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REVIEW ARTICLE

Genetic tests of biologic systems in affective disorders

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To liberate candidate gene analyses from criticisms of inexhaustiveness of examination of specific candidate genes, or incompleteness in the choice of candidate genes to study for specific neurobiological pathways, study of sizeable sets of genes pertinent to each putative pathophysiological pathway is required. For many years, genes have been tested in a 'one by one' manner for association with major affective disorders, primarily bipolar illness. However, it is conceivable that not individual genes but abnormalities in several genes within a system or in several neuronal, neural, or hormonal systems are implicated in the functional hypotheses for etiology of affective disorders. Compilation of candidate genes for entire pathways is a challenge, but can reasonably be carried out for the major affective disorders as discussed here. We present here five groupings of genes implicated by neuropharmacological and other evidence, which suggest 252 candidate genes worth examining. Inexhaustiveness of gene interrogation would apply to many studies in which only one polymorphism per gene is analyzed. In contrast to whole-genome association studies, a study of a limited number of candidate genes can readily exploit information on genomic sequence variations obtained from databases and/or resequencing, and has an advantage of not having the complication of an extremely stringent statistical criterion for association.
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Identifying susceptibility genes has long been challenging in studies of major affective disorders, as well as in other common complex diseases such as schizophrenia, asthma, diabetes, and cardiovascular diseases. Association study, which typically examines differences in allele frequency of a genetic marker between cases (affecteds) and controls, remains a major approach of disease gene mapping, and has been employed to examine possible roles of candidate genes in the etiology of a disease of interest.

Genomewide linkage analysis, in contrast, does not limit itself to a particular genomic region, apparently avoiding the risk of overlooking any genes with poor or even no information on biological functions. For more than two decades, linkage mapping has proven to be remarkably effective to guide researchers to numerous disease genes, each predisposing to a Mendelian trait. Also, development of computer algorithms for model-free linkage analysis has considerably facilitated appropriate genetic dissections of complex phenotypes with unknown mode of inheritance. In studies of major psychiatric illnesses, evidence of linkage has led to the detection of associations of specific genes with illness: dysbindin 1 (DTNBP1)[1] on chromosome 6p and neuregulin 1 (NRG1)[2] on 8p for schizophrenia, and G72/G30 on 13q for both schizophrenia[3] and bipolar disorder.[4] These genes have been demonstrated to be associated with schizophrenia and/or bipolar disorder in multiple independent data sets.[5–8] However, model-free linkage analysis is unlikely to detect genes with very weak effects (modest increase in probability of illness, given the associated allele). This has led to a resurgence of association analysis because of its much higher statistical power, particularly in the studies of complex diseases, where multiple genes are considered to exert weak effect along with environmental factors.[9]

Candidate gene association studies have historically been plagued by nonreplication. A recent meta-analysis of genes that had a large number of association studies emphasized possible contribution of false-negative underpowered studies to inconsistent results, and suggested consistent weak effects of the genes for serotonin receptor 2A (HTR2A) and dopamine receptor D3 (DRD3) on susceptibility to schizophrenia.[10] Thus, inconsistencies among reports may be consequences of what previous studies have failed to address. Until recently, it has only been feasible to interrogate a few genes in particular systems, and these interrogations have often been

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limited to very few polymorphisms in a limited number of subjects, because of limitations in the costs of genotyping, and in the knowledge of the human genome. Advances in genomics and bioinformatics, in high-throughput genotyping, in statistical analysis, and in the availability of large samples of patients with well-defined phenotypes, as well as comparable numbers of matched controls, can be expected to enhance the likelihood of detection of valid associations.

What remains as the most serious concern about the paradigm of candidate gene association study is its 'incompleteness' resulting from *ad hoc* selection of candidate genes. *A priori* hypotheses have to be made on the primary cause of the disease being studied, when starting a candidate gene study. For many years, genes have usually been tested in a 'one by one' manner for association with major affective disorders, primarily bipolar illness. However, it is also conceivable that not individual genes but abnormalities in several genes within a system or in several neuronal, neural, or hormonal systems are implicated in the functional hypotheses for etiology of affective disorders. Analysis of entire systems examining a same sample set has only rarely been undertaken,[11,12] and examples of definitive success have yet to be seen. At this time, analysis of a well-chosen and comprehensive set of candidate genes, with the support of informatics analysis of the genomic structure of each gene, may yield successful detection of specific genes and pathways associated with illness.

In the following sections, we first discuss the advantage of a hypothesis-based systematic association study on a limited number of candidate genes in contrast to the whole-genome association study, and subsequently demonstrate that, in the case of affective disorders, compilation of candidate genes pertinent to each major neurobiological system suggested for susceptibility can be reasonably carried out. The idea of testing systems can be generalized to studies of other common complex diseases.

Systematic candidate gene study *vs* whole-genome association study

Association studies are intended to capture linkage disequilibrium (LD) between genotyped markers and a disease causal variant, including when the marker being genotyped happens to be exactly the causal variant. Recent studies have revealed that chromosomal segments, spanning a few to hundreds of kilobases, can often be represented by only a few haplotypes because of strong underlying LD that associates specific alleles at each polymorphic site in the segment. Such a segment is called a 'haplotype block' and the analysis of a block can be achieved by typing a small set of SNPs (haplotype tag SNPs or htSNPs) that are most informative for discriminating haplotypes.[13,14] The International HapMap project[15] (see Electronic-Database Information) has just completed genotyping of a million SNPs in four different populations with the aim of providing information on genomic variations including the extent of LD, haplotype blocks and htSNPs. This modeling of genomic variations especially favors the idea of whole-genome LD mapping, which aims to locate disease susceptibility variants using a set of limited number of markers across the entire genome.

However, it is open to question how informative the limited number of SNPs can be in terms of sequence variations of the genome. First, it is unclear to what degree the entire genome can be captured by block-like structures. Since haplotype blocks reflect underlying LD, whose extent varies considerably across the genome, short blocks may become evident only by highly dense genotyping. According to a simulation under a recombination hot-spot model by Wall and Pritchard,[16] even genotyping with a marker density obtained by resequencing would capture only up to 71% of the entire genome as blocks. Besides, gene conversion, which is not incorporated into this model, seems to have generated discrepancies between haplotype block fractions observed in actual data and predicted by simulations. Gene conversion can give rise to a 'hole' in an LD or a haplotype block, and a susceptibility variant in such a hole is likely to be overlooked. Secondly, even when a haplotype block is evident, it is unclear if markers from the databases capture sufficient haplotype diversity. For example, a haplotype with an estimated frequency of 45% may really be a group of three haplotypes each with a frequency of 15%. This loss of information can substantially reduce the power of detecting association depending on the frequency of a causal variant. Selecting the most informative markers not depending on the haplotype block model, as suggested in Carlson *et al*,[17] would considerably circumvent these problems. Resequencing of genomic regions of interest will also be necessary (see Electronic-Database Information for current examples). From the viewpoint of the number of SNPs to be genotyped, these approaches look feasible for a study of a limited number of candidate genes, but not for whole-genome LD mapping or for its gene-focused form.[9,18,19]

Since the prior probability of association for a biologic candidate gene can be expected to be considerably higher than that for a gene randomly picked up from the genome, candidate gene approach may benefit from increased statistical power by analysis controlling 'false discovery rate'.[20] Even in the conventional statistical tests (eg Bonferroni procedure) for multiple hypotheses, which control overall type I error rate, the study of limited number of candidates derived from a few hypotheses would not suffer from the complication of a very stringent statistical criterion for association, because the number of markers would be less than in a whole-genome LD mapping. Also, a method has recently been developed to detect a set of associated genes, which may statistically interact with each other.[21] Interpretation of results of this analysis can be more

straightforward when we study multiple genes with known biologic functions. Thus, whole-genome association study does not replace the candidate gene approach using a sufficient number of informative markers, particularly when we are anxious about missing associations.

