FLJ35941, Hs.22998, KIAA0578*	Neurexin 1	600565
2q14	*IL1B*	*IL-1, IL1-BETA, IL1F2*	Interleukin 1, beta	147720
2q14.2	*IL1RN*	*DIRA, ICIL-1RA, IL-1ra3, IL1F3, IL1RA, IRAP, MGC10430, MVCD4*	Interleukin 1 receptor antagonist	147679
2q31	*GAD1*	*FLJ45882, GAD, SCP*	Glutamate decarboxylase 1 (brain, 67kDa)	605363
2q32.1	*ZNF804A*	*C2orf10*	Zinc finger protein 804A	612282
2q32.3-q33	*GULP1*	*CED-6, CED6, FLJ31156, GULP*	GULP, engulfment adaptor PTB domain containing 1	608165
2q33.3-q34	*ERBB4*	*HER4, MGC138404, p180erbB4*	v-Erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	600543
3p21.2	*GRM2*	*GLUR2, GPRC1B, MGLUR2, mGlu2*	Glutamate receptor, metabotropic 2	604099
3p21.3	*LARS2*	*KIAA0028, LEURS, MGC26121*	leucyl-tRNA synthetase 2, mitochondrial	604544
3p22-p21.3	*CCK*	*MGC117187*	Cholecystokinin	118440
3p25	*OXTR*	*OT-R*	Oxytocin receptor	167055
3p25	*PPARG*	*CIMT1, GLM1, NR1C3, PPARG1, PPARG2, PPARgamma*	Peroxisome proliferator-activated receptor gamma	601487
3p25	*SYN2*	*SYNII, SYNIIa, SYNIIb*	Synapsin II	600755

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
3p26.1-p25.1	*GRM7*	*FLJ40498, GLUR7, GPRC1G, MGLU7, MGLUR7*	Glutamate receptor, metabotropic 7	604101
3q13.3	*DRD3*	*D3DR, ETM1, FET1, MGC149204, MGC149205*	Dopamine receptor D3	126451
3q13.3	*GSK3B*		Glycogen synthase kinase 3 beta	605004
4p15.2	*PI4K2B*	*FLJ11105, PI4KIIB, PIK42B*	Phosphatidylinositol 4-kinase type 2 beta	612101
4q12	*CLOCK*	*KAT13D, KIAA0334, bHLHe8*	Clock homolog (mouse)	601851
4q31-q32	*TDO2*	*TDO, TPH2, TRPO*	Tryptophan 2,3-dioxygenase	191070
5p15.3	*SLC6A3*	*DAT, DAT1*	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	126455
5q11.2-q13	*HTR1A*	*5-HT1A, 5HT1a, ADRB2RL1, ADRBRL1*	5-Hydroxytryptamine (serotonin) receptor 1A	109760
5q11.2-q13.3	*SCZD1*		Schizophrenia susceptibility locus/chr. 5q-related	181510/181500
5q12	*PDE4D*	*DKFZp686M11213, DPDE3, FLJ97311, HSPDE4D, PDE4DN2, STRK1*	Phosphodiesterase 4D, camp-specific (phosphodiesterase E3 dunce homolog, drosophila)	600129
5q31	*PCDH12*	*VE-cadherin-2, VECAD2*	Protocadherin 12	605622
5q33	*MEGF10*	*DKFZp781K1852, FLJ41574, KIAA1780*	Multiple EGF-like-domains 10	612453
5q34	*GABRB2*	*MGC119386, MGC119388, MGC119389*	Gamma-aminobutyric acid (GABA) A receptor, beta 2	600232
5q35.1	*DRD1*	*DADR, DRD1A*	Dopamine receptor D1	126449
6p12	*VEGFA*	*RP1–261G23.1, MGC70609, MVCD1, VEGF, VEGF-A, VPF*	Vascular endothelial growth factor a	192240
6p21.3	*GRM4*	*GPRC1D, MGC177594, MGLUR4, mGlu4*	Glutamate receptor, metabotropic, 4	604100
6p21.3	*HLA-DQA1*	*CD, CELIAC1, DQ-A1, FLJ27088, FLJ27328, GSE, HLA-DQA, MGC149527*	Major histocompatibility complex, class II, DQ alpha 1	146880
6p21.3	*HLA-E*	*DAMA-277I14.1, DKFZp686P19218, EA1.2, EA2.1, HLA-6.2, MHC, QA1*	Major histocompatibility complex, class I, E	143010
6p21.3	*SYNGAP1*	*DASS-97D12.6, DKFZp761G1421, KIAA1938, MRD5, RASA1, RASA5, SYNGAP*	Synaptic Ras GTPase activating protein 1 homolog (rat)	603384
6p21.3	*TAP1*	*DAAP-57C1.5, ABC17, ABCB2, APT1, D6S114E, FLJ26666, FLJ41500, PSF1, RING4, TAP1*0102N, TAP1N*	Transporter 1, ATP-binding cassette, subfamily b (MDR/TAP)	170260
6p22.1	*MOG*	*DAQB-92E24.2, MGC26137, MOGIG2*	Myelin oligodendrocyte glycoprotein	159465
6p22.3	*DTNBP1*	*RP1–147M19.1, DBND, DKFZp564K192, FLJ30031, HPS7, MGC20210, My031, SDY*	Dystrobrevin-binding protein 1 (dysbindin)	607145
6p24-p22	*SCZD3*		Schizophrenia susceptibility locus/chr. 6p-related	600511/181500
6p24-p23	*JARID2*	*JMJ*	Jumonji, AT rich interactive domain 2	601594
6p25.1-p24.3	*MUTED*	*DKFZp686E2287, MU*	Muted homolog (mouse)	607289
6q13-q26	*SCZD5*		Schizophrenia susceptibility locus/chr. 6q-related	603175/181500
6q16	*MCHR2*	*GPR145, MCH2, MCH2R, SLT*	Melanin-concentrating hormone receptor 2	606111
6p21.2	*DAAM2*	*RP1–278E11.1, KIAA0381, MGC90515, dJ90A20A.1*	Dishevelled associated activator of morphogenesis 2	606627
6q21	*FYN*	*RP1–66H14.1, MGC45350, SLK, SYN*	FYN oncogene related to SRC, FGR, YES	137025
6q21.3	*HSPA1B*	*DAAP-21F2.7, FLJ54328, HSP70–1B, HSP70–2, HSPA1A*	Heat shock 70kDa protein 1B	603012
6q22-q23	*FABP7*	*B-FABP, BLBP, DKFZp547J2313, FABPB, MRG*	Fatty acid binding protein 7, brain	602965
6q23.1	*STX7*	*RP11–560I21.1*	Syntaxin 7	603217
6q23.2	*TAAR6*	*RP11–295F4.3, SCZD5, TA4, TRAR4*	Trace amine associated receptor 6	608923
6q23-q24	*PDE7B*	*MGC88256; bA472E5.1; PDE7B*	Phosphodiesterase 7B	

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
6q27	*TBP*	*GTF2D, GTF2D1, MGC117320, MGC126054, MGC126055, SCA17, TFIID*	TATA box binding protein	600075
6q26-q27	*QKI*	*DKFZp586I0923, Hqk, QK, QK1, QK3*	Quaking homolog, KH domain RNA binding (mouse)	609590
7p12.3	*ABCA13*	*FLJ16398; FLJ33876; FLJ33951; DKFZp313D2411; ABCA13*	ATP-binding cassette, subfamily A (ABC1), member 13	607807
7p13	*NPC1L1*	*NPC11L1*	NPC1 (Niemann-Pick disease, type C1, gene)-like 1	608010
7p15.3	*SP4*	*HF1B, MGC130008, MGC130009, SPR-1*	SP4 transcription factor	600540
7q21.1	*CYP3A4*	*CP33, CP34, CYP3A, CYP3A3, HLP, MGC126680, NF-25, P450C3, P450PCN1*	Cytochrome p450, family 3, subfamily a, polypeptide 4	124010
7q21.1	*CYP3A5*	*CP35, P450PCN3, PCN3*	Cytochrome p450, family 3, subfamily a, polypeptide 5	605325
7q21.1-q21.2	*GRM3*	*GLUR3, GPRC1C, MGLUR3, mGlu3*	Glutamate receptor, metabotropic-3	601115
7q22	*RELN*	*PRO1598, RL*	Reelin	600514
7q31.3	*LEP*	*FLJ94114, OB, OBS*	Leptin	164160
7q31.1-q31.2	*NRCAM*	*KIAA0343, MGC138845, MGC138846*	Neuronal cell adhesion molecule	601581
7q32.3-q33	*DGKI*	*DGK-IOTA*	Diacylglycerol kinase, iota	604072
7q35-q36	*KCNH2*	*ERG1, HERG, HERG1, Kv11.1, LQT2, SQT1*	Potassium voltage-gated channel, subfamily h (eag-related), member 2	152427
7q35-q36	*CNTNAP2*	*AUTS15, CASPR2, CDFE, DKFZp781D1846, NRXN4*	Contactin associated protein-like 2	604569
8p11.2	*CHRNB3*		Cholinergic receptor, nicotinic, beta 3	118508
8p11.2-p11.1	*DKK4*	*DKK-4, MGC129562, MGC129563*	Dickkopf homolog 4 (Xenopus laevis)	605417
8p11.2-p11.1	*FGFR1*	*CEK; FLG; OGD; FLT2; KAL2; BFGFR; CD331; FGFBR; HBGFR; N-SAM; FLJ99988; FGFR1*	Fibroblast growth factor receptor 1	136350
8p11.21	*CHRNA6*		Cholinergic receptor, nicotinic, alpha 6	606888
8p12	*PLAT*	*DKFZp686I03148, T-PA, TPA*	Plasminogen activator, tissue	173370
8p12	*NRG1*	*ARIA, GGF, GGF2, HGL, HRG, HRG1, HRGA, NDF, SMDF*	Neuregulin 1	142445
8p12-p11.1	*SFRP1*	*FRP, FRP-1, FRP1, FrzA, SARP2*	Secreted frizzled-related protein 1	604156
8p21	*CHRNA2*		Cholinergic receptor, nicotinic, alpha 2 (neuronal)	118502
8p21	*FGF17*	*fibroblast growth factor 17*	Fibroblast growth factor 17	603725
8p21	*FZD3*	*z-3, hFz3*	Frizzled homolog of, 3 (Drosophila)	606143
8p21	*NEFM*	*NEF3, NF-M, NFM*	Neurofilament, medium polypeptide	162250
8p21	*SCZD6*		Schizophrenia susceptibility locus/chr. 8p-related	603013/181500
8p21-p11.2	*ADRA1A*	*ADRA1C, ADRA1L1, ALPHA1AAR*	Adrenergic, alpha-1A-, receptor	104221
8p21.3	*PPP3CC*	*CALNA3, CNA3*	Protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform	114107
8p21.3	*SLC18A1*	*CGAT, VAT1, VMAT1*	Solute carrier family 18 (vesicular monoamine), member 1	193002
8p22	*NAT2*	*AAC2, PNAT*	N-acetyltransferase 2 (arylamine N-acetyltransferase)	612182
8p22-p21	*DPYSL2*	*CRMP2, DHPRP2, DRP-2, DRP2*	Dihydropyrimidinase-like 2	602463
8p22-p21.3	*FGF20*		Fibroblast growth factor 20	605558
8p22-p21.3	*PCM1*	*PTC4*	Pericentriolar material 1	600299
8p23	*ARHGEF10*	*DKFZp686H0726, GEF10, MGC131664*	Rho guanine nucleotide exchange factor (GEF) 10	608123
8p23-p21	*EGR3*	*MGC138484, PILOT*	Early growth response 3	602419
9p13.3	*SIGMAR1*	*RP11–443P11.3, FLJ25585, MGC3851, OPRS1, SR-BP1, SRBP*	Sigma non-opioid intracellular receptor 1	601978
9p24	*SLC1A1*	*RP11–6J24.1, EAAC1, EAAT3*	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	133550

