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Clinical and Neurobiological Relevance of Current Animal Models of Autism Spectrum Disorders

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication impairments, as well as repetitive and restrictive behaviors. The phenotypic heterogeneity of ASD has made it overwhelmingly difficult to determine the exact etiology and pathophysiology underlying the core symptoms, which are often accompanied by comorbidities such as hyperactivity, seizures, and sensorimotor abnormalities. To our benefit, the advent of animal models has allowed us to assess and test diverse risk factors of ASD, both genetic and environmental, and measure their contribution to the manifestation of autistic symptoms. At a broader scale, rodent models have helped consolidate molecular pathways and unify the neurophysiological mechanisms underlying each one of the various etiologies. This approach will potentially enable the stratification of ASD into clinical, molecular, and neurophenotypic subgroups, further proving their translational utility. It is henceforth paramount to establish a common ground of mechanistic theories from complementing results in preclinical research. In this review, we cluster the ASD animal models into lesion and genetic models and further classify them based on the corresponding environmental, epigenetic and genetic factors. Finally, we summarize the symptoms and neuropathological highlights for each model and make critical comparisons that elucidate their clinical and neurobiological relevance.

Key Words: Autism spectrum disorders, Animal models, Genetic factors, Environmental factors, Clinical relevance

INTRODUCTION

Autism spectrum disorder (ASD) is a prototypical pervasive developmental disorder resulting from abnormal brain development. ASD constitutes two main behavioral symptoms including impairment in social interactions and communication, and restricted, repetitive behaviors, diagnosed at an early age in development (American Psychiatric Association, 2013). The disorder is often accompanied by sensory processing abnormalities (Rogers *et al*., 2003), sleep problems (Schreck *et al*., 2004), anxiety and depression (Strang *et al*., 2012), hyperactivity (Aman and Langworthy, 2000), aggression or self-injurious behaviors (Singh *et al*., 2006), seizures (Volkmar and Nelson, 1990) and eating or digestive problems (Martins *et al*., 2008), among others. ASD is incredibly heterogeneous and is commonly comorbid with other psychiatric and neurodevelopmental disorders or syndromes (Leyfer *et al*., 2006). As one may expect, this condition causes great hardship to affected families, as it may lead to social, occupational and other functional afflictions (American Psychiatric Association, 2013).

Research over the last several decades has identified various risk factors leading to ASD, which can be classified into genetic abnormalities, epigenetic alterations and environmental insults (Gepner and Feron, 2009). Genetic risk factors take the form of monogenic mutations, single nucleotide polymorphism (SNP), and copy number variants (CNVs). Not surprisingly, many of the implicated genes have been associated with modulation of brain development and cortical organization, synapse formation and function, and neurotransmission. On the other hand, environmental insults implicated in ASD com-

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prise prenatal exposure to viral infections or chemicals, including rubella (Chess *et al*., 1978), cytomegalovirus (Yamashita *et al*., 2003), thimerosal (Bernard *et al*., 2002), thalidomide (Stromland *et al*., 2002) and alcohol (Aronson *et al*., 1997). Accordingly, it has been shown that both genetic and environmental factors associated with the disorder can directly induce epigenetic disruptions, as is the case of mutations in MeCP2 gene (Amir *et al*., 1999) and abnormal methylation of the imprinted region of the UBE3A gene (Jiang *et al*., 2004). Likewise, prenatal valproate (VPA) exposure (Christianson *et al*., 1994) is thought to mechanistically affect the epigenome at critical developmental stages and lead to ASD. More recently, the effect of increased maternal and paternal age have been linked to ASD risk, mainly by increasing the proportion of copy number variants and de novo mutations in their offspring (Lee and McGrath, 2015).

Based on the identified risk factors and possible etiology of ASD, animal models were created to mimic and understand the pathological mechanisms underlying the behavioral abnormalities of this disorder. Two main types of animal models, the lesion and genetic models thus became apparent. The lesion models include prenatal infection (neonatal Borna disease virus), neonatal amygdala lesion, and prenatal VPA exposure. Thalidomide exposure, which showed different effects between primates and rodents, may not be an appropriate animal model of ASD (Kemper and Bauman, 1993). Genetic models consist of knockout mice of various isolated genes that are thought to be involved in the pathology of both syndromic and non-syndromic ASD such as *FMR1* (Fragile X syndrome), *NF1* (Neurofibromatosis type 1), *TSC1* (Tuberous sclerosis), *DHCR7* (Smith-Lemli-Opitz syndrome), *MeCP2* (Rett syndrome), *SHANK2*, *CNTNAP2*, Eukaryotic translation initiation factor 4E (eIF4E), transgenic mouse targeting Oxytocin, Vasopressin, Reelin, Dishevelled-1, Sert (serotonin transporter), Maoa (monoamine oxidase A), HOXA1, PTEN and Neuroligins.

Although the number of animal models for ASD is rapidly expanding and will continuously increase in upcoming years, systemic efforts to concisely assess their clinical relevance and neurobiological significance are still scarce. In this review, we will tackle the two main classes of ASD animal models, lesion and genetic models, in order to dissect them into specific sub-groups to find out whether the studies of these models have neurobiological relevance to the clinical setting (Table 1).

LESION MODELS

Anatomical lesion models

Anatomical lesion models have long been used to isolate brain regions involved in the pathologic pathways of a number of neurological disorders. In the case of autism, however, brain damage induced by a gross chemical or electrolytic lesion of specific regions have not been able to even remotely replicate human ASD. The complexity of human development and the heterogeneity that is found in ASD phenotypes could perhaps be two of the main reasons that make the recapitulation of ASD much difficult in this type of postnatal lesion animal models. Moreover, the impairments found in ASD are not likely to be rooted only from a single neural circuit or brain region.

