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Exploring the Validity of Proposed Transgenic Animal Models of Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract Attention-deficit/hyperactivity disorder (ADHD) is a common, behavioral, and heterogeneous neurodevelopmental condition characterized by hyperactivity, impulsivity, and inattention. Symptoms of this disorder are managed by treatment with methylphenidate, amphetamine, and/or atomoxetine. The cause of ADHD is unknown, but substantial evidence indicates that this disorder has a significant genetic component. Transgenic animals have become an essential tool in uncovering the genetic factors underlying ADHD. Although they cannot accurately reflect the human condition, they can provide insights into the disorder that cannot be obtained from human studies due to various limitations. An ideal animal model of ADHD must have face (similarity in symptoms), predictive (similarity in response to treatment or medications), and construct (similarity in etiology or underlying pathophysiological mechanism) validity. As the exact etiology of ADHD remains unclear, the construct validity of animal models of ADHD would always be limited. The proposed transgenic animal models of ADHD have substantially increased and diversified over the years. In this paper, we compiled and explored the validity of proposed transgenic animal models of ADHD. Each of the reviewed transgenic animal models has strengths and limitations. Some fulfill most of the validity criteria of an animal model of ADHD and have been extensively used, while there are others that require further validation. Nevertheless, these transgenic animal models of ADHD have provided and will continue to provide valuable insights into the genetic underpinnings of this complex disorder.

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is a complex neurodevelopmental condition characterized by the core symptoms of hyperactivity, impulsivity, and inattention [1]. Diagnosis of ADHD has been on the rise since it was recognized as a distinct disorder in the 1970s. Currently, the worldwide prevalence rate of ADHD is approximately 5 to 7%, making it the most common psychiatric disorder among children [1–3]. Although most frequently diagnosed during childhood, ADHD may continually affect an individual throughout life. Studies have shown that about 30 to 50% of children with ADHD may continue to show symptoms of the disorder during adulthood [4, 5]. ADHD is also associated with other psychiatric disorders including anxiety, depression, personality disorders, and substance abuse [6, 7]. Thus, this disorder has serious academic, financial, and social implications that can cause a significant burden to the patient and the patient's family members.

Symptoms of ADHD are usually managed by pharmacological treatment. Currently, the most commonly used and approved medications for ADHD are methylphenidate, amphetamine, and atomoxetine [8]. Other drugs such as guanfacine, bupropion, and clonidine are also being considered as alternative medications [8]. Methylphenidate (Ritalin® or Concerta®) is the most prescribed stimulant drug for ADHD, accounting for approximately 70% of patients who are under stimulant treatment [9, 10]. Amphetamine (Adderall®) is also a psychostimulant drug proven to be effective in managing ADHD symptoms in children [11]. Methylphenidate and amphetamine work by antagonizing

the action of dopamine and norepinephrine transporters, thereby increasing extracellular dopamine and norepinephrine levels. Moreover, there is evidence that these drugs affect the serotonergic system [12–14]. Atomoxetine (Strattera®) is a nonstimulant medication pharmacologically classified as a norepinephrine reuptake inhibitor. Similar to psychostimulants, atomoxetine also increases extracellular norepinephrine and dopamine levels in the brain [15]. The fact that ADHD drugs act by increasing brain monoamine levels clearly indicates that disturbances in monoaminergic neurotransmission are involved in the pathophysiology of ADHD.

Despite this information, the exact cause of ADHD remains unknown. There are no known objective biomarkers of ADHD, and diagnosis is predominantly behavioral and based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) [1]. Further complicating the nature of this disorder is its heterogeneity; ADHD is a clinically heterogeneous disorder presenting as various combinations of hyperactivity, impulsivity, and inattention symptoms [1, 16]. Despite its heterogeneity, there is compelling evidence that ADHD has a significant genetic component. Studies have shown that ADHD is a highly heritable disorder, with heritability estimated at 76% [2, 17]. Consistent with disturbances in monoaminergic neurotransmission, associations have been found in genes that are involved in dopamine, norepinephrine, and serotonin neurotransmitter systems. Polymorphisms in genes that encode D4 and D5 subtypes of the dopamine receptor (*DRD4* and *DRD5*), dopamine transporter (*DAT*), norepinephrine transporter (*SLC6A2*), serotonin (5-hydroxytryptamine) transporter (*SLC6A4*), and serotonin 1B receptor (*HTR1B*) have been found [2, 17–21]. Positive associations have also been found in genes that generate products that interact with these neurotransmitter systems, such as catechol-O-methyltransferase (*COMT*), monoamine oxidase A (*MAOA*), dopamine β-hydroxylase (*DBH*), and *SNAP-25* (a protein-coding gene that plays a major role in the regulation of neurotransmitter release and synaptic function) [2, 17–21]. Furthermore, several other gene variants have also been associated with ADHD; these include *BDNF*, *CHRNA4*, *ADRA2A*, and others [2, 17–21]. The abundance of genes linked to ADHD indicates that the genetic factors underlying the spectrum of abnormal behaviors in this disorder are complex.

Transgenic animals have become an essential tool in uncovering the genetic underpinnings of various human psychiatric disorders, including ADHD. Although animal models cannot accurately reflect the human condition, they can yield insight into the disorder that cannot be obtained from human studies due to numerous limitations [22]. A transgenic animal pertains to an animal in which there has been a deliberate modification of the genome, either through the addition of foreign genetic information or specific inhibition of endogenous gene expression [23]. The use of transgenic animal models [knockout (KO), knockin (KI), knockdown (KD), overexpressing (OE), or mutant animals] in ADHD research has been on the rise (Fig. 1). These animal models have confirmed or refuted previous ADHD theories, have contributed novel insights into the genetic underpinnings of this complex disorder, and have provided an opportunity to screen for potential treatment strategies. In this paper, we compiled and discussed the validity of currently proposed transgenic animal models of ADHD. We included models from various species provided that the genetic modification is clearly defined. Those with unknown genetic origins or based on environmental or chemical interventions were not included (for reviews of these animal models, see [22, 24]).

