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What Gene Mutations Affect Serotonin in Mice?

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Abstract

Although serotonin neurotransmission has been implicated in several neurodevelopmental and psychological disorders, the factors that drive dysfunction of the serotonin system are poorly understood. Current research regarding the serotonin system revolves around its dysfunction in neuropsychiatric disorders, but there is no database collating genetic mutations that result in serotonin abnormalities. To bridge this gap, we developed a list of genes in mice that, when perturbed, result in altered levels of serotonin either in brain or blood. Due to the intrinsic limitations of search, the current list should be considered a preliminary subset of all relevant cases. Nevertheless, it offered an opportunity to gain insight into what types of genes have the potential to impact serotonin by using gene ontology (GO). This analysis found that genes associated with monoamine metabolism were more often associated with increases in brain serotonin than decreases. Speculatively this could be because several pathways (and therefore many genes) are responsible for the clearance and metabolism of serotonin whereas only one pathway (and therefore fewer genes) is directly involved in the synthesis of serotonin. Another contributor could be cross talk between monoamine systems such as dopamine. In contrast, genes that were associated with decreases in brain serotonin were more likely linked to a developmental process. Sensitivity of serotonin neurons to developmental perturbations could due to their complicated neuroanatomy or possibly they may be negatively regulated by dysfunction of their innervation targets. Thus these observations suggest hypotheses regarding the mechanisms underlying the vulnerability of brain serotonin neurotransmission.

Graphical abstract

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Keywords

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Introduction

Serotonin is a neurotransmitter responsible for mood regulation and influences functions such as cognition, memory, learning, appetite, immune system function, and arousal, among many others¹. Consequently, dysfunction of serotonin neurotransmission has been implicated in the pathophysiology of a variety of neurodevelopmental and psychological disorders. Likewise drugs that modify serotonin signaling are used to treat many different disorders. However, if and how serotonin dysfunctions in any specific disorders is poorly understood.²

To improve understanding of the potential vulnerabilities of serotonin neurotransmission, it might be helpful to understand how serotonin changes in different genetic models relevant to disease. To date, what mouse models have changes in serotonin neurotransmission? This question is difficult to answer because each mouse model is characterized in a unique way depending on the interests of the originating research group. In some cases, changes in serotonin neurotransmission may have been reported, but there is no centralized listing of these instances. To begin to bridge this gap, we initiate a listing of genetic mouse models that have reported effects on either brain or blood serotonin. The list is by nature partial, as it was limited by inefficiencies that are intrinsic to search. It is also subject to another important limitation, that in each case serotonin may have been measured in a slightly different manner. However, we consider the results a seed that may grow as readers contribute additional information by emailing the corresponding author to update the list now posted at: <http://www.childrenshospital.org/research-and-innovation/research/labs/commons-laboratory/ser>.

Nevertheless, at this juncture, generating this list also makes it possible to see if certain subgroups of the genes assembled have similar biological functions, and whether these functions similarly affect the serotonin system. Gene ontology (GO) was used to group genes based on their shared biological processes, molecular function, or cellular component, and can be used to inspire hypothesis for understanding the connections between a given biological function and the serotonin system.

Results and Discussion

Ninety-eight different lines of mice were identified in our search. Sixty-eight involved brain serotonin or in a few cases the serotonin metabolite 5-HIAA (Table 1) the remaining 30 affected blood, likely platelet, serotonin (supplemental Table 1). In the listing of mice we also noted if serotonin was increased or decreased in each genetic model, and refer to the associated genes as either '*increased-serotonin genes*' or '*decreased-serotonin genes*'. In every case serotonin was measured in a slightly different way, therefore these indications are not precise and don't reflect measures that are truly comparable. In addition, there were a few cases where serotonin was reported as both increased and decreased, depending on the

how it was measured. In these cases ‘both’ appears in the associated field. While the limitations of this characterization are manifold, we considered it a rough starting point to evaluate what types of genes were appearing on the overall list. Given our interest in brain serotonin, we focused on that portion of the list generated (Table 1).