Genetic testing of functional systems (pathways) in major affective disorders

Since the first monoamine hypothesis (Figure 1) of depression, based on biochemical pharmacology of antidepressants and reserpine, numerous hypotheses of dysregulation of functional systems in mood disorders have been suggested, but so far no consensus has been reached on any primary molecular mechanism underlying mood disorder susceptibility. Nonetheless, the choice of several systems (Table 1) over others for intensive genetic study can be supported by their relevance to clinical features as well as by accumulated neurobiological and neuropharmacological findings.

Phenotypic subclasses of the entire spectrum of affective disorders may have different associations with the systems in Table 1. However, we need not assume too much about a specific relationship between systems and subclasses. When samples from different types of affective disorders with abundant clinical records are available, it may be more reasonable to conduct genetic analyses on numerous phenotypic variables after completion of genotyping. Such an approach has successfully been employed in detecting association between the *PDE4D* gene and ischemic type stroke in the analysis of all the samples from broadly defined common forms of stroke.[22]

The first step of compiling candidate genes in a given functional hypothesis is to list genes involved in pathways which represent that hypothesis. GO and KEGG databases, for example (see Electronic-Database Information), help overview a set of genes involved in a particular intracellular pathway. To obtain information on genetic components specifically relevant to the phenotypes of interest, intensive literature survey or review is required. There have been a huge number of reports on specific proteins (sometimes specific subtypes) altered in post-mortem brains from bipolar disorder subjects or in brains from rodents treated with mood stabilizers. Also, animal models and systematic expression analyses by microarray or differential display assay provide information on molecules relevant to mood disorders not only at the protein level but also at the gene expression level.

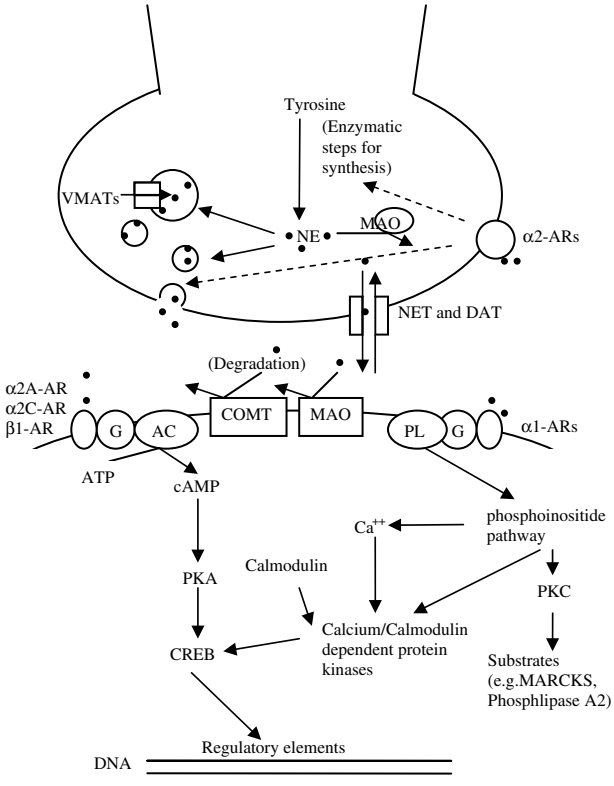

Figure 1 Evolution of 'monoamine hypothesis'. A major hypothesis for the biology of depression was developed in the 1960s, initially proposing that depletion of norepinephrine (NE), and later proposing depletion of serotonin (5-HT) and dopamine (DA), underlie the illness.[100] This 'monoamine hypothesis' was proposed because of the clinical observation that depression often occurs in subjects taking reserpine, an antihypertensive agent, which depletes monoamines from the synaptic vesicles. Also, consistent with the hypothesis was that tricyclic antidepressants and MAO inhibitors were found to increase synaptic monoamine concentrations. The hypothesis was later modified to include alterations of monoamine receptor properties so that it would encompass an explanation for the time (usually days to weeks) required for an antidepressant to take clinical effect despite its immediate action to elevate synaptic monoamine levels.[101,102] However, either the original or modified form of hypothesis has not been definitively demonstrated so far. Involvement of postsynaptic signaling is now of interest to researchers. A diagram for NE neurotransmission is shown as an example. The postsynaptic receptors for NE are coupled to guanine nucleotide binding proteins (G proteins), which transduce neurotransmitter stimulation to second messenger signaling systems such as cAMP and phosphoinositide pathways. Now that numerous components in the NE neurotransmission system have been identified, including metabolic enzymes, receptors, transporters, and postsynaptic signaling (eg one or more subtypes of G proteins, protein kinase A, protein kinase C, calcium/calmodulin-dependent protein kinases), emphasis is being placed on the broader view of dysregulation in the entire system,[103] taking interactions of each component into account. Components are presented at the gene level in Table 2. NE: norepinephrine; VMAT: vesicular monoamine transporters; MAO: monoamine oxidases, COMT: catechol-*O*-methyltransferase; αx-AR: αx-adrenerigc receptors; β1-AR: beta-1-adrenergic receptor; G: G proteins; AC: adenylate cyclases; PL: phospholipases; PKA: cAMP-dependent protein kinases; PKC: calcium-dependent protein kinases; CREB: cAMP-responsive element binding protein; NET: norepinephrine transporter; DAT: dopamine transporter.

Table 1 Major neurobiological/neuropharmacological systems suggested for roles in major affective disorder

Systems	*Subsystems or a group of genes to be analyzed*
1. Neurotransmission systems	Monoaminergic neurotransmission (adrenergic, serotonergic and dopaminergic) Cholinergic neurotransmission Amino-acid neurotransmission (GAGAergic and glutamatergic) Other neurotransmitter or neuromodulator systems (peptidergic, opioid and others)
2. A neuroendocrine system	HPA axis
3. Neurotrophic and growth factor systems	Neurotrophic/growth factors and shared signaling pathways
4. Circadian rhythm	Clock genes (eg CLOCK, ARNTL1, ARNTL2, CRY1, CRY2) Pathways for entrainment to light/darkness cycle and outputs of suprachiasmatic nucleus (eg ADCYAP1, TGFA, PROK2)
5. Genes implicated in pathophysiology of other diseases relevant to major affective disorders	Parkinson's disease genes (eg PARK2, SCNA, UCHL1) Schizophrenia-related genes (eg NRG1, DTPN1) and genes in the myelination system (eg MBP, MOG, NRG1)

Genes repeatedly reported to be associated with the phenotype of interest should be included. In addition, databases being developed (see GEO and WebQTL in Electronic-Database Information) allow for retrieving and analyzing gene expression data according to researchers' particular interest, and may contribute to more extensive compilation of candidate genes in near future.

There are problems in this approach, though. First, manual literature mining on which compilation of candidate genes mostly depends is a tedious procedure. Secondly, there is no completely objective criterion to determine genes representing each hypothesis. Microarray studies may provide valid quantitative data on difference in expression level of each gene between bipolar and healthy subjects or between disease model and wild-type animals. However, such data may represent secondary effects of illness or treatment, or species-specific effects. Although a genetic association strategy can resolve this possibility, it will be a very small fraction of differentially expressed genes that directly affect susceptibility to the illness.

Despite these challenges, we have carried out compilation of a list of candidate genes pertinent to major hypotheses of major affective disorders (Table 2).