Criteria for Validating Animal Models of ADHD

Animal models of psychiatric disorders are usually evaluated and validated with regard to three criteria: (1) face validity, (2) construct validity, and (3) predictive validity [22, 25, 26]. *Face validity* refers to the similarity of symptoms between the animal model and the human condition. In the case of ADHD, an ideal animal model must recapitulate the key symptoms of hyperactivity, impulsivity, and inattention. However, animal models that demonstrate some or specific symptoms of the disorder (e.g., inattention) can also be used to represent specific clinical forms of the disorder (predominantly inattentive ADHD) [16, 22]. There are various techniques in modeling hyperactivity, impulsivity, and inattention in animals, and the validity of these techniques has been discussed in a previous review (see [22]). *Predictive validity* involves similarity in response to pharmacological, psychological, and/or surgical treatments. In animal models of ADHD, predictive validity can be displayed as attenuation of symptoms by drugs that are effective in humans (e.g., methylphenidate, amphetamine, and atomoxetine). *Construct validity* concerns the similarity in etiology or underlying pathophysiological mechanism that induces the symptoms of the disorder. As the exact etiology of ADHD is still unknown, the construct validity of putative animal models of the disorder would always be limited [16, 22, 24]. However, it is important to note that ADHD is commonly associated with dysfunction in the monoaminergic system. Therefore, construct validity in animal models of ADHD can be established, in some measure, by demonstrating alterations of the monoaminergic system [16, 24]. In summary, animal models of ADHD must display hyperactive-, impulsive-, and/or inattentive-like behavior (face validity); respond to methylphenidate, amphetamine, and/or atomoxetine treatment (predictive validity); and display some alterations in the monoaminergic system (construct validity).

Transgenic animal models included in this review were further classified into two categories. Those with face, predictive, and construct validity that was confirmed by at least two independent researchers were classified as highly validated

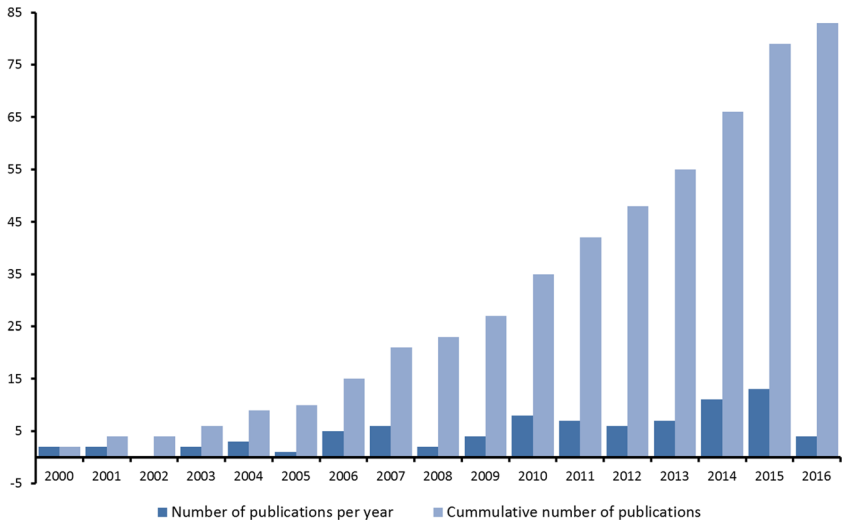

Fig. 1 Trend of publications in PubMed (Medline) that conform to the phrase "transgenic animal model of ADHD" from 2000 to 2016. Data were obtained from http://dan.corlan.net/medline-trend.html. Accessed May 3, 2017

transgenic animal models of ADHD (Table 1). Those that did not meet this criterion were classified as potential animal models of ADHD that warrant further validation (Table 2).

Proposed Transgenic Animal Models of ADHD

Highly Validated Transgenic Animal Models of ADHD

The DAT-KO Mouse

The dopamine transporter knockout (DAT-KO) mouse is perhaps the most characterized transgenic animal model of ADHD and has been extensively discussed in previous studies [16, 27, 28]. It lacks the dopamine transporter (*Slc6a3*) gene that encodes the DAT protein, which is responsible for the reuptake or clearance of dopamine from the synaptic cleft into presynaptic nerve terminals. The development of the DAT-KO as an animal model of ADHD was based partly on the therapeutic utility of methylphenidate and amphetamine [16]. As aforementioned, these psychostimulant drugs inhibit and/or reverse the function of DAT, thereby decreasing dopamine clearance and increasing extracellular dopamine levels [29]. Likewise, dopamine clearance is very slow in DAT-KO mice (approximately 300 times slower than wild-type or normal counterparts), causing a 5-fold increase in extracellular dopamine levels in the brain [16, 28]. The apparent disconnection between the rate of dopamine clearance and dopamine level (300-fold decrease in dopamine clearance vs. 5-fold increase in dopamine levels) in this mouse model is probably due to various compensatory mechanisms [16].

Table 1 Highly validated transgenic animal models of ADHD

Name	Description	Face validity	Predictive validity	Construct validity[a]
DAT-KO mouse	Mouse that lacks the dopamine transporter gene (*Slc6a3*)	Hyperactivity Impulsivity Inattention	Hyperactivity ameliorated by MPH and AMPH	Dopaminergic alterations
Coloboma mutant or Snap25-mutant mouse	Mouse with mutation on chromosome 2 and disruptions in approximately 20 genes, including *Snap25*	Hyperactivity Impulsivity Inattention	Hyperactivity ameliorated by AMPH, but not by MPH	Dopaminergic and norepinephrinergic alterations
NK1R-KO mouse	Mouse functional ablation of the neurokinin 1 receptor (NK1R) or *Tacr1* gene	Hyperactivity Impulsivity Inattention	Hyperactivity reduced by AMPH and MPH, impulsivity by ATO	Dopaminergic, norepinephrinergic, and serotonergic alterations
TRβPV-KI mouse	Mouse that carries a mutant human thyroid hormone receptor beta gene	Hyperactivity Impulsivity Inattention	Hyperactivity ameliorated by MPH	Dopaminergic alterations
P35-KO mouse	Mouse lacking the Cdk5-activating cofactor p35	Hyperactivity	Hyperactivity ameliorated by MPH and AMPH	Dopaminergic alterations

MPH methylphenidate, *AMPH* amphetamine, *ATO* atomoxetine

[a] Construct validity is always limited and, in this paper, was based on alterations in the monoaminergic system

Face Validity As an animal model of ADHD, the DAT-KO mouse shows spontaneous hyperactivity in both home cage and novel environments [12, 16]. It also exhibits impaired attention and/or learning and memory deficits in various behavioral tests, such as the Y-maze, 8-arm maze, prepulse inhibition, and novel-object recognition [16, 30–32]. Yamashita et al. [33] have also demonstrated that this mouse model displays impulsive-like behavior in the cliff-avoidance test, a test based on the natural tendency of animals to avoid a potential fall from a height. These findings show that the DAT-KO mouse displays ADHD-like behaviors (hyperactivity, inattention, impulsivity) and therefore has face validity as an animal model of ADHD.