Amygdala: Early life dysfunction and alterations in the amygdala have long been linked to autistic behaviors (Bachevalier, 1994). Indeed, autistic children have been found to have enlarged amygdala and decreased neuronal cell size within this region, despite increased cell density brain-wide (Kemper and Bauman, 1998). Interestingly, changes in amygdala volume throughout development was directly correlated with initiating communicative eye contact in autistic children (Barnea-Goraly *et al*., 2014). In addition, other studies found that ASD patients tend to avoid eye contact on facial gaze tasks and showed increased amygdala activity during gaze manipulation along with an increase in subjective threat ratings (Tottenham *et al*., 2014).

Most established animal models used to assess the contribution of amygdala to autistic behaviors have utilized rats that have undergone direct amygdala lesions or indirect impairment using other etiologic factors. Initial studies from amygdala-lesioned rats (at postnatal day 7) which were subjected to juvenile isolation prior to testing, showed that these animals developed a tendency for stereotyped walking (Wolterink *et al*., 2001), decreased social play and exploration (Wolterink *et al*., 2001), impaired social interaction, and decreased spatial learning and memory in the spontaneous alternation task (Diergaarde *et al*., 2005). However, similar lesions to the amygdala of macaque monkeys failed to affect their social behaviors, and mostly impaired their fear learning and anxiety behaviors (Amaral *et al*., 2003). These discrepancies are not surprising, as data from humans with ASD show similar inconsistencies.

Accordingly, it seems that ASD-related alterations in amygdala size vary across developmental time-points; some studies have shown that this region is enlarged in children with ASD, whereas it has been found to be smaller in size in adolescents or young adults with the disorder, compared to controls (Schumann *et al*., 2004). These findings suggest that the involvement of amygdala in ASD is rather complex, making it harder to model both with targeted lesions and in animals. Yet, even if the hallmark social behavior deficits associated with ASD are inconclusive with regards to the amygdala, it is still possible that fear and anxiety phenotypes in ASD are still linked to functional deficits in this brain region (Amaral *et al*., 2003). Recently, however, another clinical study failed to find a relationship between ASD and amygdala dysfunction, using visual tasks as a measure of impaired social attention (Lee and McGrath, 2015). Thus, further study is needed to clarify and consolidate the results regarding the involvement of amygdala in ASD pathology and to encourage its validity in the modeling of the disorder.

Cerebellum: Anatomical abnormalities of the cerebellum have been widely observed in human autistic patients (Bauman and Kemper, 1985). Reported abnormalities include hypoplasia of cerebellar vermal lobules VI and VII (Courchesne *et al*., 1994), which were negatively correlated to increased repetitive behaviors and decreased exploratory behavior in autistic children (Pierce and Courchesne, 2001), results which have been somewhat controversial. Loss of Purkinje cells in the cerebellar vermis and cortex was also reported in human autistic subjects (Allen and Courchesne, 2003). A comprehensive review had been published explaining the pathological involvement of the cerebellum in the development of autism (Fatemi *et al*., 2012). The review highlighted that in some autistic patients, there are cerebellar abnormalities covering anatomical defects, inflammation, oxidative stress, abnormal neurotransmitters and protein levels, and cerebellum-related

Table 1. Neurobiological and behavioral features of ASD animal models in relation to their clinical relevance

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
A. Lesion Models					
Amygdala lesion	• Stereotyped walking[g] Decreased social play and social exploration[g,h] • Decreased social interaction[i]	• Decreased spontaneous alteration (spatial learning and memory)[i]	• Amygdala lesion	• Enlarged amygdala in young children[a] • Increased cell density and small neuronal cell size[b,c] • Initiating eye-contact and gaze manipulation[d,e] • Impaired fear and anxiety processing[f]	[a]Schumann *et al*., 2004 [b]Bauman and Kemper, 1985 [c]Kemper and Bauman, 1998 [d]Barnea-Goraly *et al*., 2014 [e]Tottenham *et al*., 2014 [f]Amaral *et al*., 2003 [g]Wolterink *et al*., 2001 [h]Daenen *et al*., 2002 [i]Diergaarde *et al*., 2005
Cerebellum lesion	• Impaired social discrimination[e] • Repetitive behavior[f]	• Impaired visuomotor ability but not spatial memory[d] • Hyperlocomotor activity[e] • Decreased anxiety[e]	• Cerebellar lesions	• Increased repetitive behaviors and decreased exploratory behavior[a] • Hypoplasia of cerebellar vermal lobules VI and VII[b] • Loss of Purkinje cells[c] • Cerebellar injury causes high risk ratio for ASD in children[g]	[a]Pierce and Courchesne, 2001 [b]Courchesne *et al*., 1994 [c]Allen and Courchesne, 2003 [d]Joyal *et al*., 1996 [e]Bobee *et al*., 2000 [f]Martin *et al*., 2010 [g]Wang *et al*., 2014
mPFC lesion	• Decreased social play, conditioned place preference (social contact related) and social grooming[c] • *Normal social interaction in adult rats*[c]	*ND*	• mPFC lesions	• Brain overgrowth in mPFC[a] • Early PFC damage can impair social interaction and cognition[b]	[a]Carper and Courchesne, 2005; Hazlett et al., 2005 [b]Eslinger et al., 2004 [c]Schneider and Koch, 2005
Maternal BDV infection	• Increase stereotyped scale[b] • Impaired social play & social interaction[c]	*ND*	• Abnormalities in postnatal development of hippocampus and cerebellum[d]	• *MIA*[a]	[a]Mazina *et al*., 2015 [b]Hornig *et al*., 1999 [c]Pletnikov *et al*., 1999, 2002 [d]Taieb *et al*., 2001