Neurotransmission systems

The monoamine (adrenergic, dopaminergic, and serotonergic) neurotransmission systems, which were the first to be hypothesized as systems whose derangements cause mood disorders, are offered here as a detailed example of candidate gene selection in the neurotransmission systems (see also Figure 1). The genes for tyrosine hydroxylase (TH), which is a rate-limiting enzyme for dopamine and norepinephrine synthesis, and serotonin transporter (SLC6A4), which is a pump molecule for reuptake of synaptic serotonin into the presynaptic nerve terminal, have been among the most frequently studied candidates for affective disorders. Abnormalities of these genes can lead to decreased vesicular or synaptic monoamine levels as predicted by the original monoamine hypothesis. However, association has not been consistently replicated for any genes for synaptic components including TH and SLC6A4.[23] Genes for synaptic components of monoamine systems, nonetheless, still deserve genetic analysis, given the possible insufficiency of sample size and number of markers analyzed in the previous studies. In the presynaptic nerve terminal, these include genes for synthetic enzymes (eg TH, DBH, DDC), synaptic vesicle monoamine transporters (SLC18A1 and SLC18A2), and reuptake transporters (SLC6A2, SLC6A3, and SLC6A4), with many being shared between the three neurotransmitters (Table 2). Monoamines bind to pre- and postsynaptic receptors, of which numerous subtypes have been found so far. The list includes seven genes coding for adrenergic receptors, five for dopaminergic receptors, and 14 for serotonergic receptors, omitting those with limited roles in the brain such as beta-2-adrenergic receptor (ADRB2). Genes for catabolic enzymes bound to postsynaptic membrane (monoamine oxidases (MAOA and MAOB) and catechol-*O*-methyltransferase (COMT)) have also been included in the list.

Abnormality in postsynaptic signaling in bipolar disorder was first proposed in the phosphoinositide cycle because it is affected by lithium administration.[24,25] Myo-inositol monophosphatase is inhibited

Table 2 Candidate genes pertinent to each putative pathological system: 1. Neurotransmission; 2. A neuroendocrine system; 3. Neurotrophic/growth factor systems; (1–3) Intracellualr signaling largely shared by 1–3; 4. Circadian rhythm; 5. Genes implicated in the pathophysiology of other disease relevant to major affective disorders

Symbols	*Genes*	*Aliases*	*Subcategories*		*Chromosomal region*	*Genomic size (bp)*	*References*[a]
1. Neurotransmission system							
Monoaminergic neurotransmission							
ADRA1A	Alpha-1A-adrenergic receptor		Norepinephrine	Receptor	8p21.2	117 256	104
ADRA1B	Alpha-1B-adrenergic receptor		Norepinephrine	Receptor	5q33.3	55 762	
ADRA1D	Alpha-1D-adrenergic receptor		Norepinephrine	Receptor	20p13	27 844	104
ADRA2A	Alpha-2A-adrenergic receptor		Norepinephrine	Receptor	10q25.2	3650	105, 106
ADRA2B	Alpha-2B-adrenergic receptor		Norepinephrine	Receptor	2q11.2	3266	
ADRA2C	Alpha-2C-adrenergic receptor		Norepinephrine	Receptor	4p16	2819	106, 107
ADRB1	Beta-1-adrenergic receptor		Norepinephrine	Receptor	10q25.3	1714	108
QDPR	Quinoid dihydropteridine reductase		5-HT	Metabolic enzyme	4p15.32	25 691	
TPH1	Tryptophan hydroxylase 1		5-HT	Metabolic enzyme	11p15.1	19 772	109, 110
TPH2	Tryptophan hydroxylase 2		5-HT	Metabolic enzyme	12q15	93 595	111,112
HTR1A	5-Hydroxytryptamine (serotonin) receptor 1A		5-HT	Receptor	5q12.3	1269	113
HTR1B	5-Hydroxytryptamine (serotonin) receptor 1B		5-HT	Receptor	6q14.1	1173	114
HTR1D	5-Hydroxytryptamine (serotonin) receptor 1D		5-HT	Receptor	1p36.12	2835	115
HTR1E	5-Hydroxytryptamine (serotonin) receptor 1E		5-HT	Receptor	6q15	78 988	
HTR1F	5-Hydroxytryptamine (serotonin) receptor 1F		5-HT	Receptor	3q11.1	1101	
HTR2A	5-Hydroxytryptamine (serotonin) receptor 2A		5-HT	Receptor	13q14.2	62 661	113
HTR2B	5-Hydroxytryptamine (serotonin) receptor 2B		5-HT	Receptor	2q37.1	15 587	116
HTR2C	5-Hydroxytryptamine (serotonin) receptor 2C		5-HT	Receptor	Xq23	326 074	117
HTR3A	5-Hydroxytryptamine (serotonin) receptor 3A		5-HT	Receptor	11q23.2	15 195	118
HTR3B	5-Hydroxytryptamine (serotonin) receptor 3B		5-HT	Receptor	11q23.2	41 378	119
HTR4	5-Hydroxytryptamine (serotonin) receptor 4		5-HT	Receptor	5q32	172 618	120
HTR5A	5-Hydroxytryptamine (serotonin) receptor 5A		5-HT	Receptor	7q36.2	13 583	
HTR6	5-Hydroxytryptamine (serotonin) receptor 6		5-HT	Receptor	1p36.13	14 276	
HTR7	5-Hydroxytryptamine (serotonin) receptor 7		5-HT	Receptor	10q23.31	115 268	
SLC6A4	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	HTT SERT	5-HT	Transporter	17q11.2	24 118	121
ABCG1	ATP-binding cassette subfamily G member 1		5-HT	Others	21q22.3	77 974	122
DBH	Dopamine beta-hydroxylase precursor		Dopamine	Metabolic enzyme	9q34.2	22 982	123
DRD1	D1 dopamine receptor		Dopamine	Receptor	5q35.2	3127	124
DRD2	D2 dopamine receptor		Dopamine	Receptor	11q23.2	65 577	125
DRD3	D3 dopamine receptor		Dopamine	Receptor	3q13.31	50 200	126
DRD4	D4 dopamine receptor		Dopamine	Receptor	11p15.5	3400	127
DRD5	D5 dopamine receptor		Dopamine	Receptor	4p16.1	2032	
NR4A2	Nuclear receptor subfamily 4, group A, member 2	NURR1	Dopamine	Others	2q24.1	8250	128
DDC	DOPA decarboxylase		Multiple monoaminergic systems	Metabolic enzyme	7p12.2	102 610	129
MAOA	Monoamine oxidase A		Multiple monoaminergic systems	Metabolic enzyme	Xp11.3	70 206	130
MAOB	Monoamine oxidase B		Multiple monoaminergic systems	Metabolic enzyme	Xp11.3	115 765	

Table 2 Continued

Symbols	*Genes*	*Aliases*	*Subcategories*		*Chromosomal region*	*Genomic size (bp)*	*References*[a]
TH	Tyrosine hydroxylase		Multiple monoaminergic systems	Metabolic enzyme	11p15.5	7887	131, 132
COMT	Catechol-*O*-methyltransferase		Multiple monoaminergic systems	Metabolic enzyme	22q11	27 047	133
SLC6A2	Solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2	NET	Multiple monoaminergic systems	Transporter	16q12.2	46 031	
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	DAT	Multiple monoaminergic systems	Transporter	5p15.33	52 637	134, 135
SLC18A1	Solute carrier family 18 (vesicular monoamine), member1	VMAT1	Multiple monoaminergic systems	Vesicular transporter	8p21.3	38 346	64
SLC18A2	Solute carrier family 18 (vesicular monoamine), member2	VMAT2	Multiple monoaminergic systems	Vesicular transporter	10q26.11	36 203	136
Cholinergic neurotransmission							
CHAT	Choline acetyltransferase		Metabolic enzyme		10q11.23	56 010	
CHRNA3	Cholinergic receptor, nicotinic, alpha polypeptide 3		Receptor		15q24.3	25 679	137, 138
CHRNA4	Cholinergic receptor, nicotinic, alpha polypeptide 4		Receptor		20q13.33	16 298	137, 138
CHRNA5	Cholinergic receptor, nicotinic, alpha polypeptide 5		Receptor		15q24.3	27 806	137, 138
CHRNA6	Cholinergic receptor, nicotinic, alpha polypeptide 6		Receptor		8p11.21	15 857	137, 138
CHRNA7	Cholinergic receptor, nicotinic, alpha polypeptide 7		Receptor		15q13.3	184 762	137, 138
CHRNB2	Cholinergic receptor, nicotinic, beta polypeptide 2		Receptor		1q22	8827	137, 138
CHRNB3	Cholinergic receptor, nicotinic, beta polypeptide 3		Receptor		8p11.21	39 290	137, 138
CHRM1	Cholinergic receptor, muscarinic 1		Receptor		11q12.3	1383	
CHRM2	Cholinergic receptor, muscarinic 2		Receptor		7q33	1401	139
CHRM4	Cholinergic receptor, muscarinic 4		Receptor		11p11.2	1455	44
Amino-acid neurotransmission							
GABRA1	Gamma-aminobutyric acid (GABA) A receptor, alpha 1		GABA	Receptor	5q34	50 180	140
GABRA2	Gamma-aminobutyric acid A receptor, alpha 2		GABA	Receptor	4p12	140 186	141–143
GABRA3	Gamma-aminobutyric acid A receptor, alpha 3		GABA	Receptor	Xq28	283 210	141, 142
GABRA5	Gamma-aminobutyric acid A receptor, alpha 5		GABA	Receptor	15q12	34 408	141, 142
GABBR1	Gamma-aminobutyric acid B receptor 1		GABA	Receptor	6p22.1	30 856	144
SLC6A1	Solute carrier family 6 (neurotransmitter transporter, GABA), member 1		GABA	Transporter	3p25.3	21 553	145–147