Predictive Validity Similar to ADHD patients, treatment with amphetamine and methylphenidate reduced the hyperactivity in DAT-KO mice [12, 16]. Methylphenidate also ameliorated the inattentive- and impulsive-like behaviors in these mice [33, 34]. The effectiveness of these drugs on mice lacking the DAT protein seems paradoxical given that their mechanisms of action are thought to be dependent on DAT. This finding, however, suggests that the therapeutic effects of these drugs are not solely based on the dopaminergic system and most likely involve other neurotransmitter systems. Indeed, dopamine concentration in the striatum of DAT-KO mice is not affected by treatment with amphetamine and methylphenidate [12, 16]. Administration of drugs acting on the serotonergic system also reduced the hyperactivity of DAT-KO mice [16]. Moreover, the norepinephrine reuptake inhibitor, atomoxetine, rescued cognitive deficits in DAT-KO mice without affecting hyperactivity [35]. Taken together, these studies support the predictive validity of the DAT-KO mouse as an animal model of ADHD, as its ADHD-like behaviors were attenuated by treatment with methylphenidate, amphetamine, and/or atomoxetine.

Construct Validity Aside from dopaminergic alterations, the validity of the DAT-KO mouse as an animal model of ADHD is supported by numerous lines of evidence associating aberrations in the *DAT* gene and DAT-mediated processes with the pathogenesis of ADHD [16, 20, 21, 36, 37]. Brain imaging studies have also found decreased DAT levels in patients with ADHD [38, 39]. However, other studies have found conflicting results, such as increased DAT levels in the striatum of children and adults with ADHD [40–42]. Therefore, the definite role of DAT in the etiology of ADHD remains unclear, and thus, the construct validity of the DAT-KO mouse remains partial. Nevertheless, the DAT-KO mice is currently the most validated transgenic animal model of ADHD and has provided valuable information concerning the neurobiological consequences of impaired DAT function whether in relation to ADHD or not.

The Coloboma Mutant or Snap25-Mutant Mouse

The coloboma mutant mouse is a mouse strain developed from neutron irradiation bearing a mutation on chromosome 2 and disruptions in approximately 20 genes, including phospholipase C beta-1 (*Plcb1*), jagged 1 (*Jag1*), and synaptosomal-associated protein 25 kDa (*Snap25*) [43–46].

Face Validity The coloboma mutant mouse was proposed as an animal model of ADHD because it displays neurodevelopmental and behavioral deficits suggestive of ADHD [45]. In particular, this mutant mouse showed spontaneous locomotor hyperactivity in the open-field test [44, 47]. It also demonstrated impaired latent inhibition, indicating inattention, and was incapable of waiting as long as control mice to obtain a greater reinforcer on the delayed reinforcement task, indicating impulsivity [43]. These behaviors (hyperactivity, inattention, and impulsivity) give the coloboma mutant mouse face validity as an animal model of ADHD.

Predictive Validity Hyperactivity in the coloboma mutant mouse was reduced by treatment with amphetamine [44, 47]. However, methylphenidate failed to attenuate the hyperactivity, but rather increased the locomotor activity of this mutant [47]. Thus, the predictive validity of this animal model is limited due to the contradicting behavioral effects of amphetamine and methylphenidate.

Construct Validity Among the disrupted genes in the coloboma mutant mouse, the *Snap25* gene has attracted much interest since *SNAP25* polymorphisms have been associated with ADHD [48–50]. SNAP25 is an integral part of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor), a protein complex essential for the docking and fusion of synaptic vesicles with the presynaptic membrane for the release of neurotransmitters [48, 50]. The functionality of SNAP25 is deficient in the coloboma mutant mouse, and transgenic rescue of SNAP25 expression reduced the hyperactivity in this mutant [51]. This result indicates that behavioral alterations in this mutant mouse are indeed due to SNAP25 dysfunction [44]. SNAP25 dysfunction is also thought to underlie the profound reduction of dopamine release in the dorsal striatum of this mutant [52]. In addition, dopamine D2 receptor expression is increased in the ventral tegmental area and substantia nigra, a pattern consistent with inhibition of dopamine neuron activity [24, 53]. Alterations in the noradrenergic system such as an increased norepinephrine concentration in the striatum, locus coeruleus, and nucleus accumbens were also observed [54]. Experimental depletion of norepinephrine reduced hyperactivity and restored latent inhibition but not impulsivity, suggesting that the noradrenergic system is also involved in the

Table 2 Potential transgenic animal models of ADHD that warrant further validation