We subjected the genes associated with brain serotonin changes to GO analysis, separately evaluating *increased-serotonin genes* and *decreased-serotonin genes*. For this we included the genes associated with *both* increases and decreases on both lists. Thus two groups of genes from the brain serotonin database were entered independently into Princeton University’s Gene Ontology Term Finder (<http://go.princeton.edu/cgi-bin/GOTermFinder>), and the resulting top 30 GO terms ranked by p-value for each group were subjectively examined to identify similar biological processes³. We evaluated each of these terms and fit them into one of the following categories: [1] amine-related, [2] forebrain/developmental, [3] cell death/apoptosis or [4] vague (supplemental Table 2). The ‘vague’ category was subjectively created and encompassed terms that might apply to all neurons, such as terms relating to behavior, secretion, transport or synapses. By the same token genes associated with ‘cell death’ might be pleiotropic, but since they seemed to refer to a process relating to subsets of cells we considered them separately for the current discussion.

The category of ‘amine-related’ included biological processes that relate to compounds containing an amine group ($-NH_2$), including serotonin, dopamine, norepinephrine and epinephrine (supplemental Table 2). These processes are involved in amine metabolism or the transport of amine and related compounds. It was found that more *increased-serotonin genes* fell into the amine-related category (24 out of 35, or 68.6%) than *decreased-serotonin genes* (10 out of 31, or 32.3%) (Figure 1). Likewise, amine-related GO terms for *increased-serotonin genes* had more significant P values (E-9 to E-17) than for *decreased-serotonin genes* (E-6 to E-7) (see methods; statistics for GO terms are described further in Boyle et al., 15297299). The propensity for *increased-serotonin genes* to fall into this category could be attributed to the idea that multiple pathways (and therefore many genes) are responsible for the handling, clearance and metabolism of serotonin whereas only one pathway (and therefore fewer genes) is involved in the synthesis of serotonin.

Another potential factor underlying this difference could relate to dopamine, as 9 out of 35 *increased serotonin genes* were associated with the GO term ‘dopamine metabolism’, whereas ‘dopamine metabolism’ did not make the top 30 GO terms for *decreased-serotonin genes*. Some of these genes are similarly involved in metabolizing both serotonin and dopamine such as the monoamine oxidases and as such the link could be spurious, but this may not account entirely for the observation. For example, other cases could reflect the well-known reciprocal interactions between these two neurotransmitter systems⁴. We examined the 9 specific cases that were associated with the GO term ‘dopamine metabolism’, to determine if both serotonin and dopamine levels changed in these mice and if those changes were in the same direction. Six of the mutations led to elevated serotonin and dopamine levels (Atp7a, Htr1a, Maob, Park2, Park7), whereas in the other three mutations, dopamine was decreased while serotonin was increased (Nr4a2, Slc6a3, Snca)^{5,6,7,8,9,10,11}. This is fairly consistent with the literature, where interactions between these neurotransmitters exist despite conflicting reports on the directionality of the changes.

Another group of GO terms are related to cell death/apoptosis. For the *increased serotonin genes*, the genes related to apoptosis overlapped heavily with the genes in the amine-related processes group, as seen in Figure 1A. These genes included those associated with the well-known neurodegenerative disease Parkinson's (Lrrk2, Nr4a2, Park2, Park7, and Snca), as well as the rare neurodegenerative disorder, Menkes disease (Atp7a)^{5,6,10,11,12}. In Parkinson's disease, it is thought that only in advanced stages of the disease do serotonergic nuclei degenerate, whereas earlier on in disease progression, there could be increases in serotonin function^{13,14,15,16}. However, unanticipated changes in monoamine levels often exist in mouse models of Parkinson's²¹. Likewise, it is common in chemical models of Parkinson's for serotonin levels or markers of neurotransmission to change, although results vary with many technical parameters¹⁵. In the *decreased-serotonin gene* group, cell death/apoptosis and related GO terms also appeared. In contrast to the *increased-serotonin gene* group none of these genes were associated with a mouse model related to Parkinson's disease. Rather, Alzheimer's, Huntington's, and amyotrophic lateral sclerosis were among the associated diseases.¹⁴