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
9p22.3	*SMARCA2*	*BAF190, BRM, FLJ36757, MGC74511, SNF2, SNF2L2, SNF2LA, SWI2, Sth1p, hBRM, hSNF2a*	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 2	600014
9q31.1	*ABCA1*	*ABC-1, ABC1, CERP, FLJ14958, HDLDT1, MGC164864, MGC165011, TGD*	ATP-binding cassette, sub-family A (ABC1), member 1	600046
9q34	*CACNA1B*	*BIII, CACNL1A5, CACNN, Cav2.2*	Calcium channel, voltage-dependent, N type, alpha 1B subunit	601012
9q34.3	*GRIN1*	*NMDA1, NMDAR1, NR1*	Glutamate receptor, ionotropic, N-methyl D-aspartate 1	138249
10q22	*GRID1*	*RP11–93H12.1, KIAA1220*	Glutamate receptor, ionotropic, delta 1	610659
10q24	*LGI1*	*EPITEMPIN, EPT, ETL1, IB1099*	Leucine-rich, glioma inactivated 1	604619
10q22.3	*SCZD11*		Schizophrenia susceptibility locus, chromosome 10q-related	608078
10q22-q23	*NRG3*	*HRG3, pro-NRG3*	Neuregulin 3	605533
11p11.2	*FOLH1*	*FGCP, FOLH, GCP2, GCPII, NAALAD1, NAALAdase, PSM, PSMA, mGCP*	Folate hydrolase (prostate-specific membrane antigen) 1	600934
11p13	*BDNF*	*MGC34632*	Brain-derived neurotrophic factor	113505
11p15.3-p14	*TPH1*	*MGC119994, TPRH, TRPH*	Tryptophan hydroxylase 1	191060
11p15.5	*DRD4*	*D4DR*	Dopamine receptor D4	126452
11q12-q13.1	*FADS2*	*D6D, DES6, FADSD6, LLCDL2, SLL0262, TU13*	Fatty acid desaturase 2	606149
11q13	*GSTP1*	*DFN7, FAEES3, GST3, GSTP, PI*	Glutathione S-transferase pi 1	134660
11q14-q21	*SCZD2*		Schizophrenia susceptibility locus/chr. 11-related	603342/181500
11q22.3	*GRIK4*	*EAA1, GRIK, KA1*	Glutamate receptor, ionotropic, kainate 4	600282
11q22.3	*MMP3*	*CHDS6, MGC126102, MGC126103, MGC126104, MMP-3, SL-1, STMY, STMY1, STR1*	Matrix metallopeptidase 3 (stromelysin 1, progelatinase)	185250
11q22-q23	*ATM*	*AT1, ATA, ATC, ATD, ATDC, ATE, DKFZp781A0353, MGC74674, TEL1, TELO1*	Ataxia telangiectasia mutated	607585
11q23	*DRD2*	*D2DR, D2R*	Dopamine receptor D2	126450
11q23.1	*NCAM1*	*CD56, MSK39, NCAM*	Neural cell adhesion molecule 1	116930
11q24	*NRGN*	*RC3, hng*	Neurogranin (protein kinase C substrate, RC3)	602350
11q25	*OPCML*	*IGLON1, OBCAM, OPCM*	Opioid binding protein/cell adhesion molecule-like	600632
12p	*VAMP1*	*DKFZp686H12131, SYB1, VAMP-1*	Vesicle-associated membrane protein 1 (synaptobrevin 1)	185880
12p12	*GRIN2B, NMDAR2B*	*MGC142178, MGC142180, NMDAR2B, NR2B, hNR3*	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	138252
12p13.3	*CACNA1C*	*CACH2, CACN2, CACNL1A1, CCHL1A1, CaV1.2, MGC120730, TS*	Calcium channel, voltage-dependent, L type, alpha 1C subunit	114205
12q13	*ERBB3*	*ErbB-3, HER3, LCCS2, MDA-BF-1, MGC88033, c-erbB-3, c-erbB3, erbB3-S, p180-ErbB3, p45-sErbB3, p85-sErbB3*	v-Erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	190151
12q13-q14	*BLOC1S1*	*BLOS1, FLJ39337, FLJ97089, GCN5L1, MGC87455, MICoA, RT14*	Biogenesis of lysosomal organelles complex-1, subunit 1	601444
12q22-q23	*IGF1*	*IGF1A, IGFI*	Insulin-like growth factor 1 (somatomedin c)	147440
12q22-q24.2	*PAH*	*PH, PKU, PKU1*	Phenylalanine hydroxylase	612349
12q24	*DAO*	*DAAO, DAMOX, MGC35381, OXDA*	D-amino-acid oxidase	124050/181500
12q24.2-q24.31	*NOS1*	*IHPS1, NOS, nNOS*	Nitric oxide synthase 1 (neuronal)	163731
12q24.31	*GPR109A*	*HM74a, HM74b, NIACR1, PUMAG, Puma-g*	G protein-coupled receptor 109A	609163
12q24.31	*GPR109B*	*HM74, PUMAG, Puma-g*	G protein-coupled receptor 109B	606039
13q14-q21	*HTR2A*	*RP11–147L20.2, 5-HT2A, HTR2*	5-Hydroxytryptamine receptor 2A	182135

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
13q32	*SCZD7*		Schizophrenia susceptibility locus/chr. 13q-related	603176/181500
13q34	*DAOA*	*G72, LG72, SG72*	D-amino acid oxidase activator	607408/181500
14q12-q13	*NPAS3*	*FLJ10003, FLJ11138, FLJ11605, MOP6, PASD6, bHLHe12*	Neuronal PAS domain protein 3	609430
14q24.3	*NPC2*	*EDDM1, HE1, MGC1333, NP-C2*	Niemann-Pick disease, type C2	601015
14q31	*GALC*		Galactosylceramidase	606890
14q32.32	*AKT1*	*AKT, MGC99656, PKB, PKB-ALPHA, PRKBA, RAC, RAC-ALPHA*	Murine thymoma viral (v-AKT) oncogene homolog-1	164730
15q11-q12	*APBA2*	*D15S1518E, HsT16821, LIN-10, MGC99508, MGC:14091, MINT2, X11L*	Amyloid beta (a4) precursor protein-binding, family A, member 2	602712
15q11.2-q12	*GABRB3*	*ECA5, MGC9051*	Gamma-aminobutyric acid (GABA) A receptor, beta 3	137192
15q13.3	*MICRODEL15q13.3*	*EIG7, SCZD13*	Chromosome 15q13.3 microdeletion syndrome	612001
15q13-q15	*SLC12A6*	*ACCPN, DKFZp434D2135, KCC3, KCC3A, KCC3B*	Solute carrier family 12 (potassium/chloride transporters), member 6	604878
15q14	*CHRNA7, FAM7A*	*CHRNA7-DR1, D-10, MGC120482, MGC120483, CHRNA7–2, NACHRA7*	*CHRNA7* (cholinergic receptor, nicotinic, alpha 7, exons 5–10) and *FAM7A* (family with sequence similarity 7A, exons A-E) fusion	609756
15q15	*SCZD10*		Schizophrenia disorder 10 (periodic catatonia)	605419/181500
15q21.3	*ALDH1A2*	*MGC26444, RALDH(II), RALDH2, RALDH2-T*	Aldehyde dehydrogenase 1 family, member a2	603687
15q24.3	*HOMER2*	*ACPD, CPD, HOMER-2, HOMER2A, HOMER2B, Vesl-2*	Homer homolog 2 (drosophila)	604799
15q25		*TRKC, gp145(trkC)*	Neurotrophic tyrosine kinase, receptor, type 3	191316
15q26.2	*MCTP2*	*FLJ11175, FLJ33303, MGC111402*	Multiple C2 domains, transmembrane 2	
16p13.11	*NDE1*	*FLJ20101, HOM-TES-87, NUDE, NUDE1*	nudE Nuclear distribution gene e homolog 1 (A. nidulans)	609449
16p13.11	*NTAN1*	*DKFZp666E058*	N-terminal asparagine amidase	
16q12.2	*RPGRIP1L*	*CORS3, DKFZp686C0668, JBTS7, KIAA1005, MKS5, NPHP8*	RPGRIP1-like	610937
16q22.1	*HP*	*BP, HP2-ALPHA-2, HPA1S, MGC111141*	Haptoglobin	140100
17p11.2	*PEMT*	*MGC2483, PEAMT, PEMPT, PEMT2, PNMT*	Phosphatidylethanolamine N-methyltransferase	602391
17p13.1	*TP53*	*FLJ92943, LFS1, TRP53, p53*	Tumor protein p53	191170
17p13.1	*NDEL1*	*DKFZp451M0318, EOPA, MITAP1, NUDEL*	nudE nuclear distribution gene e homolog (A. nidulans)-like 1	607538
17q11.1-q12	*SLC6A4*	*5-HTT, 5-HTTLPR, 5HTT, HTT, OCD1, SERT, hSERT*	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	182138
17q12	*PPP1R1B*	*DARPP-32, DARPP32, FLJ20940*	Protein phosphatase 1, regulatory (inhibitor) subunit 1B	604399
17q21	*CNP*	*CNP1*	2',3'-cyclic nucleotide 3' phosphodiesterase	123830
17q21	*GFAP*	*FLJ45472*	Glial fibrillary acidic protein	137780
17q21.1	*ERBB2*	*CD340, HER-2, HER-2/neu, HER2, NEU, NGL, TKR1*	v-Erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	164870
17q23.3	*ACE*	*ACE1, CD143, DCP, DCP1, MGC26566, MVCD3*	Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	106180
18p	*SCZD8*		Schizophrenia disorder 8	603206/181500
18p11.2	*MC5R*		Melanocortin 5 receptor	600042

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
18p11.31-p11.2	*NDUFV2*		NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	600532
18q11-q12	*NPC1*	*FLJ98532, NPC*	Niemann-Pick disease, type C1	607623
18q21	*ME2*	*ODS1*	Malic enzyme 2, NAD^+-dependent, mitochondrial	154270
18q21.1	*TCF4*	*E2–2, ITF2, MGC149723, MGC149724, PTHS, SEF2, SEF2–1, SEF2–1A, SEF2–1B, bHLHb19*	Transcription factor 4	602272
18q21.3	*BCL2*	*Bcl-2*	B-cell CLL/lymphoma 2	151430
18q23	*MBP*	*MGC99675*	Myelin basic protein	159430
19p13.3	*ABCA7*	*ABCA-SSN, ABCX, FLJ40025*	ATP-binding cassette, sub-family A (ABC1), member 7	605414
19q13.1	*MAG*	*GMA, S-MAG, SIGLEC-4A, SIGLEC4A*	Myelin associated glycoprotein	159460
19q13.2	*APOE*	*AD2, LDLCQ5, LPG, MGC1571*	Apolipoprotein E	107741
19q13.2	*XRCC1*	*RCC*	X-ray repair complementing defective repair in chinese hamster cells 1	194360
19q13.3	*PLA2GAC*	*CPLA2-gamma, DKFZp586C0423, FLJ42247, FLJ44164*	Phospholipase A2, group IVC (cytosolic, calcium-independent)	603602
19q13.32	*BLOC1S3*	*BLOS3, FLJ26641, FLJ26676, HPS8, RP*	Biogenesis of lysosomal organelles complex-1, subunit 3	609762
20p12-p11.2	*SNAP25*	*FLJ23079, RIC-4, RIC4, SEC9, SNAP, SNAP-25, bA416N4.2, dJ1068F16.2*	Synaptosomal-associated protein, 25kDa	600322
20q11.2	*DNMT3B*	*ICF, M.HsaIIIB*	DNA (cytosine-5-)-methyltransferase 3 beta	602900
20q11.2-q13.1	*MMP9*	*CLG4B, GELB, MANDP2, MMP-9*	Matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	120361
21q22.11	*OLIG2*	*BHLHB1, OLIGO2, PRKCBP2, RACK17, bHLHe19*	Oligodendrocyte lineage transcription factor 2	606386
22q11	*DGCR6*		DiGeorge syndrome critical region gene 6	601279
22q11.2	*C22DDELS*	*C22DELq11.2*	Chromosome 22q11.2 deletion syndrome, distal	611867
22q11.2	*GNB1L*	*DGCRK3, FKSG1, GY2, KIAA1645, WDR14, WDVCF*	Guanine nucleotide binding protein (G protein), beta polypeptide 1-like	610778
22q11.2	*PRODH*	*FLJ33744, HSPOX2, MGC148078, MGC148079, PIG6, POX, PRODH1, PRODH2, SCZD4, TP53I6*	Proline dehydrogenase/proline oxidase	606810/181500
22q11-q13	*SCZD4*		Schizophrenia disorder 4	600850/181500
22q11.21	*ARVCF*	*FLJ35345*	Armadillo repeat gene deletes in velocardiofacial syndrome	602269
22q11.21	*COMT*		Catechol-O-methyltransferase	116790/181500
22q11.21	*RTN4R*	*NGR, NOGOR*	Reticulon 4 receptor	605566
22q11.21	*ZDHHC8*	*ZDHHCL1, ZNF378*	Zinc finger, DHHC-type containing 8	608784
22q11.23	*GSTT1*		Glutathione D-transferase theta 1	600436
22q11.2-q13.2	*APOL4*	*CTA-212A2.2, APOL-IV, APOLIV*	Apolipoprotein L,4	607254/181500
22q11.21	*DGCR2*	*DGS-C, DKFZp686I1730, IDD, KIAA0163, LAN, SEZ-12*	DiGeorge syndrome critical region gene 2	600594
22q12	*APOL2*	*APOL-II, APOL3*	Apolipoprotein L,2	607252/181500
22q12.3	*SYN3*	*LL22NC03–28H9.1*	Synapsin III	602705
22q12.3	*YWHAH*	*LL22NC03–44A4.1, YWHA1*	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	113508
22q13.1	*APOL1*	*RP1–68O2.2, APO-L, APOL, APOL-I*	Apolipoprotein L,1	603743/181500
22q13.1	*CSF2RB*	*CD131, CDw131, IL3RB, IL5RB*	Colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	138981
22q13	*SYNGR1*	*MGC:1939*	Synaptogyrin 1	603925