Name	Description	Face validity	Predictive validity	Construct validity[a]
GC-C-KO mouse	Mouse in which guanylyl cyclase-C gene has been knocked out	Hyperactivity Inattention Impulsivity	Hyperactivity ameliorated by AMPH	Dopaminergic alterations
per1b-KO zebrafish and Per1-KO mouse	Zebrafish and mouse with targeted mutation (inactivation) of the *per1b* and *Per1* gene, respectively	Hyperactivity Impulsivity Inattention (evaluated in zebrafish only)	Hyperactivity and impulsivity in zebrafish was ameliorated by MPH	Dopaminergic and norepinephrinergic alterations
PI3Kγ-KO mouse	Mouse lacking class IB phosphoinositide 3-kinases (PI3Kγ)	Hyperactivity Inattention	Hyperactivity and inattention ameliorated by MPH	Dopaminergic and norepinephrinergic alterations
CK1δ-OE mouse	Mouse overexpressing the δ subunit of the casein kinase 1 (CK1δ) in the forebrain	Hyperactivity	Hyperactivity ameliorated by AMPH and MPH	Dopaminergic alterations
Sts-deficient or 39XY*O mouse	Mouse with deletion of the steroid sulfatase (*Sts*) gene due to end-to-end fusion of the X and Y chromosome	Hyperactivity Inattention	–	Serotonergic alterations
GAT1-KO mouse	Mouse lacking the gamma-aminobutyric acid transporter 1 (GAT1) gene	Hyperactivity Inattention Impulsivity	Hyperactivity ameliorated by MPH and AMPH	–
nAChR β2-KO mouse	Mouse with deletion of the gene that encodes for the β2-subunit of the nicotinic acetylcholine receptor	Hyperactivity Impulsivity Inattention	–	Dopaminergic alterations
ADF/n-cofilin-KO mouse	Double mutant mouse lacking both actin depolymerizing factor (ADF) and n-cofilin	Hyperactivity Impulsivity	Hyperactivity and impulsivity ameliorated by MPH	–
GIT1-KO mouse	Mouse with deletion of the G-protein-coupled receptor kinase interacting protein 1 (GIT1) gene	Hyperactivity	Hyperactivity reduced by AMPH and MPH	–
DGKβ-KO mouse	Mouse with deletion of the DGKβ (*Dgkb*) gene	Hyperactivity Inattention	Hyperactivity, but not inattention, ameliorated by MPH	*No alteration in dopaminergic neurons and receptors*
Gβ5-KO mouse	Mouse lacking the type 5G protein beta subunit (Gβ5) gene	Hyperactivity	*Hyperactivity not ameliorated by AMPH and ATO*	Dopaminergic alterations
Fmr1-KO mouse	Mouse with deletion of the fragile X mental retardation 1 (*Fmr1*) gene	Hyperactivity Inattention Impulsivity	*Hyperactivity not ameliorated by MPH*	–
Ptchd1-KO mouse	Mouse with inactivation of the *Ptchd1* gene	Hyperactivity Inattention	*Hyperactivity not ameliorated by AMPH*	–
NOS1-KO mouse	Mouse with ablation of the neuronal nitric oxide synthase (*Nos1*) gene	Hyperactivity Impulsivity	–	–
mAChR M_1-KO mouse	Mouse with deletion of the gene that encodes for the M_1 subtype of the muscarinic acetylcholine receptor	Hyperactivity	*Hyperactivity not ameliorated by AMPH*	Dopaminergic alterations
Brinp1-KO mouse	Mouse lacking the bone morphogenetic protein (BMP)/retinoic acid (RA)-inducible neural-specific protein 1 (BRINP1)	Hyperactivity	*Hyperactivity not ameliorated by MPH*	–
Cdh13-KO mouse	Mouse with genetic ablation of the cadherin-13 (Cdh13) gene	Hyperactivity	–	–

(–) not determined or no information; italicized data indicates negative or opposite findings

MPH methylphenidate, *AMPH* amphetamine, *ATO* atomoxetine

[a] Construct validity is always limited and, in this paper, was based on alterations in the monoaminergic system

hyperactive phenotype of this animal model [16, 43, 55]. These alterations in the monoaminergic system (hypoactive dopamine, hyperactive norepinephrine systems) support the construct validity of this animal model. The coloboma mutant or *Snap25*-mutant mouse has the potential to become a useful animal model of ADHD.

The NK1R-KO Mouse

Mice with functional ablation of the neurokinin 1 receptor (NK1R) or *Tacr1* (tachykinin receptor 1) gene (NK1R-KO) have been proposed as an animal model of ADHD [56, 57]. NK1Rs are G-protein-coupled receptors that are expressed in the brain and are activated by the binding of substance P [57]. Substance P is a tachykinin neuropeptide that is concentrated in brain regions involved in motor control, mood, and cognitive performance. The NK1R-KO mouse was originally designed to investigate the mechanism of action of antidepressants.

Face Validity It was serendipitously discovered that the NK1R-KO mouse shows locomotor hyperactivity in various experimental settings [58–61]. Further studies revealed that this mouse also exhibits inattentive- (increased rate of omissions) and impulsive-like (increased premature responses) behaviors in the 5-Choice Serial Reaction-Time Task (5-CSRTT), a task which emulates procedures used to study attention and response control in patients with ADHD [62–65]. These results indicate that the NK1R-KO mouse has good face validity as an animal model of ADHD, as it displays the core behavioral symptoms (hyperactivity, inattention, and impulsivity) of the disorder.

Predictive Validity The behavioral abnormalities of the NK1R-KO mouse were ameliorated by treatment with ADHD drugs, namely methylphenidate (hyperactivity), amphetamine (hyperactivity but not impulsivity), and atomoxetine (impulsivity) [57, 61, 65, 66]. These results further strengthened the proposal that the NK1R-KO mouse can be used as an animal model of ADHD.

Construct Validity The construct validity of the NK1R-KO mouse is based on the findings that this mouse has alterations in dopaminergic, norepinephrinergic, and serotonergic neurotransmissions [57–59, 67, 68]. Moreover, evidence for an association between a polymorphism of the human *TACR1* gene and ADHD has been established [56, 61]. Thus, the NK1R-KO mouse is a promising transgenic animal model of ADHD.

The TRβPV-KI Mouse

The TRβPV knockin (TRβPV-KI) mouse carries a mutant human thyroid hormone receptor beta gene (TRβPV), which was obtained from a patient diagnosed with resistance to thyroid hormone (RTH) [16, 69, 70]. RTH is a heritable disease characterized by elevated serum thyroid hormone [triiodothyronine (T3) and thyroxine (T4)] levels and reduced responsiveness of the pituitary gland and peripheral tissues to the actions of thyroid hormone [70, 71]. Thyroid hormones are important in the development of several brain areas regulating attention, locomotion, impulsive behavior, and neurotransmitter dynamics [70, 72]. Moreover, maternal thyroid hormone dysfunction can cause severe defects in brain development which might lead to ADHD [73].

