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Transgenic Mouse Models of Childhood Onset Psychiatric Disorders

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Abstract

Childhood onset psychiatric disorders, such as Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Mood Disorders, Obsessive Compulsive Spectrum Disorders (OCSD), and Schizophrenia (SZ), affect many school age children leading to a lower quality of life, including difficulties in school and personal relationships that persists into adulthood. Currently, the causes of these psychiatric disorders are poorly understood resulting in difficulty diagnosing affected children, and insufficient treatment options. Family and twin studies implicate a genetic contribution for ADHD, ASD, Mood Disorders, OCSD, and SZ. Identification of candidate genes and chromosomal regions associated with a particular disorder provide targets for directed research, and understanding how these genes influence the disease state will provide valuable insights for improving the diagnosis and treatment of children with psychiatric disorders. Animal models are one important approach in the study of human diseases, allowing for the use of a variety of experimental approaches to dissect the contribution of a specific chromosomal or genetic abnormality in human disorders. While it is impossible to model an entire psychiatric disorder in a single animal model, these models can be extremely valuable in dissecting out the specific role of a gene, pathway, neuron subtype, or brain region in a particular abnormal behavior. In this review we discuss existing transgenic mouse models for childhood onset psychiatric disorders. We compare the strength and weakness of various transgenic animal models proposed for each of the common childhood onset psychiatric disorders, and discuss future directions for the study of these disorders using cutting-edge genetic tools.

Childhood onset psychiatric disorders including Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Mood Disorders, Obsessive Compulsive Spectrum Disorders (OCSD), and Schizophrenia (SZ) affect many school age children. These children typically have a lower quality of life, including difficulties in school and personal relationships, and these problems persist into adulthood. Additionally, the treatment and support of these individuals causes severe financial and social burdens on society. Currently, the causes of these psychiatric disorders are poorly understood. This lack of knowledge results in difficulty diagnosing affected children, and insufficient treatment options.

Family and twin linkage studies implicate a genetic contribution for ADHD, ASD, Mood Disorders, OCSD, and SZ (Hudziak and Faraone, 2010). In some cases single, rare genetic mutations lead to childhood onset psychiatric disorders (Hudziak and Faraone, 2010). Additionally, there is a hypothesis that other cases are multigenic, with many genes

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contributing small effects leading to the overall disease state (Hudziak and Faraone, 2010). Developmental and environmental factors can also influence the severity of symptoms observed in affected individuals leading to a “spectrum” of behaviors (Dick et al., 2010). Identification of candidate genes and chromosomal regions associated with a particular disorder provide targets for directed research, and understanding how these genes influence the disease state will provide valuable information for improving the diagnosis and treatment of children with psychiatric disorders.

Animal models are one method commonly utilized in the study of human diseases. Specifically, animal models can overcome many of the confounding factors that limit research in human patients including genetic variability and environmental diversity. Some benefits of using transgenic mice to model human diseases include genetically homogeneous populations, greater control over environmental conditions, shorter time between generations, pharmacological studies, and the opportunity for genetic manipulations. The generation of transgenic mouse models can therefore allow for a controlled approach in evaluating the consequences of a specific chromosomal or genetic abnormality observed in human patients.

There are however limitations to using animal models to study psychiatric disorders. Most importantly, there are many behaviors of psychiatric disorders that are currently impossible to evaluate in a mouse model. For example, obsessive thinking in OCD, and hallucinations in SZ cannot be assessed in mice. Thus, researchers are limited to modeling behaviors of psychiatric disorders that can be assessed in a mouse including hyperactivity, social interactions, anxiety, and some types of learning and memory (Crawley, 2007). However, it is important to note that even behaviors that can be assessed in a mouse are not an exact replica of human behavior. At best, we can make correlations between the observed mouse behavior and known human behaviors in these disorders.

It is also impossible to model an entire psychiatric disorder in a single animal model. Psychiatric disorders are complex disorders, and current technology cannot expect to encompass the entirety of such a complex disorder within a single model (Laporte et al., 2008). A more realistic approach is to model a specific behavior, or single genetic mutation associated with a disorder in an individual model. These models can then be used to dissect out the specific role of a gene, pathway, neuron subtype, or brain region in a particular behavior.

Establishing a transgenic mouse as a model of a psychiatric disorder requires face, construct, and predictive validity. Face validity refers to the resemblance of the mouse model phenotype to the symptoms of the human disorder. In some cases, rodent behaviors can be directly correlated to human symptoms. For example, pre-pulse inhibition (PPI), a test of sensory-motor gating, can be evaluated in both humans and rodents (Geyer, 2008). Other behaviors in mice are correlative to human behaviors. For example, tests to show anxiety-like behaviors in a mouse include time spent in the open section of the elevated plus maze and emergence to light in the light dark emergence test. These particular behaviors are not observed in humans with anxiety; however the observation of the behavior in the mouse is sufficient to draw a positive correlation in some cases. Table 1 lists behavior tests commonly used in characterizing mouse models of psychiatric disorders.

Construct validity refers to similarities in the mouse model to the underlying cause of the human disorder. Gene association and linkage studies can implicate certain genes which are then targeted in transgenic mouse models and therefore partially address construct validity. Finally, predictive validity refers to the expected response in the mouse model to treatments

as observed in human patients. Establishing predictive validity is helpful for evaluating the potential of future novel therapies for a particular disorder.

In this review we will discuss transgenic mouse models for childhood onset psychiatric disorders. We will introduce the currently proposed transgenic animal models for common childhood onset psychiatric disorders, and discuss future directions for the study of these disorders using cutting-edge genetic tools. We apologize that due to page limitations, we were unable to list all relevant references in this review.

I. Attention Deficit Hyperactivity Disorder

ADHD is one of the most prevalent childhood psychiatric disorders affecting an estimated 8–12% of school age kids (Biederman and Faraone, 2005). ADHD was originally described by Bradley et al. in the 1930s. They observed that treatment with sedatives paradoxally resulted in increased activity in children with what they called minimal brain damage (now called ADHD) (Bradley, 1937). Additionally, administration of stimulants to these children resulted in normalized behavior (Bradley, 1937). Today ADHD is characterized by hyperactivity, impaired sustained attention, impulsivity, and distractibility (APA, 2000).

Family, twin, and adoption studies confirm genetics play an important role in susceptibility to ADHD (Sharp et al., 2009). Genome wide linkage analysis studies identified peak regions on chromosome 3, 4, 5, 6, 7, 9, 10, 11, 15, 16,17, and 20 (Sharp et al., 2009). Genetic studies of candidate genes within these ADHD linkage regions found association of genes involving the dopamine, serotonin, glutamatergic and adrenergic systems (Sharp et al., 2009).

Many of the current animal models of ADHD are pharmacological or environmental models, which will not be discussed in this review (For an extensive review of these models see (Kostrzewa et al., 2008)). Here we will focus on transgenic mouse models of ADHD.

DAT KO

The dopamine transporter (DAT) facilitates the recycling of extracellular dopamine (DA) (Giros et al., 1996). DAT is a major target for psychostimulants including cocaine and amphetamine as found through pharmacological studies (Giros and Caron, 1993, Heikkila et al., 1975). In addition, genetic studies show polymorphisms in the *DAT* gene are associated with increased risk of ADHD (Xu et al., 2009), although there are also studies that fail to identify an association (Langley et al., 2005).

Generation of DAT null (DAT KO) mice led to overall and specific growth disorders, such as dwarfism, as well as increased premature death (Bosse et al., 1997). Behavior studies show DAT KO mice are more active in home cage environments and novel environments as found in the open field test, and show defects in spatial memory as measured by performance in the radial arm test (Gainetdinov et al., 1999). Administration of psychostimulants (methylphenidate, dextroamphetamine, and cocaine) attenuates hyperactivity in DAT KO mice (Gainetdinov et al., 1999). The ability of psychostimulants to attenuate hyperactivity in DAT KO mice suggests a possible secondary mechanism of action for psychostimulants, possibly through their effect on other monoamine transporters (Hall et al., 2009, Riddle et al., 2007).

Administration of the selective serotonin reuptake inhibitor (SSRI) fluoxetine and the nonselective 5-HT receptor agonist quipazine blocks hyperactivity in DAT KO mice (Gainetdinov et al., 1999). The selective 5-HT2A R antagonist M100907 also reduced hyperactivity in DAT KO mice (Barr et al., 2004). This effect of serotonin on hyperactivity may be mediated by glutamatergic signaling, as blockade of NMDARs prevented the

inhibitory effects on locomotor activity in DAT KO mice by psychostimulants and serotonin drugs (Gainetdinov et al., 2001). In particular, glutamatergic and dopaminergic signaling in the cortico-striatal pathway appears to be important for effects of hyperactivity in DAT KO mice (Gainetdinov et al., 2001). There are some cases of adults with ADHD responding positively to duloxetine, a selective serotoninnorepinephrine reuptake inhibitor (SSNRI) (Tourjman and Bilodeau, 2009). However, currently few studies have explored the effectiveness of SSRIs and other antidepressants in ADHD (Verbeeck et al., 2009).

DAT KD

The DAT KO (previously described above) had developmental deficits and high levels of premature death with only 68% survival at 10 weeks of age in knockout animals (Bosse et al., 1997). Zhuang et al thought to avoid these development issues by creating a DAT knockdown (DAT KD) by introducing an additional 4Kb of sequence in the promoter region resulting in decreased transcription to 10% of the normal DAT levels. This approach successfully prevented the growth defects and high mortality rates observed in the DAT KO (Zhuang et al., 2001).

DAT KD mice exhibit hyperactive behaviors like the DAT KO mice that are alleviated by administration of amphetamines or valproate, treatments for ADHD and mania respectively (Ralph-Williams et al., 2003, Zhuang et al., 2001). Additionally, DAT KD mice show increased motivation for food rewards (Pecina et al., 2003). Specifically, DAT KD mice had higher learning acquisition and greater incentive performance for a sweet reward in a runway test (Pecina et al., 2003). The increased “wanting” in the DAT KD mouse is likened to drug seeking in models of addiction in humans. However, the increased focus on obtaining the sweet reward and how this relates to a possible contradiction of inattention in ADHD has not been addressed.

Another study looked at instrumental learning in the DAT KD mice (Yin et al., 2006). This study found DAT KD mice do not have impaired learning abilities. Interestingly though, the DAT KD mice did show a deficit in selectivity of cue control during Pavlovian training. DAT KD mice would enter the food magazine before the conditional stimulation (CS) as frequently as during the CS even though no reward was present in the magazine before the CS (Yin et al., 2006). WT mice showed clear discrimination by entering significantly more frequently during the CS than the pre-CS. The authors suggest this lack of discrimination could also represent higher “wanting” (Yin et al., 2006). How this higher “wanting” and decreased discrimination behavior might relate to impulsivity in ADHD has yet to be explored. (See also OCSD)

Coloboma Mice

The coloboma mouse was generated by neutron irradiation (Searle, 1966), which resulted in a mutation on Chromosome 2 affecting the genes *SNAP-25* (synaptosomal-associated protein 25), *PCLB-1* (phospholipase c beta-1), and *Jag1* (Jagged 1) (Hess et al., 1994). The coloboma mouse was characterized as a model of ADHD when increased spontaneous activity compared to control animals was observed in the open field test (Hess et al., 1992). Some human genetic studies show an association of *SNAP-25* to ADHD (Forero et al., 2009). However, other studies have failed to associate *SNAP-25* and ADHD (Hess et al., 1995). SNAP-25 mutant mice show deficits in PPI, however their ataxia precludes the ability to assess hyperactivity and other behaviors characteristic of ADHD (Jeans et al., 2007). Therefore, the current SNAP-25 mouse model cannot confirm *SNAP-25* is the gene causing the ADHD-like behaviors in the Coloboma mice.

Coloboma pups exhibit delayed neurodevelopmental milestones, hypersensitivity to touch, and persistent head bobbing which is not observed in control mice (Heyser et al., 1995). Unfortunately, these mice also have eye dysmorphia, delayed lens attachment, and micropthalmia (Theiler and Varnum, 1981). Therefore evaluation of behavioral tests in these mice must be interpreted cautiously.