Table 1. Continued

Locus	Symbol	Aliases	Title	OMIM
22q13.2	*MCHR1*	*GPR24, MCH1R, MGC32129, SLC1*	Melanin-concentrating hormone receptor 1	601751
22q13.3	*SHANK3*	*DEL22q13.3, KIAA1650, PROSAP2, PSAP2, SPANK-2*	SH3 and multiple ankyrin repeat domains 3	606230
22q13.31	*BIK*	*BIP1, BP4, NBK*	BCL2-interacting killer (apoptosis-inducing)	603392
22q13.33	*BRD1*	*BRL, BRPF1, BRPF2, DKFZp686F0325*	bromodomain containing 1	604589
22q13.33	*MLC1*	*RP3–355C18.4, KIAA0027, LVM, MLC, VL*	MLC1 gene	605908
22q13.33	*ZBED4*		Zinc finger, BED-type containing 4	612552
Xp11.23	*MAOB*	*RP1–201D17__B.1, MGC26382*	Monoamine oxidase B	309860
Xq13.1	*NLGN3*	*HNL3, KIAA1480*	Neuroligin 3	300336
Xp22.1	*SAT1*	*DC21, KFSD, KFSDX, SAT, SSAT, SSAT-1*	Spermidine/spermine N1-acetyltransferase 1	313020
Xp22.32-p22.31	*NLGN4*	*ASPGX2, AUTSX2, HLNX, HNLX, KIAA1260, MGC22376, NLGN, NLGN4*	Neuroligin 4, X-linked	300427
Xq24	*HTR2C*	*RP11–810O3.1, 5-HT2C, 5-HTR2C, HTR1C*	5-Hydroxytryptamine (serotonin) receptor 2C	312861
Xq28	*MECP2*	*AUTSX3, DKFZp686A24160, MRX16, MRX79, MRXS13, MRXSL, PPMX, RS, RTS, RTT*	Methyl CPG binding protein 2 (Rett syndrome)	300005
Xp22.3 or Yp11.3	*IL3RA*	*RP11–261P4.2, CD123, IL3R, IL3RAY, IL3RX, IL3RY, MGC34174, hIL-3Ra*	Interleukin 3 receptor, alpha (low affinity)	308385, 430000
GWA 10q2613				
GWA 11p141				
GWA 16p1312				

predominantly controlled by the Liver X receptor (LXR) transcription factor, have been detected. Stimulation of cellular lipid biosynthesis by amphiphilic psychotropic drugs is followed by a transcriptional activation of cholesterol transport and efflux pathways. Such effects may be relevant for both therapeutic effects and metabolic adverse effects of psychotropic drugs [28].

Apoptotic Engulfment Pathway

Apoptosis has been speculated to be implicated in SCZ. The apoptotic engulfment pathway involving the *MEGF10, GULP1, ABCA1,* and *ABCA7* genes have been investigated in SCZ. Nominally significant associations were found in *GULP1* (rs2004888), *ABCA1* (rs3858075), and *ABCA7* genes. A significant 2-marker (rs2242436 ∗ rs3858075) interaction between the *ABCA1* and *ABCA7* genes and a 3-marker interaction (rs246896 ∗ rs4522565 ∗ rs3858075) among the *MEGF10, GULP1,* and *ABCA1* genes were found in different samples [29].

Brain-Derived Neurotrophic Factor (*BDNF*)

A variety of evidence suggests *BDNF* as a candidate gene for SCZ, and several genetic studies have shown a significant association between the disease and certain SNPs within *BDNF* (specifically, Val66Met and C270T). The functional microsatellite marker *BDNF-LCPR* (BDNF-linked complex polymorphic region), which affects the expression level of BDNF, is associated with BD. A meta-analysis of the two most extensively studied polymorphisms (Val66Met and C270T) revealed no association in single-marker or multimarker analysis and no association of Val66Met polymorphism with SCZ, whereas C270T showed a trend for association in a fixed model, but not in a random model. These findings suggest that if BDNF is indeed associated with SCZ, the A1 allele in *BDNF-LCPR* would be the most promising candidate [30]. In a Taiwanese population no association between the *BDNF* Val66Met polymorphism and SCZ was found; however, this polymorphism may reduce psychopathology, in particular negative symptoms [31]. Patients with schizoaffective disorder and other affective disorders are significantly more likely to carry two copies of the most common *BDNF* haplotype compared with healthy volunteers. When compared with SCZ patients, individuals with schizoaffective disorder are significantly more likely to carry two copies of the common haplotype [32]. Defective BDNF has been proposed as a candidate pathogenic mechanism in SCZ and dementia. BDNF transcription is regulated during the protracted period of human frontal cortex development. Expression of the four most abundant alternative 5′ exons of the *BDNF* gene (exons I, II, IV, and VI) has been studied in RNA extracted from the prefrontal cortex. Expression of transcripts I-IX and VI-IX was highest during infancy, whereas that of transcript II-IX was lowest just after birth, slowly increasing to reach a peak in toddlers. Transcript IV-IX was significantly upregulated within the first year of life, and was maintained at this level until school age. Quantification of BDNF

Table 2. Top polymorphisms in top 30 genes at SZ gene [15,159]

SZGene	Gene	SNPs	Allele (minor/major)
1	*DISC1*	rs3737597	A*/G
2	*SLC18A1*	rs2270641	C*/A
3	*GABRB2*	None	
4	*DRD2*	rs1079597 (TaqI-B)	A/G*
		rs6277	C*/T
		rs1801028	G*/C
		rs6275	T*/C
5	*GWA 10q2613*	rs17101921	A*/G
6	*AKT1*	rs3803300	A*/G
7	*GRIN2B*	rs1019385	T/G*
		rs7301328	G*/C
8	*DGCR2*	rs2073776	A*/G
9	*PLXNA2*	rs1327175	G/C*
10	*RPGRIP1L*	rs9922369	A*/G
11	*TPH1*	rs1800532	A*/C
12	*DRD4*	120-bp TR	S/L*
		rs1800955	C*/T
13	*DAOA*	rs3916971	T/C*
		rs778294	T/C*
		rs2391191 (M15)	A*/G
14	*GWA 11p141*	rs1602565	C*/T
15	*DRD1*	none	
16	*HTR2A*	rs6311	A/*G
17	*RELN*	rs7341475	A/G*
18	*APOE*		e2/3/4*
19	*NRG1*	rs2439272	A/G*
		rs35753505	C*/T
		rs473376	G*/A
20	*IL1B*	rs1143634	T/C*
21	*MTHFR*	rs1801133	T*/C
22	*COMT*	rs4680	A/G*
		rs737865	C/T*
23	*HP*	Hp1/2	1/2*
24	*DAO*	rs2111902	G*/T
		rs3741775	C/G*
		rs3918346	A*/G
		rs4623951	C/T*
25	*TP53*	rs1042522	C*/G
26	*ZNF804A*	rs1344706	G/T*
27	*GWA 16p1312*	rs71992086	T*/A
28	*DTNBP1*	rs1011313	T*/C
		rs1018381	T/*C
		rs2619538(SNPA)	T*/A
		rs3213207(P1635)	G/A*
29	*OPCML*	rs3016384	T/C*
30	*RGS4*	rs2661319 (SNP16)	A/G*

protein revealed that levels followed a similar developmental pattern as transcript IV-IX. *In situ* hybridization of mRNA in cortical sections showed the highest expression in layers V and VI for all four BDNF transcripts, whereas moderate expression was observed in layers II and III. These findings reported by Wong et al. [33] show that dynamic regulation of BDNF expression occurs through differential use of alternative promoters during the development of the human prefrontal cortex, particularly in the younger age groups, when the prefrontal cortex is more plastic. Alterations in BDNF processing during brain maturation cannot be neglected as a potential mechanism for prefrontal cortex dysfunction in SCZ. The levels of (pro)BDNF and receptor proteins, TrkB and p75, are altered in hippocampus in SCZ and mood disorder and polymorphisms in each gene influence protein expression [34]. Neurodegenerative processes may be involved in the pathogenesis of tardive dyskinesia (TD), and a growing body of evidence suggests that BDNF plays a role in both the antipsychotic effects and the pathogenesis of TD. BDNF and glycogen synthase kinase (GSK)-3beta are important in neuronal survival, and thus abnormal regulation of BDNF and GSK-3beta may contribute to TD pathophysiology. Park et al. [35] studied the relationship between two polymorphisms, Val66Met in the *BDNF* coding region and 50T/C in the *GSK-3beta* promoter, and susceptibility to TD among a matched sample of patients having SCZ with TD, patients with SCZ without TD, and normal control subjects. Polymerase chain reaction (PCR) analysis revealed no significant difference in the occurrence of the polymorphisms among the TD, non-TD, and control subjects, but a significant interaction was observed among the groups possessing *BDNF* Val allele in compound genotypes. The schizophrenic subjects with the C/C *GSK-3beta* genotype, who carry the Val allele of the *BDNF* gene, are expected to have a decreased risk of developing neuroleptic-induced TD [35].

Biogenesis of Lysosome-Related Organelles Complex 1 (*BLOC-1*)

BLOC-1 is a protein complex formed by the products of eight distinct genes. Loss-of-function mutations in two of these genes, *DTNBP1* and *BLOC1S3*, cause Hermansky–Pudlak syndrome, a human disorder characterized by defective biogenesis of lysosome-related organelles. Haplotype variants within the same two genes have been postulated to increase the risk of developing SCZ [36].

Calcium Channel, Voltage-Dependent, L Type, Alpha 1C Subunit (*CACNA1C*)

Strong evidence of association at the polymorphism rs1006737 (within *CACNA1C*, the gene encoding the alpha-1C subunit of the L-type voltage-gated calcium channel) with the risk of BD has recently been reported in a meta-analysis of three genome-wide association studies of BD. The risk allele also conferred increased risk for SCZ and recurrent major depression with similar effect sizes to those previously observed in BD [37,38].

Cannabinoid Receptors

Two endocannabinoid receptors, CB1 and CB2, are found in the brain. The R63 allele of rs2501432 (R63Q), the C allele of rs12744386 and the haplotype of the R63-C allele of *CB2* were significantly increased among patients with SCZ [39].

Cholecystokinin A Receptor (*CCK-AR*) Gene

CCK-AR has been implicated in the pathophysiology of SCZ through its mediation of dopamine-release in the CNS. Association between the *CCK-AR* gene and SCZ has been observed, especially between the 779T/C polymorphism and auditory hallucinations or positive symptoms of SCZ [40].

Alpha-7 Nicotinic Acetylcholine Receptor (*CHRNA7*)

Multiple genetic linkage studies support the hypothesis that the 15q13–14 chromosomal region contributes to the etiology of SCZ. Among the putative candidate genes in this area are *CHRNA7* and its partial duplication, *CHRFAM7A*. A large chromosomal segment including the *CHRFAM7A* gene locus, but not the *CHRNA7* locus, is deleted in some individuals. The *CHRFAM7A* gene contains a polymorphism consisting of a 2 base pair (2 bp) deletion at position 497–498 bp of exon 6. The 2 bp polymorphism was associated with SCZ in African-Americans, and in Caucasians [41]. The rs3087454 SNP, located at position –1831 bp in the upstream regulatory region of *CHRNA7*, was significantly associated with SCZ in African-American and Caucasian-Non-Hispanic case-control samples [42].

CNTNAP2, *NRXN1*, and the Neurexin Superfamily

Heterozygous CNV and SNPs of *CNTNAP2* and *NRXN1*, two distantly related members of the neurexin superfamily, have been repeatedly associated with a wide spectrum of neuropsychiatric disorders, such as developmental language disorders, autism spectrum disorders, epilepsy, Pitt–Hopkins syndrome, and SCZ [43].

Catechol-O-Methyltransferase (*COMT*)

The *COMT* gene, which is located in the 22q11 microdeletion, has been considered as a candidate gene for SCZ due to its ability to degrade catecholamines, including dopamine. Human *COMT* contains three common polymorphisms (A22S, A52T, and V108M), two of which (A22S and V108M) render the protein susceptible to deactivation by temperature or oxidation. The A52T mutation had no significant effect on COMT structure. The A22S and V108M polymorphisms evolved independently in Northern European and Asian populations. While the decreased activities of both A22S and V108M *COMT* are associated with an increased risk for SCZ, the V108M-induced destabilization is also linked with improved cognitive function. Polymorphisms within this hotspot may have evolved to regulate COMT activity, and heterozygosity for either mutation may be advantageous [44]. Some studies revealed potential epistatic effects of two intronic SNPs located in the *COMT* and aldehyde dehydrogenase 3B1 (*ALDH3B1*) genes, which conferred genetic risk to paranoid SCZ. Among the individuals carrying the rs3751082 A allele in the *ALDH3B1* gene, the rs4633 T allele in the *COMT* gene was associated with susceptibility to paranoid SCZ, development of hallucination, delay of P300 latency, and increased expression of the *COMT* gene; however, the rs4633 T allele did not show any association in the rs3751082 G/G genotype carriers [45].