Face Validity The proposition that the TRβPV-KI mutant mouse can be utilized as an animal model of ADHD was based on the observation that this mouse demonstrates increased locomotor activity in a familiar, but not in a novel environment [69, 70, 74]. In addition, this mutant mouse also exhibited inattentive- (slow reaction times and inaccuracy in an operant task) and impulsive-like (inability to inhibit response in an operant task) behaviors [69, 70, 74]. In addition, similar to human ADHD, behavioral deficits in the TRβPV-KI mouse persist into adulthood even after normalization of thyroid hormone levels [70].

Predictive Validity Treatment with methylphenidate alleviated the hyperactivity in the TRβPV-KI mutant mouse, but the effect was only transient as values returned to baseline levels within an hour [70]. This result suggests that this mouse has a degree of predictive validity as an animal model of ADHD.

Construct Validity The TRβPV-KI mouse showed elevated dopamine turnover in the striatum [70]. This alteration in dopamine availability and the response to methylphenidate treatment suggest that behavioral changes in this mouse are related to the dopaminergic system. Adding support to the construct validity of the TRβPV-KI mouse is the observation that 50–70% of children with RTH also show symptoms of ADHD [71, 75], suggesting a correlation or a common mechanism between abnormalities of the thyroid system and ADHD. Further studies with the TRβPV-KI mouse might contribute to elucidating the role of the thyroid system in the pathophysiology of ADHD.

The P35-KO Mouse

Cyclin-dependent kinase 5 (Cdk5) is a neuronal serine/threonine protein kinase that plays an important role in normal brain development, neuronal migration and differentiation, membrane transport, and corticogenesis [76–78]. Moreover, Cdk5 influences dopamine neurotransmission by regulating synthesis, vesicle release, and postsynaptic responses [76, 77]. The activity of Cdk5 is dependent upon its association with either the p35 or p39 cofactors [79–81]. Given its role in neuronal development and dopamine signaling, there is possibility that Cdk5 dysregulation may contribute to the etiology of ADHD. Mice with targeted disruption of Cdk5 display severe brain abnormalities and are nonviable [82]. On the other hand, mice lacking the Cdk5-activating p35 cofactor (P35-KO) are viable but with defects in cortical lamination.

Face Validity The P35-KO mouse manifests locomotor hyperactivity reminiscent of ADHD [76, 77]. Interestingly, this hyperactivity was observed only in juvenile and not in adult P35-KO mice [77]. Currently, however, there is no information regarding the inattention- and impulsivity-related behaviors of this mutant mouse.

Predictive Validity

The validity of the P35-KO mouse as an animal model of ADHD is supported by the findings that hyperactivity in this mouse is ameliorated by treatment with methylphenidate and amphetamine [76, 77].

Construct Validity Dopaminergic activity is altered in the brain of P35-KO mice; increased tyrosine hydroxylase (TH) protein levels, increased dopamine synthesis and content, decreased dopamine degradation, increased prefrontal cortex (PFC) innervation by TH-positive fibers, and increased protein kinase A activity were observed in the PFC and/or striatum [76, 77]. Furthermore, the P35-KO mice exhibited glucose uptake in their cerebral cortex, which is indicative of hypermetabolic brain activity [76]. These findings support the predictive validity of the P35-KO mouse as an animal model of ADHD.

Potential Transgenic Animal Models of ADHD That Warrant Further Validation

The GC-C-KO Mouse

Guanylyl cyclase-C (GC-C), also known as guanylate cyclase 2c, is a membrane receptor for the gastrointestinal peptide hormones guanylin and uroguanylin and was thought to be mainly expressed on intestinal mucosal cells [83, 84]. However, Gong et al. [84] discovered that GC-C is also strongly and selectively expressed in dopaminergic neurons in the ventral tegmental area and substantia nigra compacta of mice. It was also found that GC-C can affect the firing of midbrain dopaminergic neurons by potentiating the responses mediated by acetylcholine and glutamate receptors via the activity of protein kinase G (PKG) [84]. Knockout of the GC-C gene in mice (GC-C-KO) significantly reduced extracellular dopamine levels in the striatum, further indicating that GC-C plays a role in dopaminergic neurotransmission. Behavioral phenotypes of GC-C-KO mice mimic the core symptoms of ADHD, displaying behaviors of locomotor hyperactivity in a familiar environment, and impaired behavioral inhibition (impulsivity) and lower ratio of correct responses (inattention) in a go/no-go task [84]. Treatment with amphetamine and 8-Br-cGMP (a PKG activator) reduced the hyperactive behavior of GC-C-KO mice [84]. Thus, the GC-C-KO mouse has face, predictive, and construct validity. With further validation and confirmation by other researchers, the GC-C-KO is a promising animal model of ADHD.

The per1b-KO Zebrafish and Per1-KO Mouse

Dysfunctions in circadian rhythm have been implicated in various psychiatric disorders, including ADHD [85, 86]. However, the role of the circadian clock on the pathogenesis of ADHD is not entirely clear. A recent study by Huang et al. [85] showed that targeted mutation (knockout) of the circadian gene *period1b* (*per1b*), an ortholog of the human *PER1* gene, resulted in the manifestation of ADHD-like behaviors in zebrafish (*Danio rerio*) (per1b-KO zebrafish). Specifically, per1b-KO zebrafish displayed swimming hyperactivity, learning deficits, or inattentive-like behavior in the active avoidance conditioning paradigm—a well-established method for examining learning in fish, and impulsivity (i.e., inability to wait) in a two-choice serial reaction-time task. Treatment with methylphenidate or selegiline, a monoamine oxidase inhibitor, rescued the hyperactivity and impulsivity of this mutant. Further analysis revealed that per1b-KO zebrafish has low levels of dopamine, high levels of norepinephrine, and altered dopaminergic neuron development. Moreover, knockout of the *Per1* gene in mice (Per1-KO mouse) also resulted in hyperactive and impulsive-like behaviors, reduced dopamine levels, and dysregulation of dopamine-related genes [85]. This result indicates that the role of this circadian gene in ADHD is highly conserved. Taken together, these findings suggest that disruption of the *Per1* or *per1b* circadian gene produces ADHD-like behaviors and that per1b-KO zebrafish and Per1-KO mice have face (hyperactivity, inattention, and impulsivity), predictive (respond to methylphenidate treatment), and construct (altered dopaminergic and norepinephrinergic transmission) validity as animal models of ADHD. The use of mice or zebrafish as animal models of ADHD has its advantages and disadvantages. For instance, the mouse, as a mammal, may be more behaviorally similar to humans, while zebrafish as a diurnal species may be more useful in studying circadian-related processes and are readily available for high-throughput drug screens.