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
Prenatal LPS exposure	• Deficits in social interaction[c]	• Increased anxiety[c,d] • Impaired learning and memory[e] • Decreased PPI[f]	• Increased cell density[g] • Increased excitability of pyramidal neurons and postsynaptic glutamatergic responses[h] • Decreased NMDA-induced synaptic plasticity[i]	• *MIA*[a] • Increased TNF-α, IL-1β and IL-6 in peripheral blood mononuclear cells of ASD patients after LPS stimulation[b]	[a]Mazina *et al*., 2015 [b]Jyonouchi *et al*., 2005 [c]Hava *et al*., 2006 [d]Wang *et al*., 2010 [e]Golan *et al*., 2005 [f]Romero *et al*., 2007 [g]Patterson, 2009 [h]Lowe *et al*., 2008 [i]Lante *et al*., 2008
Prenatal Poly (I:C) exposure	• Stereotypic repetitive behavior[b,c] • Deficits in social interaction and communication[d] • Impaired social preference[d]	• Increased anxiety[b,c] • Impaired sensorimotor coordination[d] • Decreased PPI[b,c]	• Spatially localized deficit in Purkinje cells[d,e] • PSD malformation, purinergic receptors downregulation and reduced phosphorylation of ERK1/2 and CAMKII[d]	• *MIA*[a]	[a]Mazina *et al*., 2015 [b]Meyer *et al*., 2011; [c]Patterson, 2009 [d]Naviaux *et al*., 2013 [e]Shi *et al*., 2009
Prenatal VPA exposure	• Stereotypic repetitive behavior[f] • Impaired social interaction[e,f,g,h] • Decreased social preference for social novelty[e,h]	• Macrocephaly • Increased anxiety[e,f] • Impaired reversal learning and fear memory processing[e,f] • Abnormal nest seeking behaviors[e,f] • Decreased PPI[f] • Seizure susceptibility[h] • Male preponderance	• Neural tube defects & smaller brain mass at birth[e] • Hyper-connectivity and hyper-plasticity in the mPFC region[j] • Increased ratio between NMDA and AMPA receptor function[k] • Reduced synaptic function of LTP and NMDAR-mediated currents[l] • Abnormal neuronal migration[m] • Reduced GAD and $GABA_A$ receptor subunit expression and dysfunction of benzodiazepine bin induced extensive neurogenesis ding site[n] • Increased $GABA_A$ receptor driving force (DF_{GABA})[o] • Induced extensive neurogenesis *in vitro*[p] • Reduced natural apoptosis of neural progenitor cells (NPCs) and increased neurogenesis[q] • Increased PSD-95, α-CaMKII, vGluT1 and synaptophysin expressions and elevated kinetic profiles of the glutamatergic NMDA, AMPA and mGluR5 pathways in the PFC through attenuation of MeCP2[r]	• Gestational VPA treatment can induce ASD in children[a] • Neural tube defects[b] • Intellectual impairments[c] • ASD related neurobehavioral impairments[d] • Increased seizure susceptibility[i]	[a]Christianson *et al*., 1994 [b]Ornoy, 2009 [c]Moore *et al*., 2000 [d]Moore *et al*., 2000 [e]Ornoy, 2009; Kataoka *et al*., 2013; Kim *et al*., 2014c [f]Schneider and Koch, 2005; Schneider *et al*., 2008; Patterson, 2009 [g]Dufour-Rainfray *et al*., 2010; [h]Kim *et al*., 2011 [i]Spence and Schneider, 2009 [j]Rinaldi *et al*., 2008 [k]Rinaldi *et al*., 2007 [l]Martin and Manzoni, 2014 [m]Kuwagata *et al*., 2009 [n]Fukuchi *et al*., 2009 [o]Tyzio *et al*., 2014 [p]Jung *et al*., 2008 [q]Go *et al*., 2012 [r]Kim *et al*., 2014b

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
BTBR T+ tf/J mice	• Low level of social interaction[b] • Stereotyped repetitive behaviors such as repetitive grooming[c] • Ultrasonic vocalization abnormalities[d]	*ND*	• Absent corpus callosum and reduction of hippocampal commissure[a] • Altered brain connective tissue and reduced level of heparan sulfate[e] • Reduction of adult hippocampal neurogenesis[f] • No difference in GAD65/67[f]	*ND*	[a]Wahlsten *et al*., 2003 [b]Bolivar *et al*., 2007 [c]Amodeo *et al*., 2012; McFarlane *et al*., 2008 [d]Wohr *et al*., 2011a [e]Blanchard *et al*., 2012; [f]Stephenson *et al*., 2011
B. Genetic Models					
BDNF$^{-/+}$ mice	• *Male BDNF-tg mice exhibited less marble burying*[f] • Female BDNF-tg mice had higher self-grooming[g]	• High seizure susceptibilities[f,g] • Male BDNF-tg mice exhibited less anxiety- and depressive-like behaviors-[f] • Female BDNF-tg mice had higher anxiety scores and no change in depression-like behaviors[g] • Hyperactivity • Increased aggression	• Serotonergic defects	• Higher BDNF levels in the blood of children with ASD[a] but decreased serum BDNF levels in other ASD patients[e] • Basal forebrain of autistic adults showed increased BDNF levels[b] • BDNF mutation may underlie the overgrowth of brain in ASD[c] • A candidate gene for ASD susceptibility[d]	[a]Bryn *et al*., 2015 [b]Perry *et al*., 2001 [c]Tsai, 2005 [d]Pardo and Eberhart, 2007 [e]Taurines *et al*., 2014 [f]Weidner *et al*., 2014 [g]Papaleo *et al*., 2011
DHCR7 mutant mice	• Low exploratory activity in the social preference test[d]	• Low exploration in open field test[d]	• Increased ventricular size[e] • Hippocampus abnormalities[f] • Serotonergic neurons abnormalities[f,g]	• Main cause of SLOS from a defective DHCR7[a] • 50% of SLOS are relevant to autism[b] • Low cholesterol observed in children with ASD[c] • SLOS patients have hyperactivity, irritability, aggression, insomnia, self-injurious behavior, repetitive and ritualistic behaviors as well as impaired communication[b]	[a]Irons *et al*., 1993 [b]Tierney *et al*., 2000 [c]Tierney *et al*., 2006 [d]Moy *et al*., 2009 [e]Correa-Cerro *et al*., 2006 [f]Waage-Baudet *et al*., 2003 [g]Korade *et al*., 2013