The group of GO terms related to forebrain functionality are unique to *decreased-serotonin genes*, which included 'learning or memory,' 'cognition,' or some element of brain development. All these GO terms had a very high overlap of members. Not only were these terms unique to *decreased serotonin genes*, but they also encompassed a majority of the group (18 out of 31 genes, 58.1%). Genes associated with this GO term are involved in both development disorders that appear in youth (Mecp2/Rhett syndrome, En2/Autism spectrum disorder, Pex13/Zellweger spectrum disorder, Hprt/Lesch-Nyhan Syndrome), and neurodegenerative diseases that appear later in life (Htt/Huntington's disease, App/Alzheimer's disease, Nr4a2/Parkinson's disease, Sod1/Amyotrophic Lateral Sclerosis)^{17,18-19,5,20,21,22,23,24,25,26,27,28,29}. Some of the genes in this group are involved in pattern formation, neuronal specification or act as a trophic factor for serotonin neurons themselves (Lmx1B, Fev, En2, and Bdnf)^{17,19,30,31}.

We can provide two speculative reasons for why decreased serotonin genes fell into our forebrain/developmental category. One is that serotonin neurons have massive axons that ramify throughout the neuroaxis. These axons appear to follow highly organized patterns of innervation, although in a complex way that is not easy to tease apart. The combination of the magnitude and pattern of innervation could make these axons particularly sensitive to any disruption in developmental pattern or axon guidance. Another possibility is that serotonin axons may be sensitive to the proper function of their innervation targets, and dysfunction of these target areas could have a negative feedback on serotonin neurotransmission.

One thing worth taking into consideration with these observations is that brain monoamine content is often only assayed when it is suspected to have changed. Thus, the mouse models with altered serotonin that we have obtained in our database likely represent a biased sampling. On the other hand, it is interesting to speculate why serotonin levels appear commonly altered in many mouse models. One reason could be that, since serotonin is involved in so many behavioral endpoints that it may change as a compensatory response to many types of genetic abnormalities that perturb behavior. That is, in the case of multiple

genetic mutations and by extension multiple disease states, an allostatic process may serve to shift serotonin neurotransmission. Although under that premise, if serotonin pharmacotherapy improves symptoms of the disease state, one would have to posit that these adaptations are maladaptive. Certainly there are a mix of reasons at play.

Conclusion

We generated a compilation of mutations affecting brain or blood serotonin. The creation of this database provides a stepping-stone for the future of serotonin research, creating associations with different genes and the serotonin system. One goal for example could be to further understand the basis for vulnerability of the serotonin system to various genetic manipulations. In addition, further insight could be attained on the mechanism of action of these genes by using publically available databases of serotonin neurons genes expression to further examine if these mutations have the potential to be acting within serotonin neurons themselves and directly impact their function or are more likely to act indirectly through network phenomena.^{32–34} A common effect on the serotonin system from a group of genes with a similar function may provide insight as to how serotonergic neurotransmission can be changed to bring about neuropsychiatric disorders.

Methods

The goal of this study was to create a database detailing rodent genotypes that affect the serotonin system. We sought to identify both mutations that likely impact serotonin neurons directly (i.e. targeting genes involved in serotonin biosynthesis), as well as other mutations that may have physiological effects that indirectly alter serotonin levels.

The Jackson Laboratory's database of mice was used as an initial reference³⁵. "Serotonin" was entered as a search term in the mouse search bar. This resulted in a list of mice with mutations that impact serotonin levels. Mutations that affect serotonin metabolite levels or serotonin neuron production were also included. A summary of these impacts could be found by clicking the "show more" tab underneath the name of the mouse strain. Clicking on the mouse strain reveals its genotype, associated disorder, etc. All information from the Jackson Laboratory cited PubMed literature.

Search of the Jackson Laboratory inventory identified many mice with mutations affecting serotonin output, however, additional mice with similar mutations might not be available through the Jackson Laboratory. In order to find such mice, PubMed searches were performed. Terms such as "serotonin HPLC" and "serotonin ELISA" were used, since HPLC (high performance liquid chromatography) and ELISA (enzyme-linked immunosorbent assay) are two common methods used to measure serotonin levels. In order to make the searches rodent specific, another approach was to search terms such as "'increased serotonin' AND mice". Regardless of the search, when the results were returned the abstract of each publication was perused to ascertain if a genetic model was studied and if serotonin seemed to be impacted. If it seemed like these criteria were met, the publication itself was examined for confirmation. In a few cases, the measure relating to serotonin was

normal but there were changes in the serotonin metabolite (5-HIAA), since this might suggest altered metabolism of serotonin those cases were included in the database.