Altered DA and norepinephrine (NE) concentration is found in the striatum and the Nucleus Acumbens (NAc) of coloboma mice, which may be a result of altered presynaptic function (Jones et al., 2001). Mutations in the *SNAP-25* gene may contribute to this phenotype as this protein is involved in docking synaptic vesicles (Jones et al., 2001). The striatum and NAc play important roles in regulating motor activity, therefore a phenotype of hyperactivity in these mice is consistent with altered transmission in these brain regions (Wachtel et al., 1979). Amphetamine administration normalizes hyperactivity in coloboma mice, which is consistent with treatment of ADHD patients (Hess et al., 1996). A recent study shows the effect of amphetamine on hyperactivity is mediated specifically through the dopamine 2 (D2) receptor subtype (Fan et al., 2010). Methylphenidate, another psychostimulant, however results in dose-dependent increases in locomotor activity (Hess et al., 1996). The difference in response to these psychostimulants is proposed to be likely due to the difference in mechanistic action between the two drugs (Hess et al., 1996). Specifically, psychostimulants are categorized on their sensitivity to pretreatment with reserpine, a drug that disrupts vesicular release by depleting vesicular stores of catecholamines. Amphetamine is not inhibited by pretreatment with reserpine, and therefore is thought to increase synaptic DA independent of vesicular release. Methylphenidate is inhibited by pretreatment with reserpine, and is therefore sensitive to vesicle depletion. The authors suggest that the opposing effects of amphetamine and methylphenidate may highlight a presynaptic defect involving SNAP-25 in coloboma mice, however the exact mechanism underlying this effect has not been explored (Hess et al., 1996).

Decreasing NE transmission by blocking the α-2C adrenergic receptor, or decreasing NE levels with systemic administration of DSP-4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride), also led to decreased hyperactivity in the coloboma mice (Bruno and Hess, 2006, Jones and Hess, 2003). This evidence further suggests the NE system plays a role in affecting hyperactivity.

Coloboma mice also exhibit inattention and impulsivity, two additional characteristics of ADHD. Specifically, coloboma mice have disrupted latent inhibition (LI), and show impaired performance in the delayed reinforcement paradigm (Bruno et al., 2007). Thus, coloboma mice demonstrate several characteristics associated with ADHD though physical defects limit the usefulness of this model.

Other ADHD Models

Some ADHD patients show evidence of subtle reductions in the thickness of the anterior and posterior corpus callosum, a structure connecting the two hemispheres of the brain and possibly involved in the control of sustained attention (Baumgardner et al., 1996). The Acallosal I/LN J mouse model is an inbred mouse line that completely lacks the corpus callosum. This mouse shows poor impulse control and learning difficulties in the Y-maze and avoidance test, and hyperactivity in the open field (Magara et al., 2000). Human cases with altered corpus callosum are associated with disorders that have both physical and mental characteristics that are unrelated to ADHD (Paul et al., 2007). Therefore, the role of the corpus callosum in human cases of ADHD might be difficult to assess due to the comorbidity of these disorders.

Thyroid hormones are critical for normal brain development, and abnormal thyroid hormone levels in utero have been linked to ADHD like behaviors (Hauser et al., 1998). Resistance to thyroid hormone (RTH) is caused by mutations in thyroid receptor β (Thrb), which results in a failure to down-regulate thyroid stimulating hormone (TSH). 70% of children diagnosed with RTH syndrome are also diagnosed with ADHD (Siesser et al., 2006). Thus, exploring the potential role of Thrb involvement in ADHD is an intriguing question. Generation of a transgenic mouse model that expresses a mutated human Thrb, Thrb knock-in (Thrb KI), results in hyperactivity in the open field test, impulsivity in the delayed reinforcement test, and inattentiveness in the reaction-time task selectively in male mice in some test conditions (Siesser et al., 2006). However, to date it is unclear how these sex differences and conditional responses may relate to ADHD in humans.

Casein Kinase 1 (CK1) is a conserved family of Ser/Thr kinases important for many cellular processes including cell signaling, circadian rhythm, and cellular trafficking (Knippschild et al., 2005). The CK1δ isoform is highly enriched in the brain (Zhou et al., 2010), and CK1 regulates the phosphorylation state of DARPP-32 (dopamine and c-AMP regulated phospho-protein MW 32 kDa), an important, striatum expressed, protein phosphatase inhibitor which integrates synaptic inputs from various sources including glutamatergic and dopaminergic inputs (Svenningsson et al., 2004). Thus, DARPP-32 is an important modulator of the Cortico-Striato-Thalamic-Cortico (CSTC) loop. Overexpression of CK1δ (CK1δ OE) in the forebrain led to down-regulation of dopamine receptors, increased hyperactivity in the open field, and decreased anxiety in the elevated plus maze and the novelty suppressed feeding paradigm, which measures the latency to initiate eating in a novel environment (Zhou et al., 2010). This hyperactivity was attenuated by treatment with methlyphenidate, sub-maximal doses of amphetamine, the dopamine 1 (D1)R agonist SKF81297, and the D2R agonist quinprole (Zhou et al., 2010). Thus, CK1δ OE is proposed as a potential new model for ADHD.

II. Autism Spectrum Disorder

ASD is a developmental disorder occurring in as many as 1:150 children, with males four times more likely to be diagnosed than females (CDC, 2009). Clinical diagnosis criteria for ASD are aberrant reciprocal social interactions, deficits in communication, and stereotyped repetitive behavior with restricted interest (APA, 2000). Currently, there are no effective pharmacological treatments for ASD.

Family and twin studies show that ASD is highly heritable (O'Roak and State, 2008). Additionally, linkage and association studies have identified several potential susceptibility loci and multiple candidate genes potentially involved in ASD (Abrahams and Geschwind, 2008). Advances in detection of copy number variations (CNVs), rare deletions, duplications, and single nucleotide polymorphisms (SNPs) identified cases of ASD with rare, single locus genetic changes that can either be inherited or de novo (Marshall et al., 2008). Finally, there is a high incidence of ASD symptoms in individuals with monogenetic disorders such as Rett Syndrome, Fragile X, Angelman Syndrome, and Downs Syndrome (Moss and Howlin, 2009). Thus ASD arises from many different genetic sources that are in some cases further influenced by environmental factors leading to high levels of variability in the severity of behaviors in affected individuals (Herbert et al., 2006).

There are several mouse models of ASD currently being investigated including environmental, pharmacological, and inbred strains that will not be covered by the scope of this review (Benno et al., 2009, Kuwagata et al., 2009, Marin et al., 2008, Patterson, 2009, Singer et al., 2009). In this review we will focus on transgenic mouse models thought to have characteristics of ASD.

Developmental Disorders with Autism-like Features

Several developmental disorders with known monogenetic causes display autistic characteristics (Reiss, 2009). Therefore, mouse models targeting these disorders may be useful in discovering brain circuits involved in the expression of autism related behaviors. While one must be cautious of non-autism related physical and mental handicaps associated with these disorders, these models are still very useful in the study of autism.

Fragile X—Fragile X is a genetic disorder that predominantly affects males and is caused by a mutation of the *Fmr1* (Fragile X mental retardation 1) gene resulting in the loss of fragile X mental retardation protein (FMRP) (Oostra, 1996). Characteristics of Fragile X include mental retardation, facial dysmorphology, macroorchidism, seizures, and autistic-like behaviors (Garber et al., 2008).

Transgenic mouse models of Fragile X show increased susceptibility to limbic seizures (Qiu et al., 2009). Additionally, deficits in spatial learning by radial arm maze, deficits in object recognition, deficits in acquiring lever-press/avoidance, and deficits in learning in the Morris water maze were observed in FMRP null mice (Brennan et al., 2006, D'Hooge et al., 1997, Mineur et al., 2002, Ventura et al., 2004). Tests of the effect of loss of FMRP on social behaviors resulted in conflicting data. Some groups identified deficits in social approach and social anxiety using the three-chamber social approach test (Mineur et al., 2006, Liu and Smith, 2009), while others found equal or increased social approach (McNaughton et al., 2008, Spencer et al., 2005). Currently, it is not clear why there are contradictory results. Differences in experimental design, controls, and animal age are potential reasons (Brodkin, 2008).

FMRP null mice have increased dendritic spine length and altered spine morphology similar to changes observed in patients with Fragile X and ASD (Irwin et al., 2000). FMRP is an mRNA binding protein that associates with polyribosomes, including dendritic polysomes, and is thought to be involved in translational regulation of specific mRNAs (Brown et al., 2001). FMRP null mice show deficits in cortical long-term potentiation (LTP), and enhanced mGluR dependent long-term depression (LTD) (Nosyreva and Huber, 2006, Zhang et al., 2009). Importantly, FMRP is hypothesized to repress mRNA translation in response to mGluR5 activation (Bear et al., 2004). In support of this hypothesis, transgenic mice with 50% reduction of mGuR5 on the FMRP null background corrected many of the phenotypes observed in the FMRP null mice including basal protein synthesis, sensitivity to audiogenic seizures, and spine density in cortical pyramidal neurons (Dolen et al., 2007). Also, the mGluR5 antagonist, MPEP, can rescue PPI in FMRP null mice (de Vrij et al., 2008). Additionally, inhibition of p21-activated kinase (PAK), a downstream target of FMRP, also rescues some phenotypes of FMRP null mice. Expression of a dominant negative PAK (dnPAK) in the forebrain corrected dendritic spine morphology, cortical LTP, and hyperactivity and anxiety as measured by the open field test in the FMRP null mice (Hayashi et al., 2007). These studies implicate potential new therapeutic targets in treating fragile X patients.

Rett Syndrome—Another genetic disorder with autistic-like behaviors is Rett syndrome (Nomura, 2005). Rett syndrome is characterized by normal development for the first 6–18 months of life followed by regression of social, language, and cognitive function, and the emergence of stereotyped hand movements, decreased brain growth, and motor impairments (Glaze, 2004). While some cases do see improvement in behavior and communication in later stages of Rett syndrome, there is not a complete return to normal behavior (APA, 2000). Rett syndrome is an X-linked disorder like Fragile X, however Rett syndrome primarily affects females with most males dying either in utero or shortly after birth

(Hoffbuhr et al., 2001). Most cases of Rett syndrome are caused by a mutation in methyl CpG binding protein 2 (Mecp2), a protein that binds to methylated DNA resulting in both gene silencing and activation (Chahrour et al., 2008).

Mecp2 mutant mice exhibit phenotypes similar to behaviors observed in patients with Rett syndrome (Stearns et al., 2007). Generation of Mecp2 null mouse lines led to onset of symptoms around 5–6 weeks of age with neurological characteristics similar to Rett syndrome including motor coordination defects (Guy et al., 2001, Chen et al., 2001a). A truncated mutation of Mecp2 also led to similar onset of characteristic features of Rett syndrome (Shahbazian et al., 2002). Studies to investigate social interactions show mice expressing truncated Mecp2 have reduced social interaction with no effect on social recognition as assessed by the partition test (Moretti et al., 2005). These mice also show deficits in long-term social memory using the social recognition test, deficits in nest building and other home cage behaviors, and impaired learning and memory in the Morris water maze and contextual fear conditioning test (Moretti et al., 2005, Moretti et al., 2006).

A Mecp2 mutant mouse with postnatal loss of expression or forebrain specific deletion still exhibits social interaction deficits in the partition test and resident intruder paradigm suggesting loss of Mecp2 plays a critical role in adult neurons in addition to its role during development (Gemelli et al., 2006, Chen et al., 2001a). Additionally, studies showing that replacement of Mecp2 in adult mice can correct defects in Mecp2 null mice including survival, motor defects, and locomotor defects, suggesting some characteristics of Rett syndrome are not irreversible developmental defects (Guy et al., 2007, Jugloff et al., 2008, Luikenhuis et al., 2004). Both Mecp2 null mice, and mice expressing truncated Mecp2 show decreased numbers of synaptic connections and deficits in synaptic plasticity (Belichenko et al., 2009, Dani and Nelson, 2009, Moretti et al., 2006). Treatment with the growth factors brain derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1) ameliorate some of the symptoms of Rett syndrome found in Mecp2 null mice (Chang et al., 2006, Tropea et al., 2009). BDNF and IGF-1 are both known to affect spine morphology through pathways involving phosphoinositide-3-kinase (PI3K) (Zheng and Quirion, 2004). Cerebrolysin (CBL), a drug known to have neuroprotective and neurotrophic activity, can ameliorate symptoms of neurodegeneration and aging, and can also ameliorate dendritic simplification in mice expressing truncated Mecp2 (Doppler et al., 2008). These studies suggest defects in dendritic spine morphology may be a contributing factor in the expression of Rett Syndrome.