The PI3Kγ-KO Mouse

Phosphoinositide 3-kinases (PI3Ks) are a family of intracellular signaling enzymes that regulate important cellular functions, such as cell growth, proliferation, migration, differentiation, and survival [87, 88]. Studies have found that class IB PI3Ks (PI3K**γ**) are present in neurons and are involved in synaptic plasticity and behavioral flexibility [89, 90]. A recent study by D'Andrea et al. [91] found that *PI3Kγ*-deficient (PI3Kγ-KO) mice show some symptoms of ADHD, such as hyperactivity, deficits in attention in an attentional set-shifting test, impaired spatial memory, and social dysfunction. The

hyperactivity and attention deficits in this mouse were ameliorated by methylphenidate treatment. Brain analysis demonstrated that dopamine and norepinephrine levels were altered in the prefrontal cortex and striatum of these mutants. Moreover, it was found that PI3Kγ is particularly enriched in the noradrenergic neurons of the locus coeruleus and that PI3Kγ regulates ADHD-related behaviors through modulation of cAMP-CREB signaling in this brain region [91]. Thus, the PI3Kγ-KO mouse has a degree of face (hyperactivity and inattention), predictive (response to methylphenidate treatment), and construct (altered dopamine and norepinephrinergic system) validity as an animal model of ADHD.

The CK1δ-OE Mouse

Another proposed model of ADHD is mice overexpressing the δ subunit of the casein kinase 1 (CK1δ) in the forebrain. CK1δ is a member of the highly conserved protein kinase family and plays a crucial role in numerous biological functions [92]. In the CNS, CK1δ regulates the phosphorylation of DARPP-32 (dopamine- and cAMP-regulated phosphoprotein MW of 32 kDa), a protein that integrates synaptic signals from dopaminergic and glutamatergic afferents [93]. Zhou et al. [94] reported that mice overexpressing the CK1δ in the forebrain (CK1δ-OE mouse) showed locomotor hyperactivity, reduced anxiety, and nesting behavior deficiencies. Treatment of methylphenidate and amphetamine not only reduced hyperactivity but induced hypoactivity in this mutant mouse. The dopamine antagonists, SCH23390 and haloperidol, also rescued the hyperactivity of CK1δ-OE mouse. Moreover, CK1δ overexpression led to reduced dopamine D1 and D2 receptor expression in the brain, indicating that CK1δ dynamics have a profound effect on the dopaminergic system. Taken together, the CK1δ overexpressing mice have some face (hyperactivity), predictive (response to amphetamine and methylphenidate treatment), and construct (alteration in the dopaminergic system) validity as an animal model of ADHD.

*The Sts-Deficient or 39XY*O Mouse*

The 39XY*O mouse possesses an end-to-end fusion of the X and Y chromosome pseudoautosomal region [95]. As a result of this genetic manipulation, the 39XY*O mice lack the ADHD-associated gene, steroid sulfatase (*Sts*) [95, 96]. *Sts* encodes for the steroid sulfatase enzyme that catalyzes the desulfation of endogenous steroids, notably the neurosteroid hormone dehydroepiandrosterone (DHEAS) to DHEA [95]. This hormone is involved in various neuronal functions, including cognition and attention [95, 97]. Several studies have shown that 39XY*O mice display behavioral phenotypes associated with ADHD such as hyperactivity, inattention, and occasional aggression [95, 98, 99]. Interestingly, however, this mutant mouse exhibited lower levels of impulsive-like behavior than its wild-type counterpart [97]. This result provides evidence that attention and impulsivity are dissociable, and suggests that the 39XY*O mouse can be useful in modeling ADHD without impulsivity (i.e., the inattentive subtype of ADHD). Behavioral alterations in this mutant mouse are attributed to increased serotonin levels in the striatum and hippocampus [98, 99]. Thus, the 39XY*O (Sts-deficient) mouse has a degree of face (hyperactivity and inattention) and construct (altered serotonergic system) validity as an animal model of ADHD. However, the predictive validity of this promising animal model still needs to be established.

The GAT1-KO Mouse

It has been hypothesized that ADHD is caused by "disinhibition" of neuronal activities in the brain. In line with this view, researchers are examining the role of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, in ADHD [100, 101]. Like other neurotransmitters, the action of GABA in the synaptic cleft is terminated by its transporter, the gamma-aminobutyric acid transporter (GAT). Mice in which the gene for the GAT subtype 1 (GAT1) (*Slc6a1*), the major isoform in the central nervous system, was knocked out (GAT1-KO) displayed hyperactive-, inattentive-, and impulsive-like behaviors [101, 102]. GAT1-KO mice also exhibited impairments in spatial learning and memory in the Morris water maze [102]. The hyperactivity in these mice was reduced by both methylphenidate and amphetamine [101]. These results indicate that the GAT1-KO mouse has face and predictive validity as an animal model of ADHD. However, the construct validity of this mouse is still limited, as the state of the monoaminergic system in this mouse and the role of GAT and the GABAergic neurotransmission in relation to ADHD are still unclear.

The nAChR β2-KO Mouse

Mice with deletion of the gene that encodes the β2 subunit of the nicotinic acetylcholine receptor (nAChR β2-KO) have been proposed as an animal model of ADHD [103]. The utility of this mouse as a model of ADHD is supported by the findings that patients with ADHD showed polymorphism of nicotinic acetylcholine receptor subunits and other ADHD models showed dysregulation of nicotinic pathways [104–106]. In addition, nicotinic acetylcholine receptors are known to affect monoamine dynamics in the brain [104, 105, 107]. The nAChR β2-KO mouse manifests the behavioral symptoms of ADHD: hyperactivity, inattention, and impulsivity [103, 108, 109]. It also displayed abnormal mesolimbic dopamine neuron firing [103]. These behavioral and dopaminergic abnormalities can be rescued by nicotine treatment [103, 108]. However, there are currently no reports regarding

the effects of ADHD drugs on these mutants. Thus, the nAChR β2-KO mouse has face (hyperactivity, inattention, and impulsivity) and construct (alterations in mesolimbic dopamine neuron firing) validity, but no studies have yet confirmed its predictive validity. Further studies are needed to establish the suitability of this mouse as an animal model of ADHD.