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
EN2$^{-/-}$ mice	• Decreased social play[b]	• Increased aggression, impaired learning and memory and motor coordination[b]	• Decreased cerebellar size and abnormal foliation patterns[c] • Major cell types of the olivocerebellar circuit e.g. Purkinje, were reduced up to 30-40%[d]	• Mutations of this gene were found to have some associations with ASD[a]	[a]Benayed *et al*., 2005; [b]Cheh *et al*., 2006 [c]Kuemerle *et al*., 2007 [d]Kuemerle *et al*., 1997
FMR1 knockout mice	• Repetitive behaviors[c] • Decreased social interaction[c] • *Controversy in social approach & social anxiety behaviors*[f]	• Increased anxiety & hyperactivity[c] • High seizure susceptibility[d] • Decreased spatial learning ability & impaired object recognition[e]	• Increased dendritic spine length[g] • Increased mGluR-dependent LTD[h] • 50% reduced mGluR5 expression[i] • Imbalance between excitation and inhibition in the brain circuitry[d] • Increased dendritic spine length • Cortical LTP decrement[j] • Delayed GABA polarity developmental switch (i.e. from depolarizing to hyperpolarizing) and dysregulated intracellular chloride levels[k] • Dysfunctional endocannabinoid system (ECS), i.e altered CB1 and CB2 receptors[l] • Increased excitatory synaptic plasticity and abnormal mGlu5R/2-AG coupling[l]	• Main cause of FXS, from *FMR1* mutation, i.e. expanded CGG trinucleotide repeats (55-230) in the 5' untranslated region (5'UTR) & halts the production of FMRP[a] • 10-30% of FXS are diagnosed with autism[b]	[a]Garber *et al*., 2008; [b]Hatton *et al*., 2006 [c]Bernardet and Crusio, 2006 [d]Silva and Ehninger, 2009 [e]Brennan *et al*., 2006 [f]Spencer *et al*., 2005; McNaughton *et al*., 2008 vs Mineur *et al*., 2006; Liu and Smith, 2009 [g]Irwin *et al*., 2000 [h]Nosyreva and Huber, 2006 [i]Bear *et al*., 2004 [j]Zhang *et al*., 2009 [k]He *et al*., 2014; Tyzio *et al*., 2014 [l]Maccarrone *et al*., 2010; Jung *et al*., 2012; Busquets-Garcia *et al*., 2013;
GABRB3 knockout mice	• Stereotyped circling[g] • Decreased social interaction[g] • Impaired nesting behaviors[g]	• Increased neonatal mortality and seizure susceptibility[f] • Hyperactivity[g] • Impaired learning and memory with low exploratory behaviors[g]	• 50% reduction of the binding capacity to the GABAA receptor sites in newborns and adults[h]	• Maternal deletion of 15q11-13 containing *UBE3A* and *GABRB3* causes Angelman syndrome[a] • *UBE3A* and *GABRB3* downregulations have overlapping genotypes and phenotypes with autism especially those with *MECP2* mutations causing Rett syndrome[b] • Reduced GABAergic receptor system[c] • Decreased GAD expression[d] • *GABRB3* polymorphism[e]	[a]Wagstaff *et al*., 1991; Nakao *et al*., 1994; [b]Samaco *et al*., 2005 [c]Blatt *et al*., 2001 [d]Fatemi *et al*., 2002 [e]Buxbaum *et al*., 2002 [f]Homanics *et al*., 1997 [g]DeLorey *et al*., 2008 [h]Sinkkonen *et al*., 2003