15q11–13 Deletion/Duplication—Angelman Syndrome (AS) is a genomically imprinted disorder that is linked to the 15q11–13 region, and displays autistic-like behaviors (Veltman et al., 2005). Imprinted genes show expression from only one inherited copy of a gene, therefore if there is a mutation or deletion of the gene copy that should be expressed, the second copy cannot compensate resulting in loss of function. AS results from loss of the maternal copy of Ube3A (ubiquitin protein ligase E3A), a ubiquitin ligase (Clayton-Smith and Laan, 2003). Interestingly, decreased Ube3A expression has also been observed in a small number of cases of ASD and Rett syndrome (Samaco et al., 2005). Mice with a maternal deficit in Ube3a have enhanced seizure susceptibility, deficits in motor coordination, and reduced spatial learning in the Morris water maze (Miura et al., 2002). Recent studies address how Ube3a may be affecting neurological processes including cognitive impairment. Specifically, these studies show Ube3a plays an important role in experience-dependent plasticity and synapse development (Greer et al., 2010, Yashiro et al., 2009).

15q11–13 also contains several $GABA_A$ receptor (GABR) subunit genes including the *GABRB3*, *GABRA5*, and *GABRG3* genes (DeLorey et al., 2008). GABAergic signaling plays

an important role in brain development (Manent and Represa, 2007), and altered GABAergic signaling is found in some patients with ASD (Blatt, 2005). Additionally, polymorphisms in *GABRB3* have been associated with autism by a linkage and association study (Buxbaum et al., 2002).

Gabrb3 null mice have high rates of neonatal mortality (Homanics et al., 1997). Mice that survive show enhanced seizure susceptibility, abnormal motor coordination, and impaired learning and memory in the contextual fear conditioning and passive avoidance test (DeLorey et al., 1998, Homanics et al., 1997). A later study shows Gabrb3 KO mice have impaired social interaction in the partition test, and impaired nesting behaviors (DeLorey et al., 2008). Gabrb3 KO mice are also hyperactive but show stereotyped circling and decreased exploratory behavior in the open field with a novel object, which is suggested as being an index of non-selective attention in this model (DeLorey et al., 2008).

Duplication of the 15q11–13 chromosomal region is also associated with ASD. This duplication is present in up to 5% of ASD cases, and is most commonly maternally derived although evidence for paternally derived duplications is accumulating (Bolton et al., 2004, Dykens et al., 2004, Roberts et al., 2002, Schroer et al., 1998). On the basis of conserved human/mouse linkage, generation of a transgenic mouse carrying a 6.3 Mb duplication of mouse chromosome 7 mirroring the human chromosome 15q11–13 duplication was generated by Nakatani et al. Mice carrying a paternally derived 15q11–13 duplication results in poor social interaction in the three chamber social approach test, behavioral inflexibility in the Morris water maze and Barnes maze test, and abnormal ultrasonic vocalizations in both neonatal pups separated from their mother and adult mice in the resident intruder test (Nakatani et al., 2009). These mice also exhibit anxiety as measured by the elevated plus maze, and depression as measured by the forced swim test (Nakatani et al., 2009). However, mice carrying a maternally derived duplication did not show any behavioral differences when compared to WT mice (Nakatani et al., 2009). Thus, while in humans the 15q11–13 duplication is usually maternally derived, these mice do mimic a chromosomal duplication found in human ASD patients, and several autistic-like behaviors are present in the paternally derived mice suggesting this could be a good model for studying mechanisms in ASD-like behavior.

Other Developmental Disorders with Autism-like Features—Other developmental disorders with autistic-like phenotypes include tuberous sclerosis (TSC), Smith-Lamli-Ortiz Syndrome (SLOS), and Downs Syndrome (Moss and Howlin, 2009). A mouse model of TSC, Tsc1 conditional knockout, has enhanced cortical excitability, abnormal spine density and morphology, and seizures (Meikle et al., 2007). SLOS is a neurodevelopmental disorder associated with high rates of autism (Sikora et al., 2006). SLOS is caused by mutations in *DHCR7* (7-dehydrocholesterol reductase), which leads to disruption of cholesterol formation (Fitzky et al., 1998). Cholesterol levels have been shown to be important for synapse formation (Renner et al., 2009). One study has reported that cholesterol levels are low in children with autism suggesting that proteins involved in cholesterol synthesis could be candidate genes for ASD (Tierney et al., 2006). Dhcr7 null mice die soon after birth. A complex heterozygous model with a single copy deletion of Dhcr7 on one allele and a human missense mutation in the other allele, $Dhcr7^{ms/-}$ results in increased ventricular size (Correa-Cerro et al., 2006).

Overall, these studies show genes that cause various neurodevelopmental disorders may also be relevant to specific changes in autism. It is important to note that these developmental disorders also have characteristics not associated with ASD. Therefore results from behavior studies should be critiqued carefully and should consider potential complications from phenotypes not associated with ASD. One thing we can learn from these models is neural

circuits and pathways potentially involved in ASD, which may be beneficial in identifying other potential targets for the study of autism. While not all developmental disorders with autistic-like behaviors may prove to be useful in studying ASD, there is a wealth of information to be gained from these models.

Synaptic and Signaling Genes Implicated in ASD

Altered brain growth is a common characteristic of ASD (Courchesne et al., 2004). Specifically, abnormal growth in the frontal lobe cerebellum and limbic structures are observed(Courchesne, 2004). These brain regions are important for development of social behaviors, communication, and motor coordination which are disrupted in patients with ASD (Sacco et al., 2007). Many proteins and pathways critical for neuronal growth and organization have been implicated in ASD including extracellular matrix proteins, neurotrophic factors, neurotransmitters, and transcription factors.

Alterations in synaptic function have also been proposed as a fundamental mechanism underlying ASD (Zoghbi, 2003). Additionally, as mentioned previously studies in mouse models of developmental disorders with ASD-like behaviors (FMRP, Mecp2, and Ube3a) exhibit synaptic defects. Not surprisingly, many of the candidate genes identified in the new genetic studies are synaptic proteins (Freitag, 2007). Many of these candidate genes have been made into transgenic animal models and are discussed below.

Neuroligin and Neurexin—Neuroligins and neurexins are trans-synaptic cell adhesion molecules involved in the formation and maintenance of excitatory and inhibitory synapses (Craig and Kang, 2007). Genetic studies have identified variations in the neuroligin genes *NLGN1, NLGN4X*, and *NLGN3* in a few cases of ASD (Betancur et al., 2009). Genetic studies involving individuals affected with ASD also identified variations in neurexins including a 2p16.3 deletion involving *NRXN1*, rare *NRXN1* specific deletions, sequence variants in *NRXN1*, and chromosomal abnormalities involving 2p16.3/*NRXN1* (Betancur et al., 2009). However, other studies show individuals with deletions and chromosomal abnormalities involving *NRXN1* in non-affected individuals (Betancur et al., 2009). Overall, there is evidence to support a role of neuroligins and neurexins in a small number of cases of ASD, and several transgenic models have been generated to explore the role of these proteins in ASD.

Two independent groups generated a transgenic mouse model that mimicked a point mutation in *NLGN3* found in human ASD patients, NLGN R451C. Tabuchi et al reported their mice show impaired social interactions in the three chamber social approach test, enhanced spatial learning in the Morris water maze, and enhanced inhibitory synaptic transmission with no effect on excitatory transmission (Tabuchi et al., 2007). The second group, Chadman et al, did not observe the same ASD-like phenotypes in their R451C line (Chadman et al., 2008). Specifically, using the same behavioral tests, they observed no difference in social approach or spatial memory in R451C mice compared to WT mice (Chadman et al., 2008). It is not clear why there is a discrepancy between the two lines. Possible reasons include the use of different inbred strains for the genetic background, or differences in methodology between the two studies.

In addition to point mutation knock-in mice, NLGN null mice for NLGN 1, 2, 3, and 4 have also been generated. NLGN1 null mice show impaired spatial memory using the Morris water maze, and increased repetitive stereotyped grooming (Blundell et al., 2010). These mice also exhibit reduced NMDA/AMPA ratios in cortico-striatal synapses and impaired hippocampal LTP (Blundell et al., 2010). NLGN3 and NLGN4 null mice both exhibit deficits in ultrasonic vocalization and social behaviors (Jamain et al., 2008, Radyushkin et al., 2009). NLGN4 null mice display deficient social approach and social memory in the

three chamber social approach test (Jamain et al., 2008). Additionally, male NLGN4 null mice showed decreased ultrasonic vocalization when exposed to a female mouse in estrous (Jamain et al., 2008). These deficits in ultrasonic vocalization are likened to deficits in communication found in human ASD cases. NLGN3 null mice also display decreased social memory in the three chamber social approach test and decreased ultrasonic vocalizations when exposed to a female mouse in estrous (Radyushkin et al., 2009). However, NLGN3 null mice did not show deficits in social interaction (Radyushkin et al., 2009). Finally, NLGN3 null mice exhibit olfactory deficits in the buried food finding test which may account for the lack of social memory. Interestingly, some ASD patients also exhibit olfactory deficits (Bennetto et al., 2007, Suzuki et al., 2003). These models suggest NLGN variations could be important in some cases of ASD.

There are three NRXN genes (1–3), and each gene encodes for a long (α) and short (β) isoforms which differ in their extracellular domains (Betancur et al., 2009). Abnormalities in α-NRXNs but not β-NRXNs are associated with ASD (Yan et al., 2008). Triple α-neurexin KO mice were not viable, double α-neurexin KO mice survived approximately one week, and even single α-neurexin KO mice experienced impaired survival (Missler et al., 2003). Double α-neurexin KO mice show α-neurexins are not critical for synapse formation but are important in synapse function (Dudanova et al., 2007). Altered functional coupling of Ca^{2+} channels to the presynaptic membrane and decreased Ca^{+2}-mediated neurotransmitter release is observed in brain slices from α-NRXN KO mice (Missler et al., 2003). This phenotype is rescued specifically by α-NRXN not β-NRXN (Zhang et al., 2005). A study using the single deletion NRXN1-α KO mice reveals altered excitatory transmission in the hippocampus (Etherton et al., 2009). Behavioral studies show decreased PPI, impaired nest building activity, and improved motor learning on the rotorod, which measures the ability of a mouse to maintain balance on a revolving rod over increasing speeds, but no obvious social defects (Etherton et al., 2009). Thus, NRXN also shows promise as a model for studying ASD.

22q13.3/SHANK3—SHANK (SH3 and multiple ankyrin repeat domains) is a family of scaffold proteins highly enriched in postsynaptic densities (Sheng and Hoogenraad, 2007). Shanks interact with many synaptic proteins including neuroligins, glutamate receptor complexes, and the cytoskeleton acting as a master scaffold in the PSD (Gerrow et al., 2006). Interestingly, over-expression of Shank1 in vitro results in dendritic spine enlargement (Sala et al., 2001). Additionally, expression of Shank3 is sufficient to induce dendritic spine formation in aspiny neurons (Roussignol et al., 2005). Alternatively, knockdown of Shank3 leads to decreased dendritic spine size in hippocampal neurons in vitro (Roussignol et al., 2005).