SLC6A11	Solute carrier family 6 (neurotransmitter transporter, GABA), member 11	GAT1	GABA	Transporter	3p25.3	122230	145
SLC6A12	Solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12	BGT1	GABA	Transporter	12p13.33	23 241	145
VIAAT	Vesicular inhibitory amino-acid transporter		GABA	Transporter	20q11.23	4887	148
DBI	Diazepam binding inhibitor (GABA receptor modulator, acyl-Coenzyme A binding protein)		GABA	Others	2q14.2	4975	
GAD2	Glutamate decarboxylase 2	GAD65	Glutamate GABA	Metabolic enzyme	10p12.1	87 894	149
GAD1	Glutamate decarboxylase 1	GAD67	Glutamate GABA	Metabolic enzyme	2q31.1	25 848	149, 150
ABAT	4-Aminobutyrate aminotransferase precursor	GABA-T	Glutamate GABA	Metabolic enzyme	16p13.2	109 987	151
GLRA3	Glycine receptor, alpha 3		Glutamate	Receptor	4q34.1	186 168	152
GLRB	Glycine receptor, beta		Glutamate	Receptor	4q32.1	95 517	152
GRIA1	Glutamate receptor, ionotropic, AMPA 1		Glutamate	Receptor	5q33.2	364 262	153
GRIA2	Glutamate receptor, ionotropic, AMPA 2		Glutamate	Receptor	4q32.1	143 068	
GRIA3	Glutamate receptor, ionotropic, AMPA 3		Glutamate	Receptor	Xq25	304 502	
GRIA4	Glutamate receptor, ionotrophic		Glutamate	Receptor	11q22.3	368 731	
GRIK1	Glutamate receptor, ionotropic kainate 1		Glutamate	Receptor	21q21.3	402 421	
GRIK2	Glutamate receptor, ionotropic kainate 2		Glutamate	Receptor	6q16.3	669 205	
GRIK3	Glutamate receptor, ionotropic kainate 3		Glutamate	Receptor	1p34.3	233 113	
GRIK4	Glutamate receptor, ionotropic kainate 4		Glutamate	Receptor	11q23.3	325 942	154
GRIK5	Glutamate receptor, ionotropic kainate 5		Glutamate	Receptor	19q32.2	64 020	
GRIN1	*N*-methyl-D-aspartate receptor subunit zeta 1 (precursor)		Glutamate	Receptor	9q34.3	28 919	155
GRIN2A	*N*-methyl-D-aspartate receptor subunit 2A		Glutamate	Receptor	16p13.2	421 920	156
GRIN2B	*N*-methyl-D-aspartate receptor subunit 2B		Glutamate	Receptor	12q13.1	418 909	
GRIN2C	*N*-methyl-D-aspartate receptor subunit 2C		Glutamate	Receptor	17q25.1	18 802	
GRIN2D	*N*-methyl-D-aspartate receptor subunit 2D		Glutamate	Receptor	19q13.33	49 262	157
GRM1	Glutamate receptor, metabotropic 1		Glutamate	Receptor	6q24.3	408 316	
GRM2	Glutamate receptor, metabotropic 2 precursor		Glutamate	Receptor	3p21.31	9131	158
GRM3	Glutamate receptor, metabotropic 3 precursor		Glutamate	Receptor	7q21.12	220 113	158
GRM4	Metabotropic glutamate receptor 4		Glutamate	Receptor	6p21.31	111 816	
GRM5	Glutamate receptor, metabotropic 5		Glutamate	Receptor	11q14.3	540 352	159
GRM6	Glutamate receptor, metabotropic 6 precursor		Glutamate	Receptor	5q35.3	16 793	
GRM7	Glutamate receptor, metabotropic 7		Glutamate	Receptor	3p26.1	880 272	160
GRM8	Metabotropic glutamate receptor 8 precursor		Glutamate	Receptor	7q31.33	804 658	
SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	EAAT3	Glutamate	Transporter	9p24.2	96 815	161–163
SLC1A2	Solute carrier family 1 (glial high-affinity glutamate transporter), member 2	EAAT2	Glutamate	Transporter	11p13	158 150	161–163
SLC1A3	Solute carrier family 1 (glial high-affinity glutamate transporter), member 3	EAAT1	Glutamate	Transporter	5p13.2	81 750	161–163
SLC1A6	Solute carrier family 1 (high-affinity aspartate/glutamate transporter), member 6	EAAT4	Glutamate	Transporter	19p13.12	22 740	161, 163
SLC6A9	Solute carrier family 6 neurotransmitter transporter, glycine), member 9	GLYT1	Glutamate	Transporter	1p34.1	25 587	164
DAO	D-amino-acid oxidase		Glutamate	Metabolic enzyme	12q24.11	20 831	3
SRR	Serine racemase		Glutamate	Metabolic enzyme	17p13.3	21 306	165
Other neurotransmitter or neuromodulator systems							
AVP	Arginine vasopressin–neurophysin II		Peptide	Transporter	20p13	2873	166
AVPR1A	Arginine vasopressin receptor 1A		Peptide	Receptor	12q14.2	6375	166

Table 2 Continued

Symbols	*Genes*	*Aliases*	*Subcategories*		*Chromosomal region*	*Genomic size (bp)*	*References*[a]
CCK	Cholecystokinin		Peptide	Neurotransmitter Intercellular signaling	3p22.1	6802	
CCKAR	Cholecystokinin A receptor		Peptide	Receptor	4p15.2	9025	
CCKBR	Cholecystokinin B receptor		Peptide	Receptor	11p15.4	12 202	
HCRT	Orexin precursor		Peptide	Neurotransmitter Intercellular signaling	17q21.2	1393	167
HCRTR1	Orexin receptor 1		Peptide	Receptor	1p35.2	8074	167
HCRTR2	Orexin receptor 2		Peptide	Receptor	6p12.1	108 347	167
NPY	Neuropeptide Y		Peptide	Neurotransmitter Intercellular signaling	7p15.3	417	168
NPY1R	Neuropeptide Y receptor Y1		Peptide	Receptor	4q32.2	2797	168
NPY2R	Neuropeptide Y receptor Y2		Peptide	Receptor	4q32	1152	168
NPY5R	Neuropeptide Y receptor Y5		Peptide	Receptor	4q32	4165	
NTS	Neurotensin		Peptide	Neurotransmitter Intercellular signaling	12q21.31	8689	169
NTSR1	Neurotensin receptor 1		Peptide	Receptor	20q13.33	53 934	169
NTSR2	Neurotensin receptor 2		Peptide	Receptor	2p25.1	12121	169
SST	Somatostatin		Peptide	Neurotransmitter Intercellular signaling	3q27.3	1227	
TAC1	Tachykinin, precursor 1		Peptide	Neurotransmitter Intercellular signaling	7q21.3	8408	
TACR1	Tachykinin receptor 1		Peptide	Receptor	2p12	150 044	
TACR2	Tachykinins receptor 2		Peptide	Receptor	10q22.1	11 498	
TACR3	Tachykinins receptor 3		Peptide	Receptor	4q24	130 349	170
VIP	Vasoactive intestinal peptide		Peptide	Neurotransmitter Intercellular signaling	6q25.2	8857	
VIPR2	Vasoactive intestinal peptide receptor 2	VPAC2	Peptide	Receptor	7q36.3	116 783	66
PMCH	Pro-melanin-concentrating hormone		Peptide	Neurotransmitter Intercellular signaling	12q23.2	1364	52
GPR24	G-protein-coupled receptor 24	MCHR1	Peptide	Receptor	22q13.2	3582	52
PDYN	Beta-neoendorphin–dynorphin preproprotein		Peptide	Neurotransmitter Intercellular signaling	20p13	15 300	171
OPRD1	Opioid receptor, delta1		Opioid	Receptor	1p35.3	51 552	
OPRK1	Opioid receptor, kappa1		Opioid	Receptor	8q11.23	21 771	
OPRM1	Opioid receptor, kappa1		Opioid	Receptor	6q25.2	80 118	
ADORA1	Adenosine A1 receptor		Others	Receptor	1q32.1	76 750	172
ADORA2A	Adenosine A2a receptor		Others	Receptor	22q11.23	9234	
ADORA2B	Adenosine A2b receptor		Others	Receptor	17p12	30 980	
ADORA3	Adenosine receptor A3		Others	Receptor	1p13.2	4689	62