D-amino Acid Oxidase Activator (*DAOA*)

The *DAOA* gene locus on chromosome 13q32-q34 has been implicated in the etiology of SCZ. Three SNPs (rs778294, rs779293, and rs3918342) have been identified in this region, and two of them (rs778293 and rs3918342) have shown significant transmission disequilibrium and a highly significant under-transmission between haplotype CAT and SCZ [46]. *G72* is one of the most widely tested genes for association with SCZ. As G72 activates the D-amino acid oxidase (DAO), G72 is termed DAOA. Ohi et al. [47] found nominal evidence for association of alleles, M22/rs778293, M23/rs3918342, and M24/rs1421292, and the genotype of M22/rs778293 with SCZ, although there was no association of allele or genotype in the other 5 SNPs. They also found nominal haplotypic association, including M15/rs2391191 and M19/rs778294 with SCZ [47]. Association of the *G72/G30* locus with SCZ and BD has been reported in several studies. The *G72/G30* locus spans a broad region of chromosome 13q. One meta-analysis of published association studies shows highly significant evidence of association between nucleotide variations in the *G72/G30* region and SCZ, along with compelling evidence of association with BD [48]. This locus has been associated with panic disorder, SCZ, and BD, specially the 3 SNPs rs2391191, rs3918341, and rs1935062, with controversial results [49].

Disrupted-In-Schizophrenia (DISC)-1 (*DISC1*)

The *DISC1* locus is located at the breakpoint of a balanced t(1;11)(q42.1;q14.3) chromosomal translocation in a large and unique Scottish family. This translocation segregates in a highly statistically significant manner with a broad diagnosis of psychiatric illness, including SCZ, BD and major depression, as well as with a narrow diagnosis of SCZ alone. Two novel genes were identified at this locus and due to the high prevalence of SCZ in this family, they were named DISC-1 (*DISC1*) and DISC-2 (*DISC2*). *DISC1* encodes a novel multifunctional scaffold protein, whereas DISC2 is a putative noncoding RNA gene antisense to *DISC1*. A number of independent genetic linkage and association studies in diverse populations support the original linkage findings in the Scottish family and genetic evidence now implicates the DISC locus in susceptibility to SCZ, schizoaffective disorder, BD and major depression, as well as various cognitive traits [50].

DISC1 interacts directly with phosphodiesterase 4B (PDE4B), an independently identified risk factor for SCZ. DISC1-PDE4B complexes are therefore likely to be involved in molecular mechanisms underlying psychiatric illness. PDE4B hydrolyzes cAMP and DISC1 may regulate cAMP signaling through modulating PDE4B activity. There is evidence that expression of both genes is altered in some psychiatric patients. *DISC1* missense mutations that give rise to phenotypes related to SCZ and depression in mice are located within binding sites for *PDE4B*. These mutations reduce the association between *DISC1* and *PDE4B*, and one results in reduced brain PDE4B activity. Altered DISC1-PDE4B interaction may thus underlie the symptoms of some cases of SCZ and

depression [51]. DISC1 protein binding partners include the Nuclear Distribution Factor E Homologs (NDE1 and NDEL1), LIS1, and phosphodiesterases 4B and 4D (PDE4B and PDE4D) [52]. A *DISC1* haplotype, *HEP3*, and an *NDE1* spanning tag haplotype are associated with SCZ in Finnish families. Tomppo et al. [53] identified 3 SNPs to be associated with SCZ in *PDE4D* (rs1120303), *PDE4B* (rs7412571), and *NDEL1* (rs17806986). Greater significance was observed with allelic haplotypes of *PDE4D*, *PDE4B*, and *NDEL1* that increased or decreased SCZ susceptibility, highlighting the potential importance of DISC1-related molecular pathways in the etiology of SCZ and other major mental illnesses [53]. Kähler et al. [54] have genotyped and analyzed 40 and 72 tagSNPs in SCZ and BP multicenter samples, respectively, from the Scandinavian Collaboration on Psychiatric Etiology (SCOPE), involving 837 SCZ cases and 1473 controls plus 594 BP cases and 1421 partly overlapping controls. Six and 16 tagSNPs were nominally associated with SCZ and BP, respectively, in the combined samples or in gender-specific subgroups. None of these findings remained significant after correction for multiple testing. However, a number of tagSNPs found to be nominally associated with SCZ and BP were located in a high linkage disequilibrium (LD) region spanning the splice site of *PDE4B3*, an isoform with altered brain expression in BP patients.

DNA Methyltransferase 3B

Aberrant DNA methylation may be involved in the development of SCZ. DNA methyltransferase 3B (DNMT3B) is the key methyltransferase in DNA methylation regulations. Case-control and family-based studies were performed through genotyping two tag SNPs (rs2424908 and rs6119954) covering the whole *DNMT3B* gene. The frequency of G allele of rs6119954 was significantly higher in SCZ. Genotype distribution of rs6119954 was significantly different between patients and controls. A haplotype-wise analysis revealed a higher frequency of the T-G (rs2424908-rs6119954) haplotype in SCZ [55]. In SCZ a functional down-regulation of the prefrontal cortex GABAergic neuronal system is mediated by a promoter hypermethylation, presumably catalyzed by an increase in DNA-methyltransferase-1 (DNMT-1) expression. This promoter hypermethylation may be mediated not only by DNMT-1 but also by an entire family of *de novo* DNA-methyltransferases, such as DNA-methyltransferase-3a (DNMT-3a) and -3b (DNMT-3b) [56].

Dopamine-Related Genes

DARPP-32 (PPP1R1B)

Recent findings have highlighted the importance of DARPP-32 (dopamine- and cAMP-regulated phosphoprotein, 32 kDa), a key regulatory molecule in the dopaminergic signaling pathway for dopamine-related phenotypes like antisocial-behavior, drug addiction, and SCZ [57].

Dopamine Beta-Hydroxylase

The SNP rs1108580 A/G in *DBH* has been associated with SCZ [58].

Dopamine Transporter (DAT) 3′ UTR VNTR

Dopamine has a crucial role in the modulation of neurocognitive function, and synaptic dopamine activity is normally regulated by DAT and COMT. Altered dopamine function is a key pathophysiological feature of SCZ [59].

Dopamine Receptor D2 (DRD2)

Associations of two SNPs for *DRD2* (rs11608185, rs6275) were found [60].

Dopamine D4 Receptor (DRD4)

Associations have been reported between the variable number of tandem repeat (VNTR) polymorphisms in the exon 3 of *DRD4* and multiple psychiatric illnesses/traits. The size of allele "7R" is less frequent (0.5%) in the Japanese than in Caucasian populations (20%). The most common 4R variant is considered to be the ancestral haplotype [61]. A haplotype containing rs3732782, rs905568, and rs7620754 in the 5′ region of *DRD3* was associated with TD [62].

Tyrosine Hydroxylase (TH)

TH (EC 1.14.16.2) is involved in the conversion of phenylalanine to dopamine. As the rate-limiting enzyme in the synthesis of catecholamines, TH has a key role in the physiology of adrenergic neurons. The *TH* variant rs6356 A/G has been associated with SCZ [58].

Dystrobrevin Binding Protein 1 (*DTNBP1*) and Dysbindin

DTNBP1, a gene encoding dysbindin protein, is a susceptibility gene for SCZ identified by family-based association analysis. Up to 14 SNPs spanning the *DTNBP1* locus may show association with SCZ in different studies [63]; however, a high-resolution melting analysis (HRMA) to screen the 11 *DTNBP1* exons with their corresponding DNA variants in a sample from United Kingdom revealed no significant associations with SCZ [64]. *DTNBP1* and *MUTED*, encode proteins that belong to the endosome-localized BLOC-1 complex. BLOC-1 plays a key role in endosomal trafficking and as such has been found to regulate cell-surface abundance of the D2 dopamine receptor, the biogenesis and fusion of synaptic vesicles, and neurite outgrowth [65]. BLOC-1 interacts with the adaptor protein (AP)-3 complex, which is essential for vesicle or protein sorting. A 3-marker C-A-T dysbindin haplotype is associated with increased risk for SCZ, decreased mRNA expression, reduced gray matter volume in both the right dorsolateral prefrontal and left occipital cortex, poorer cognitive performance, and early sensory processing deficits [66]. Four SNPs (rs3213207, rs1011313, rs760761, and rs2619522) have been genotyped in a large Korean SCZ sample. Haplotype analyses revealed a significant association with SCZ with the haplotypes A-C-C-C and A-C-T-A having an eminent protective effect toward SCZ. The major

contribution to the difference in the haplotype distribution between patients and controls was the rs760761 (C/T) and rs2619522 (A/C) haplotypes [67]. Seven *DTNBP1* SNPs (rs2743852 (SNP C), rs760761 (P1320), rs1011313 (P1325), rs3213207 (P1635), rs2619539 (P1655), rs16876571, and rs17470454) were investigated in BP, and significant differences in genotypic and allelic frequencies of rs3213207 and rs760761 of *DTNBP1* were found between bipolar patients and controls [68].

Estrogen Signaling

Estrogen signaling may be altered in the brains of people with SCZ. DNA sequence variation in the estrogen receptor (*ER*) alpha gene, lower ERalpha mRNA levels, and/or blunted ERalpha signaling is associated with SCZ. Reductions in the transcriptionally active form of *ErbB4* comprising the intracytoplasmic domain (ErbB4-ICD) have been found in SCZ. Convergence between *ERalpha* and *ErbB4-ICD* in the transcriptional control of *ERalpha*-target gene expression may represent a convergent pathway that may be disrupted in SCZ [69]. Li et al. [70] investigated the *ERBB3* gene given the putative functional nature of the gene and population heterogeneity between Asian and Caucasian. Scottish case and control samples were sequenced with 4 SNPs (rs705708 at intron 15, rs2271189, rs773123, rs2271188 at exon 27), and association of rs773123, which is a nonsynonymous Ser/Cys polymorphism located 7 bases downstream of rs2271189, with SCZ was detected in the Caucasian population [70]. The estrogen protection hypothesis proposes that estrogen has a protective effect against onset of SCZ. Epidemiological studies have shown that young women are less likely to develop SCZ than men of the same age, and women are more likely to develop late-onset SCZ after menopause. Clinical studies have shown higher psychotic symptoms in perimenopausal women, and women at the low estrogen phase of the menstrual cycle [71].

FADS2: Delta-6 Desaturase

Emerging evidence suggests that SCZ might be associated with peripheral and central polyunsaturated fatty acid (PUFA) deficits. Abnormalities in fatty acid composition have been reported in peripheral tissues from drug-naïve first-episode schizophrenic patients, including deficits in omega-3 and omega-6 PUFAs, which are partially normalized following chronic antipsychotic treatment. Postmortem cortical tissue from patients with SCZ also exhibit deficits in cortical docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (AA; 20:4n-6) relative to normal controls, and these deficits tend to be greater in drug-free SCZ patients [72]. Delta-5 desaturase (*FADS1*), Delta-6 desaturase (*FADS2*), elongase (*HELO1* [*ELOVL5*]), peroxisomal (*PEX19*), and Delta-9 desaturase (stearoyl-CoA desaturase, *SCD*) mRNA expression has been studied in the postmortem prefrontal cortex of patients with SCZ. *FADS2* mRNA expression was significantly greater in SCZ patients relative to controls (+36%), and there was a positive trend found for *FADS1* (+26%). Drug-free SCZ patients (+37%), and SCZ patients treated with typical (+40%) or atypical (+31%) antipsychotics, exhibited greater *FADS2* mRNA expression relative to controls. Consistent with increased Delta6 desaturase activity, SCZ patients exhibited a greater PUFA (product:precursor) 20:3/18:2 ratio (+20%) and a positive trend was found for 20:4/18:2 (+13%) [73].

Fyn

Fyn, a Src-family kinase, is highly expressed in brain tissue and blood cells. Fyn participates in brain development, synaptic transmission through the phosphorylation of NMDA receptor subunits, and the regulation of emotional behavior. Fyn is required for the signal transduction in striatal neurons that is initiated by haloperidol. Fyn abnormalities are present in patients with SCZ. At the mRNA level, the splicing patterns of *Fyn* were altered in the patients and their relatives; specifically, the ratio of *FynDelta7*, in which exon 7 is absent, was elevated [74]. Fyn plays a key role in the interaction between BDNF and glutamatergic receptor NMDA. An association was found between *FYN* polymorphisms and cognitive test performance in schizophrenic patients. rs706895 (-93A/G in the 5′-flanking region), rs6916861 (Ex12 + 894T/G in the 3′-UTR), and rs3730353 (IVS10 + 37T/C in intron 10) were investigated in BD, and a significant association was found between rs6916861 T/G and rs3730353 T/C and BD [75].