The smallest deletion capable of causing 22q13.3 deletion syndrome contains three genes including the *Shank3* gene and is characterized by global developmental delays, delayed or absent speech, and autistic behaviors (Cusmano-Ozog et al., 2007). Genetic studies of individuals with 22q13.3 syndrome indicate that *Shank3* is the critical gene in this disorder (Bonaglia et al., 2006). Specifically, individuals with balanced translocations involving *Shank3* or breakpoints within the *Shank3* gene display ASD characteristics (Bonaglia et al., 2006). Additionally, individuals with ringed chromosome 22 typically have deletion of the long arm and exhibit 22q13.3 deletion syndrome characteristics. However, individuals with a ringed chromosome 22 with no disruption of *Shank3* are phenotypically normal (Jeffries et al., 2005). Additional genetic studies identified variations within the *Shank3* gene including CNVs and SNPs that are associated with ASD (Sykes et al., 2009).

Currently, there are no published transgenic models of a Shank3 knockout. A Shank1 KO generated by Hung et al exhibits increased anxiety as assessed in the light dark emergence

test and the open field, impaired contextual fear memory, and impaired long-term memory retention using the radial arm test (Hung et al., 2008). Shank1, like Shank3, affects synaptic strength and dendritic spine maturation (Sala et al., 2001). Thus, a Shank3 mutant mouse could prove to be an interesting model for the study of ASD.

BDNF—BDNF is a neurotrophic factor important for axon guidance, dendritic growth during development, synaptic modulation, induction of LTP, and certain forms of learning and memory (Greenberg et al., 2009). *BDNF* has been identified as a candidate gene for ASD susceptibility (Pardo and Eberhart, 2007). Additionally, increased plasma levels of BDNF have been reported in children diagnosed with ASD (Connolly et al., 2006).

While BDNF-null mice die shortly after birth, BDNF heterozygous (BDNF+/−) mice and conditional BDNF knockouts are viable and show altered behavioral phenotypes (Chan et al., 2006, Lyons et al., 1999). Forebrain specific deletion of BDNF resulted in males showing increased locomotor activity in the open field test, while females show increased depression-like behaviors as determined by the forced swim test and the sucrose preference test, a test of anhedonia (Monteggia et al., 2007). Targeted deletion of BDNF in either fetal or postnatal brains and BDNF+/− mice exhibit hyperactivity, increased aggression in the resident intruder test, and altered serotonergic signaling (Chan et al., 2006, Daws et al., 2007, Lyons et al., 1999, Rios et al., 2001, Rios et al., 2006). Treatment of BDNF+/− mice with fluoxetine, an SSRI, ameliorated the increased aggression (Lyons et al., 1999).

Interestingly, BDNF levels are increased in the brains of 5-HT_{2C} knockout mice (Hill et al., 2010). Reciprocally, 5-HT clearance and function are deficient in BDNF+/− mice suggesting an association between BDNF levels and serotonin signaling (Daws et al., 2007, Lyons et al., 1999). Finally, behavioral deficits found in SERT null mice are exacerbated when crossed to BDNF +/− mice suggesting the effects of SERT and BDNF may have cumulative detrimental effects (Murphy et al., 2003, Ren-Patterson et al., 2006, Ren-Patterson et al., 2005). Thus, BDNF may play a role in ASD and other psychiatric disorders, including Mood Disorders, by modulating serotonin signaling.

Another transgenic model, CADPS-2 (Ca^{2+}-dependent activator protein for secretion 2), further implicates altered BDNF function as a potential contributor of ASD characteristics. CADPS-2 is a member of a family of proteins involved in exocytosis of dense-core vesicles, and is involved in the activity-dependent release of BDNF (Sadakata et al., 2004). Cadps-2 knockout mice show impaired BDNF release (Sadakata et al., 2007). These mice also exhibit ASD-like behaviors including decreased social interactions when paired in a novel cage, maternal neglect, decreased interest in novel environments in the open field test, and home cage hyperactivity (Sadakata et al., 2007).

Serotonin Signaling—Serotonin (5-HT) signaling is involved in many neurodevelopmental processes including neurogenesis, cell migration, cell survival, synaptogenesis, and plasticity (Azmitia, 2001). Hyperserotonemia is one of the most consistent findings in patients with ASD (Hranilovic et al., 2008). Additionally, genetic studies in ASD patients identified genes involved in serotonin signaling, though some studies fail to identify these correlations (Huang and Santangelo, 2008). Finally, treatment with the SSRI fluoxetine mildly improves social behavior and decreases aggression and stereotyped behavior in children with autism (West et al., 2009). However, a new report shows no effect. Citalopram, an SSRI commonly prescribed to children with ASD, was found to be no more effective than placebo at reducing repetitive behaviors in children with ASD (King et al., 2009, Myers, 2010).

Several animals with targeted disruption of the serotonin transporter (5-HTT, SERT, SLC6A4) were generated to investigate the role of serotonin signaling. Bengel et al generated a 5-HTT null (5-HTT KO) mouse that resulted in insufficient clearing of 5-HT (Bengel et al., 1998). These 5-HTT KO mice have altered cortical thickness and cell density (Altamura et al., 2007). Interestingly, patients with variations in the 5-HTT gene have slower extracellular 5-HT clearance and show decreased gray matter volumes (Canli et al., 2005). 5-HTT null mice show greater anxiety in the elevated-plus maze, the light dark emergence test, and the open field (Carroll et al., 2007, Holmes et al., 2003). These mice also demonstrate hypoactivity, and decreased vertical activity (Kalueff et al., 2007). Additionally, these mice are more sensitive to stress than WT controls, and have altered hypothalamic-pituitary-adrenal (HPA) axis signaling (Jiang et al., 2009).

Veenstra-VanderWeele et al. identified a rare nonsynonymous variation in the serotonin transporter (Gly56Ala) in pedigrees carrying diagnoses of ASD and OCD. This Gly56Ala variant resulted in constitutively elevated SERT activity in human patients (Veenstra-Vanderweele et al., 2009). Generation of a transgenic mouse carrying the Gly56Ala variant showed normal gross morphology, though to date there has been no behavioral characterization (Veenstra-Vanderweele et al., 2009). Thus, the potential for this model is currently unknown.

PTEN—PTEN (Phosphatase and tensin homolog on chromosome ten) is a phosphatase for Phosphatidilinositol 3,4,5 triphosphate (PI3) that antagonizes signaling through the PI3K pathway and affects cellular proliferation, differentiation, and migration (Stiles, 2009). PTEN abnormalities are usually associated with syndromes including Cowden's syndrome (a disorder characterized by the development of hamartomas) and TSC, and often exhibit features such as macroencephaly, seizures, and mental retardation (Pilarski and Eng, 2004). Genetic studies show some ASD patients have variations in the *PTEN* gene (Buxbaum et al., 2007). Additionally, many individuals affected with Cowden's syndrome and TSC are also diagnosed with ASD (Goffin et al., 2001). *PTEN* variations have also been identified in some ASD patients with macroencephaly (Butler et al., 2005).

Conditional deletion of PTEN in a select population of mature neurons in the cortex and hippocampus using neuron-specific enolase (Nse)-cre results in decreased social approach when paired in a neutral cage or in the three chamber social approach test, increased activity in the open field, and impaired PPI (Kwon et al., 2006, Ogawa et al., 2007). Additionally, these mice show progressive macroencephaly. This correlates well with abnormalities observed in Cowden syndrome and may model the increased head circumference seen in autistic children (Hazlett et al., 2005). In addition to the macroencephaly and behavioral abnormalities observed in the Nse-Cre PTEN mice, there are also changes in neuronal morphology observed including loss of polarity and neuronal hypertrophy (Kwon et al., 2006, Ogawa et al., 2007). mTORC1 (Mammalian target of rapamycin complex 1) is a downstream target of PTEN (Stiles, 2009). Interestingly, a recent study shows rapamycin, a specific inhibitor of mTORC1, can reverse many of the behavioral abnormalities seen in the Nse-Cre PTEN mice (Zhou et al., 2009). These studies suggest downstream targets of PTEN may be useful therapeutic targets for treating ASD, particularly in cases associated with macroencephaly.

Oxytocin/ Vasopressin—Oxytocin (OT) is a hypothalamic neuropeptide with receptors located in various brain regions associated with anxiety and social behavior including the olfactory bulb, piriform cortex, amygdala, and lateral septum (Landgraf and Neumann, 2004). In particular, OT release can facilitate decreases in anxiety and stress responses (Parker et al., 2005). Genetic studies have identified *OT* as a candidate gene of ASD

(Gregory et al., 2009). Additionally, treatment with OT inhalation increased social interactions in individuals with ASD (Andari et al., 2010).

Three different OT null mice were generated to study the role of endogenous OT (Gross et al., 1998, Nishimori et al., 1996, Young et al., 1996). The line generated by Young and colleagues showed reduced maternal retrieval and reduced aggression when OT null mice were paired in a neutral cage (DeVries et al., 1997, Pedersen et al., 2006). Odorant detection defects were observed in female knockouts from the line generated by Gross and colleagues (Kavaliers et al., 2003). Social memory as assessed in the resident intruder test was deficient in male knockout mice from the lines generated by Nishimori and colleagues with no deficits in normal social interactions (Ferguson et al., 2000, Winslow and Insel, 2002). Additional studies found deletion of either OT or the OT receptor (OTR KO) decreased social recognition, social memory, and ultrasonic vocalizations of male pups subjected to social isolation (Lee et al., 2008, Takayanagi et al., 2005). No difference in social approach in the OT KO was found using the three chamber social approach test (Crawley et al., 2007). There were some differences in social recognition between the total OTR and the forebrain specific OTR knockout ($OTR^{FB/FB}$) (Lee et al., 2008). A follow-up studyfound male $OTR^{FB/FB}$ mice can differentiate between inter-strain females but not intra-strain females (Macbeth et al., 2009). These differences between the total and conditional OTR knockouts could be due to differences in temporal or spatial expression. Further studies to dissect the specific role of OT in the various social paradigms will be helpful in determining how OT affects social behavior.

Arginine Vasopressin (AVP), another hypothalamic neuropeptide, may also be altered in ASD (Yirmiya et al., 2006). Normal AVP function is implicated in typical male social behaviors in animals including aggression, scent marking, courtship, and pair-bonding (Carter et al., 2008). Two of the AVP receptors are expressed in the CNS, V1aR and V1bR. V1aR is located throughout the brain while V1bR is most highly expressed in the amygdala (de Vries and Miller, 1998). V1aR knockout mice show profound deficits in social recognition using ovariectamized females introduced to the home cage, and decreased anxiety in the elevated plus maze and the light dark emergence test (Bielsky et al., 2004). Social discrimination is rescued with viral reintroduction of the V1aR specifically in the lateral septum (Bielsky et al., 2005). V1bR knockout mice show reduced social aggression, reduced social motivation, and impaired social memory (Caldwell et al., 2008). V1bR KO mice also exhibit decreased ultrasonic vocalizations in social environments both as pups and adults (Scattoni et al., 2008).

Overall, OT and AVP are thought to be important for social behavior. Transgenic mouse models of OT and AVP both exhibit ASD-like behaviors. Thus, models of OT and AVP show great promise for understanding mechanisms involved in social recognition and interactions, behaviors that are severely affected in ASD.

Other ASD Models

Reelin (RELN) is an extracellular matrix protein involved in cell guidance, dendrite formation, and synaptogenesis (Tissir and Goffinet, 2003). Genetic studies show a CGG trinucleotide repeat in the 5'UTR of the *Reln* gene is associated with cases of ASD (Zhang et al., 2002). However, a separate study failed to identify an association (Krebs et al., 2002). Reeler mice have a spontaneous deletion that resulted in a loss of the majority of the *Reln* gene (Goffinet, 1984). Homozygous mice completely lack reelin, have severe structural alterations in several brain regions including the cortex, cerebellum and hippocampus, have severe ataxia or altered gait, and deficits in ultrasonic vocalizations have been recorded selectively in socially isolated male pups (Goffinet, 1984, Ognibene et al., 2007). Alternatively, heterozygous reeler mice show loss of Purkinje cells in the cerebellum and

subtle neuro-anatomical abnormalities (Tueting et al., 1999). Studies with heterozygous reeler mice show decreased PPI, deficits in odor discrimination, decreased anxiety in the elevated plus maze, and impaired conditioned fear in the active avoidance test (Marrone et al., 2006, Tueting et al., 1999), though some studies do not support these findings (Podhorna and Didriksen, 2004, Salinger et al., 2003).