The ADF/n-Cofilin-KO Mouse

The actin depolymerizing factor (ADF)/cofilin family members are abundant in the brain and play an important role in neuronal development and synaptic function [110, 111]. Double mutant mice lacking genes that encode for ADF and n-cofilin (ADF/n-cofilin-KO mouse) exhibited hyperactivity, impulsivity, and impaired working memory [112]. Treatment of methylphenidate ameliorated the hyperactivity and impulsivity in these mutants [112]. Pharmacological blockade of dopamine and glutamate transmission also normalized locomotor activity [112]. Interestingly, ADHD-like behaviors were not exhibited by single-mutant mice lacking the gene for ADF or n-cofilin only [112]. This result indicates that the ADHD-like behaviors in the ADF/n-cofilin-KO mice are produced by specific gene-gene interactions. Altogether, the ADF/n-cofilin-KO mice presented face (hyperactivity and impulsivity) and predictive (response to methylphenidate) validity as an animal model of ADHD and highlight the involvement of gene-gene interactions in ADHD.

The GIT1-KO Mouse

The G-protein-coupled receptor kinase interacting protein 1 (GIT1) is known to regulate the endocytic traffic of β2-adrenergic receptors and interact with other G-protein-coupled receptors, such as dopamine receptors [113, 114]. A study by Won et al. [115] has implicated the *GIT1* gene in the pathophysiology of ADHD. In a study conducted among Korean children, they found that polymorphism in the *GIT1* gene is strongly associated with susceptibility to ADHD [115]. Mice with genetic deletion of the *Git1* gene (GIT1-KO) exhibited hyperactive behavior, impaired learning and memory, and enhanced electroencephalogram theta rhythms. The hyperactivity of the GIT1-KO mouse was ameliorated by methylphenidate and amphetamine treatment [115]. In addition, impaired learning and memory and enhanced theta rhythms were also normalized by amphetamine treatment [115]. In contrast, however, another strain of GIT1-KO mice did not demonstrate hyperactivity [116]. Other studies also failed to find an association between the *GIT1* gene and ADHD [117, 118]. In summary, the GIT1-KO mouse might have a degree of face (hyperactivity) and predictive validity (hyperactivity reduced by methylphenidate and amphetamine), but its suitability as an animal model of ADHD is hampered by conflicting reports. Thus, further study and validation are required to establish the GIT1-KO mouse as an animal model of ADHD.

The DGKβ-KO Mouse

Diacylglycerol kinase β (DGKβ) is an enzyme that regulates many intracellular signaling pathways in the central nervous system, including those that mediate dopaminergic neurotransmission [119, 120]. The gene that encodes for DGKβ (*DKGB*) has been implicated in neuropsychiatric disorders (e.g., bipolar disorder) [121]. Deletion of the *Dgkb* gene in mice results in hyperactivity, careless behavior, and attentional deficits [122, 123]. Methylphenidate treatment ameliorated attentional deficits but not hyperactivity in this mouse. No difference in dopaminergic neurons and receptors was found when compared to its wild-type counterpart. Thus, the DGKβ-KO mouse showed some face (inattention and hyperactivity) and predictive (responded to MPH) validity as an animal model of ADHD. Detailed investigations are required to elucidate the involvement of DGKβ in the pathophysiology of ADHD.

The Gβ5-KO Mouse

The type 5G protein beta subunit (Gβ5) is a regulator of downstream signaling from G-protein-coupled receptors. As polymorphisms in monoaminergic G-protein-coupled receptors have been associated with ADHD, there is a possibility that regulators of GPCRs, such as Gβ5, may play a role in ADHD. Mice lacking the Gβ5 gene (Gβ5-KO) display hyperactivity, accompanied by motor learning deficits and impaired habituation to a novel environment [124]. They also showed deficits in basal levels, release, and reuptake of dopamine in the dorsal striatum [124]. However, treatment with amphetamine and atomoxetine failed to reduce hyperactivity [124]. Interestingly, treatment with an NMDA receptor antagonist reversed the hyperactivity in these mice [124]. Altogether, the Gβ5-KO mouse displays some face (hyperactivity) and construct (alterations in dopaminergic system) validity as an animal model of ADHD. However, as ADHD drugs failed to alleviate ADHD-like behavior, this animal model is found to have poor predictive validity. Hence, further studies are necessary to validate its potential role as a putative animal model of ADHD.

The Fmr1-KO Mouse

Fragile X syndrome is a genetic disorder caused by a mutation in the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome. It is one of the most commonly inherited forms of intellectual disability [125, 126]. Patients with fragile X syndrome often display autism- and ADHD-like features

[125, 127–129]. The *Fmr1* knockout (Fmr1-KO) mouse, the most characterized rodent model of fragile X syndrome, showed hyperactive-, inattentive-, and impulsive-like behaviors in various behavioral tests [130, 131]. However, the opposite observation has also been reported: no impairments in inhibitory control and sustained attention [131]. Moreover, it was reported that methylphenidate failed to ameliorate the hyperactivity in this mutant mouse [132]. Thus, the Fmr1-KO mouse has face validity (hyperactive-, inattentive-, and impulsive-like behavior), but there is insufficient data to support its predictive and construct validity as an animal model of ADHD.

The Ptchd1-KO Mouse

The X-linked Patched-domain containing protein 1 (PTCHD1) gene has been implicated in developmental disabilities such as intellectual disability and autism spectrum disorder [133, 134]. Individuals with *PTCHD1* deletion displayed sleep abnormality and variable degrees of intellectual disability- and autism-related behaviors [133, 134]. Interestingly, these individuals also exhibit ADHD-like symptoms of hyperactivity and attentional deficits [134, 135], suggesting an overlap between these neurodevelopment disorders. Deletion of the *Ptchd1* gene in mice (Ptchd1-KO) resulted to the development of locomotor hyperactivity and attentional and learning deficits [135]. The behavior abnormalities in this mutant were attributed to dysfunctions in calcium-dependent potassium currents in the thalamic reticular nucleus [135]. Treatment with amphetamine failed to rescue the hyperactivity of Ptchd1-KO mouse [135]. Thus, the Ptchd1-KO has some face validity (hyperactivity and inattention) but very limited predictive and construct validity. Regardless, further studies are encouraged to improve our understanding of the role of this gene in neurodevelopmental disorders.