GABAergic Gene Expression

Prefrontal deficits in gamma-aminobutyric acid (GABA) and GABAergic gene expression, including neuropeptide Y (*NPY*), somatostatin (*SST*), and parvalbumin (*PV*) messenger RNAs (mRNAs), have been reported for multiple SCZ cohorts. Preclinical models suggest that a subset of these GABAergic markers (NPY/SST) is regulated by BDNF, which in turn is under the inhibitory influence of small noncoding RNAs. Subjects with SCZ show deficits in NPY and PV mRNAs [76].

Glutamatergic Neurotransmission

GCLM

Glutathione and its rate-limiting synthesizing enzyme, the glutamate-cysteine ligase (GCL), are involved in the pathogenesis of SCZ. Genetic association was reported between 2 SNPs lying in noncoding regions of the glutamate cysteine ligase modifier (*GCLM*) gene, which specifies for the modifier subunit of GCL and SCZ [77]. Other genes involved in glutamate neurotransmission include glutamate transporter genes (*EAAT1, EAAT2, EAAT3, EAAT4, vGluT1*) [78], glutamic acid decarboxylase 2 (*GAD2*), and the glutamine synthetase (*GLUL*) genes, glutamate receptor genes (*GRIA4, GRIN2D, GRIK3, GRIK4, GRIK5, GRM3, GRID1*), glutaminase, glutamate carboxypeptidase II (*GCPII*), group III metabotropic glutamate receptor genes (*GRM4* and *GRM7*), *NMDAR*, and glycine- and serine-related genes (*PHGDH*, *SHMT1*, *SRR*, and *DAO*).

Golli-MBP

Multiple studies have reported oligodendrocyte and myelin abnormalities, as well as dysregulation of their related genes, in brains

of SCZ patients. One of these genes is the myelin-basic-protein (*MBP*) gene, which encodes two families of proteins: classic-MBPs and golli-MBPs. While the classic-MBPs are predominantly located in the myelin sheaths of the nervous system, the golli proteins are more widely expressed and are found in both the immune and the nervous systems. Association between 6 (out of 26 genotyped) SNPs has been found in Jewish Ashkenazi cohorts. Of these, three (rs12458282, rs2008323, rs721286) are from one LD block, which contains a CTCF binding region. Haplotype analysis revealed significant "risk"/"protective" haplotypes for SCZ, suggesting that *golli-MBP* is a possible susceptibility gene for SCZ [79].

Growth Factor Signaling Pathways

Evidence has accumulated that the activity of the signaling cascades of Neuregulin-1, Wnt, TGF-beta, BDNF-p75, and DISC1 is different between control subjects and patients with SCZ. These pathways are involved in embryonic and adult neurogenesis and neuronal maturation. Clinical data indicate that in SCZ the Wnt pathway is most likely hypoactive, whereas the Nrg1-ErbB4, the TGF-beta- and the BDNF-p75-pathways are hyperactive. Haploinsuffiency of the *DISC1* gene is currently the best established SCZ risk factor.

Interleukins

SCZ has been associated with abnormalities in cytokines and cytokine receptors potentially link to a defective immunological function in psychotic disorders. Some reports have shown that *IL-1B*, *IL-3* gene, colony stimulating factor 2 receptor alpha (*CSF2RA*), and IL-3 receptor alpha (*IL3RA*) are associated with SCZ [80].

KCNH2 (Potassium Voltage-Gated Channel, Subfamily h [Eag-Related], Member 2)

Organized neuronal firing is crucial for cortical processing and this is disrupted in SCZ. In SCZ hippocampus, KCNH2-3.1 expression is 2.5-fold greater than KCNH2-1A expression. A meta-analysis of 5 clinical data sets shows association of SNPs in *KCNH2* with SCZ [81].

Kynurenine Pathway

Some studies of mRNA expression, protein expression, and pathway metabolite levels have implicated dysregulation of the kynurenine pathway in the etiology of SCZ and BD. A SNP in each of 6 genes, *TDO2*, *HM74*, *HM74A*, *MCHR1*, *MCHR2*, and *MC5R*, was tested for association with SCZ. An A allele in *HM74* was significantly associated with SCZ and with SCZ plus BD combined [82].

MCTP2

The *MCTP2* gene is involved in intercellular signal transduction and synapse function. Djurovic et al. [83] genotyped 37 tagging SNPs across the *MCTP2* gene to study a possible association with SCZ in three independent Scandinavian samples, and found a possible involvement of *MCTP2* as a potential novel susceptibility gene for SCZ [83].

Major Histocompatibility Complex (MHC)

The International Schizophrenia Consortium [84] and the European SGENE-plus [85] found significant association with several markers spanning the MHC region on chromosome 6p21.3–22.1. In the MCH region, the 5 genome-wide significant markers (*MCH/HIST1H2BJ*: rs6913660-C; *MHC/PRSS16*: rs13219354-T; *MHC/PRSS16*: rs6932590-T; *MHC/PGBD1*: rs13211507-T; *MHC/NOTCH4*: rs3131296-G) have risk alleles with average control frequencies between 78 and 92%. The 5 chromosome 6p markers, spanning about 5 Mb, cover 1.4 cM and exhibit substantial linkage disequilibrium. Rs3131296 shows correlation with classical HLA alleles (*HLA-A∗0101*, *HLA-B∗0801*, *HLA-C∗0701*, *HLA-DRB∗0301*, *HLA-DQA∗0501*, *HLA-DQB∗0201*) [84,85]. This finding might give support to the infective-neuroimmune hypothesis of SCZ.

Methylenetetrahydrofolate Reductase (*MTHFR*)

The frequency of homozygosity for the 677T allele of the *MTHFR* gene was found higher in Chinese patients with SCZ than in controls. Both elevated plasma homocysteine levels and variation in the *MTHFR* 677C–>T gene is related to increased rates of SCZ and is risk factor for psychosis [86].

Neuregulin (*NRG1*, *NRG3*)

Chromosome 8p22-p11 has been identified as a locus for SCZ in several genome-wide scans and confirmed by meta-analysis of published linkage data. Systematic fine mapping using extended Icelandic pedigrees identified an associated haplotype in the gene neuregulin 1 (*NRG1*), also known as heuregulin, glial growth factor, *NDF43*, and *ARIA*. A 290 kb core at risk haplotype at the 5′ end of the gene (*HAP[ICE*]), defined by 5 SNPs and 2 microsatellite polymorphisms was found to be associated with SCZ in the Icelandic and Scottish populations. Significant association was found with 5 SNPs located in the second intron of *NRG1* [87]. Li et al. [88] analyzed data from the SNP markers SNP8NRG241930, SNP8NRG243177, SNP8NRG221132, and SNP8NRG221533, and the microsatellite markers 478B14–848, 420M9–1395, and found strong positive association for all 6 polymorphisms. Gong et al. [89] performed a meta-analysis of 26 published case-control and family-based association studies up to September 2008 covering 8049 cases, 8869 controls, and 1515 families. Across these studies, the conclusions are as follows: (1) only SNP8NRG221132, 420M9–1395(0) and 478B14–848(0) showed significant association in the relatively small sample size; (2) the association analysis of case-control studies was statistically consistent with that of family studies; and (3) the matrix of coancestry coefficient suggested obvious population stratification. The study reveals that 1 SNP of the *NRG1* gene does not contribute significantly to SCZ and that population stratification is evident [81]. Quantitative real-time PCR was used to check the genotypes

of 4 SNPs-rs221533(C/T), rs7820838(C/T), 433E1006(A/G), and rs3924999(C/T), located at the 5′ terminus of the *NRG1* gene, in 258 Chinese Han schizophrenic parent-proband trios. There was significant transmission disequilibrium in allelic transmission of C, A, T from rs221533, 433E1006, rs3924999 loci, respectively (rs221533, 433E1006, rs3924999). Haplotype was analyzed at frequency exceeding 1%. In 3-marker-haplotype, C/C/G and C/C/A (rs221533, rs7820838, 433E1006) transmitted predominantly. In 4-marker-haplotype (rs221533, rs7820838, 433E1006, rs3924999), C/C/G/T, C/C/A/C, and C/C/A/T showed transmission disequilibrium. According to these studies, the *NRG1* gene polymorphism is significantly associated with SCZ in Chinese Han, especially in the positive subtype of SCZ [90].

Linkage studies have implicated 10q22-q23 as a SCZ susceptibility locus in Ashkenazi Jewish (AJ) and Han Chinese from Taiwan populations. Chen et al. [91] performed a peakwide association fine mapping study by using 1414 SNPs across approximately 12.5 Mb in 10q22-q23 of Ashkenazi Jewish, and found strong evidence of association by using the "delusion" factor as the quantitative trait at 3 SNPs (rs10883866, rs10748842, and rs6584400) located in a 13 kb interval in intron 1 of *NRG3*. NRG3 is primarily expressed in the CNS and is 1 of 3 paralogs of NRG1 [91].

Neurogranin (*NRGN*)

A marker located 3457 bases upstream of the *NRGN* gene on 11q24.2 (rs128078009-T) has been associated with SCZ [92]. This marker has an average risk allele control frequency of 83%. Another *NRGN* SNP (rs7113041) has been reported to be associated with SCZ in Portuguese patients [93]. Altered NRGN activity might mediate the effects of NMDA hypofunction implicated in SCZ pathogenesis [92].

Reelin (*RELN*)

RELN is a large secreted protein of the extracellular matrix that has been proposed to participate to the etiology of SCZ. The *RELN* gene encodes a secretory glycoprotein critical for brain development and synaptic plasticity. Postmortem studies have shown lower RELN protein levels in the brains of patients with SCZ and BP compared with controls. In a genome-wide association study of SCZ, the strongest association was found in a marker within *RELN*, although this association was seen only in women. *RELN* is also associated with BP in women [94]. There is association between *RELN* intragenic STR allele and working memory, impaired cognitive functioning, and more severe positive and negative symptoms of SCZ [95]. RELN plays a pivotal role in neurodevelopment. Excessive *RELN* promoter methylation and/or decreased *RELN* gene expression have been described in SCZ and autism. Temporocortical tissue (Brodmann Area 41/42) of postpuberal individuals are heavily methylated, especially at CpG positions located between −131 and −98 bp. Sex hormones thus seemingly boost DNA methylation at the *RELN* promoter. This physiological mechanism might contribute to the onset of SCZ and the worsening of autistic behaviors during the puberal period [96]. During development, RELN is crucial for the correct cytoarchitecture of laminated brain structures and is produced by a subset of neurons named Cajal-Retzius. After birth, most of these cells degenerate and RELN expression persists in postnatal and adult brain. In hippocampal cultures, RELN is secreted by GABAergic neurons displaying an intense RELN immunoreactivity (IR). Secreted RELN binds to receptors of the lipoprotein family on neurons with a punctate RELN IR. Blocking protein secretion rapidly and reversibly changes the subunit composition of N-methyl-D-aspartate glutamate receptors (NMDARs) to a predominance of NR2B-containing NMDARs. Addition of recombinant or endogenously secreted RELN rescues the effects of protein secretion blockade and reverts the fraction of NR2B-containing NMDARs to control levels. The continuous secretion of RELN is necessary to control the subunit composition of NMDARs in hippocampal neurons. Defects in RELN secretion could play a major role in the development of neuropsychiatric disorders, particularly those associated with deregulation of NMDARs such as SCZ [97]. RELN is downregulated in the brain of schizophrenic patients and of heterozygous reeler mice (rl/+). The behavioral phenotype of *rl*/– mice, however, matches only partially the SCZ hallmarks. Homozygous reeler mutants (*rl*/*rl*) exhibit reduced density of parvalbumin-positive (PV+) GABAergic interneurons in anatomically circumscribed regions of the neostriatum. The striatal regions in which *rl*/*rl* mice exhibited decreased density of PV+ interneurons are either unaltered (rostral striatum) or equally altered (dorsomedial and ventromedial intermediate striatum, caudal striatum) in *rl*/+ mice. *RELN* haploinsufficiency alters the density of PV+ neurons in circumscribed regions of the striatum and selectively disrupts behaviors sensitive to dysfunction of these targeted regions [98]. Brain abnormalities in +/*rl* are similar to psychotic brain and include a reduction in glutamic acid de carboxylase 67 (GAD67), dendritic arbors and spine density in cortex and hippocampus, and abnormalities in synaptic function including long-term potentiation (LTP). *RELN* and *GAD67* promoters are hypermethylated in GABAergic neurons of psychotic postmortem brain and DNA methyltransferase 1 (DNMT1) is upregulated. Hypermethlyation of *RELN* and *GAD67* promoters can be induced by treating mice with methionine, and these mice display brain and behavioral abnormalities similar to +/*rl*. [99,100].