Dishevelled-1(Dvl-1) is a protein involved in the Wingless-Int (WNT) signaling pathway. WNT signaling is involved in cell migration, cell survival, dendritic morphogenesis, and synapse formation. *WNT2* has been identified as a candidate gene for ASD susceptibility (Wassink et al., 2001). Targeted disruption of Dvl1 leads to altered home cage behavior, social interaction deficits including subordinate behavior in social dominance paradigms, and changes in synapse formation (Long et al., 2004). However, these mice demonstrate normal ultrasonic vocalization, spatial learning, and hippocampal synaptic plasticity (Long et al., 2004). (See also Mood Disorders)

Engrailed 2 (EN2) is a transcription factor important in neurodevelopment and is critical in the formation of specific serotonergic and noradrenergic nuclei in the mid- and hindbrain (Simon et al., 2004). EN2 is also important for the survival of specific subpopulations of dopaminergic neurons (Sgado et al., 2006). Genetic studies show SNPs of *EN2* are associated with ASD (Benayed et al., 2005), though some studies fail to confirm this (Zhong et al., 2003). EN2 knockout and missense mutant mice show a decrease in the number of purkinje neurons (Baader et al., 1998). Additionally, EN2 knockout mice show social deficits as juveniles in reduced social play and as adults in decreased aggression when paired in a neutral environment (Cheh et al., 2006). EN2 knockout mice show reduced spatial learning in the Morris water maze, and are hyperactive with impaired motor coordination as observed in the open field test (Cheh et al., 2006). A better understanding of the genes regulated by EN2 and how these genes may be involved in pathways important for the development of social behaviors may be useful in the study of ASD.

III. Mood Disorders

Bipolar disorder (BD) is a mood disorder characterized by recurrent episodes of mania (type 1) or hypomania (type 2) and episodes of depression in a single individual (APA, 2000). Other mood disorders include major depressive disorder (MDD), cyclothymia, and BD not otherwise specified. The risk of developing BD in a lifetime is approximately 1–4% (Merikangas et al., 2007). BD is highly heritable with many cases having a clear genetic basis (Barnett and Smoller, 2009). Twin studies show the concordance in MZ twins is 38.5–43% while DZ twins is only 4.5–5.6% (Kieseppa et al., 2004). Additionally, linkage and association studies have identified many chromosomal regions and candidate genes for BD (For a detailed review of BD genetics see (Barnett and Smoller, 2009))

The development of mouse models of BD with the critical feature of cycling between mania and depression is currently not established. However, there has been success in generating unipolar models of mania and depression. The discovery of genes directly linked to BD and a better understanding of the neurological basis of cycling between mania and depression will facilitate the development of more effective treatment. Several pharmacological, nutritional, and environmental models are used in the study of Mood Disorders, for a review of these models see Kato et al (Kato et al., 2007). Here we will focus on transgenic models of mood disorders.

Clock Mutant

Altered circadian processes including sleep, activity, and hormonal secretions are common characteristics found in mood disorder patients (Wood et al., 2009). Disruption of sleep/

wake cycles can trigger manic phases, while stabilization of sleep/wake cycles is often essential for mood stabilization (Boivin, 2000). Additionally, depression symptoms are more prevalent in winter months and regions that receive significantly less daylight (Saeed and Bruce, 1998). Association studies identified several circadian genes as susceptibility genes for BD including *CLOCK*, *BMAL1* (aryl hydrocarbon receptor nuclear translocator-like), *PERIOD3*, *ARNTL* (aryl hydrocarbon receptor nuclear translocator-like), *DBP* (D site of albumin promoter (albumin D-box) binding protein), and *TIMELESS* (Mansour et al., 2006).

CLOCK is a transcription factor that forms a complex with BMAL1 and induces the expression of several genes that are involved in regulating circadian rhythm through a time-delayed transcription-translation feedback loop (King and Takahashi, 2000). Disruption of the *CLOCK* gene in mice led to hyperactivity in the open field, disrupted circadian rhythms and decreased sleep determined by the running wheel test and monitoring of brain wave patterns, decreased anxiety in the open field and elevated plus maze, increased reward for sucrose and cocaine using the reward/aversion test, and reduced depression-like behavior in the forced swim test and the learned helplessness test (King et al., 1997, McClung et al., 2005, Naylor et al., 2000, Roybal et al., 2007, Easton et al., 2003). Importantly, clinically relevant doses of lithium improved the manic-like phenotype in the CLOCK mice (Gelenberg et al., 1989, Roybal et al., 2007). Additionally, reintroduction of WT CLOCK in the ventral tegmental area (VTA) returned locomotor activity and anxiety levels to near wild type control levels (Roybal et al., 2007).

The clock gene D-box binding protein (*Dbp*) is also a candidate gene for BD (Niculescu et al., 2000). Dbp null mice show lower locomotor activity in the open field and blunted response to stimulants compared to control animals as seen by atypical reduction in stereotypy behavior with administration of methamphetamines (Le-Niculescu et al., 2008). Interestingly, upon infliction of chronic stress, these mice demonstrate a change in phenotype. Specifically, sleep deprivation leads to increased activity levels, and exposure to stress leads to increased alcohol intake (Le-Niculescu et al., 2008).

POLG

Defects in mitochondrial DNA (mtDNA) and calcium homeostasis have been found in patients with BD (Stork and Renshaw, 2005). Additionally, variations in mtDNA have been associated with BD (Kato, 2002), though one study did not replicate these findings (Munakata et al., 2004).

mtDNA polymerase (POLG) mutant mice were generated to study chronic progressive external ophthalmoplegia (CPEO), a mitochondrial disorder that often has comorbidity with mood disorders (Kasahara et al., 2006). Transgenic mice with forebrain specific expression of mutant POLG exhibit several behavioral characteristics of BD including altered circadian rhythm and reduced overall wheel running activity in the running wheel test (Kasahara et al., 2006). Additionally, female but not male mice show periodic activity changes in relation to estrous (Kasahara et al., 2006). Treatment with the tricyclic antidepressant, amitriptyline, which can causes a manic-switch in BD patients also led to a manic switch-like behavioral change in the POLG mice (Kasahara et al., 2006). Specifically, administration of amitriptyline resulted in increased wheel running during the light phase and increased locomoter activity selectively in POLG mice. Importantly, lithium improves the periodic activity changes associated with the estrous cycle and circadian rhythm disruptions observed in these mice, but not the overall wheel running activity. The authors suggest the responses to tricyclic antidepressants and lithium indicate the POLG mice may be a good model for studying BD.

Glucocorticoid Receptor

Clinical studies show a majority of patients with depression have hyperactivity of the hypothalamic-pituitary-adrenal (HPA) system and elevated plasma cortisol levels (Holsboer, 2000). The glucocorticoid receptor (GR) modulates many neuronal functions including stress responsiveness and cognitive function (de Kloet et al., 1999). Additionally, BAG-1(BCL2-associated athanogene), a GR co-chaperone, was found to be a target of mood stabilizers further implicating this pathway as important in BD (Zhou et al., 2005). Finally, genetic association studies have found gene variations in *GR* to be associated with Major Depression (MD) (van West et al., 2006).

Several animal models with altered GR function have been generated including a point mutation to prevent GR dimerization (GRdim), a brain specific knockout of GR (GRnescre), and a GR missense model with reduced GR expression in the brain and some peripheral tissues (Pepin et al., 1992, Reichardt et al., 1998, Tronche et al., 1999). The GRdim model did not show any depressive, manic, or anxiety-like differences (Oitzl et al., 2001). GRnescre mice show deficient acquisition of stress-coping as determined by the forced swim test, and decreased anxiety in the elevated plus maze and light dark emergence test (Tronche et al., 1999). Missense GR mice show decreased anxiety in the elevated plus maze, but increased anxiety in the open field (Montkowski et al., 1995, Strohle et al., 1998). The difference in anxiety phenotypes is suggested to be related to the stress-inducing environment of the open field (Strohle et al., 1998).

Generation of a transgenic mouse model with forebrain specific over-expression of GR (GRov) by Wei et al resulted in an animal model with increased sensitivity to both positive and negative stimulation. Specifically, these mice exhibit increased depression-like behaviors in the forced swim test, anxiety-like behaviors in the elevated plus maze, high sensitivity to anti-depressants, and hypersensitivity to cocaine administration (Wei et al., 2004).

Ridder et al evaluated a pair of GR mutant mice, one with a 50% reduction in GR expression (GR+/−), and one with over-expression of GR. Under basal conditions the GR+/- mice show normal levels of cortisol and normal behaviors (Ridder et al., 2005). Stress inducing protocols generated higher levels of cortisol as well as depression-like behaviors in the forced swim test and learned helplessness test in GR+/− mice compared to WT. Alternatively, the GR over-expression mice show greater resistance to depression-like behaviors compared to WT controls. The GR over-expression mice however, do not exhibit an anxiety-like phenotype in the elevated zero maze and the light dark emergence test as observed in the GRov mice that specifically over-express GR in the forebrain (Ridder et al., 2005, Wei et al., 2004). The authors suggest the use of different promoters in the two lines could explain the differences in behavioral characteristics between the two lines.

Other Mood Disorder Models

GSK-3β (Glycogen synthase kinase-3β) is a serine/threonine kinase involved in many different cellular processes (Doble and Woodgett, 2003). One role of GSK-3β is regulation of circadian rhythm, which as mentioned above is disrupted in BD (Kaladchibachi et al., 2007). Interestingly, GSK3β activity is inhibited by the WNT signaling cascade through Dvl1 (a model described in the ASD section) (Chen et al., 2001b). Dvl1 KO mice show deficits in sensory motor gating, which is impaired in individuals with BD (Lijam et al., 1997). Importantly, GSK-3β is inhibited by both lithium and valproic acid, which are both used to treat BD (Chen et al., 1999, Klein and Melton, 1996). However, an association study failed to identify *GSK-3*β as a genetic risk factor for BD (Nishiguchi et al., 2006). Transgenic mice over-expressing GSK-3β have increased locomotor activity and decreased

habituation, hypophagia, increased acoustic startle response, and increased mobility in the forced swim test (Prickaerts et al., 2006). Thus it is suggested this could be a model for hyperactivity as seen in mania.

Wolfram syndrome (WFS) is an autosomal recessive disorder that is defined by the occurrence of diabetes mellitus and bilateral optic atrophy, and is often accompanied by depression (Swift et al., 1990). Additionally, the *WFS1* gene was mapped to a region on chromosome 4p16.1, a linkage locus of BD (Polymeropoulos et al., 1994). Interestingly, variations in the *WFS1* gene have been found in patients with BD, MD, SZ, suicide victims, as well as several other psychiatric disorders without comorbidity of Wolfram syndrome (Swift and Swift, 2000). Initial characterization of a WFS1 knockout (WFS1 KO) found these mice show increased endoplasmic reticulum (ER) stress and increased vulnerability to cell death (Yamada et al., 2006), which is alleviated with administration of valproate, a drug used in treatment of BD (Kakiuchi et al., 2009). More recent studies with WFS1 KO mice show normal circadian rhythm in the running wheel test (Kato et al., 2008). However these mice did show decreased social interaction when paired in a neutral cage, increased behavioral despair in the active avoidance test and latency to escape the Morris water maze, and decreased behavioral despair in the forced swim test (Kato et al., 2008, Raud et al., 2009).

PKCI/HINT1 (Protein Kinase C interacting protein) is a member of the histidine triad (HIT) protein family (Klein et al., 1998). *PKCI* was identified as a candidate gene for BD and SZ through microarray analysis of human postmortem brains diagnosed with BD or SZ respectively (Elashoff et al., 2007, Vawter et al., 2002). An expression analysis study found that PKCI expression was primarily found in parvalbumin positive interneurons in the cortex and limbic regions, which are regions implicated in mood disorders (Liu et al., 2008). PKCI/HINT1 null mice show normal locomotor activity in the open field, and exhibit greater sensitivity to amphetamine than WT controls (Barbier et al., 2007). PKCI/HINT1 KO mice exhibit decreased immobility in the tail suspension test, and this is partially alleviated with administration of valproate. Additionally, PKCI/HINT1 KO mice exhibit less immobility in the forced swim test, increased HPA axis basal activity, and increased time spent in the light compartment during the light dark emergence test, which is consistent with mania-like behavior (Barbier and Wang, 2009).