Lastly we searched the OMIM-Online Mendelian Inheritance in Man website using the search term ‘serotonin’. Each entry found was examined to see the context that the word ‘serotonin’ was used. If it seemed that the entry referred to a gene that when mutated caused changed levels of serotonin it was included in the database. Due to the limitations of all of these search strategies it is likely that many relevant genes were missed. Therefore the current database should be considered a preliminary sub-sample of the entire group of relevant genes. Readers can submit additions to the list by emailing the corresponding author.

In sum these searches resulted in a database listing approximately 100 mice, the majority of which were either heterozygous or homozygous single-gene knockouts. However, a few were more complex genetic models such as over-expressers or knock-ins of specific alleles, etc.

For the GO analysis we used Princeton University Lewis-Sigler Institute for Integrative Genomics “GOTERMFINDER” website at <http://go.princeton.edu/cgi-bin/GOTermFinder>. This tool is based on “GO::TermFinder” software written by Gavin Sherlock and Shuai Weng at Stanford University and the “GO::View” module by Shuai Weng³⁶. We selected the ontology aspect “process” with the *M. musculus* annotation. The results return a list of GO terms ordered by statistical significance (Bonferroni corrected P-values) for more details on the statistical analysis see reference ³⁶. We arbitrarily analyzed the first 30 GO terms returned, which had a P value less than E-6 and a false discovery rate of 0.00.

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Figure 1. Two Venn diagrams of genes that affect brain serotonin levels separated by which category of biological process each gene affects, as determined by Princeton University's Gene Ontology Term Finder. The graphs were created in MATLAB, and the sizes of each circle are relative to how many genes fall under each category. (A) Mutations that increase serotonin. The red circle is for amine-related biological processes (n=24), and the yellow circle is for apoptosis-related biological processes (n=20). (B) Mutations that decrease serotonin. The red circle is for forebrain/developmental biological processes (n=17), the yellow circle is for apoptosis-related biological processes (n=10), and the blue circle is for amine-related biological processes (n=10).

Table 1

A list of mouse models with changes in the brain serotonin system (serotonin or in a few cases the serotonin metabolite 5-HIAA). Serotonin was measured in a variety of different ways therefore changes in serotonin levels are accurate only to a first approximation and cannot be rigorously compared between cases.

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
<i>Adra2c</i> ³⁷	• Knockout of adrenergic receptor alpha 2c (<i>Adra2c</i>)	• Decreased	None	Yes	9016344
APP 21,23	• Triple transgenic mouse model B6; 129- <i>Psen1^{tm1MprTg}</i> (APPSwe, tauB301L) <i>1LfaJ</i>)	• Decreased	Alzheimer's disease	No	25947203; 12895417
<i>Apt7a</i> ⁶	• X-linked mottled locus mutation of <i>Apt7A^{Mo-br}</i> gene	• Increased	Menkes disease	Yes	8174230
<i>BDNF</i> ³⁰	• Knockdown of brain-derived neurotrophic factor (BDNF) • Genotype: +/-	• Decreased	None	No	17156118
CACNA 1B ^{38, 39}	• Knockout of N-type Ca ²⁺ channel α_{1B} subunit (<i>Cav2.2</i>)	• Both	Myoclonic dystonia	No	19963013; 19004821
<i>Cdk5r1</i> ⁴⁰	• Knockout of cyclin-dependent kinase 5 (<i>Cdk5r1</i>)	• Increased	Attention-deficit/hyperactivity disorder (ADHD)	Yes	20832057
<i>Celf6</i> ³²	• Knockout of CUGBP Elav-like family member 6 (<i>Celf6</i>)	• Decreased	Autism spectrum disorder (ASD)	Yes	23407934
<i>Cnr1</i> ⁴¹	• Transgenic construct inserted in-frame with the start codon of the bacterial artificial chromosome (BAC) RP240-370M5 containing the cannabinoid receptor locus (<i>Cnr1</i>)	• Increased	Schizophrenia	yes	24239560