Serotonin (5-Hydroxytryptamine [5-HT]) Transporter (*SLC6A4*)

SLC6A4 is known to influence mood, emotion, cognition, and efficacy of antidepressants, particularly that of selective serotonin reuptake inhibitors. Atypical antipsychotics exert their effects partially through serotonergic systems, and hence, variation in 5-HT uptake may affect antipsychotic action mediated through the serotonergic system. The genetic roles of 5 polymorphisms of *SLC6A4*, including those of the widely studied 44 bp VNTR in the promoter region of *SLC6A4* (the serotonin transporter gene-linked polymorphic region: *5HTTLPR*) and a VNTR polymorphism (STin2) in the second intron, have been studied in SCZ. Significant allelic and genotypic associations with rs2066713, *5HTTLPR*, and STin2 polymorphisms have been detected. A haplotype linking these three risk alleles, 5HTTLPR/S-rs2066713/C-STin2/12-repeat, was also significantly associated with disease in a South Indian population [101]

SMARCA2/BRM and the SWI/SNF Chromatin-Remodeling Complex

Chromatin remodeling may play a role in the neurobiology of SCZ. The *SMARCA2* gene encodes BRM in the SWI/SNF chromatin-remodeling complex, and associations of SNPs with SCZ were found in two linkage disequilibrium blocks in the *SMARCA2* gene after screening of 11,883 SNPs (rs2296212) and subsequent screening of 22 genes involved in chromatin remodeling (rs3793490) in a Japanese population. A risk allele of a missense polymorphism (rs2296212) induced a lower nuclear localization efficiency of BRM, and risk alleles of intronic polymorphisms (rs3763627 and rs3793490) were associated with low SMARCA2 expression levels in the postmortem prefrontal cortex. A significant correlation in the fold changes of gene expression from schizophrenic prefrontal cortex was seen with suppression of *SMARCA2* in transfected human cells by specific siRNA, and of orthologous genes in the prefrontal cortex of *Smarca2* knockout mice. *Smarca2* knockout mice showed impaired social interaction and prepulse inhibition. Psychotogenic drugs lowered Smarca2 expression while antipsychotic drugs increased it in the mouse brain. According to Koga et al. [102] these findings support the role of BRM in the pathophysiology of SCZ [102].

TAPASIN

Chlamydiaceae species has been identified as a major factor in the pathogenesis of SCZ, suggesting defective immune responses of schizophrenic patients against this environmental factor. Immune responses against Chlamydiaceae species are controlled by immunogenetic factors. Successful responses against microbes depend on the presentation of immunogenic peptides by HLA molecules, which are encoded by a highly polymorphic gene system. Several *HLA* alleles or HLA antigens have been found associated with SCZ in some studies. It has been proposed that variants of these genes, which control transportation and loading of microbial peptides onto HLA molecules, could prevent clearing of immune cell infection by selection of nonimmunogenic peptides for HLA presentation. To generate support for this hypothesis Fellerhoff and Wank [103] determined in a small group of schizophrenic patients and control individuals allele frequencies of the transporter proteins TAP1/TAP2, which select the immunoproteasome-tailored peptides for transportation. Frequencies of *TAPASIN* alleles, which encode chaperons and also may select peptides for loading on MHC molecules have also been studied, and significant associations between SCZ and *TAP1* allele frequencies as well as *TAPASIN* allele frequencies were found, suggesting that variants of these two genetic systems could influence SCZ. These genes belong to the family of ABC transporter proteins and may also influence the efficiency of drugs [103].

TATA Box-Binding Protein Gene (*TBP*)

Spinocerebellar ataxia type 17 (*SCA17*) is a rare autosomal dominant neurodegenerative disorder with ataxia and psychotic symptoms. *SCA17* is caused by an expanded polyglutamine tract in the TATA box-binding protein (*TBP*) gene. Ohi et al. [104] investigated the association between SCZ and CAG repeat length in common *TBP* alleles with fewer than 42 CAG repeats in a Japanese population. Higher frequency of alleles with greater than 35 CAG repeats was found in patients with SCZ compared with that in controls. A negative correlation between the number of CAG repeats in the chromosome with longer CAG repeats out of 2 chromosomes and age at onset of SCZ was also observed. *TBP* genotypes with greater than 35 CAG repeats, which were enriched in patients with SCZ, were significantly associated with hypoactivation of the prefrontal cortex measured by near-infrared spectroscopy during the tower of Hanoi, a task of executive function. These findings suggest possible associations of the genetic variations of the *TBP* gene with risk for SCZ, age at onset and prefrontal function [104].

Transcription Factor 4 (*TFC4*)

A marker in intron 4 of the transcription factor 4 (*TFC4*) on 18q21.2 (rs9960767-C) has been associated with SCZ [85]. The risk allele control frequency of this marker is about 6%. TCF4 is essential for normal brain development. Mutations in this gene were found to be responsible for Pitt-Hopkins syndrome, an autosomal-dominant neurodevelopmental disorder characterized by mental and psychomotor retardation, microcephaly, epilepsy, and facial dysmorphism.

Tripartite Motif Protein 32 (*TRIM32*)

Mutations in the gene encoding tripartite motif protein 32 (*TRIM32*) cause two seemingly diverse diseases: limb-girdle muscular dystrophy type 2H (LGMD2H) or sarcotubular myopathy (STM) and Bardet–Biedl syndrome type 11(BBS11). TRIM32 is involved in protein ubiquitination, acting as a widely expressed ubiquitin ligase that is localized to the Z-line in skeletal muscle. TRIM32 binds and ubiquitinates dysbindin, a protein implicated in the genetic aetiology of SCZ, augmenting its degradation. Small-interfering RNA-mediated knock down of *TRIM32* in myoblasts resulted in elevated levels of dysbindin. The LGMD2H/STM-associated *TRIM32* mutations, D487N, and R394H, impair ubiquitin ligase activity toward dysbindin and were mislocalized in heterologous cells. These mutants were able to self-associate and also coimmunoprecipitated with wild-type TRIM32 in transfected cells. D487N mutant could bind to both dysbindin and its E2 enzyme but was defective in monoubiquitination. The BBS11 mutant P130S did not show any biochemical differences compared with the wild-type protein. TRIM32 is a regulator of dysbindin and LGMD2H/STM mutations may impair substrate ubiquitination [105].

Tyrosine 3-monooxygenase/Tryptophan 5-monooxygenase Activation Protein, Eta Isoform (*YWHAH*)

Brain protein 14-3-3, eta isoform, or tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein 1 (YWHA1; 14-3-3-ETA) is a protein kinase-dependent

activator of tyrosine and tryptophan hydroxylases and an endogenous inhibitor of protein kinase C. The 14-3-3 protein exists in several distinct forms: for example, beta (YWHAB), gamma (YWHAG), epsilon (YWHAE), zeta (YWHAZ), theta (YWHAQ), sigma (SFN), and eta (YWHAH). *YWHAH* (22q12) is a positional and functional candidate gene for both SCZ and BP. This gene has been previously shown to be associated with both disorders, and the chromosome location (22q12.3) has been repeatedly implicated in linkage studies for these disorders. It codes for the eta subtype of the 14-3-3 protein family, is expressed mainly in brain, and is involved in HPA axis regulation. Five tag SNPs and the $(GCCTGCA)_n$ polymorphic locus present in this gene have been genotyped and the rs2246704 SNP was associated with BP and psychotic BP. The polymorphic repeat and two other SNPs were also modestly associated with psychotic BP [106].

Vesicular Monoamine Transporters (*VMAT1/SLC18A1*)

Vesicular monoamine transporters (VMAT1 and VMAT2) mediate accumulation of monoamines such as serotonin, dopamine, adrenaline, and noradrenaline from the cytoplasm into storage organelles in monoaminergic neurons. VMAT1 is preferentially expressed in neuroendocrine cells and VMAT2 is primarily expressed in the CNS. The *VMAT1* gene (*SLC18A1*) is a locus with strong evidence of linkage with SCZ and, thus, the polymorphic forms of the *VMAT1* gene may confer susceptibility to SCZ [107]. The vesicular monoamine transporter 1 gene (*VMAT1/SLC18A1*) maps to the shared BD/SCZ susceptibility locus on chromosome 8p21. Variations in the *VMAT1* gene might affect transporter function and/or expression, and might be involved in the etiology of SCZ. Genotypes of 62 patients with SCZ and 188 control subjects of European descent were obtained for 4 missense SNPs (Thr4Pro, Thr98Ser, Thr136Ile, Val392Leu) and 2 noncoding SNPs (rs988713, rs2279709) [108,109]. The previously reported association of Pro4Thr of the *VMAT1* gene with SCZ could not be replicated; however, evidence was obtained for a possible role of the Thr98Ser in giving susceptibility to SCZ in women [110].

X-ray Repair Complementing Defective Repair in Chinese Hamster Cells 1 (*XRCC1*)

Human cells fused with Chinese hamster ovary (CHO) mutant lines, defective at different genes for excision repair of DNA following ultraviolet (UV) irradiation or defective in repair following X-irradiation, produce hybrids that retain the human gene that complements the defect in the CHO line when selected under conditions that require repair. The 1893-bp open reading frame of this gene encodes a protein of 631 amino acids, compared with the 633-amino acid polypeptide of human XRCC1, which shares 86% sequence identity with mouse proteins. Association between genetic polymorphism of *XRCC1* Arg194Trp and risk of SCZ has been reported [111].

Zinc Finger Protein 804A (*ZNF804A*)

Two recent genome-wide association studies reported association between SCZ and the *ZNF804A* gene on chromosome 2q32.1 (rs1344706, rs7597593, rs1344706) [112,113].

Pharmacogenomics of Neuroleptics

Historically, the vast majority of pharmacogenetic studies of CNS disorders have been addressed to evaluate the impact of cytochrome P450 enzymes on drug metabolism. 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 [114]. 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 [115–117].

Pharmacogenomics relates to the application of genomic technologies, such as genotyping, gene sequencing, gene expression, genetic epidemiology, transcriptomics, proteomics, metabolomics, and bioinformatics, to drugs in clinical development and on the market, applying the large-scale systematic approaches of genomics to speed up the discovery of drug response markers, whether they act at the level of drug target, drug metabolism, or disease pathways [4,10–12,118]. The final aim of pharmacogenomics is therapeutics optimization and personalized pharmacotherapy [3,4,6].

The pharmacogenomic outcome depends upon many different determinant factors including (1) genomic profile, (2) disease phenotype, (3) concomitant pathology, (4) genotype–phenotype correlations, (5) nutritional conditions, (6) age and gender, (7) pharmacological profile of drugs, (8) drug–drug interactions, (9) gene expression profile, (10) transcriptomic cascade, (11) proteomic profile, and (12) metabolomic networking. The dissection and further integration of all these factors is of paramount importance for the assessment of the pharmacogenomic outcome in terms of safety and efficacy [4].

Cytochrome P450-Related Pharmacogenetics

Drug metabolism includes phase I reactions (i.e., oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e., acetylation, glucuronidation, sulphation, methylation). The principal enzymes with polymorphic variants involved in phase I reactions are the following: CYP3A4/5/7, CYP2E1, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2, epoxide hydrolase, esterases, NQO1 (NADPH-quinone oxidoreductase), DPD (dihydropyrimidine dehydrogenase), ADH (alcohol dehydrogenase), and ALDH (aldehyde dehydrogenase). Major enzymes involved in phase II reactions include the following: UGTs

(uridine 5′-triphosphate glucuronosyl transferases), TPMT (thiopurine methyltransferase), COMT , HMT (histamine methyltransferase), STs (sulfotransferases), GST-A (glutathion S-transferase A), GST-P, GST-T, GST-M, NAT2 (N-acetyl transferase), NAT1, and others [3–5,11].

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

The microsomal, membrane-associated, P450 isoforms CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2E1, and CYP1A2 are responsible for the oxidative metabolism of over 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 3). CYP3A4 metabolizes more drug molecules than all other isoforms together. Most of these polymorphisms exhibit geographic and ethnic differences [119–122]. 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), intermediate metabolizers (IMs), poor metabolizers (PMs), and ultrarapid metabolizers (UMs). Approximately 20–30% of CNS drugs are metabolized by CYP2D6 enzymes, which are deficient in 10–20% of Caucasians. Only 26% of Southern Europeans are pure EMs for the trigenic cluster integrated by CYP2D6+CYP2C19+CYP2C9 variants, indicating that by trial-and-error only one-quarter of the population might be good responders to the conventional drugs of current prescription worldwide [3,4,6,123].

Most drugs act as substrates, inhibitors, or inducers of CYP enzymes. 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 [114,124,125]. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4 (Table 3); 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 [3,4]. About 80% of patients with resistant depression, 60% of patients nonresponsive 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 [4].