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
MeCP2 knockout mice	• Impaired social interaction and nest building ability[b,d] • Impaired long-term social memory[b,d]	• Increased anxiety[b] • Decreased motor coordination[c] • Impaired learning and memory[b,d]	• Increased neuronal transcription through enhanced histone acetylation[e] • Neurotoxicity due to excessive glutamate release from microglia[f] • *MeCP2*-null astrocytes cannot support normal dendritic morphology in the wild-type hippocampal neurons[g] • Abnormal dendrites and axon development[h] • Reduced inhibitory quantal size of GABAergic neurons[i] • Decreased GAD expression[i]	• Main cause of x-linked, female –prevalent Rett syndrome, an MeCP2 mutation disorder[a]	[a]Rett, 1966 [b]Chahrour and Zoghbi, 2007 [c]Guy *et al*., 2001 [d]Moretti *et al*., 2006 [e]Guy *et al*., 2011 [f]Maezawa and Jin, 2010 [g]Ballas *et al*., 2009 [h]Larimore *et al*., 2009 [i]Chao *et al*., 2010
MAOA deficient mice	• Social and communication impairments[h] • Repetitive behavior responses & behavioral rigidity[h]	• Increased aggression[e] • Increased fear and eye-blink conditioning[f] • Hyper-responsiveness to acoustic stimuli[g] • Motor abnormalities[h]	• Increased hippocampal LTP and NMDAR expression[g] • Thinning of the corpus callosum[i] • Increased pyramidal neurodendrite arborization in the PFC[h] • Disrupted microarchitecture of the cerebellum[h] • Increased levels of serotonin, dopamine and norepinephrine[e,g,h]	• Mutation of MAOA causes Brunner syndrome and is linked to antisocial behaviors[a] • The alleles regulating the levels of MAOA were correlated with autism and the severity of autistic symptoms[b] • Causative role of MAOA-up stream variable number of tandem repeats (uVNTR) in ASD hyperserotone*MIA*[c] • Cortical enlargement in autism is associated with a functional variable number tandem repeats in MAOA[d]	[a]Hunter, 2010 [b]Cohen *et al*., 2003 [c]Hranilovic *et al*., 2008 [d]Davis *et al*., 2008 [e]Cases *et al*., 1995 [f]Singh *et al*., 2013 [g]Popova *et al*., 2000 [h]Bortolato *et al*., 2013

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
$NF1^{+/-}$ mice	*ND*	• Defects in spatial learning and memory[c,d] • Delayed acquisition of motor skills[d] • Impaired fear conditioning[d]	• Cortical neurons and astrocytes fail to form cortical barrels in the somatosensory cortex[e]	• Mutations of the NF1 gene causes a life-shortening condition known as neurofibromatosis[a] • NF1 was suggested to underlie mental retardation and learning deficits[b] • Overexpression of *NF1* gene and polymorphisms in some NF1 allele region were correlated with autism[f]	[a]Rasmussen and Friedman, 2000 [b]Husi *et al*., 2000 [c]Silva *et al*., 1997 [d]Costa *et al*., 2002 [e]Lush *et al*., 2008 [f]Mbarek *et al*., 1999; Marui *et al*., 2004
NLGN1 knockout mice	• Repetitive/stereotype grooming[b]	• Impaired spatial memory[b]	• Decreased NMDA/AMPA ratios in cortico-striatal synapses[b] • Decreased hippocampal LTP[b]	• In-depth molecular genetic analysis concluded that neuroligin mutations may cause autism only in rare occasions and neuroligin allele variations would be unlikely major risk factor for autism[a]	[a]Ylisaukko-oja *et al*., 2005 [b]Blundell *et al*., 2010
NLGN3 R451C mutant mice	• Impaired social interaction[c] • Deficits in USV and preference for social novelty[d,e] • *No changes in time spent in social interaction*[e]	• Enhanced spatial learning ability[c] • Olfactory defects[e] • *No changes in PPI and seizure susceptibility*[e]	• Increased inhibitory synaptic transmission with no apparent effect in excitatory synapses in the somatosensory cortex[d] • Increased excitatory transmission in the hippocampal region for both AMPAR and NMDAR–mediated currents[c] • Enhanced LTP[c] • Increased dendritic branching and synaptic structure abnormalities in hippocampus[c]	• Mutations of *NLGN3* and *NLGN4* are associated with X-linked intellectual disability, seizures, and autism[a] • Arg451Cys (R451C) mutation of *NLGN3* is associated with autism[b]	[a]Jamain *et al*., 2003 [b]Comoletti *et al*., 2004 [c]Etherton *et al*., 2011 [d]Jamain *et al*., 2008; [e]Radyushkin *et al*., 2009
NLGN4 mutant mice	• Impaired social interaction and social memory[c,d] • *No change in repetitive behaviors*[c]	• *No change in exploratory activity, anxiety, learning and memory*[c]	• Reduced brain volume[c]	• Mutations of *NLGN3* and *NLGN4* are associated with X-linked intellectual disability, seizures, and autism[a] • Attributed to many comorbid neurodevelopmental conditions and may only contribute to ASD at a small fraction[b]	[a]Jamain *et al*., 2003; [b]Gauthier *et al*., 2005; [c]Jamain *et al*., 2008; [d]Radyushkin *et al*., 2009