2. A neuroendocrine system

HPA axis						
POMC	Proopiomelanocortin	ACTH	Neurotransmitter Intercellular signaling	2q23.3	7665	
CRH	Corticotropin-releasing hormone precursor		Neurotransmitter Intercellular signaling	8q13.1	2080	
CRHR1	Corticotropin-releasing hormone receptor 1		Receptor	17q21.31	51 525	
CRHR2	Corticotropin-releasing hormone receptor 2		Receptor	7p14.3	29 697	
MC2R	Melanocortin 2 receptor (adrenocorticotropic hormone)		Receptor	18p11.21	894	173
NR3C1	Nuclear receptor subfamily 3, group C, member 1	(Glucocorticoid receptor)	Receptor	5q31.3	123 763	174
NR3C2	Nuclear receptor subfamily 3, group C, member 2	(Mineralocorticoid receptor)	Receptor	4q31.23	363 604	174
MC4R	Melanocortin 4 receptor		Receptor	18q21.32	999	52
HSPA5	Heat shock 70 kDa protein 5 (glucose-regulated protein, 78 kDa)	GRP78	Others	9q33.3	6478	175
SERPINA6	Corticosteroid binding globulin precursor	CBG	Others	14q32.13	19 088	55
ABCB1	ATP-binding cassette subfamily B member 1	ABCB1	Others	7q21.12	209 617	55
HSD11B1	11-Beta-hydroxysteroid dehydrogenase 1		Enzyme		48 746	56
Neurotrophic/growth factor systems						
BDNF	Brain-derived neurotrophic factor		Neurotransmitter Intercellular signaling	11p14.1	63 295	39, 60, 61
EGF	Epidermal growth factor		Neurotransmitter Intercellular signaling	4q25	99 370	176
FGF2	Fibroblast growth factor2		Neurotransmitter Intercellular signaling	4q27	71 528	
IGF1	Insulin-like growth factor I		Neurotransmitter Intercellular signaling	12q23.2	84 649	62
TGFB1	Transforming growth factor, beta 1		Neurotransmitter Intercellular signaling	19q13.2	23561	177
IGF1R	Insulin-like growth factor 1 receptor precursor		Receptor	15q26.3	308 747	178
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	TrkB	Receptor	9q21.33	352 717	
NTRK3	Neurotrophin receptor 3		Receptor	15q25.3	379 607	62
(1–3) Intracellular signaling largely shared by 1-3						
ADCY2	Adenylate cyclase 2		cAMP signaling	5p15.31	433 850	179
ADCY9	Adenylate cyclase 9		cAMP signaling	16p13.3	150 555	180
ADRBK2	Beta adrenergic receptor kinase 2	GRK3	cAMP signaling	22q12.1	158 971	62
CREB1	CAMP-responsive element binding protein 1		cAMP signaling	2q33.3	68 897	35, 179
CREM	CAMP-responsive element modulator		cAMP signaling	10p11.21	84 983	36, 179
GNAI2	Guanine nucleotide binding protein		cAMP signaling	3p21.31	22 633	33
GNAL	Guanine nucleotide binding protein (G protein), alpha-activating activity polypeptide, olfactory type		cAMP signaling	18p11.21	129 640	181

Table 2 Continued

Symbols	*Genes*	*Aliases*	*Subcategories*	*Chromosomal region*	*Genomic size (bp)*	*References*[a]
GNAS	Guanine nucleotide binding protein (G protein), alpha-stimulating activity polypeptide 1 (LL)		cAMP signaling	20q13.32	71 451	33
PDE4A	Phosphodiesterase 4A, cAMP-specific		cAMP signaling	19p13.2	47 837	37, 182
PDE4B	Phosphodiesterase 4B, cAMP-specific		cAMP signaling	1p31.2	580 324	37, 183
PDE4D	Phosphodiesterase 4D, cAMP-specific		cAMP signaling	5q11.2	615 565	184
PRKACA	Protein kinase, cAMP-dependent, catalytic, alpha		cAMP signaling	19p13.13	26 045	185, 186
PRKAR2B	Protein kinase, cAMP-dependent, regulatory, type II, beta		cAMP signaling	7q22.3	116 687	185
RGS20	Regulator of G-protein signaling 20		cAMP signaling	8q11.23	78 299	187
RGS4	Regulator of G-protein signaling 4		cAMP signaling	1q23.3	5184	30, 73, 188
RGS7	Regulator of G-protein signaling 7		cAMP signaling	1q43	581 608	179
PPP1R1B	Protein phosphatase 1, regulatory (inhibitor) subunit 1B	DARPP-32	cAMP signaling Calcium signaling	17q12	9699	41
PPP1R9B	Protein phosphatase 1 regulatory subunit 9B	Spinophilin	cAMP signaling Calcium signaling	17q21.33	15 179	41, 189
CAMK2A	Calcium/calmodulin-dependent protein kinase II alpha		cAMP signaling Calcium signaling	5q33.1	70 277	39, 40, 190
KCNN3	Calcium-activated potassium channel SK3	hSK3	Calcium signaling	1q22	162 714	191
MARCKS	Myristoylated alanine-rich protein kinase C		Calcium signaling Phosphoinositide	6q21	4425	192
PRKCA	Protein kinase C, alpha		Calcium signaling Phosphoinositide	17q24.1	499 979	192, 193
PRKCE	Protein kinase C, epsilon		Calcium signaling Phosphoinositide	2p21	532 811	192, 193
PLA2G1B	Phospholipase A2, group IB (pancreas)		Calcium signaling Phosphoinositide Neurotrophic factors	12q24.31	5674	194, 195
PLCG1	Phospholipase C, gamma 1		Calcium signaling Phosphoinositide Neurotrophic factors	20q12	38 197	196
GNB3	Guanine nucleotide-binding protein beta-3		Calcium signaling cAMP signaling Phosphoinositide	12p13.31	7183	197, 198
BCL2	B-cell CLL/lymphoma 2		Neurotrophic factors	18q21.33	195 352	199
DUSP6	Dual-specificity phosphatase 6		Neurotrophic factors	12q21.33	4023	200
MAP2K2	Mitogen-activated protein kinase kinase 2		Neurotrophic factors	19p13.3	33 805	64, 199
MAPK1	Mitogen-activated protein kinase 1		Neurotrophic factors	22q11.21	105 092	64, 193