The impaired metabolic capacity of the *CYP2D6*-PM genotype results in higher steady-state plasma concentrations at a given dose, thus increasing the risk of toxic effects from medication. Extrapyramidal syndrome or TD (EPS/TD) is significantly more frequent among PM patients than among the matched IM and EM control subjects. [126].

Risperidone is converted to 9-hydroxyrisperidone by CYP2D6. The *CYP2D6*10* polymorphism, which is a prevalent mutant allele among East Asians, and the presence of comedication, exert significant influences on the pharmacokinetics of risperidone [127]. The plasma levels of risperidone and 9-OH-risperidone are significantly different among *CYP2D6* genotype groups. *CYP3A5* nonexpressors exhibit higher plasma concentrations of both risperidone and 9-OH-risperidone than its expressors [128].

Drug- and Disease-Related Pharmacogenomics

Targets that show promise for pharmacologic focus in SCZ include the dopamine receptors in the prefrontal cortex, the serotonin receptors in the prefrontal cortex, and anterior cingulate cortex, the glutamatergic excitatory synapse, the acetylcholine nicotinic receptors in the hippocampus, the acetylcholine muscarinic receptors, and the brain GABA system [129,130]. In addition to Cytochrome P450 enzymes, many other gene products influence both efficacy and safety of psychotropic drugs [3,4,114,117,131–133].

Analysis of polymorphic variants in *5-HT2A* receptors (5-HT2AR-A-1438G) revealed that schizophrenic carriers of the G/G genotype receiving olanzapine showed a significant tendency toward improvement in the PANSS positive syndrome score in comparison with patients who did not have a G gene (AA and AG) [134].

Aripiprazole acts as a partial agonist at dopamine D2 (DRD2) and D3 (DRD3) and serotonin 1A (HTR1A) receptors and as an antagonist at serotonin 2A receptors (HTR2A) [135]. Since aripiprazole acts as an antagonist at HTR2A, genetic variants of *HTR2A* may be important in explaining variability in response to aripiprazole. The GG/CC genotype group of *HTR2A* A-1438G/T102C polymorphisms predicts poor aripiprazole response specifically for negative symptoms. In addition, the clinical factors, including dosage of aripiprazole, age, duration of illness, and diagnostic subtype, were found to influence Positive and Negative Syndrome Scale (PANSS) performance after aripiprazole treatment [136]. Aripiprazole was associated with increased *BDNF* promoter activity. Treatment with aripiprazole at 10 μM increased the levels of BDNF by 85%, compared with control levels, whereas haloperidol had no effect. Cells treated with aripirazole effectively increased the levels of GSK-3beta phosphorylation and Bcl-2 at doses of 5 and 10 μM (30 and 58 and 31 and 80%, respectively); however, haloperidol had no effects on p-GSK-3 beta and Bcl-2 expression [137].

The prototypical atypical antipsychotic agent, clozapine (CLZ), is more efficacious for refractory SCZ than the "typical" antipsychotics. Since 2002, at least 22 association studies have shown that the *DTNBP1* can be associated with the risk for SCZ, and it has also been hypothesized that *DTNBP1* might influence the response to antipsychotic treatments. Patients with diplotype ACCCTC/GTTGCC, genotypes T/T+T/C, or allele T of marker rs742105 (P1333) have better response to CLZ, and

Table 3. Neuroleptics metabolized via enzymes of the CYP gene family and other gene-related enzymes [4,15,161,162]

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Other genes
Aripiprazole	Atypical antipsychotic	*CYP2D6, CYP3A4*			*ADRA1A, DRD2, DRD3, HTR1A, HTR2A, HTR2C*
Benperidol	Neuroleptic antipsychotic				*DRD2*
Bromperidol	Antipsychotic, neuroleptic butyrophenone				*ABCB1, HTR2, DRD2*
Chlorpromazine	Phenothiazine antipsychotic	*CYP2D6*	*CYP1A2, CYP3A4*	*CYP2D6, CYP2E1*	*ABCB1, ACACA, ADRA1, BDNF, DRD2, DRD3, HTR2C, KCNE2, LEP, NPY, SCN5A*
Clozapine	Atypical antipsychotic	*CYP1A2*	*CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP3A4*	*CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4*	*ADRA1, ADRB3, APOA5, APOD, APOC3, DRD2, DRD3, DRD4, GNB3, GNAS1, HLAA1, HRH1, HRH2, HTR1A, HTR2A, HTR2C, HTR6, RGS2, SLC6A2, SLC6A4, TNF-A*
Droperidol	Atypical antipsychotic				*ADRA1,DRD2,KCNE2, KCNH, SCN5A*
Fluphenazine	Typical antipsychotic phenothiazine	*CYP2D6*		*CYP1A2, CYP2C9, CYP2D6, CYP2E1*	*DRD1, DRD2*
Flupenthixol	Typical antipsychotic				*DRD1*
Haloperidol	Typical antipsychotic	*CYP2D6, CYP3A4*	*CYP1A2*	*CYP2D6, CYP3A4*	*ABCB1, ADR1A, DRD1, DRD2, DRD4, DTNBP1, GRIN2B, HTR2A, IL1RN, KCNE2, SCN5A*
Loxapine	Typical antipsychotic				*ADR1A, DRD1, DRD2, HTR2A,,KCNE2, SCN5A*
Mesoridazine	Typical antipsychotic				*ADR1A, DRD2, KCNE2, SCN5A*
Molindone	Typical antipsychotic				*ADRA1, DRD2*
Olanzapine	Atypical antipsychotic	*CYP1A2*	*CYP1A2, CYP2D6*	*CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP3A4*	*ABCB1, ADRA1, ADRB3, APOA5, APOC3, COMT, DRD2, DRD3, GNB3, GRM3, HRH1, HRH2, HTR2A, HTR2C, HTR6, LEP, LEPR, LPL, RGS2, SLC6A2, TNF-A*
Paliperidone	Atypical antipsychotic				*ADRA1A, ADRA1B, ADRA1D, DRD2, HRH1, HTR2A,*
Perphenazine	Typical antipsychotic phenothiazine	*CYP2D6*	*CYP1A2, CYP2C8/9, CYP2C19, CYP3A4*	*CYP1A2, CYP2D6*	*ADRA1A, DRD1, DRD2, DRD3*
Periciazine	Typical, antipsychotic phenothiazine, piperidine	*CYP2D6, CYP3A4*			*DRD1, DRD2*
Pimozide	Typical antipsychotic	*CYP1A2, CYP3A4*		*CYP2C19, CYP2D6, CYP2E1, CYP3A4*	*ADRA1A, DRD2, KCNE1, KCNE2, KCNQ1, KCNH2, SCN5A*
Pipotiazine	Typical antipsychotic	*CYP2D6, CYP3A4*			*DR*
Prochlorperazine	Typical antipsychotic				*ADRA1A, ABCB1, DRD2*
Quetiapine	Atypical antipsychotic	*CYP3A4*	*CYP2D6*		*ADRA1A, DRD1, DRD2, HRH1, HTR1A, HTR2A, HTR2B, KCNE1, KCNE2, KCNH2, KCNQ1, SCN5A*
Risperidone	Atypical antipsychotic	*CYP2D6*	*CYP2A4*	*CYP2D6, CYP3A4*	*ABCB1, ADRA1A, ADRA1B, DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C, KCNE2, RGS2, SLC6A2, SCN5A*
Sulpiride	Atypical antipsychotic				*DRD2*
Thioridazine	Typical antipsychotic phenothiazine	*CYP2D6*	*CYP2C19*	*CYP1A2, CYP2C8/9, CYP2D6, CYP2E1*	*ADRA1A, DRD2, KCNE2, SCN5A*

Table 3. Continued

Drugs	Pharmacological category	Major substrate	Minor substrate	Inhibitors	Other genes
Thiothixene	Typical antipsychotic	*CYP1A2*		*CYP2D6*	*ADRA1A, DRD2, KCNE2, KCNQ1, KCNH6, SCN5A,*
Trifluoperazine	Typical antipsychotic phenothiazine	*CYP1A2*			*ADRA1A, DRD2*
Ziprasidone	Atypical antipsychotic		*CYP1A2, CYP3A4*	*CYP2D6, CYP3A4*	*ADRA1, AOX1, DRD2, DRD3, HTR2C, HTR1A, HTR2A, KCNE2, KCNH2, RGS4, SCN5A*
Zonisamide	Anticonvulsant	*CYP3A4*	*CYP2C19*		
Zuclopenthixol	Typical antipsychotic	*CYP2D6*			*ADRA1, DRD1, DRD2, KCNE2, SCN5A*

ABCB1, ATP-binding cassette, sub-family B (MDR/TAP), member 1; *ACACA*, Acetyl-Coenzyme A carboxylase alpha; *ADRA1*, Adrenergic, alpha-1 receptor; *ADRA1A*, Adrenergic, alpha-1A-, receptor; *ADRA1B*, Adrenergic, alpha-1B-, receptor; *ADRB3*, Adrenergic, beta-3-, receptor; *ADRA1D*, Adrenergic, alpha-1D-, receptor; *AOX1*, Aldehyde oxidase 1; *APOA5*, Apolipoprotein A-V; *APOC3*, Apolipoprotein C-III; *APOD*, Apolipoprotein D; *BDNF*, Brain-derived neurotrophic factor; *COMT*, Catechol-O-methyltransferase; *CYP1A2*, Cytochrome P450, family 1, subfamily A, polypeptide 2; *CYP2A6*, Cytochrome P450, family 2, subfamily A, polypeptide 6; *CYP2C19*, Cytochrome P450, family 2, subfamily C, polypeptide 19; *CYP2C8*, Cytochrome P450, family 2, subfamily C, polypeptide 8; *CYP2C9*, Cytochrome P450, family 2, subfamily C, polypeptide 9; *CYP2D6*, Cytochrome P450, family 2, subfamily D, polypeptide 6; *CYP2E1*, Cytochrome P450, family 2, subfamily E, polypeptide 1; *CYP3A4*, Cytochrome P450, family 3, subfamily A, polypeptide 4; *DR*, Dopamine receptor; *DRD1*, Dopamine receptor D1; *DRD2*, Dopamine receptor D2; *DRD3*, Dopamine receptor D3; *DRD4*, Dopamine receptor D4; *DTNBP1*, Dystrobrevin binding protein 1; *GNAS*, GNAS complex locus; *GNB3*, Guanine nucleotide binding protein (G protein), beta polypeptide 3; *GRIN2B*, Glutamate receptor, ionotropic, N-methyl D-aspartate 2B; *GRM3*, Glutamate receptor, metabotropic 3; *HLA*, Major histocompatibility complex; *HRH1*, Histamine receptor H1; *HRH2*, Histamine receptor H2; *HTR1A*, 5-Hydroxytryptamine (serotonin) receptor 1A; *HTR2A*, 5-Hydroxytryptamine (serotonin) receptor 2A; *HTR2B*, 5-Hydroxytryptamine (serotonin) receptor 2B; *HTR2C*, 5-Hydroxytryptamine (serotonin) receptor 2C; *HTR6*, 5-Hydroxytryptamine (serotonin) receptor 6; *IL1RN*, Interleukin 1 receptor antagonist; *KCNE1*, Potassium voltage-gated channel, Isk-related family, member 1; *KCNE2*, Potassium voltage-gated channel, Isk-related family, member 2; *KCNH*, Potassium voltage-gated channel, subfamily H (eag-related), member 1–8; *KCNH2*, Potassium voltage-gated channel, subfamily H (eag-related), member 2; *KCNH6*, Potassium voltage-gated channel, subfamily H (eag-related), member 6; *KCNQ1*, Potassium voltage-gated channel, KQT-like subfamily, member 1; *LEP*, Leptin; *LEPR*, Leptin receptor; *LPL*, Lipoprotein lipase; *NPY*, Neuropeptide Y; *RGS2*, Regulator of G-protein signaling 2, 24kDa; *RGS4*, Regulator of G-protein signaling 4; *SCN5A*, Sodium channel, voltage-gated, type V, alpha subunit; *SLC6A2*, Solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2; *SLC6A4*, Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4; *TNF*, Tumor necrosis factor (TNF superfamily, member 2).

patients with diplotype ACCCTC/GCCGCC, genotype A/G, or allele A of marker rs909706 (P1583) have better response to haloperidol in European-Americans, African-Americans, and/or the combined sample. European-American patients with diplotype ACCCTC/GCCGCC have worse response to CLZ on positive symptoms. These results might indicate that *DTNBP1* gene modulates the effects of both the atypical antipsychotic CLZ and the typical antipsychotic haloperidol and that SCZ patients with different DTNBP1 diplotypes, haplotypes, genotypes, or alleles might have different responses to these antipsychotics [138].