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
NRXN1α deficient mice	• Impaired nesting ability[b] • Increased grooming activity[b] • *No obvious social defects*[b]	• Impaired pre-pulse inhibition[b] • *Enhanced motor learning*[b]	• Defects in excitatory synaptic transmission[b]	• *NRXN1* deletion was implicated with ASD along with other disorders[a]	[a]Ching *et al*., 2010 [b]Etherton *et al*., 2009
Oxt deficient mice	• Impaired social recognition[f] • Decreased social odor memory in females[g] • Normal social approach[h]	• *Reduced aggression*[h]	• Oxytocin administration into the amygdala region showed enhanced social recognition in Oxt knockout mice[i]	• Oxytocin has a key role in the process of social recognition and interactions[a] • Reduced plasma levels of oxytocin observed in autistic children[b] • Administration of oxytocin in autistic patients resulted to enhanced social interactions[c], reduced repetitive behaviors[d], and improved emotional recognition[e]	[a]Guastella *et al*., 2008; Savaskan *et al*., 2008 [b]Insel, 2010 [c]Andari *et al*., 2010 [d]Hollander *et al*., 2003 [e]Guastella *et al*., 2010 [f]Ferguson *et al*., 2001; [g]Kavaliers *et al*., 2003 [h]Winslow and Insel, 2002
Oxtr-null mice	• Reduced social memory[b] • Defective USVs[b] • Deficits in social behaviors[c,d] • *No changes in stereotyped behaviors*[c]	• Increased aggression[d] • High seizure susceptibility[d]	• Decreased ratio of GABAergic presynapses in the hippocampus[d]	• Polymorphisms in *Oxtr* from various ethnic populations revealed an associations to ASD[a] • OXTR SNPs as predictors of social impairments in children with or without ASD[e]	[a]Jacob *et al*., 2007; Gregory *et al*., 2009; Wu *et al*., 2005; Liu *et al*., 2010; [b]Lee *et al*., 2008 [c]Pobbe *et al*., 2012 [d]Sala *et al*., 2011 [e]Parker *et al*., 2014
MAGEL2-deficient mice	• Impaired social recognition and interaction in adulthood[c]	• Learning difficulties in adulthood[c] • Decreased suckling behavior leading to 50% mortality[d]	• Reduced production of oxytocin in the hypothalamus during neonatal period[d]	• *MAGEL2* is a paternally imprinted gene located in chromosome 15q11-q13 found to have a genetic role in the development of PWS[a] • *MAGEL2* has been introduced as a causative gene for the complex ASD and contributes to PWS and ASD comorbidity[b]	[a]Boccaccio *et al*., 1999 [b]Schaaf *et al*., 2013 [c]Meziane *et al*., 2015 [d]Schaller *et al*., 2010

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
PTEN mutant mice	• Abnormal social interaction[b]	• Excessive responses to stimuli[b] • Hyperactivity[c] • Decreased PPI[c]	• Macrocephaly and neuronal hypertrophy[b] • Increased net excitatory drive onto granule neurons with a preferential increase in excitatory synaptic neurons[d] • Increased cell proliferation capacity[e]	• PTEN variations were observed in ASD with macrocephaly phenotypes[a]	[a]Butler *et al*., 2005 [b]Kwon *et al*., 2006 [c]Ogawa *et al*., 2007 [d]Luikart *et al*., 2011 [e]Gregorian *et al*., 2009; Bonaguidi *et al*., 2011
Reeler (rl/rl) and mutant (+/rl) mice	• Deficits in USV[a]	• Increased seizure susceptibility[d]	• Disorganizations in the cerebrum, cerebellum, hippocampus, subcortical regions, and spinal cord[c] • Decreased density of striatal GABAergic interneurons[e]	• Downregulation of Reelin in the cortical GABAergic interneurons has been frequently observed in schizophrenia, bipolar disorders and autism[a]	[a]Ognibene *et al*., 2007 [b]Gillberg, 1998; [c]Martin, 1981; Goffinet, 1983; Yip *et al*., 2000; D'Arcangelo, 2005 [d]Patrylo *et al*., 2006 [e]Marrone *et al*., 2006 [f]Tueting *et al*., 1999 [g]Salinger *et al*., 2003 [h]Podhorna and Didriksen, 2004 [i]Iafrati *et al*., 2014
Heterozygous *reeler* (+/rl) mice	*ND*	• Deficits in PPI and decreased exploration in the EPM[f] • *Normal social aggressive behaviors*[g] • *No behavioral abnormalities*[h] • Abnormal fear memory[i]	• Reduction in dendritic spine density and abnormal LTP in the prefrontal cortex[d]	• Mutation of 7q22-23 resulting to longer triplet repeats in the 5'UTR of *RELN* gene were observed in autistic patients[b]	
SERT knockout mice	• Reduced social interactions[c]	• Decreased exploration[d] • Increased anxiety[d] • Increased sensitivity to stress[e]	• Altered HPA axis signaling[e] • Altered cortical thickness and cell density[f]	• Hyperserotone*MIA* is a consistent finding ASD[a] • Conflicting results regarding the involvement of SERT variants in autism hyperserotone*MIA*[b] • Variations of SERT including Gly56Ala, Ile425Leu, Ile425Val, Phe465Leu, Leu550Val, and Lys605Asn all increase the serotonin uptake activity of SERT[g] • SERT variation may overlap between ASD and OCD[h]	[a]Hranilovic *et al*., 2008 [b]Betancur *et al*., 2002; Huang *et al*., 2008 [c]Kalueff *et al*., 2007 [d]Holmes *et al*., 2003; [e]Jiang *et al*., 2009 [f]Altamura *et al*., 2007 [g]Prasad *et al*., 2009 [h]Veenstra-Vanderweele *et al*., 2009
$SHANK1^{-/-}$ mice	• *No defects in social interaction*[d]	• Increased anxiety[b,d] • Impaired contextual fear memory[b] • *Enhanced spatial learning*[b] • Deficits in USV and scent marking behaviors[c] • Motor disability[d]	• Altered composition of PSD proteins[b] • Reduced size of dendritic spines and weaker basal synaptic transmission[b]	• Synaptic dysfunction hypothesis in ASD pathophysiology could be supported by studies of *Shank* mutation neurobiology in mice[a] • Male-heritable *SHANK1* locus microdeletions in ASD patients	[a]Jiang and Ehlers, 2013 [b]Hung *et al*., 2008 [c]Wohr *et al*., 2011b [d]Silverman *et al*., 2011 [e]Sato *et al*., 2012

