TABLE 465e-1 EXAMPLES OF GENES IMPLICATED IN AUTISM

Gene Symbol	Gene Name	Function
PTEN	Phosphatase and tensin homolog	Signal transduction Synaptic function
TSC1	Tuberous sclerosis 1	Signal transduction Translation and protein stability Synaptic function
TSC2	Tuberous sclerosis 2	Signal transduction Translation and protein stability Synaptic function
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase	Signal transduction
FMR1	Fragile X mental retardation 1	Translation and protein stability Synaptic function
UBE3A	Ubiquitin protein ligase E3A	Translation and protein stability Synaptic function
CNTN3	Contactin 3	Synaptic function
CNTN4	Contactin 4	Synaptic function
CNTNAP2	Contactin-associated protein-like 2	Synaptic function
NLGN3	Neuroligin 3	Synaptic function
NLGN4	Neuroligin 4	Synaptic function
NRXN1	Neurexin 1	Synaptic function
PCDH10	Protocadherin 10	Synaptic function
SHANK3	Shank 3	Synaptic function
SLC6A4	Serotonin transporter	Neurotransmitter signaling
AVPR1	Arginine vasopressin receptor 1	Neurotransmitter signaling
OXTR	Oxytocin receptor	Neurotransmitter signaling
CACNA1C	Voltage-gated calcium channel–alpha 1C subunit	Ion channel
CACNA1H	Voltage-gated calcium channel–alpha 1H subunit	Ion channel
SCN1A	Sodium channel, voltage-gated, type I, alpha subunit	Ion channel
SCN2A	Sodium channel, voltage-gated, type II, alpha subunit	Ion channel
SLC9A9	Sodium/hydrogen exchanger	Transporter
GRIN2B	Glutamate receptor, ionotropic, *N*-methyl-D-aspartate 2B	Neurotransmitter signaling
DHCR7	7-Dehydrocholesterol reductase	Metabolism
PAH	Phenylalanine hydroxylase	Metabolism
ARX	Arx transcription factor	Gene expression
EN2	Engrailed 2 transcription factor	Gene expression
MECP2	Methyl CpG–binding protein 2 (Rett's syndrome)	Gene expression
RNF8	Ring finger protein 8	Gene expression
CHD8	Chromodomain helicase DNA binding protein	Gene expression
TBR1	T-box, brain 1	Gene expression

with multiple psychiatric syndromes. For example, mutations in *MECP2*, *FMR1*, and *TSC1* and *TSC2* (see Table 465e-1 for abbreviations) can cause mental retardation without ASD, others in *MECP2* can cause obsessive-compulsive and attention-deficit hyperactivity disorders, some alleles of *NRXN1* are associated with symptoms of both ASD and schizophrenia, and common polymorphisms in *CACNA1C* are strongly associated with both schizophrenia and bipolar disorder. Likewise, duplication of chromosome 16p is associated with both schizophrenia and autism, whereas DiGeorge's (velocardiofacial) syndrome region deletions and the *DISC1* (disrupted in schizophrenia 1) locus on chromosome 22 are associated with schizophrenia, autism, and bipolar disorder. The association of genes with multiple syndromes attests to the complexity of psychiatric disorders and the influence of additional factors that combine to specify the ultimate phenotype, including regulatory variants that determine cell-type specificity and timing of gene expression, protective variants, and epigenetic effects.

SIGNAL TRANSDUCTION

Studies of signal transduction have revealed numerous intracellular signaling pathways that are perturbed in psychiatric disorders, and such research has provided insight into development of new therapeutic agents. For example, lithium is a highly effective drug for bipolar disorder and competes with magnesium to inhibit numerous magnesium-dependent enzymes, including the enzyme GSK3β and several enzymes involved in phosphoinositide signaling that lead to activation of protein kinase C. These findings have led to discovery programs focused on developing GSK3β or protein kinase C inhibitors as potential novel treatments for mood disorders.

The observations that tricyclic antidepressants (e.g., imipramine) inhibit serotonin and/or norepinephrine reuptake and that monoamine oxidase inhibitors (e.g., tranylcypromine) are effective antidepressants initially led to the view that depression is caused by a deficiency of these monoamines. However, this hypothesis has not been substantiated. A cardinal feature of these drugs is that long-term administration is needed for their antidepressant effects. This means that their short-term actions, namely promotion of serotonin or norepinephrine function, are not per se antidepressant but rather induce a cascade of adaptations in the brain that underlie their clinical effects. The nature of these therapeutic drug-induced adaptations has not been identified with certainty. One theory holds that, in a subset of depressed patients who display upregulation of the hypothalamic-pituitary-adrenal (HPA) axis characterized by increased secretion of corticotropin-releasing factor (CRF) and glucocorticoids, excessive glucocorticoids cause atrophy of hippocampal neurons, which is associated with reduced hippocampal volumes seen clinically. Chronic antidepressant administration might reverse this atrophy by increasing brain-derived neurotrophic factor (BDNF) in hippocampus. A role for stress-induced decreases in the generation of newly born hippocampal granule cell neurons, and its reversal by antidepressants through BDNF and other growth factors, has also been suggested.

A major advance in recent years has been the identification of several rapidly acting antidepressants with non–monoamine-based mechanisms of action. The best established is ketamine, a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors, which exerts rapid (hours) and robust antidepressant effects in severely depressed patients who have not responded to other treatments. Ketamine, which at higher doses is psychotomimetic and anesthetic, exerts these antidepressant effects at low doses with minimal side effects. However, the response to ketamine is transient, which has led to several approaches to maintain treatment response, such as repeated ketamine delivery. The mechanism underlying ketamine's antidepressant action is not known, but its striking clinical efficacy has stimulated animal research on the role of glutamate neurotransmission and synaptic plasticity in key limbic regions. Recent evidence supports a role for TORC1 activation because administration of rapamycin blocks the antidepressant-like effects of ketamine in animal models. Mechanisms by which ketamine activates TORC1 are currently an active area of investigation.