Disruption of the RELN and GABAergic signaling systems have been observed in psychiatric disorders including autism, SCZ, BD, and major depression. Chronic administration of psychotropic medications (CLZ, fluoxetine, haloperidol, lithium, olanzapine, and valproic acid) used in the treatment of psychiatric disorders alters levels of RELN, its receptor Vldlr, downstream molecules Gsk3 beta, Dab-1, and Gad65/67 in the prefrontal cortex. mRNAs for *RELN, Vldlr, Dab-1, Gsk3 beta,* and *Gad65* were each significantly altered by at least one of the drugs tested, and in the case of *RELN, Dab-1,* and *Gsk3* beta, by multiple drugs, suggesting that the RELN signaling and GABAergic systems are affected by commonly used psychotropic medications [139]. Valproic acid facilitates chromatin remodeling when it is associated with CLZ or sulpiride but not with haloperidol or olanzapine. This remodeling might contribute to *RELN* - and *GAD67*-promoter demethylation and might reverse the GABAergic-gene-expression downregulation associated with SCZ morbidity [140].

Flavin-containing monooxygenase 3 (*FMO3*) genotype data for European-, Latin-, African-, and Asian-American SCZ patients treated with olanzapine were compared to age-, gender-, and race/ethnicity-matched controls. For European Americans, significant differences in individual cases versus controls were observed between *FMO3* 158 and 257 alleles and genotype frequencies and SCZ delusions, hallucinations, and weight gain/increased appetite. For Latin Americans, a significant difference in individual cases versus controls was observed for *FMO3* 158 and 257 for SCZ delusions as well as hallucinations and delusions. Sleepiness and weight gain were associated with allele 308. In African-Americans, a comparison of allele frequency and diagnosis showed a significant dependence on allele 158 in individual cases versus controls [141].

Haplotype analysis showed highly significant association of 7 *COMT* marker haplotypes with SCZ, and allelic associations of two SNPs (rs4633, rs4680) with drug response were also found. A

significant association of markers located between intron 1 and intron 2 (rs737865, rs6269), and in exon 4 (rs4818, rs4680) with drug response was detected, indicating that the interacting effects within the *COMT* gene polymorphisms may influence the disease status and response to neuroleptics in SCZ patients [142].

Olanzapine is a second-generation antipychotic that may cause weight gain and metabolic syndrome in some cases. The peroxisome proliferator-activated receptor (*PPAR*)-*gamma* is an important gene in the progress of type II diabetes and metabolic syndrome. Significant differences were found between pretreatment and posttreatment body mass index (BMI) and weight change in Pro12Ala polymorphism of *PPARG2* in Turkish patients [143].

Twenty-one loci of diverse candidate genes encoding dopamine, serotonin (5-HT), histamine, and adrenergic receptors, tumor necrosis factor-alpha, ghrelin, adiponectin, and *PPARG2*, were analyzed as candidate genes for olanzapine-related body weight gain. Olanzapine-induced weight gain correlated negatively with baseline BMI and positively with clinical global improvement and the length of olanzapine treatment, but it did not correlate with the daily dose of olanzapine, concomitant antipsychotics, sex, age, or smoking. Four genetic variants, the 102T allele of *HTR2A*, the 825T allele of *GNB3*, the 23Cys allele of *HTR2C*, and the 64Arg/Arg genotype of *ADRB3*, were significantly associated with olanzapine-induced weight gain. Stepwise regression analysis revealed that the baseline BMI predicted 12.5% of the weight gain, and the 2 latter genetic factors added 6.8%. The patients with double and triple genetic risk factors showed 5.1 and 8.8% BMI increases, respectively, during olanzapine treatment, whereas the patients with a single or no risk factor showed approximately a 1% BMI increase [144].

Genetic predisposition to CLZ -induced weight gain has also been suggested. Ten genetic polymorphisms across 9 candidate genes, including the serotonin 2C, 2A, and 1A receptor genes (*HTR2C/2A/1A*); the histamine H_1 and H_2 receptor genes (*H1R/H2R*); the cytochrome P450 1A2 gene (*CYPIA2*); the beta3 and alpha,alpha-adrenergic receptor genes (*ADRB3/ADRAIA*); and tumor necrosis factor alpha (*TNF-alpha*) have been studied. Trends were observed for *ADRB3, ADRA1A, TNF-alpha*, and *HTR2C* [145].

5-HT2C and 5-HT2A antagonisms are hypothesized to play a role in the metabolic adverse effects induced by olanzapine and CLZ. Associations between polymorphisms in *5-HT2C* and *5-HT2A* receptor coding genes, *HTR2C*, and *HTR2A*, with antipsychotic-induced weight gain have been reported. Olanzapine-treated patients with *HTR2C* haplotype C (-759C, -697C, and 23Ser) had higher BMI and C peptide levels compared with patients with haplotype B (-759T, -697C, and 23Cys). The frequency of patients homozygous for the *HTR2C* haplotype A (-759C, -697G, and 23Cys) was significantly higher among CLZ -treated patients with obesity (BMI >30 kg/m) compared with nonobese patients. Patients carrying the *HTR2A* haplotype 2 (-1438A, 102T, and 452His) had significantly higher C peptide levels compared with haplotype 3 (-1438A, 102T, and 452Tyr) carriers in the olanzapine group and in the overall study population [146]. An association between *HTR2C* polymorphisms and the occurrence of the metabolic syndrome in patients using antipsychotics has also been reported. Primary determinants were polymorphisms in the promoter region of the *HTR2C* gene (HTR2C:c.1–142948$[GT]_n$, rs3813929 [–759 C/T], and rs518147 [–697 G/C]) and an intragenic polymorphism (rs1414334:C>G). The variants of HTR2C:c.1–142948$(GT)_n$ and rs1414334 were not significantly associated with the metabolic syndrome in the replication sample but did show significance in the pooled analysis. The variant rs1414334 C allele was specifically associated with the metabolic syndrome in patients using CLZ or risperidone. The increased risk for the metabolic syndrome is particularly strong in carriers of the rs1414334 C allele using CLZ or risperidone [147].

The *LEPR* Q223R polymorphism (rs1137101) and the *LEP* promoter 2548G/A polymorphism (rs7799039) were postulated as candidate genes to be associated with obesity in patients using atypical antipsychotic drugs. In females, the *LEPR* 223QR and *LEPR* 223RR genotypes were associated with a lower risk of obesity. In males, this association was not found. In females, the average body weight was 13.6 kg more in the *LEPR* 223QQ group compared with the *LEPR* 223RR group. No significant association was found between the *LEP* promoter 2548G/A polymorphism and obesity [148].

Sequence variations in the glutamate transporter gene *SLC1A1* (A/C/G haplotype at rs2228622-rs3780413-rs3780412) have been associated with susceptibility to atypical antipsychotic-induced obsessive-compulsive symptoms [149].

Several polymorphisms previously associated with the efficacy of the novel antipsychotic iloperidone could be used together to predict clinical response and provide practical information for individualized treatment. A recent study using 6 genetic markers of iloperidone response as measured by change in the Positive and Negative Syndrome Scale-Total (PANSS-T) score demonstrated that the 6-marker genotype combinations defined 4 groups of patients with distinct probabilities of response. Over 75% of iloperidone-treated patients in the group with the optimal genotype combinations showed a 20% or greater improvement, compared with 37% for patients with other genotypes [150].

Genome-wide expression profiling microarrays to study effects of typical antipsychotics and atypical antipsychotics in the postmortem liver of SCZ patients revealed that typical antipsychotics affected genes associated with nuclear protein, stress responses, and phosphorylation, whereas atypical antipsychotics affected genes associated with Golgi/endoplasmic reticulum and cytoplasm transport. Comparison between typical antipsychotics and atypical antipsychotics further identified genes associated with lipid metabolism and mitochondrial function. Analyses on individual antipsychotics identified a set of genes (151 transcripts) that are differentially regulated by 4 antipsychotics, particularly by phenothiazines, in the liver of SCZ patients [151].

Growing genetic evidence has implicated a role for *NRG-1* in SCZ pathogenesis as well as alterations in SNAP receptor (SNARE) proteins at both gene and protein levels in postmortem investigations. CLZ has been shown to increase both NRG-1 levels and synaptic markers in rodents. CLZ has the ability to upregulate *NRG-1* (+3.58-fold change) and *VAMP-1* (+1.92) while SNAP-25 remaines unchanged [152].

Drug-Related Proteomics

An increasing number of experiments have found anomalies in mitochondria in the brains of psychotics, which suggests that mitochondrial dysfunction or abnormal cerebral energy metabolism might play an important role in the pathophysiology of SCZ. Differential mitochondrial protein expressions were assessed using two-dimensional (2D) gel electrophoresis for three groups with chlorpromazine (CPZ), CLZ, quetiapine (QTP), and a control group. A total of 14 proteins, of which 6 belong to the respiratory electron transport chain (ETC) of oxidative phosphorylation (OXPHOS), showed significant changes in quantity including NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 10 (Ndufa10), NADH dehydrogenase (ubiquinone) flavoprotein 2 (Ndufv2), NADH dehydrogenase (ubiquinone) Fe-S protein 3 (Ndufs3), F1-ATPase beta subunit (Atp5b), ATPase, H^+ transporting, lysosomal, beta 56/58 kDa, isoform 2 (Atp6v1b2) and ATPase, H^+ transporting, V1 subunit A, isoform 1 (Atp6v1a1). These data show proteomic changes induced by neuroleptics in rodents [153]. Label-free liquid chromatography tandem mass spectrometry (LC-MSE) was used to identify differentially expressed proteins in rat frontal cortex following subchronic treatment with haloperidol or olanzapine. LC-MSE profiling identified 531 and 741 annotated proteins in fractions I (cytoplasmic-) and II (membrane enriched-) in the 2 drug treatments. Fifty-nine of these proteins were altered significantly by haloperidol treatment, 74 by olanzapine, and 21 were common to both treatments. Pathway analysis revealed that both drugs altered similar classes of proteins associated with cellular assembly/organization, nervous system development/function (particularly presynaptic function), and neurological disorders, which indicate a common mechanism of action. The top affected canonical signaling pathways differed between the two treatments. The haloperidol data set showed a stronger association with Huntington's disease signaling, while olanzapine treatment showed stronger effects on glycolysis/gluconeogenesis [154].

Selective serotonin reuptake inhibitor (SSRI) and antipsychotic coadministration is a widely used strategy to treat both psychotic depression and depressive symptoms in SCZ. Coadministration of SSRIs and antipsychotics may result in molecular changes different from their individual effects. Studies have been carried out on the acute effects of two SSRIs, citalopram, and escitalopram, alone or in combination with haloperidol, on the expression of *Homer1a* together with its splice variant *ania-3*, and *p11*, 2 genes linked respectively to dopaminergic and serotonergic neurotransmission and involved in synaptic plasticity. *Homer1a* and *ania-3* were induced in the striatum by haloperidol, alone and in combination with SSRIs, but not by SSRIs alone. Haloperidol+citalopram co-administration induced a stronger *Homer1a* expression than haloperidol alone in the ventrolateral caudate-putamen. *Homer1a* was significantly downregulated in the parietal cortex by all treatments. These results show that haloperidol + citalopram combination exerts synergistic effects on *Homer* expression, suggesting that citalopram may influence the impact of haloperidol on dopaminergic neurotransmission. *Homer1a* and *ania-3* are strongly induced in striatum by haloperidol, while they are not influenced by citalopram or escitalopram in this region. In the cortex the two transcripts are modulated by both haloperidol and SSRIs, suggesting a possible role of both dopamine and serotonin in their cortical regulation [155].

Conclusions

SCZ is a multifactorial, polygenic/complex disorder in which more than 100 different genes distributed across the human genome might be involved. Polymorphic variants in many SCZ-related candidate genes may give rise to proteomic dysfunctions associated with SCZ pathogenesis (e.g., neurodevelopmental defects, neurotransmitter dysregulation). As an example, altered expression of DISC1 and/or its molecular partners (nuclear distribution element-like [NUDEL], fasciculation and elongation protein zeta-i [FEZ1], and lissencephaly 1 [LIS1]) may underlie its pathogenic role in SCZ and partially explain its genetic association [156,157]. Epigenetic factors may also play a major role in SCZ pathogenesis and response to therapeutic intervention. Both CYP-related genes and genes associated with SCZ and/or with drug mechanism of action are responsible for efficacy and safety issues in the pharmacotherapy of SCZ. An effective, personalized treatment of SCZ patients would require a pharmacogenomic approach in order to optimize the use of neuroleptics and other psychotropic drugs. Excluding exogenous factors, the therapeutic response to these compounds mainly depends upon genetic and epigenetic factors, including CYP variants and SCZ-related genomic profiles. From a practical point of view, pharmacoeconomic studies have to validate the utility of genetic testing in CNS disorders to optimize therapeutics with conventional drugs [158]. In terms of drug development, novel pharmacogenomic approaches have to be incorporated into current strategies in drug primary screening, preclinical studies (transfected cells, transgenic animals, disease-specific biochips), and clinical trials.

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Conflict of Interest

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

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