AKT1	v-Akt murine thymoma viral oncogene homolog 1		Neurotrophic factors		14q32.33	23 856	42, 43
GNAQ	Guanine nucleotide binding protein (G protein), q		Phosphoinositde		9q21.2	311 000	201
GNA11	Guanine nucleotide binding protein (G protein), alpha 11 (Gq class)		Phosphoinositide		19p13.3	26 923	201
IMPA1	Inositol(myo)-1(or 4)-monophosphatase 1		Phosphoinositide		8q21.13	28 365	
IMPA2	Inositol(myo)-1(or 4)-monophosphatase 2		Phosphoinositide		18p11.21	49 422	26, 202
INPP5F	Inositol polyphosphate-5-phosphatase F		Phosphoinositide		10q26.12	103 044	203
ITPKA	1D-Myo-inositol-trisphosphate 3-kinase A		Phosphoinositide		15q15.1	9624	203
ITPKB	Inositol-1,4,5-triphosphate-3 kinase B		Phosphoinositide		1q42.12	104 439	203
PIB5PA	Phosphatidylinositol (4,5) bisphosphate		Phosphoinositide		22q12.2	11 703	203
PIK3C2B	Phosphoinositide-3-kinase, class 2, beta polypeptide		Phosphoinositide		1q32.1	67 707	203
PIK3C3	Phosphoinositide-3-kinase, class 3		Phosphoinositide		18q12.3	126 246	203
PIK4CA	Phosphatidylinositol 4-kinase, catalytic, alpha peptide		Phosphoinositide		22q11.21	131 028	203
PIP5K2A	Phosphatidylinositol-4-phosphate 5-kinase type		Phosphoinositide		10p12.2	177 663	203
KIAA0274	Sac domain-containing inositol phosphatase 3		Phosphoinositide		6q21	134 167	203
SYNJ1	Synaptojanin 1		Phosphoinositide		21q22.11	96 978	204
4. Circadian rhythm							
Clock genes							
ARNTL	Aryl hydrocarbon receptor nuclear translocator-like	BMAL1			11p15.3	109 433	66
ARNTL2	Transcription factor BMAL2	BMAL2			12p11.23	87 479	66
BHLHB2	Differentiated embryo chondrocyte expressed gene	1-Dec			3p26.1	5654	66
aBHLHB3	Basic helix–loop–helix domain containing, class B, 3	2-Dec			12p12.1	4886	66
CLOCK	Clock				4q12	114 338	66, 205
CRY1	Cryptochrome 1 (photolyase-like)				12q23.3	102 181	66
CRY2	Cryptochrome 2 (photolyase-like)				11p11.2	35 768	66
CSNK1D	Casein kinase 1, delta isoform 1				17q25.3	29 332	66
CSNK1E	Casein kinase 1 epsilon				22q13.1	25 461	66
PER1	Period 1				17p13.1	11 913	66
PER2	Period 2				2q37.3	44 407	66
PER3	Period 3				1p36.23	60 475	66
TIMELESS	Timeless (*Drosophila*) homolog				12q13.3	32 260	206
DBP	D site of albumin promoter (albumin D-box)				19q13.33	6642	66
NR1D1	Nuclear receptor subfamily 1, group D, member 1	Rev-ErbAalpha			17q21.1	7933	66
Pathways for entrainment to light/darkness cycle and outputs of suprachiasmatic nucleus							
PROK2	Prokineticin 2	PK2	Clock output		3p13	13 406	73
GPR73L1	G-protein-coupled receptor 73-like 1	PKR2	Clock output		20p12.3	12 330	73
TGFA	Transforming growth factor alpha		Clock output		2p13.3	106 512	72
EGFR	ERBB1		Clock output		7p11.2	137 918	72
AANAT	Arylalkylamine *N*-acetyltransferase		Clock output	Melatonin	17q25.1	2549	
MTNR1A	Melatonin receptor 1A		Clock output	Melatonin	4q35.2	22 675	207–209

Table 2 Continued

Symbols	*Genes*	*Aliases*	*Subcategories*		*Chromosomal region*	*Genomic size (bp)*	*References*[a]
MTNR1B	Melatonin receptor 1B		Clock output	Melatonin	11q14.3	13 160	210, 208, 211
CRX	Cone–rod homeobox		Photoreception		19q13.33	5524	66
OPN4	Opsin4	Melanopsin	Photoreception		10q23.2	11 815	66
ADCYAP1	Adenylate cyclase-activating polypeptide	PACAP	Photoreception		18p11.32	5664	212, 213
ADCYAP1R1	Type I adenylate cyclase-activating polypeptide receptor		Photoreception		7p14.3	43 503	69, 212
FYN	Protein-tyrosine kinase fyn				6q21	212 143	66
GDI1	GDP dissociation inhibitor 1				Xq28	6293	66
RAB3A	RAB3A, member RAS oncogene family				19p13.11	7230	66
NPAS2	Neuronal PAS domain protein 2				2q11.2	175 551	214
5. Genes implicated in pathophysiology of other diseases relevant to major affective disorders							
Genes implicated in the pathophysiology of Parkinson's disease							
PARK2	Parkinson disease (autosomal recessive, juvenile) 2, parkin	PARK2 PARKIN			6q26	1 379 130	76
SNCA	Synuclein, alpha	PARK1			4q22.1	111 429	76
PNUTL1	Peanut-like 1	CDCREL1			22q11.21	8818	76
SNCAIP	Synuclein alpha-interacting protein	Synphilin1			5q23.2	151 817	76
UCHL1	Ubiquitin carboxyl-terminal esterase L1	PARK5			4p13	11 518	76
GPR37	G-protein-coupled receptor 37	PAELR			7q31.33	19 566	76
UBB	Ubiquitin B precursor				17p11.2	1688	76
UBE1	Ubiquitin-activating enzyme E1				Xp11.3	24 267	76
STUB1	STIP1 homology and U-box containing protein 1	CHIP			16p13.3	2277	76, 79
UBE2L3	Ubiquitin-conjugating enzyme E2L 3	UBCH7			22q11.21	56 367	76
UBE2L6	Biquitin-conjugating enzyme E2L 6	UBCH8			11q12.1	16 325	76
PARK7	Parkinson disease (autosomal recessive, early onset) 7 (PARK7)	DJ1			1p36.23	23 544	215
Genes implicated in the pathophysiology of schizophrenia							
RELN	Reelin		Cell migration		7q22.1	517 727	150
DISC1	Disrupted in schizophrenia 1		Cell migration		1q42.2	399 739	93, 216, 217
NDEL1	nudE nuclear distribution gene E homolog like 1	NUDEL	Cell migration		17p13.1	32 293	217
PAFAH1B1	Platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit 45 kDa	LIS1	Cell migration		17p13.3	91 953	217, 218
PTAFR	Platelet-activating factor receptor		Cell migration		1p35.3	27 328	219
CHL1	Cell adhesion molecule with homology to L1CAM		Cell migration		3p26.3	212 449	220
L1CAM	L1 cell adhesion molecule isoform 1 precursor		Cell migration		Xq28	13 925	221, 222
NCAM1	Nerural cell adhesion molecule		Cell migration		11q23.1	314 048	66, 223
DTNBP1	Dysbindin1		Schizophrenia gene		6p22.3	140 167	1
NRG1	Neuregulin1		Schizophrenia gene		8p12	1 103 459	2
PRODH	Prolin dehydrogenase (oxidase) 1		Schizophrenia gene		22q11	23 771	224
CLDN11	Oligodendrocyte transmembrane protein		Myelination		3q26.2	13 827	94