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
Ddc ⁴²	<ul style="list-style-type: none"> Knock-in of aromatic L-amino acid decarboxylase gene (Ddc or Aadc) 	<ul style="list-style-type: none"> Decreased 	Dyskinesia	No	23275025
Deaf1 ⁴³	<ul style="list-style-type: none"> Knockout of deformed epidermal autoregulatory factor-1 (Deaf1) gene 	<ul style="list-style-type: none"> Decreased 	Depression	No	22232550
Dhcr7 ⁴⁴	<ul style="list-style-type: none"> Inborn error in 3β-hydroxysteroid 7-reductase (Dhcr7), Homozygous recessive 	<ul style="list-style-type: none"> Increased 	Smith-Lemli-Opitz syndrome	No	14659996
En2 17,19	<ul style="list-style-type: none"> Knockout of engrailed 2 gene (En2) 	<ul style="list-style-type: none"> Both 	Autism spectrum disorder (ASD)	No	26002543; 16935268
Esr2 ⁴⁵	<ul style="list-style-type: none"> Knockout of estrogen receptor 2 (Esr2) Nonsense mutation 	<ul style="list-style-type: none"> Decreased 	Anxiety	Yes	15642619
Fev 46, ⁴⁷	<ul style="list-style-type: none"> Knockout of Pet-1 transcription factor 	<ul style="list-style-type: none"> Decreased 	None	No	26529643; 19204984
Gabra1 ⁴⁷	<ul style="list-style-type: none"> GABA-A receptor agonist inhibits the medullary raphe 	<ul style="list-style-type: none"> Decreased 	None	No	19204984
Gpx1 ¹⁰	<ul style="list-style-type: none"> Triple knockout of Park2, Park7, and Gpx1 genes 	<ul style="list-style-type: none"> Increased 	Parkinson's disease (PD)	Yes	24075852
Gria1 ^{48, 49}	<ul style="list-style-type: none"> Knockout of glutamate receptor, ionotropic, AMPA1 alpha 1 (Gria1) 	<ul style="list-style-type: none"> Decreased 	Major depressive disorder (MDD)	Yes	18492725; 15344919
Gtf2ird 1 ⁵⁰	<ul style="list-style-type: none"> Knockout of Gtf2ird1 gene 	<ul style="list-style-type: none"> Increased 5-HIAA 	Williams-Beuren syndrome (WBS)	No	17680805
Hmbs ⁵¹	<ul style="list-style-type: none"> Heterozygous mutation in third heme pathway enzyme porphobilinogen deaminase (Hmbs or Pbgd) 	<ul style="list-style-type: none"> Increased 	Acute intermittent porphyria (AIP)	No	8550820

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
Hmox1 ⁵²	<ul style="list-style-type: none"> • GFAP:HMOX1 transgenic mice • Overexpression of heme oxygenase-1 (HO-1) 	<ul style="list-style-type: none"> • Increased 	Schizophrenia	No	22875919
Hprt1 ^{25,26,27,28,29}	<ul style="list-style-type: none"> • Knockout of purine salvage pathway enzyme hypoxanthine-guanine phosphoribosyl transferase (Hprt)⁴ 	<ul style="list-style-type: none"> • Decreased 	Lesch-Nyhan syndrome	No	2573408; 27206901; 27029809; 1777100; 27185277
Htr1a ^{7,8}	<ul style="list-style-type: none"> • Knockout of 5-hydroxytryptamine (serotonin) receptor 1a (5-HT1A or HTR1A) 	<ul style="list-style-type: none"> • Increased 	Anxiety	Yes	11483665; 11080193
Htt ²⁴	<ul style="list-style-type: none"> • CAG repeat expansion in Huntingtin gene (HTT) • Autosomal dominant 	<ul style="list-style-type: none"> • Decreased 	Huntington disease (HD)	No	21483838
Ido1 ⁵³	<ul style="list-style-type: none"> • Knockout of IDO1 gene 	<ul style="list-style-type: none"> • Decreased 	None	No	27316339
Kcnj6 ⁵⁴	<ul style="list-style-type: none"> • Point mutation of KCNJ6 gene • Homozygous recessive • Creates the weaver mutant mice 	<ul style="list-style-type: none"> • Increased 	None	No	8490719
Kif1c ⁵⁵	<ul style="list-style-type: none"> • Knockdown of homeobox gene Sax2 	<ul style="list-style-type: none"> • Increased 	None	No	17879320
Lep ^{56,57}	<ul style="list-style-type: none"> • Leptin-deficient ob/ob mouse 	<ul style="list-style-type: none"> • Increased 	Obesity	Yes	21903748; 1382044
Lmx1b ³¹	<ul style="list-style-type: none"> • Conditional knockout of Lmx1b gene • -/- mice are embryonic lethal 	<ul style="list-style-type: none"> • Decreased 	Depression	No	21945798
Lphn3 ⁵⁸	<ul style="list-style-type: none"> • Knockout of latrophilin 3 gene (Lphn3) 	<ul style="list-style-type: none"> • Increased 	Attention deficit hyperactivity disorder (ADHD)	No	27247960