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
SHANK2$^{-/-}$ mice	• Repetitive grooming and jumping[c,d] • Impaired USVs and social interaction behaviors[c,d]	• Hyperactivity[c]	• Fewer dendritic spines and lower basal synaptic transmission with increased excitatory currents by NMDA receptors[c] • Decreased NMDA receptor function (another study)[d]	• Mutations in the *SHANK2* gene were reported in ASD patients[a] • Spine volume alterations and smaller *SHANK2* cluster sizes (R462X & T1127M *SHANK2* variants)[b] • Defective dendritic branching and decreased postsynaptic clustering (R4623X variant)[b]	[a]Berkel *et al*., 2010; Leblond *et al*., 2012 [b]Berkel *et al*., 2012 [c]Schmeisser *et al*., 2012 [d]Won *et al*., 2012
SHANK3 mutant mice	• Deficits in social interaction[c] • Mild social deficits in juvenile but not adults[e] • Repetitive grooming (variable)[c,e] • Decreased USVs (variable)[e,f] • Reduced social sniffing[f]	• Decreased reversal learning (variable)[e] • Impaired novel object recognition and motor coordination[e]	• Cortico-striatal circuit and striatal synaptic defects[c] • Decreased EPSCs in the pyramidal neurons of hippocampal CA1[f] • Reduced basal neurotransmission in these animals in an AMPAR mediated manner[f] • Reduced GluR1-immunoreactive puncta of the stratum radiatum[f] • Impaired LTP but not LTD[f]	• Mutations of the *SHANK3* genes, such as the microdeletions of 22q13, have been implicated in ASD[a] • Heterozygous mutations of *SHANK3* may cause ASD in a gene-dosage-dependent manner[b] • Possible link between autism and schizophrenia due to similar findings regarding *SHANK3* mutations[d]	[a]Manning *et al*., 2004 [b]Durand *et al*., 2007; [c]Peca *et al*., 2011 [d]Gauthier *et al*., 2010 [e]Yang *et al*., 2012 [f]Bozdagi *et al*., 2010
Conditional *TSC1* knockout mice	• Abnormal social interactions[g] • Repetitive behaviors[g] • Impaired vocalizations[g]	• Increased seizure susceptibility[c,d]	• Significant brain pathology[c] • Cortical excitability[d] • Enhanced AMPAR and NMDAR-mediated EPSCs[e] • Increased brain size and elevated mTORC1 signaling but declined mTORC2 signaling[f] • Decreased Purkinje cells[g]	• Mutations of *TSC1* or *TSC2* cause Tuberous sclerosis complex (TSC)[a] • 20-60% of TSC patients have ASD[a] • *TSC1*/*TSC2* mutations are associated with neurological deficits including cognitive dysfunction, epilepsy, and autism[b]	[a]Bolton *et al*., 2002; Curatolo *et al*., 2004 [b]DiMario, 2004; Goorden *et al*., 2007 [c]Uhlmann *et al*., 2002 [d]Meikle *et al*., 2007 [e]Bateup *et al*., 2011 [f]Carson *et al*., 2012 [g]Tsai *et al*., 2012 [h]Ehninger *et al*., 2012 [i]Onda *et al*., 2002 [j]Young *et al*., 2010 [k]Chevere-Torres *et al*., 2012 [l]Reith *et al*., 2011 [m]Auerbach *et al*., 2011 [n]Tang *et al*., 2014 [o]Lozovaya *et al*., 2014
Conditional *TSC2* knockout mice	• TSC (+/-) mutant mice with MIA by poly I:C induced impaired social interactions[h] • Altered USVs[j] • Impaired social interaction[k,n]	• Seizure behaviors early in life[o]	• No significant brain pathology in *TSC2*$^{w/-}$ mice[i] • Purkinje cell degeneration and apoptosis via ER and oxidative stress[l] • Deficient mGluR-LTD in the hippocampus[m] • mTOR over activity leading to abnormal postnatal dendritic pruning through normal autophagic inactivation in the brain[n] • mTOR-dependent upregulation of NMDARs that contain GluN2C[o]		

Table 1. Continued

Animal model of ASD	Features of animal model			Clinical behavioral and neurobiological findings	Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects		
UBE3A mutation	• Core symptoms of autism (increased *UBE3A*)[b] • Increased emissions of USVs[c]	• Increased seizure susceptibility[d]	• Reduced glutamate synaptic transmission (increased *UBE3A*)[b] • Weakened synaptic functions through excessive internalization of AMPA receptors[e]	• Mutations of 15q11-13 containing *UBE3A* and *GABRB3* results to Angelman syndrome[a] • Italian ASD patients have *UBE3A* mutation[f]	[a]Wagstaff *et al.*, 1991; Nakao *et al.*, 1994; [b]Smith *et al.*, 2011 [c]Jiang *et al.*, 2010 [d]Miura *et al.*, 2002 [e]Greer *et al.*, 2010 [f]Guffanti *et al.*, 2011
Brattleboro rats	• Decreased social recognition[c]	• No cardiovascular response to social isolation[d]	• Could not synthesize AVP due to a frameshift mutation of its gene[b]	• Autistic individuals and their immediate family members usually have an associated defect in *AVPR1a* gene[a] • Transmission disequilibrium in the AVR intronic microsatellite of ASD patients[a]	[a]Wassink *et al.*, 2004; Yirmiya *et al.*, 2006 [b]Schmale *et al.*, 1989 [c]Engelmann and Landgraf, 1994 [d]Gardiner and Bennett, 1983 [e]Bielsky *et al.*, 2005; Insel, 2010 [f]Wersinger *et al.*, 2004; Caldwell *et al.*, 2008
V1aR knockout mice	• Deficits in social interaction and recognition[e]	• Decreased anxiety[e]	*ND*		
V1bR knockout mice	• Decreased social aggression, social aggression and social memory[f] • Deficits in USV[f]	*ND*	*ND*		
CNTNAP2$^{-/-}$ mice	• All core symptoms of ASD[b]	• Hyperactivity and epileptic seizures[b]	• Abnormal neuronal migration and network activity[b] • Reduced GABAergic interneuron population[b]	• Variants of CNTNAP2 have been identified in a number of ASD patients[a] • CNTNAP2 mutations were found in a certain Australian population and in a boy with autism that have exhibited speech delays; an implication of this gene's involvement in language development[c] • CNTNAP2 mutations impaired the frontal lobe circuitry in ASD[d] • Not all variants of the CNTNAP2 gene may relate to ASD[e]	[a]Alarcón *et al.*, 2008; Arking *et al.*, 2008 [b]Peñagarikano *et al.*, 2011 [c]Whitehouse *et al.*, 2011 [d]Scott-Van Zeeland *et al.*, 2010 [e]Sampath *et al.*, 2013