ERBB3	v-Erb-b2 erythroblastic leukemia viral oncogene	Myelination	12q13.2	22 605	94
GALC	Galactosylceramidase precursor	Myelination	14q31.3	60 484	94
MBP	Myelin basic protein	Myelination	18q23	37 252	94
MOG	Myelin oligodendrocyte glycoprotein	Myelination	6p22.1	15 621	94
OLIG1	Oligodendrocyte transcription factor 1	Myelination	21q22.11	2276	94
OLIG2	Oligodendrocyte lineage transcription factor 2	Myelination	21q22.11	3209	94
PLP1	Proteolipid protein 1	Myelination	Xq22.2	15 706	94
SOX10	SRY (sex determining region Y)-box 10	Myelination	22q13.1	12 220	94
TF	Transferrin	Myelination	3q22.1	32 401	94

The total number of candidate genes: 257; total genomic size: 26 620 628 bp.
[a]When a gene has not intensively been studied despite its putative key biologic role in one of the pathways, it may lack a reference. Conversely, when numerous studies have been conducted, review articles, meta-analyses, and large-scale studies are preferentially given.

by lithium,[24,25] and its coding gene (IMPA2) is a promising candidate.[26,27] Another gene in this pathway, phosphoinositide-3-kinase class 3 (PIK3C3), was recently reported to be associated with bipolar disorder and schizophrenia.[28] Calcium signaling is closely linked to the phosphoinositide pathway, and expression of protein kinase C subtypes (PRKCA and PRKCE) and its substrate myristoylated alanine-rich protein kinase C (MARCKS) are reduced in the rat brain after chronic treatment with lithium.[29]

Monoamine neurotransmitter receptors, such as alpha2 and beta-1-adrenergic receptors, are coupled to G proteins, which, upon stimulation, activate enzymes in the cAMP-signaling pathway. The gene for regulator of G-protein signaling 4 (RGS4) was initially brought into attention by a microarray study and recently reported to be associated with schizophrenia.[30] Selecting candidates based on expression data also led to the detection of associations of G-protein-coupled receptor kinase3 (GRK3)[31] and other promising gene[32] with bipolar disorder. Altered expression level of G protein AS and AI2 subunits (GNAS, GNAI2) in the post-mortem brains from bipolar or lithium receiving subjects has also been reported,[33] although variants in the former gene are not apparently associated with bipolar disorder.[34] Recent animal studies demonstrated that chronic administration of antidepressants induces elevation of cAMP-responsive element binding protein gene (CREB1) expression-[35] and cAMP-responsive element modulator (CREM)-deficient mice showed emotional and behavioral changes.[36] Also, chronic antidepressant administration increases cAMP phosphodiesterase (PDE4A and PDE4B) expression in rat frontal cortex.[37] A phosphodiesterase inhibitor, rolipram, has been reported to have an antidepressive effect.[38]

Further, abnormalities of molecules that overarch multiple intracellular signaling pathways (eg calcium/calmodulin-dependent protein kinase II alpha (CAMK2A),[39,40] DARPP-32 (PPP1R1B),[41] and v-akt murine thymoma viral oncogene homologs (AKT1),[42,43] are also suggested in psychiatric illnesses.

Roles of other neurotransmission systems including cholinergic, amino acid (glutamate and GABA) and peptidergic neurotransmission in bipolar disorder or related physiological functions such as appetite and anxiety are also supported by neuropharmacological findings,[44–48] although not detailed here.

A neuroendocrine system

The hypothalamic-pituitary-adrenocortical (HPA) axis has a long history as a stress-response pathway and has been repeatedly suggested to play a role in major depressive disorder.[49] A recent hypothesis that elevated levels of cortisol in depressed patients may contribute to neuronal death and to reduced dendritic arborizations in hippocampus[50–52] seems to have a potential for elucidating the etiology of mood disorder. This hypothesis is consistent with the

previous neuroimaging findings reporting reductions of hippocampal volume in some mood disorder subjects.[53,54]

Obvious candidates based on these formulations are genes encoding peptide hormones (proopiomelanocortin (POMC) and corticotrophin-releasing hormone precursor (CRH)) and their receptors (MC2R, MC4R, CRHR1, and CRHR2). In addition, glucocorticoid receptor (NR3C1), which binds to glucocorticoids and then enters the nucleus to enhance or inhibit gene expression by direct binding to glucocorticoid response elements or by interactions with other transcriptional factors such as CREB, can be considered an important signaling component. Other candidates include genes for heat-shock proteins such as HSPA5, which associate with the glucocorticoid receptor as chaperones, multidrug-resistant protein 1 (ABCB1), which pumps out cortisol from the cell,[55] and 11-beta-hydroxysteroid dehydrogenase 1 (HSD11B1), which metabolizes cortisol.[56]

Neurotrophic factor systems

There has been growing evidence supporting roles of neurotrophic factors and growth factors, which regulate neuronal growth, development, survival, and plasticity, in mood disorders. The gene for brain-derived neurotrophic factor (BDNF), which is involved in neuronal survival and arborization in hippocampus, is an unusually promising candidate. The expression of BDNF is decreased by stress and glucocorticoids[57] and is increased by chronic antidepressant or electroconvulsive treatment in rat hippocampus.[58,59] Association between BDNF and bipolar disorder has been replicated in independent pedigree samples.[60,61] Also, the gene for insulin-like growth factor I (IGF1) would be worth studying based on its role in neurogenesis and reported altered expression level in the brains of metamphetamine-treated rats.[62] Recently, a requirement was demonstrated for hippocampal neurogenesis for behavioral effects of antidepressants, consistent with importance of genes involved in neurogenesis in studies of depression.[63]

As in the neurotransmission systems and HPA axis, genes for molecular components of the neurotrophic factor system have not been systematically studied for association with bipolar disorder. Genes such as NTRK2 and NTRK3 coding for neurotrophic factor receptors collectively called Trk are candidates as well as genes for ligands. Among the several intracellular cascade systems activated upon Trk stimulation are phosphoinositide signaling and protein kinase C pathway, whose components are shared with neurotransmission systems described above. It may be challenging to select candidates from the mitogen-activated protein (MAP) kinase cascade, another intracellular signaling pathway downstream of Trk, because of the large number of subtypes for each protein. However, an expression study on PC12 cells differentiated by nerve growth factor (NGF) showed that lithium administration altered expression of two genes (MAP2K2 and MAPK1) encoding kinases of this pathway.[64]

Circadian rhythm

Abnormalities in circadian rhythm are found in seasonal affective disorder as well as in a fraction of patients with major depression. The fact that interventions on circadian rhythm such as light therapy and sleep deprivation can improve the symptoms of depression or provoke mania might be indicative of an etiological role of this system.[65] The mammalian circadian pacemaker is located within the suprachiasmatic nucleus (SCN) in the hypothalamus. 'Clock genes' (eg CLOCK, ARNTL (BMAL1), ARNTL2 (BMAL2), PER1, PER2, and PER3) play crucial roles in generating and regulating circadian rhythm, and mutations of these genes have already been reported to cause abnormal circadian locomotion in rodents. In the past several years, many clock genes have been identified in various species such as Drosophilae, fungi, and rodents. As human counterparts or homologues have already described for most clock genes,[66] the circadian rhythm system is amenable to genetic dissection.

Although the clock genes are probably the first candidates to be studied in the circadian rhythm system, it is noteworthy that these gene loci did not show major effect on strain variability in mouse circadian behavior in a genomewide analysis.[67] Studying nonclock genes with suggested roles in circadian rhythm would also be important. Since the SCN can be entrained to light/dark cycle, genes encoding components involved in photoreception in the retinohypothalamic tract are intriguing candidates. For example, pituitary adenylate cyclase-activating polypeptide (ADCYAP1) is a major neurotransmitter of this tract as well as glutamate.[68] Lack of either of its receptor genes, ADCYAP1R1 or VIPR2, leads to abnormal circadian phenotype in rodents.[69] In addition, since diurnal rhythmicity in physiological functions and behaviors is eventually affected in mood disorder, output pathways from the SCN, including pineal melatonin secretion,[70,71] cannot be omitted. Recently, transforming growth factor-α (TGFA)[72] and prokineticin 2 (PROK2),[73] substances secreted from the SCN to adjacent hypothalamic areas, have been reported to regulate behavioral circadian rhythm in mice.