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
Lrrk2 ¹²	<ul style="list-style-type: none"> • Transgene insertion 340 (Tg(PDGFβ-LRRK2*G2019S)/340Djmo) 	<ul style="list-style-type: none"> • Increased 	Parkinson's disease (PD)	Yes	21494637
Mage12 ⁵⁹	<ul style="list-style-type: none"> • Knockout of Type II melanoma-associated antigen (Mage12) gene 	<ul style="list-style-type: none"> • Decreased 	Prader-Willi Syndrome (Gene is in-activated, along a few others)	No	19199291
Maoa ⁶⁰	<ul style="list-style-type: none"> • Knockout of monoamine oxidase A (Maoa) 	<ul style="list-style-type: none"> • Increased 	None	No	9159177
Mao-a/b ⁹	<ul style="list-style-type: none"> • Knockout of monoamine oxidase A/B genes (Mao-A/B) 	<ul style="list-style-type: none"> • Increased 	Serotonin syndrome	No	22964922; 15272015
Mao-a/b ⁶¹	<ul style="list-style-type: none"> • Transversion at nucleotide in exon 8 of monoamine oxidase A (Maoa) creates spontaneous nonsense mutation at residue 284, replacing a lysine • Disruption of monoamine oxidase B (Maob) by insertion of neo cassette in exon 6, causing nonsense mutation 	<ul style="list-style-type: none"> • Increased 	None	Yes	15272015
Mecp2 ^{18, 62, 63}	<ul style="list-style-type: none"> • Knockout of X-linked methyl-CpG binding protein 2 (MECP2), causing deficiency 	<ul style="list-style-type: none"> • Decreased 	Rett syndrome	Yes	21609470; 15002050; 20633611
Mouse chromosome 7C ⁶⁴	<ul style="list-style-type: none"> • Duplication of mouse chromosome 7C (orthologous to human chromosome 15q11-13) 	<ul style="list-style-type: none"> • Decreased 	Autism spectrum disorder (ASD)	No	21179543
Nos1 ⁶⁵	<ul style="list-style-type: none"> • Nitric oxide synthase 1 (Nos1) knockout 	<ul style="list-style-type: none"> • Increased 	None	Yes	14609545
Nos3 ⁶⁶	<ul style="list-style-type: none"> • Knockout of endothelial nitric oxide synthase (eNOS) 	<ul style="list-style-type: none"> • Decreased 	Implicated in stroke, renal and heart failure	No	12882365