IV. Obsessive-Compulsive Spectrum Disorders (OCSD)

Obsessive Compulsive Disorder (OCD) is a disorder characterized by persistent intrusive thoughts (obsessions) and the expression of ritualistic repetitive behaviors (compulsions) which are often performed in an attempt to alleviate intense anxiety caused by the obsession (Leckman et al., 2007). Common obsessions include fear of contamination and fear of harming oneself or others (Lochner et al., 2008). Common compulsions include excessive hand washing or grooming, counting, checking, telling or confessing, repeating, and hoarding (Lochner et al., 2008). OCD affects 1–3% of the world's population, with approximately equal ratios of affected adult males to females (Rasmussen and Eisen, 1994). In children, however, there is a 2–3:1 ratio of affected males to females (Kalra and Swedo, 2009). Current treatment of OCD consists of pharmacotherapy, cognitive-behavioral therapy (CBT), or both. However, treatment at best only partially relieves OCD behaviors. Thus a better understanding of OCD is necessary to improve the treatment options available.

Other disorders classified as OCSDs include Tourette Syndrome (TS), Trichotillomania (TTM) or compulsive hair pulling, Body Dysmorphia Disorder (BDD), and Dermatillomania or Compulsive Skin Pulling (CSP) (Phillips, 2002). Additionally, compulsive hoarding and eating disorders including anorexia are proposed OCSDs (Bellodi

et al., 2001, Samuels et al., 2007). In considering the relevant disorders, OCSDs may affect as much as 10% of the general population (Dell'Osso et al., 2007).

Several genetic studies including twin studies, family studies, and association and linkage studies show that OCD has a strong genetic component (Nicolini et al., 2009). Twin studies show monozygotic twins have a greater concordance rate for OCD (80–87%) than dizygotic twins (47–50%) (Carey and Gottesman, 1981). A family study by Pauls et al. showed individuals with first-degree relatives diagnosed with OCD have a greater incidence of OCD (7.9–10%) than relatives of control individuals (2.0%) (Pauls et al., 1995). These findings were confirmed by additional family studies analyzed by other groups (Grabe et al., 2006, Nestadt et al., 2000). Linkage studies of families with at least two affected family members identified a strong association with 9p24, 10p15, 11p15, and 14 (Nicolini et al., 2009). Large scale analysis studies will be important for confirming these linkage sites. In particular, an ongoing collaborative genetic study by six universities will collect information from hundreds of families with individuals diagnosed with OCD (Samuels et al., 2006). This consortium of data and samples will be available to researchers and is sponsored by the NIMH. To date, over 60 candidate genes for association with OCD have been identified. These genes implicate the involvement of the serotonergic, glutamatergic, and dopaminergic systems in OCD (Nicolini et al., 2009). One particular circuit gaining support as a major factor in OCD is the cortico-striatal-thalamo-cortical (CSTC) circuit (Ting and Feng, 2008).

D1CT transgenic mouse

The D1CT transgenic mouse model was generated by expressing an intracellular form of cholera toxin (CT), a neuro-potentiating enzyme, under the control of the D1 promoter (Campbell et al., 1999). These transgenic mice have chronic potentiation of D1 positive subsets of neurons in the brain. Expression in the D1CT-7 line was predominantly restricted to neurons within the intercalated nucleus of the amygdala and cortical area that project to the striatum and orbitofrontal cortex.

Behavioral studies in D1CT mice show several abnormalities resembling OCD-like behaviors. Specifically, these mice demonstrated repetitive non-aggressive biting of siblings during grooming, repetitive climbing/leaping, and extended bouts of repetition during normal behavior (Campbell et al., 1999). D1CT-7 mice also exhibit increased levels of anxiety as observed in open field and light dark emergence tests when compared to WT littermates (McGrath et al., 1999). Additionally, D1CT-7 mice exhibit TS-like behaviors including juvenile-onset tics defined as isolated head and/or body jerks or shakes (Nordstrom and Burton, 2002). Importantly, administration of clonidine to D1CT-7 mice reduced tics observed in these mice similar to results found in human TS patients (Cohen et al., 1979). Unfortunately, the effect of SSRIs in these mutant mice has yet to be evaluated.

5-HT_{2C} Receptor

The 5-HT_{2C} serotonin receptor (5-HT_{2C}-R) subtype is broadly expressed in the brain and mediates much of the serotonin signaling in the brain (Goddard et al., 2008). Additionally, the 5-HT_{2C}-R is thought to mediate the actions of serotonin underlying the therapeutic benefits of SSRI treatment in OCD (Goddard et al., 2008). The initial characterization of 5-HT_{2C}-R null mice found that these mice experience mid-life obesity due to hyperphagia, are prone to death from spontaneous seizures, and exhibit altered sleep homeostasis (Tecott et al., 1995, Chou-Green et al., 2003b). Later studies observed compulsive behaviors in the 5-HT_{2C}-R null mice more characteristic of some OCD-like behaviors (Chou-Green et al., 2003a). Specifically, the 5-HT_{2C}-R null mice show increased chewing of non-nutritive clay and “neat” chewing patterns in plastic screens suggesting compulsive behavior (Chou-Green et al., 2003a). This study also observed increased head dipping in knockout mice compared

to wild type mice (Chou-Green et al., 2003a). The authors suggest the clay and screen chewing and increased head dipping are comparable to compulsive behaviors observed in OCD patients. Finally, 5-HT_{2C}-R null mice show less anxiety symptoms than WT mice (Heisler et al., 2007). These mice show increased time and activity in the open quadrant of the elevated plus maze, increased time spent in the center of the open field, increased exploration of novel objects, and increased time in a mirrored chamber (Heisler et al., 2007). These mice also show decreased corticotropin hormone release from the extended amygdala in response to anxiety stimuli compared to control mice.

Recently, Kimura et al. generated a transgenic mouse with overexpression of 5-HT_{2C}-R in the forebrain (C2CR) driven by the CamKIIα promoter (Kimura et al., 2009). These mice showed elevated anxiety as measured by the elevated plus maze and hypo-locomotion as measured in the open field. This mouse line does not exhibit weight or eating issues as the hypothalamus is not affected in this mouse. Thus, 5-HT_{2C}-R mice may be useful in exploring neuronal circuitry mediating anxiety, which is commonly increased in OCD patients.

SAPAP3

SAPAP3 (SP90/PSD95-associated protein 3) belongs to a family of four homologous genes encoding proteins that are widely yet differentially expressed in the nervous system (Welch et al., 2004). The SAPAP family of proteins are scaffold proteins that localize to excitatory synapses (Takeuchi et al., 1997). Recent human genetic studies have identified multiple rare *SAPAP3* missense variants in TTM and OCD patients, which suggest an association of OCD/TTM with *SAPAP3* disruption (Zuchner et al., 2009).

Deletion of SAPAP3 (SAPAP3 KO) led to compulsive self-grooming to the point of hair loss and the development of skin lesions (Welch et al., 2007). Importantly, there was no evidence for skin abnormalities or sensory innervation defects in these mice suggesting that the increased grooming is a result of compulsive behavior not skin aggravation. Additionally, the SAPAP3 KO mice showed increased anxiety in the open field, the light dark emergence test, and the elevated zero maze (Welch et al., 2007).

SAPAP3 is the only family member that is highly expressed in the striatum (Welch et al., 2004). Therefore, SAPAP3 KO mice were evaluated for defects in cortico-striatal synaptic transmission by electrophysiology. Field excitatory postsynaptic currents (fEPSCs) were decreased in SAPAP3 KO mice (Welch et al., 2007). Importantly, rescue of both the cortico-striatal dysfunction and compulsive grooming was achieved through viral reintroduction of WT SAPAP3 specifically into the striatum. These results suggest that synaptic dysfunction in the striatum might be a central mechanism for the expression of compulsive grooming. Interestingly, DAT KD mice also show disruption in cortico-striatal synapses, and the D1CT mice also are suggested to have cortico-striatal defects though it has not been directly tested. If other models of OCD, specifically models with compulsive/repetitive behaviors, are found to have similar corticostriatal defects, this could establish a link between a common circuitry defect with a specific OCD-like behavior.

Administration of 5mg/kg fluoxetine, an SSRI, for six days was able to partially rescue the compulsive grooming behavior in SAPAP3 KO mice. Fluoxetine treatment also seems to alleviate anxiety levels as observed through decreased latency in the light dark emergence test. While a single dose of fluoxetine was not sufficient to alleviate the overgrooming, the treatment dose and timecourse is lower and shorter than typical treatment with fluoxetine in OCD patients (Ackerman et al., 1998, Jenike, 2004). Overall, the SAPAP3 KO mouse is a promising model for understanding the circuitry involved in compulsive/repetitive behavior.

Slitrk5

Slitrk (SLIT and NTRK-like family, member) proteins (Slitrk1–6) are single-pass transmembrane proteins that control neurite outgrowth (Aruga and Mikoshiba, 2003). Variations in *Slitrk1* (discussed below) have been identified in patients with TS and TTM (Abelson et al., 2005, Zuchner et al., 2006). Currently, the potential involvement of other Slitrk family members in psychiatric disorders is not well characterized. To fully characterize the expression pattern and evaluate the functional role of Slitrk5, Shmelkov et al replaced the Slitrk5 gene with a lacZ reporter gene to generate a Slitrk5 knockout (Slitrk5 KO). Expression analysis showed a wide expression pattern including the cortex, hippocampus, and striatum (Shmelkov et al., 2010).

Behavioral observations of the Slitrk5 KO showed these mice have increased grooming compared to WT littermates which results in severe skin lesions. Chronic treatment with the SSRI fluoxetine alleviated the overgrooming behavior in Slitrk5 KO mice but had no effect on WT mice. Additionally, Slitrk5 KO mice showed increased anxiety-like behaviors as determined by the elevated plus maze, the open field, and compulsive-like behavior in the marble burying test (Shmelkov et al., 2010).

Slitrk5 is expressed in many brain regions, however FosB expression, a marker of neuronal activity, was found to be elevated exclusively in the orbitofrontal cortex of Slitrk5 KO mice (Shmelkov et al., 2010). Interestingly, imaging studies in patients with OCD also showed increased activity in the orbitofrontal cortex (Menzies et al., 2008). Slitrk5 KO mice also had decreased volume and dendritic arbor complexity selectively in the striatum (Shmelkov et al., 2010). As mentioned previously, defects in cortico-striatal circuitry have been implicated in OCD, therefore Slitrk5 KO mice were evaluated for defects in cortico-striatal signaling by electrophysiology. Slitrk5 KO mice had decreased fEPSCs recordings, indicating these mice have defects in cortico-striatal signaling. Biochemical studies also showed total and synaptic glutamate receptor subunits were decreased in the striatum. Overall, the Slitrk5 KO mice exhibit OCD-like behaviors of compulsive grooming and anxiety, and have selective defects in cortico-striatal signaling. Thus the Slitrk5 KO is a promising model for the study of cortico-striatal defects in OCD.