The NOS1-KO Mouse

Nitric oxide (NO) is an important signaling molecule in the human body and modulates a variety of physiological processes such as neurotransmission, synaptic plasticity, and neurodevelopment [136, 137]. NO production in the brain is catalyzed by the enzyme, neuronal nitric oxide synthase (NOS), which is encoded by the *NOS1* gene. Clinical studies have linked the *NOS1* gene with ADHD [20, 138]. A mouse model with ablation of the gene coding for neuronal nitric oxide synthase (*Nos1*) (NOS1-KO mouse) was explored as a possible animal model for ADHD [136]. The NOS1-KO mouse exhibited sustained locomotor hyperactivity in the open-field test and learning impairments or impulsive-like behavior in a two-way active avoidance and passive avoidance task. These behavioral features (hyperactivity and impulsivity) support the face validity of the NOS1-KO mouse as animal model of ADHD. However, the effects of ADHD drugs and the state of the monoaminergic systems in this mutant mouse remain to be characterized.

The mAChR M_1-KO Mouse

Muscarinic acetylcholine receptors (mAChR) play critical roles in the regulation of several important functions of the CNS including cognitive processing, emotional behavior, and locomotor activity [139]. There are five subtypes of mAChR, namely M_1, M_2, M_3, M_4, and M_5. The M_1 subtype of the mAChR is abundantly expressed in higher brain regions, including the amygdala, striatum, hippocampus, and cerebral cortex [140, 141]. Mice with deletion of the gene that encodes for the M_1 subtype (mAChR M_1-KO mouse) consistently displayed hyperactivity under various conditions [142, 143]. No other ADHD-related behavior alterations were found. This mouse also showed elevated dopaminergic transmission in the striatum [142]. However, hyperactivity was not ameliorated by treatment with amphetamine; instead, this mouse showed an increased response to the stimulatory effects of the drug [142]. In conclusion, the mAChR M_1-KO mouse showed some face (hyperactivity) and construct (elevated dopaminergic transmission) validity but currently lacks predictive validity as an animal model of ADHD.

The Brinp1-KO Mouse

Genome-wide association studies have associated *BRINP1* (bone morphogenetic protein (BMP)/retinoic acid (RA)-inducible neural-specific protein 1) with various neurological disorders including Parkinson's disease, schizophrenia, and dementia [144–146]. BRINP1 is a member of the Membrane Attack Complex/Perforin (MACPF) family and is predominantly expressed in the nervous system [147]. The physiological role of this protein is not entirely understood but is suggested to function in cell cycle regulation, neurogenesis, neuronal maturation, and neural plasticity [147–149]. Recent studies have found that *Brinp1*-knockout (Brinp1-KO) mice display reduced sociability, impaired ultrasonic vocalization, altered short-term memory, reduced anxiety-like behavior, and locomotor hyperactivity [148, 149]. These behaviors seem to show face validity for schizophrenia, the social communication deficits of autism spectrum disorder, and the hyperactivity phenotype of ADHD. However, methylphenidate does not affect hyperactivity in these mice [149], indicating that more studies are needed before Brinp1-KO mice can be considered as an animal model of ADHD.

The Cdh13-KO Mouse

Cadherin-13 is a cell adhesion molecule that plays a major role in neuronal development and plasticity [150]. Clinical studies

have identified Cadherin-13 (*CDH13*) as a risk gene for ADHD and other comorbid neuropsychiatric conditions, including substance abuse or drug addiction [21, 150, 151]. Recent studies have shown that mice with genetic ablation of the *Cdh13* gene (Cdh13-KO) show hyperactivity and learning difficulties, with no inattention and impulsivity [152, 153]. Thus, the Cdh13-KO mouse might be useful in modeling the hyperactive aspect of ADHD. Currently, however, there is no information regarding the effect of ADHD drugs and the state of monoaminergic systems in this mouse model. Further studies are needed to establish the worth of this transgenic mouse as an animal model of ADHD.

Conclusion

Animal models are valuable tools in untangling the complicated nature of complex psychiatric disorders such as ADHD. Although they cannot completely reflect the human condition, they can provide insights into the disorder that cannot be obtained from human studies due to various constraints. An ideal animal model of ADHD must have face (similarity in symptoms), predictive (similarity in response to treatment or medications), and construct (similarity in etiology or underlying pathophysiological mechanism) validity. The construct validity of putative animal models of ADHD would always be limited as the exact etiology of ADHD remains unclear.

The use of transgenic animals in ADHD research has substantially increased and diversified over the years, concurrently with the progress in human ADHD genetic studies and consistently with the heterogeneous nature of this disorder. Here, we have accumulated and discussed the validity of these transgenic animals. Since our understanding of ADHD is still limited, it is not possible to conclude which transgenic animal would best represent ADHD. Each of the proposed transgenic animal models of ADHD has strengths and limitations. Some fulfill most of the validity criteria of an animal model of ADHD, while there are others that only show specific behaviors, which may be useful in modeling distinct clinical isoforms of the disorder. There are also some that carry mutation on genes implicated by human ADHD genetic studies (e.g., *DAT*, *SNAP25*, *PER1*, *SLC6A1*, *GIT1*, *NOS1*, and *CDH13*) [17, 20, 21]. Several other ADHD-related behaviors have not been modeled or characterized yet (see [17, 20, 21]) and continued efforts in establishing and validating transgenic animal models are encouraged. However, it is most likely that no single gene or transgenic animal model can represent the whole spectrum of ADHD, and that complex gene-gene, gene-environment interactions must also be taken into consideration. Nevertheless, findings obtained from current transgenic animal models of ADHD have provided unprecedented insights into the genetic underpinnings of this complex disorder.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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