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
Nr4a2 ⁵	• Knockout of nuclear receptor subfamily 4, group A, member 2 (Nurr1 or NR4A2)	• Increased	Schizophrenia, Parkinson's disease	Yes	17457314
Pah ^{67, 68}	• Homozygous recessive mutation of <i>Pah^{tm2}</i> gene	• Decreased	Phenylketonuria	Yes	22107842; 12499868
Park2 ¹⁰	• Triple knockout of Park2, Park7, and Gpx1 genes	• Increased	Parkinson's disease (PD)	Yes	24075852
Park7 ¹⁰	• Triple knockout of Park2, Park7, and Gpx1 genes	• Increased	Parkinson's disease (PD)	Yes	24075852
Pex13 ²⁰	• Missense mutation (I326T) in peroxisome biogenesis 13 gene (PEX13)	• Decreased	Zellweger syndrome	no	24881576
Pitx3 ⁶⁹	• Knockout of paired-like homeodomain transcription factor 3 (Pitx3)	• Increased	Parkinson's disease (PD)	Yes	23159831
Plat ⁷⁰	• Knockout of tissue plasminogen activator (tPA)	• Decreased	None	No	20156421
Pen1 ^{21, 23}	• Triple transgenic mouse model B6; 129- <i>Psen1^{tm1MparTg}</i> (APPswe, tauB301L)1LfaJ	• Decreased	Alzheimer's disease	No	25947203; 12895417
Pen ⁷¹	• Knockdown of phosphatase and tensin homolog (PTEN) gene	• Decreased	Cancer/Autism Spectrum Disorder	No	21508359
Pis ⁷²	• Knockout of 6-pyruvoyltetrahydropterin synthase gene (Pis)	• Decreased	Hyperphenylalaninemia	No	12734191
Rn4 ⁷³	• Knockdown of Nogo-A gene	• Increased	Schizophrenia	No	24478657
Sirt1 ⁷⁴	• Knockout of Sirtuin 1 gene (Sirt1)	• Increased	Anxiety	No	22169038

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
Slc13a1 ⁷⁵	• Knockout of NaS1 sulfate transporter	• Decreased	None	No	18007198
Slc6a3 ⁷⁶	• Knockout of dopamine transporter (DAT)	• Increased	None	No	23417514
Slc6a4 ^{77,78,79}	• Knockout of solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (Slc6a4 or 5-HTT or SERT)	• Decreased	Autism spectrum disorder (ASD)	Yes	9547354; 10841514; 16380550
Slc6a8 ⁸⁰	• Knockout of CrT; slc6a8 gene	• Increased	Creatine deficiency	Yes	21249153
Sncα ⁸¹	• Expression of human A53T mutant alpha-synuclein (or SNCA) under PDGFβ promoter • <i>PDGF-βA53T-synuclein-transgenic</i> mice	• Decreased	Parkinson's disease	No	26201615
Sncα ¹¹	• Conditional expression of mutant Sncα in dopamine neurons	• Increased	Parkinson's disease	yes	19630976
Sod1 ²²	• Transgenic mice that carry SOD1 (G86R) mutation	• Decreased	Amyotrophic lateral sclerosis ¹⁴	No	23114367
SPR ⁸²	• Knockout of sepiapterin reductase gene (Spr)	• Decreased	Phenylketonuria	No	16532389
Tacr1 ⁸³	• Knockout of NK1 receptor	• Increased	Depression	No	22155476
Tat ⁸⁴	• Transgenic mice with brain-specific doxycycline-induced TAT expression	• Increased	HIV	No	27211061
Tau B301L ^{21,23}	• Triple transgenic mouse model B6; 129- <i>Psen1^{ImMport}Tg</i> (APPswe, tauB301L)1LfaJ	• Decreased	Alzheimer's disease	No	25947203; 12895417

Gene Name	Mutation	Serotonin Change: Increased, Decreased, or Both	Related Disorder	Available at Jackson Laboratory?	Source PMID
Tdo2 ⁵³	• Knockout of TDO2 gene	• Increased	None	No	27316339
Tgfa ⁸⁵	• Transgene insertion 42 (Tg(MTGF42Lmb))	• Increased	None	yes	7617706
Tph2 ⁸⁶	• R439H Tph2 Knock-in mice	• Decreased	Major depressive disorder (MDD)	Yes	18212115
Tph2 ⁸⁷	• Knockout of tryptophan hydroxylase 2 gene in dark agouti rats	• Decreased	None	No	26869713
Ube3a ⁸⁸	• Maternal deletion of Ube3a gene	• Increased	Angelman syndrome (AS)	Yes	22916201
Ucn/Ucn2 ⁸⁹	• Double knockout of urocortin 1 and 2 genes (Ucn1/2)	• Increased	Anxiety	No	19884890