Other OCD models

Hoxb8 is a member of the mammalian HOX (homeobox-containing) family of transcription factors best characterized for their role in early development (Capecchi, 1997). Hoxb8 is broadly expressed in the adult brain including the basal ganglia, hippocampus, cortex, and cerebellum (Greer and Capecchi, 2002). To address the role of Hoxb8, Greer and Capecchi generated a transgenic mouse line that was homozygous for a loss-of-function allele of Hoxb8. These mice exhibited excessive self and cage mate grooming that resulted in hair removal and skin lesions both on themselves and wild type cage mates (Greer and Capecchi, 2002). Importantly, these mice were found to have no underlying skin abnormalities and the lesions developed with 100% penetrance (Greer and Capecchi, 2002). Recently Chen et al. found that in the brain, Hoxb8 exclusively labels a sub-population of microglia. This sub-population seems to have a bone marrow origin. They also observed a reduction in the total number of microglia in Hoxb8 mutant mice compared to WT mice (Chen et al., 2010). Importantly, their data shows that transplantation of wild-type bone marrow rescues the excessive grooming in the Hoxb8 mutant mice (Chen et al., 2010). Additionally, deletion of Hoxb8 selectively in hematopoietic cells using a conditional knockout line was sufficient to induce pathological grooming in mice (Chen et al., 2010). The authors suggest three potential mechanisms for the role of microglia in modulating neuronal activity. First, the release of cytokines could work in parallel with neurotransmitters to stimulate or inhibit neuronal activity (Chen et al., 2010). Microglia have also been shown to function in

regulated neuronal cell death during embryogenesis (Frade and Barde, 1998, Marin-Teva et al., 2004). Therefore, another potential mechanism is through possible loss of appropriate cell death leading to altered neuronal connectivity resulting in aberrant behavior (Chen et al., 2010). Finally, microglia processes are very dynamic and have been shown to contact synapses in an activity dependent manner (Wake et al., 2009). Thus, a third potential mechanism is through altered microglia modulation of neuronal networks leading to altered behavior. Importantly, the Hoxb8 subpopulation of microglia are most abundant in the cortex including the orbital regions, and basal ganglia (Chen et al., 2010). This is intriguing as the orbitofrontal cortex and basal ganglia are two brain regions implicated in human OCD (Graybiel and Rauch, 2000, Huey et al., 2008). While these potential mechanisms have yet to be explored, they propose a very interesting role for the immune system in modulating behavior.

The DAT KD mouse, previously described above as a model for ADHD and mania, also exhibits OCD-like behaviors. The hyper-dopaminergic DAT KD mice exhibit sequential super-stereotypy, and showed greater resistance to disruption of this pattern than control animals (Berridge et al., 2005). Interestingly, the basal ganglia is thought to organize sequential patterns of movement and thought, including grooming patterns (Lieberman, 2001, Marsden, 1984). The importance of DAT in regulating dopaminergic neurotransmission in the basal ganglia suggests that DAT disruption might be directly associated with OCD.

Aromatase cytochrome P450 (P450arom), the product of the *cyp19* gene, catalyzes the final step of biosynthesis of estrogen from androgens. Estrogen plays an important role in the development of both males and females. To study the role of aromatase activity in mice, targeted disruption of the *cyp19* gene led to the generation of aromatase knockout (Arko) mice which are estrogen deficient (Fisher et al., 1998). The absence of estrogen in male Arko mice, but not female Arko mice, resulted in compulsive behaviors including excessive grooming, barbering, increased wheel running, and reduced PPI up to 18 months of age (Hill et al., 2007, van den Buuse et al., 2003). Male Arko mice also exhibit a decrease in the expression of catechol-O-methyltransferase (COMT), a major enzyme regulating dopamine degredation, in the hypothalamus with no difference in the frontal cortex (Hill et al., 2007). Interestingly, low COMT activity has been suggested as a risk factor in human OCD, specifically in males (Karayiorgou et al., 1999, Pooley et al., 2007, Schindler et al., 2000). Additionally, some evidence does exist for involvement of the hypothalamus in grooming and wheel running behaviors (Rhodes et al., 2003). Thus, male Arko mice may be a good model to evaluate the role of the hypothalamus in OCD-like behaviors.

Expression of Slitrk1, another member of the Slitrk family of proteins, is abundant in the olfactory bulb, frontal cortex, hippocampus, and amygdala (Katayama et al., 2010). Variations in *Slitrk1* have been identified in patients with TS and TTM (Abelson et al., 2005, Zuchner et al., 2006). Slitrk1 KO mice show decreased locomotor activity in light cycles, anxiety-like behaviors in the elevated plus maze and the light dark emergence test, and depression like behaviors in the forced swim test (Katayama et al., 2010). Neurochemical analysis of Slitrk1 KO mice show increased NE levels in the mPFC and NAc, while choline (CH) and acetylcholine (Ach) levels were decreased in the striatum (Katayama et al., 2010). Both NE and CH/Ach signaling are involved in mediating fear and anxiety (Brioni et al., 1993, Hu et al., 2007). Interestingly, clonidine, an alpha2-adrenergic agonist known to be effective in treating some TS patients (Robertson, 2006), was effective in treating the anxiety in Slitrk1 KO mice but had no effect on locomotor activity (Katayama et al., 2010).

V. Schizophrenia

Schizophrenia (SZ) is a neuropsychiatric disorder that affects approximately 1% of the world's population (Wu et al., 2006). SZ is characterized by the presence of three categories of symptoms: positive symptoms (hallucinations, delusions, and psychosis), negative symptoms (anhedonia, social defects, impaired motivation), and cognitive deficits (impaired working memory, attention, and execution) (APA, 2000). Although onset of SZ typically occurs in early adulthood (AOS), rare cases of childhood onset SZ (COS) occur in children as early as six years old (Rapoport et al., 2005). Studies show there is a significant genetic component for SZ (O'Donovan et al., 2009). Additionally, several pathways have been implicated in SZ including glutamatergic and GABA-ergic transmission (O'Tuathaigh et al., 2007).

Many SZ susceptibility genes are also associated with other childhood onset psychiatric disorders. Therefore many transgenic mouse models of SZ susceptibility genes were presented in previous sections of this review. For example, *PKCI/HINT1* is associated with both SZ and Mood Disorders. Additionally, *reln*, *BDNF*, and *neuregulin 1* are associated with SZ and ASD. Because SZ is mostly an adult onset psychiatric disorder, we have limited our presentation of SZ models to those genes associated with other disorders discussed in this review, and in this section the most prominently characterized SZ transgenic models to date.

22q11 deletion syndrome

22q11 deletion is a chromosomal abnormality associated with mental disorders. The smallest known deletion affects a minimum of 30 genes, and several of these genes have been associated with SZ and BD (Lindsay et al., 1995). In fact, patients with the 22q11 deletion exhibit both SZ and BD symptoms (Paylor and Lindsay, 2006). Several models of 22q11 exist including models that mimic the deletion seen in human patients, models with smaller deletion regions, and models with targeted deletion of specific genes contained within the deleted region (Jerome and Papaioannou, 2001, Kimber et al., 1999, Lindsay et al., 1999, Lindsay et al., 2001, Puech et al., 2000, Long et al., 2006).

One model, the Df(16)A+/− transgenic mouse, deletes a subset of genes affected in 22q11 syndrome (Mukai et al., 2008, Stark et al., 2008). Studies involving the Df(16)A+/− mouse model show impaired PPI, decreased working memory in the T maze, impaired response to contextual fear-conditioning, hyperactivity in open field, and male mice show higher levels of anxiety as determined by the light dark emergence test (Stark et al., 2008). Additionally, lower levels of miRNAs, and synaptic defects in the hippocampus were identified in Df(16)A+/− mice, which are suggested to contribute to some of the cognitive defects found in these mice (Mukai et al., 2008, Stark et al., 2008).

DISC1

DISC1 (Disrupted in Schizophrenia 1) was initially identified as a putative susceptibility gene through analysis of a Scottish pedigree with a (1; 11) (q42.1; q14.3) translocation that resulted in the disruption of the *DISC1* gene (Millar et al., 2000). Family members carrying the deletion were affected with SZ, depression, and BD (Ishizuka et al., 2006). Additional independent linkage and association studies in diverse populations have confirmed *DISC1* as a susceptibility gene for SZ (Palo et al., 2007). Several mouse models have been generated that disrupt DISC1 to evaluate its role in SZ including a truncated DISC1 ($DISC1_{tr}$) mimicking the break in the Scottish pedigree, a missense DISC1 ($DISC1_{L100P}$), and a dominant negative DICS1 (DN-DISC1) driven by the CaMKII promoter(Clapcote et al., 2007, Hikida et al., 2007, Shen et al., 2008).

The DISC1tr mice exhibit several SZ hallmarks including increased lateral ventricles, decreased cerebral cortex volume, and decreased parvalbumin (PV) expression in the medial prefrontal cortex (mPFC) (Shen et al., 2008). Additionally, these mice exhibit decreased LI, and increased immobility in forced swim test (Shen et al., 2008). This model shows promise as it mimics a break point found in human patients, and possesses some SZ-like pathology.

The $DISC1_{L100P}$ mice also exhibit neuro-anatomical changes seen in schizophrenia patients, and exhibit behaviors that may be relevant to SZ including decreased PPI, decreased LI, increased activity in the open field, and decreased performance in the T-maze (Clapcote et al., 2007). Importantly, treatment with antipsychotics such as haloperidol and clozapine correct the deficits in PPI, LI, and reduce mobility in these mice (Clapcote et al., 2007). While this model is a promising model of SZ it does not reflect a mutation found in human patients.

The DN-DICS1 showed increased volume of the left lateral ventricle, and has decreased immunoreactivity of PV positive inhibitory neurons (Hikida et al., 2007). These mice exhibited hyperactivity in the open field, increased immobility in the forced swim test, and a small deficit in PPI at 74 decibels only (Hikida et al., 2007). This mouse did not show any difference in Y-maze, Morris water maze, or social paradigms (Hikida et al., 2007). Overall, DISC1 transgenic mouse models show promise as models of SZ.

Other SZ models

Deficits in glutamatergic transmission through the NMDAR have been implicated in the expression of SZ (Olney et al., 1999). This hypothesis emerged after the discovery that phencyclidine (PCP), which primarily acts through blockade of the NMDAR, led to a SZ-like psychosis and the exacerbation of symptoms in SZ patients (Lodge and Anis, 1982, Luby et al., 1959). Later studies showed that the use of NMDAR antagonist such as MK-801 also induced psychosis that could be reversed by the administration of antipsychotics such as clozapine (Olney et al., 1999). Additional studies using brain imaging, postmortem staining, and genetic manipulation have further implicated NMDAR hypofunction in SZ (Kehrer et al., 2008). One model which reduces expression of the NR1 subunit of the NMDAR ($NR1_{hypo}$) generated by Mohn et al. shows increased sensitivity to PCP, increased open field activity, decreased social investigation in the resident intruder test , and decreased PPI that is reversed by treatment with antipsychotics (Duncan et al., 2006b, Duncan et al., 2006a, Mohn et al., 1999, Moy et al., 2006).

Recently, generation of a transgenic mouse model selectively deleting NR1 expression in PV positive neurons of the forebrain show increased activity in the open field, increased anxiety in the elevated plus maze, decreased PPI, mild anhedonia in the saccharine-preference test after social isolation, and impaired nesting behavior (Belforte et al., 2010). Thus the glutamate hypothesis and the role of the NMDAR in SZ is a promising model for studying SZ.

Many other transgenic mouse models are currently being characterized as models of SZ including ErbB4, Adenosine Kinase, Complexin 1, mGluR1, and many more. Additionally, there are many developmental, drug induced, and lesion preparation models that are outside the scope of this review. For a comprehensive list of mouse models of schizophrenia go to http://www.schizophreniaforum.org/res/models/Animal_Models_04_09.pdf.

VI. Future Directions

Transgenic animal models are important tools for studying the molecular, cellular, and circuitry mechanisms of childhood onset psychiatric disorders. In this review we attempted

to introduce current transgenic models for ADHD, ASD, Mood Disorders, OCSD, and SZ. Here we will focus on general future directions for designing useful animal models. We will highlight the newest technologies available and discuss the advantage and limitations of these technologies.