Systems implicated in Parkinson's disease and schizophrenia

Other CNS diseases may also provide clues for susceptibility genes for mood disorders, if they share etiological mechanisms with mood disorders. Symptoms of depression occur in approximately half of the subjects with Parkinson's disease. Although neuropathological changes characteristic of Parkinson's

disease such as Lewy body formation and demise of dopaminergic neurons in the substantia nigra are not generally observed in the post-mortem brains of mood disorder subjects, depression is reported to be a risk factor for developing Parkinson's disease,[74,75] suggesting a mechanism shared in part by both illnesses. Recent studies have revealed that genes playing roles in the ubiquitin–proteasome pathway cause some familial forms of Parkinson's disease (SNCA, PARK2 (PARKIN), UCHL1).[76] Several other components that play crucial roles in this pathway have also been reported; for example, Parkin-associated endothelin receptor-like receptor (Pael-R)[77] and CDCrel-1 (PNUTL1)[78] suggested for one of the substrates for PARKIN-mediated ubiquitination. Also, a protein called carboxy-terminus of Hsp70p-interacting protein (CHIP) is known to modulate the function of PARKIN.[79]

Also, the hypothesis that one subclass of major affective disorders shares susceptibility genes in common with schizophrenia is particularly promising. Genetic epidemiology has provided evidence for this overlap, primarily in family studies. Gershon *et al* observed an excess of major depression and schizoaffective disorder in the relatives of both mood disorder and schizophrenia probands.[80,81] The excess of major depression in relatives of both mood disorders and schizophrenia has been a consistent finding.[82] Studies from three data sets have addressed the issue of psychotic mood disorder/schizophrenia overlap. Two of the data sets found elevated rates of psychotic mood disorder in relatives of schizophrenic probands, and *vice versa*;[83–86] the third also suggested shared liability.[87] In addition, some twin studies have found evidence of shared heritability between psychotic mood disorder and schizophrenia.[88,89] Further, linkage studies of bipolar illness and schizophrenia have implicated overlapping chromosomal regions, including 10p12–13, 13q31–33, 18p11.2, and 22q11–13,[90,91] although not all analyses agree.[92] There has been considerable progress in identifying genes associated with schizophrenia, particularly in chromosomal regions where evidence of linkage was suggested. Among them, the G72/G30 gene locus on 13q33 has been demonstrated to be associated with both schizophrenia and bipolar disorder.[3,4,6–8] The notion of shared susceptibility gene is also supported by a very recent association study on DISC1 gene.[93] Other schizophrenia genes such as NRG1 and DTNBP might also be worth studying for possible association with mood disorders. In addition, a recent study has demonstrated convergent expression alterations of genes involved in myelination in both schizophrenia and bipolar disorder.[94] Such genes would be good candidates for susceptibility genes shared by major psychiatric illnesses. Studying these genes implicated in the pathophysiology of schizophrenia may contribute to eventual reconstruction of the current diagnostic nosology, and to identification of new molecular targets with broad therapeutic spectra.

Prioritizing candidate genes by quantitative trait loci (QTL) analysis

Combining microarray gene expression data and gene mapping methods to identify genetic determinants of gene expression (expression phenotypes) has recently been applied in several species, including mouse and human.[95–97] This has resulted in the successful identification of QTLs, which control the baseline expression levels of some genes. We have used this approach to identify regulators of the expression of the candidate genes we compiled, in the adult BXD recombinant inbred mice. We decided to use QTL mapping data in mouse instead of human, because the only available human QTL mapping results are from lymphoblast cell lines, and it has been shown in mouse that QTLs in brain and hematopoietic stem cells differ greatly.[98] Interval mappings were performed at the WebQTL site (see Electronic-Database Information), using UTHSC Brain mRNA U74Av2 (Mar04) RMA Orig database. QTL with an empirical genome-wide *P*-value less than 0.05 was detected for six genes, namely HTR2B, HTR4, GRIN2B, PRKCE, PER3, and BCL2.

We then determined if any of the QTLs is in syntenic regions to human bipolar linkage findings. If a *cis*-acting QTL, for which the QTL is in the target gene itself, overlaps with bipolar linkage, the target gene itself merits testing in association studies as positional candidate for bipolar linkage. If the overlapping QTL is a *trans*-acting QTL, the regulator at the QTL is a new candidate gene for association study. Thus, linkage results to gene expression may point to new candidate genes and underlying regulatory pathways for the bipolar linkage. We found that two QTLs overlap with bipolar linkage regions. A *trans*-linked QTL for two genes, HTR4 and BCL2, is mapped to the same region in mouse genome, and may thus represent a single linkage. This *trans*-linked QTL for the two genes can be divided into four segments, three of which are in syntenic regions to bipolar linkage findings at 2q,[92] 6q,[99] and 10q,[92] respectively. In addition, a *cis*-QTL for the gene PER3 is in syntenic region to bipolar linkage finding at 1p.[92] This suggests that PER3 is a good candidate for this bipolar linkage. With the identification of more bipolar linkages and the improvement of QTL mapping methods, the list of genes with QTLs overlapping with bipolar linkage will certainly grow.

Requirements for implementation of the systems genetic approach and future directions

The approach being suggested would benefit from the feasibility of much denser genotyping compared to the whole-genome LD mapping. It requires collection of information on functional importance of polymorphic markers, as well as positions, flanking sequences, validation status, and allele frequencies. Since the information is scattered on multiple web-based databases such as those from UCSC Genome

Bioinformatics, dbSNP, HapMap, and SNP Consortium (see Electronic-Database Information), manual mining of information can be tedious and sometimes infeasible. What is needed is a sophisticated informatics system facilitating compilation of pieces of information from different resources into a single platform. We might further assign priority of genotyping to each polymorphism according to its potential functional effect and the degree of LD with other polymorphisms.

Genotype data obtained by the study of multiple genes in a biologic system may provide a set of multiple susceptibility genes either through conventional association analyses or through multilocus association analyses such as the one developed by Hoh *et al*.[21] Although the latter may provide a list of susceptibility genes, in which some of them are exerting interacting effects, we further need computational modeling, which allows for systems analysis describing specific relationships between genes and clinical features. This would provide a basis for putting genetic results back into biological and clinical context. The systems listed in Table 1 are considered more complex in reality than described above, and it is also possible that interactions between systems rather than within a system increase the risk for major affective disorders. For example, a suggested integral model views multiple systems from a single perspective of neuronal death/survival. Hyperfunction of glutamatergic neurotransmission and HPA axis can lead to neuronal death, whereas adrenergic/serotonergic neurotransmission and neurotrophic factors favor neuronal survival/arborization or neurogenesis, with each system interacting with several others.[50–52] The hypothesis-based study described so far is expected to increase the likelihood of obtaining outputs that can be reasonably interpreted through the current biological and epidemiological knowledge of major affective disorders. The systems functioning conclusions from the genetic outputs, although, would not necessarily be completely consistent with the current hypothesis-based systems. The biological meaning of the genetic outputs could be tested by further research designs such as multiple gene manipulations in rodents.

Electronic-Database Informaion

Databases for biologic pathways
Gene Ontology (GO) Consortium:
http://www.geneontology.org/
Kyoto Encyclopedia of Genes and Genomes (KEGG) databases:
http://www.genome.ad.jp/kegg/pathway.html

Databases for genomic information and gene expression
UCSC Genome Bioinformatics:
http://genome.ucsc.edu/
dbSNP: http://www.ncbi.nlm.nih.gov/SNP/
The International HapMap Project:
http://www.hapmap.org/
The SNP Consortium: http://snp.cshl.org/
Gene Expression Omnibus (GEO):
http://www.ncbi.nlm.nih.gov/geo/
WebQTL: http://www.genenetwork.org/

Candidate gene projects involving resequencing
The NIEHS SNPs program:
http://egp.gs.washington.edu/
The Cardiogenomics program:
http://www.cardiogenomics.org
The SeattleSNPs program:
http://pga.gs.washington.edu/

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