

Table 1. Monoamine-Related Gene Knockouts That Affect Depression-Related Behavior in Mice.*

Gene or Protein	Function	Depression-Related Changes	Corroboration of Monoamine-Deficiency Hypothesis	Other Behavior Elicited by Knockout of Gene	
<i>sert</i>	Serotonin transporter	Increased depressive behavior, reduced serotonin level, desensitized postsynaptic 5-HT1AR, and reduced presynaptic 5-HT1AR function ³²	No	Excessive anxiety ³²	
<i>net</i>	Norepinephrine transporter	Reduced depressive behavior, prolonged norepinephrine clearance, elevated extracellular norepinephrine levels ³³	Yes	Increased locomotion response to amphetamines and cocaine ³³	
<i>5-ht1ar</i>	Serotonergic 1A receptor (presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior, normal serotonin level and release, impaired SSRI-induced neurogenesis ³²	No	Excessive anxiety, impaired hippocampal learning ³²	
<i>5-ht1br</i>	Serotonergic 1B receptor (presynaptic autoreceptor and postsynaptic)	Reduced response to SSRI in forced swim test, reduced serotonin level and increased serotonin release, increased SSRI-induced serotonin release, decreased serotonin-transporter expression ³²	Yes	Increased aggressiveness, reduced anxiety, increased exploration, increased use of cocaine ³²	
p11 (protein)	Interacts with and enhances signaling efficiency of 5-HT1BR	Increased depressive behavior, increased serotonin turnover ²⁰	No	Not reported ²⁰	
<i>5-ht2ar</i>	Serotonergic 2A receptor	No change ³⁴	No	Reduced inhibition in conflict-anxiety paradigms ³⁴	
<i>5-ht7</i>	Serotonergic 7 receptor (possibly presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior and REM sleep duration ³⁵	No	Normal locomotion ³⁵	
<i>α_{2a}ar</i>	α _{2A} -Adrenergic receptors (presynaptic autoreceptor)	Reduced norepinephrine levels, presynaptic inhibition of release, ³⁶ increased depressive behavior ³⁷	No	Altered sympathetic regulation, ³⁶ impaired motor coordination	
<i>α_{2c}ar</i>	α _{2C} -Adrenergic receptors (presynaptic autoreceptor restricted to central nervous system)	Reduced depressive behavior ³⁸	Yes	Increased aggressiveness, ³² increased locomotion response to amphetamines ³⁶	
<i>mao-a</i>	Monoamine oxidase A	Increased brain serotonin and epinephrine levels ³⁹	No	Increased aggressiveness and response to stress, ³⁰ decreased exploration ³²	
<i>ac VII</i> (heterozygotes)	Adenylyl cyclase type 7	Reduced depressive behavior ⁴⁰	No	Unchanged anxiety ⁴⁰	
<i>impa1</i>	Inositol monophosphatase 1	Reduced depressive behavior, unaltered brain inositol levels ⁴¹	Yes	Increased hyperactivity and sensitivity to pilocarpine-induced seizures ⁴¹	
<i>smit1</i>	Sodium-myoinositol transporter 1	Reduced depressive behavior and brain inositol levels ⁴²	Yes	Increased sensitivity to pilocarpine-induced seizures ⁴²	
<i>creb</i>	Cyclic AMP–response element–binding protein	Reduced depressive behavior, normal antidepressant-induced behavior ⁴³	No	No increase in BDNF after long-term use of antidepressants ⁴³	
<i>bdnf</i>	Male mice	Brain-derived neurotrophic factor	No depressive behavior ⁴⁴	No	Increased aggressiveness, hyperphagia, ⁴⁵ hyperactivity ⁴⁴
	Female mice	Brain-derived neurotrophic factor	Increased depressive behavior ⁴⁴	Yes	Increased aggressiveness, hyperphagia ⁴⁵

* BDNF denotes brain-derived neurotrophic factor, 5-HT1AR 5-hydroxytryptamine 1A receptor, 5-HT1BR 5-hydroxytryptamine 1B receptor, REM rapid eye movement, and SSRI selective serotonin-reuptake inhibitor.