Modeling Human Variations/Mutations in Mice

Many of the models presented in this review aim to delete or overexpress genes implicated in childhood onset psychiatric disorders. These mouse models have been very helpful in confirming the involvement of these genes in psychiatric disorders, and in some cases have provided insight into specific brain regions that may be involved in the expression of some of the disorders features. However, in many human patients, psychiatric disorders do not arise from a complete deletion or duplication of a gene. Human genetic studies have identified many rare variations or mutations within genes of interest which are thought to contribute to the expression of psychiatric disorders (Hudziak and Faraone, 2010). Some labs have begun to generate mice that mimic break points or variations observed in human patients, and these models show promise as models for their respective disorders (Chadman et al., 2008, Shen et al., 2008, Tabuchi et al., 2007, Veenstra-Vanderweele et al., 2009). Thus, generating mouse models that replace the endogenous gene with a variation or mutation identified in human populations will reflect conditions observed in human patients, and may allow for better elucidation of the etiology of these childhood onset psychiatric disorders.

New Tools for the Study of Brain Function

Cre-Lox System—The concept of using cre-lox systems to target specific brain regions or neuronal populations is not new, however this technique is continually advancing. Cre can be expressed either globally or conditionally in subpopulations of cells/organs (Gaveriaux-Ruff and Kieffer, 2007, Wolf and Woodside, 2005). Currently, traditional and inducible cre lines are available (Heldt and Ressler, 2009, Utomo et al., 1999). Traditional cre lines express cre in the temporal and spatial pattern of the selected promoter. Inducible cre lines express cre in the specific pattern after administration of a drug such as tamoxefin (Cre-ER) (Feil et al., 1997). As the temporal and spatial expression patterns of more genes are characterized, the available cre-lines will greatly increase. Many groups, along with gene expression nervous system atlas (GENSAT) project and Allen Brain Institute, have characterized hundreds of genes and their expression patterns to date. The advantage of this method over a global knockout/over-expression is that using specific promoters allow for targeting and manipulation of specific brain regions or sub-populations of neurons. Importantly, this method can be beneficial when global effects result in lethality or developmental problems not associated with the disorder of interest. One limitation of this approach is that genes are generally expressed in many brain areas. Thus, while scientists can target selected sub-populations of neurons using different promoters, it is difficult to target specific brain regions without expression in other areas using transgenic cre mouse lines. Viral injection of cre driven by a specific promoter circumvents this problem. Additionally, the expression pattern has not been characterized for all genes, therefore a transgenic cre mouse line may not currently exist that targets the specific population of interest. As more and more genes are characterized, this limitation will be marginalized. Another issue to be mindful of in using this technique is that often cre-lines do not affect 100% of the target population, and sometimes ectopic expression of cre occurs. Careful characterization of new cre-lines using reporter lines that express fluorescence in the presence of cre will be required to verify the expression pattern (Wang, 2009).

One advancement to the cre-lox system is the inverted and double floxed with LoxP and mutant LoxP (mLoxP) FLEX switch (Atasoy et al., 2008, Nyabi et al., 2009, Schnutgen et

al., 2003). This system allows for flanking of a genomic region of interest, where in the presence of Cre a region of DNA is inverted to change the expression pattern of the gene of interest. For example, exons can be inverted leading to the generation of a knockout mouse in the absence of cre. In the presence of cre the exons will be inverted again restoring protein expression. Additionally, this method can be used to flank exons with loxP/mloxP sites where in the absence of cre there is normal gene expression and in the presence of cre the exons are inverted resulting in a loss of gene expression. Thus, the FLEX method can be used to generate a cre-induced gene rescue using the original gene locus as well as a traditional cre-induced knockout. The FLEX method maintains the advantages of using cre-lines including temporal and spatial control over gene replacement/knockout expression.

Optogenetics—Another new method available is optogenetics, channelrhodopsin and halorhodopsin (Arenkiel et al., 2007, Zhang et al., 2008, Zhao et al., 2008). Channelrhodopsin is a non-selective cation channel that is activated by blue light (473nm), which leads to neuronal activation. Halorhodopsin is a chloride pump that is activated by yellow light (580nm) and leads to neuronal silencing. These channels can be expressed using any of the currently available techniques including cre-lox, viral delivery, or knock-in. The advantage of this method is the ability to stimulate or silence specific neurons rapidly and effectively both in vivo and in vitro (Airan et al., 2009, Cardin et al., 2009, Cardin et al., 2010, Zhang et al., 2010). Importantly, in vivo recording of neuronal activation by field local potentials (FLPs) or specific regulation of single neurons by whole cell recordings is a rapidly advancing technique used to study psychiatric disorders in animal models (Stuber, 2010, Zhang et al., 2010). These recording techniques allow for the study of neuronal signaling in an intact system, and can be used in both anesthetized and awake behaving animals (Adamantidis et al., 2010, Cardin et al., 2009). Optogenetics facilitates the effectiveness of these recording techniques by allowing for rapid and precise stimulation/silencing of specific neurons or brain regions to generate specific firing patterns (Cardin et al., 2009, Cardin et al., 2010). The greatest limitation of this technique is that light is required to activate the channels, therefore direct access to the brain region of interest is necessary. Currently, in vivo experiments require surgery to place cannulas and attachment of a fiberoptic cable to deliver the light pulses. Thus, damage to other brain regions is a confounding issue. Additionally, the ability to perform behavioral studies is severely limited due to the fiberoptic cables attached to the head of the animal.

Chemicogenetics—The final method we will introduce is chemicogenetics (Conklin et al., 2008, Dong et al., 2010, Nichols and Roth, 2009, Pei et al., 2010). One example is the “designer receptor exclusively activated by a designer drug” (DREADD) strategy. DREADD receptors are mutated muscarinic acetylcholine (mAch) receptors that no longer respond to Ach and are selectively activated by clozapine-N-oxide (CNO) (Alexander et al., 2009, Armbruster et al., 2007). M4 receptors are G_i coupled receptors that leads to neuronal silencing by inhibiting adenylate cyclase (AC) levels and prolonging potassium channel, non-specific cation channel and transient receptor channel opening (Eglen, 2006). The M3 receptor is a G_q coupled receptors that leads to neuronal activation by mobilizing phosphoinositides and decreasing intracellular calcium levels (Eglen, 2006). Thus, M4-DREADDs lead to neuronal silencing while the M3-DREADDs result in neuronal activation. DREADD receptors, like channelrhodopsin and halorhodopsin can be introduced using any of the currently available techniques. Importantly, this method can be used in vivo as CNO can pass through the blood brain barrier (Alexander et al., 2009). Advantages to this method are that behavioral studies are not limited as there is no external equipment attached to the mouse. Additionally, CNO is completely inert in cells not expressing DREADD receptors, therefore complications due to drug related side effects are not an issue. Thus, this technique shows great promise for behavioral studies.

One limitation for this method is that delivery of CNO is on a much slower time scale than the rapid control of optogenetics so studies of direct stimulation/silencing effects on signaling are limited in this model. A second limitation is that the method has not been characterized in all cell types and may not work in all systems due to differential expression of signaling pathways required for DREADD receptor-mediated neuronal activation/silencing.

VII. Conclusions

In conclusion, studies using animal models have greatly increased our understanding of childhood onset psychiatric disorders. As discussed earlier, it is impossible to model an entire psychiatric disorder in a single mouse model, however these models can be very useful in characterizing a specific behavior or physical feature of a disorder. Additionally, many characteristics of childhood onset psychiatric disorders are shared between disorders. For example, repetitive behaviors are seen in both OCD and ASD. Therefore, when considering the validity of a transgenic mouse model, one should evaluate the validity for select behaviors or a particular feature rather than the validity of a mouse for a particular psychiatric disorder. Thus far, animal models have played important roles in validating candidate genes related to specific disorders, identifying and confirming the involvement of signaling pathways in specific behaviors/disorders, and in identifying potential targets for development of new therapeutics. One future goal is to compare different models that share a common behavior or characteristic to identify common neuronal circuitry defects involved in the expression of that behavior. The newest technologies discussed in this review can then be used to test and confirm the involvement of a particular circuitry network or population of neurons allowing for a deeper understanding of the underlying causes of psychiatric disorders.

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Table 1

Table of common behavior tests used to characterize animal models of childhood onset psychiatric disorders.

Behavior Test	Description
Anxiety/Fear:	
Active/Passive Avoidance	Measures the avoidance of an area where a foot shock was given. Passive avoidance required the mouse to not enter the area where the foot shock was presented. Active avoidance requires the mouse to exit the area where the foot shock was presented upon a cue.
Contextual Fear Conditioning	Measures the amount of freezing when placed in an environment where a previous negative stimulus (foot shock) was given
Elevated Plus Maze	Measures time spent in the open arm versus protected arm of a cross-shaped arena
Elevated Zero Maze	Measures time spent in the open area versus protected area of a circular arena
Light Dark Emergence	Measures latency to emerge from the dark chamber to the light chamber. Also measure total time spent in light and dark chambers, and activity levels in these chambers
Open Field	Measures time spent in the center of the open field arena versus the perimeter or corners of the arena
Reward/Aversion	Measures the latency to obtain a reward in the presence of an aversive stimulus (ex. predator urine, brightly lit novel arena)
Compulsive Behavior:	
Marble Burying	Measures the number of marbles buried as a result of compulsive digging or shifting in bedding
Non-nutritive Chewing	Measures amount of chewing of non-nutritive clay or substances
Repetitive Grooming	Measures number of grooming sessions and total time spent grooming in a 24 hour period. Also measures time spent grooming relative to other adaptive behaviors (eating, sleeping)
Depression:	
Learned Helplessness	Measures latency to escape a foot shock after repetitive training with foot shock in an inescapable chamber
Porsolt Forced Swim	Measures the time spent in vigorous swimming relative to the time spent floating in a tall cylinder filled with water
Tail Suspension	Measures the time spent struggling relative to the time spent immobile when suspended by the tail
Learning and Memory:	
Barnes Maze	Measures the ability to learn the location of an escape hole in a circular maze with 18 evenly spaced holes using spatial environmental cues
Morris Water Maze	Measures the ability to learn the location of a hidden platform using extra-maze spatial environmental cues
Radial Arm	Measures the number of entries into one of eight arms that are baited with food or water using spatial environmental cues; may tap into cognitive preservation
T Maze/Y-Maze	Measures the correct initial entry into an alternating arm of the maze bated with food or water using spatial environmental cues; may tap into cognitive preservation
Social Paradigms:	
Nest Building	Evaluates size and organization of nest building; may also assess procedural cognitive function
Pairing in Novel Environment	Measures amount of social approach of two mice paired in a novel environment
Resident Intruder	Measures amount of social approach when an intruder mouse is introduced into the home cage of the test mouse following social isolation
Social Approach-Partitioned	Measures amount of time spent near the partition dividing the test mouse from either a stranger or known mouse.
Social Approach- Three Chamber	Measures amount of time spent in an empty chamber versus a chamber containing a stranger mouse. Second trial measures the time spent in the chamber with a known mouse versus a stranger mouse versus an empty chamber

Behavior Test	**Description**
Social Recognition	Measures the amount of social interaction between the test mouse and a second mouse on the first and subsequent exposures
Ultrasonic Vocalization-Adults	Measures the number and duration of ultrasonic vocalizations of male mice exposed to female mice in estrous OR male mice during a resident intruder test
Ultrasonic Vocalization- Neonates	Measures the number and duration of ultrasonic vocalizations of pups during brief isolation from the dam and/or littermates
Other:	
Delayed Reinforcement	Measures the ability to wait for a preferred reinforcer (ex. water) over the immediately available less-preferred reinforce (ex. quinine). The time for the preferred reinforcer increases with each trial.
Reaction-Time Task	Measures the number of nose poke entries to receive a reward during a cued time period.
Home Cage Activity	Measures the amount of total, horizontal, and vertical activity in a home cage environment to test for habituation
Latent Inhibition	Measures the impaired performance during an active avoidance task when test training includes exposure to the cued stimulus but without any reinforcement contingencies
Open Field Activity	Measures the amount of total, horizontal, and vertical activity in a novel environment; other activities including stereotypic or repetitive patterns of movement can also be assessed
Pre-pulse Inhibition/Sensory Motor Gating	Measures the inhibition of a reflexive acoustic startle response to be inhibited when weaker stimuli are presented prior to the startle stimulus
Running Wheels	Measures the amount and duration of activity in a 24 hour period. Manipulation of light and dark cycles can allow for measuring circadian rhythm based on activity patterns over several months