Table 1. Continued

Animal model of ASD	Features of animal model				Citations
	Core symptoms of ASD	Other symptoms	Neurobiological defects	Clinical behavioral and neurobiological findings	
eIF4E overexpression mice	• Social interaction deficits[b] • Repetitive behaviors[b]	*ND*	• mPFC, striatal and hippocampal synaptic abnormalities through increased cap-dependent translation in the brain[b]	• Variants of the eIF4E gene promoter had been found were found in patients with ASD[a]	[a]Szatmari *et al*., 2007 [b]Santini *et al*., 2013

All descriptions with supercript alphabets correspond to their authors in the citation area and these alphabet sets have unique citations for each animal model.
ND: no data, *MIA*: maternal immune activation, Italicized sentences-negative, controversial or normal findings, USVs: ultrasonic vocalizations.

motor and cognitive impairments. Moreover, the pathological onset of cerebellar defects in autism is at an early age, which affects the development later in life. Lastly, various risk factors involving genetics, environment, or their combination can affect the development of the cerebral circuitry found in autism (Fatemi *et al*., 2012).

In rats, lesions in the midline of the cerebellum cause visuomotor defects in the Morris water maze test, despite any spatial memory defects in the spontaneous alternation test (Joyal *et al*., 1996). Moreover, early postnatal cerebellum lesions have been shown to increase spontaneous motor activity and decrease anxiety-like behavior in rodents (Bobee *et al*., 2000). Using the lurcher mutation model, which provides a reasonable mouse model of cerebellar defects (Martin *et al*., 2004), it was shown that the loss of Purkinje cells in mice induced significantly increased repetitive behaviors (Martin *et al*., 2010). As a whole, these cerebellum lesion studies in rodents confirm a potential role of this structure in producing some of the motor, repetitive and exploratory behavioral deficits or anxiety-like behaviors, observed in autism (Pierce and Courchesne, 2001). This is also consistent with the fact that cerebellar injury at birth is a risk factor for ASD in children (Wang *et al*., 2014). Indeed, cerebellar damage animal models could be an important tool for isolating the role of the cerebellum in specific autistic symptoms.

Medial prefrontal cortex (mPFC): Studies have shown that brain overgrowth in the mPFC and dorsolateral PFC is generally pronounced in autistic patients (Carper and Courchesne, 2005; Hazlett *et al*., 2005). Aside from PFC overgrowth, early PFC damage in humans has also been shown to impair social interaction and cognition (Eslinger *et al*., 2004). In rats, neonatal mPFC lesions decrease social play, conditioned place-preference associated with social contacts, and social grooming (Schneider and Koch, 2005). Interestingly, similar lesions in adult rats do not seem to affect social interactions as much (Schneider and Koch, 2005), suggesting that these deficits arise early in development. As morphological changes in mPFC have been linked to ASD, the exact neurobiological pathway pertaining to social deficits should be further studied. When doing so, nonetheless, it is important to be aware of the fact that alterations in mPFC function are not unique to ASD, as they also overlap with other neurological conditions.

Maternal infection

Maternal immune activation (MIA) is a proposed risk factor for abnormal fetal brain development leading to neurodevelopmental disorders such as ASD (Mazina *et al*., 2015). It has been shown that MIA during pregnancy in rodents leads to a dysregulated immune system in offspring and also results in autism-related phenotypes that persist well into adulthood (Patterson, 2011). In more detailed molecular studies, interleukin-6 (IL-6) has been suggested to play a mechanistic role in the transcriptional and behavioral abnormalities of MIA in offspring (Smith *et al*., 2007). This could parallel some reports from human ASD cases, where mothers of affected individuals display elevated IL-6 levels, as is observed in depression and schizophrenia (Daniels *et al*., 2008). This overlap with other neuropsychiatric disorders is also to be taken into consideration when using animal models of MIA. Yet, the fact that IL-6 has consistently been found to be increased in ASD brains (Benvenuto *et al*., 2009) and plasma (Ashwood *et al*., 2011), makes it a very worthy line of study. Furthermore, recent progress in animal models of MIA have shown promising results, yet further studies will be needed to connect immune dysregulation with ASD pathophysiology (Hsiao *et al*., 2012). Below, we briefly describe the three most commonly used MIA models of ASD.

Prenatal BDV (Borna Disease Virus) infection was the first virus-induced animal model of ASD (Pletnikov *et al*., 2002). BDV, a transmissible, progressive and lethal virus that causes encephalomyelitis in horses and sheep, is associated with neurologic impairments and behavioral disorders in humans (Richt *et al*., 1997). Prenatally BDV-infected rats, which have been commonly used to investigate pathogenic mechanisms (Taieb *et al*., 2001), show increased stereotypy (Hornig *et al*., 1999), decreased social play (Pletnikov *et al*., 2002) and impaired social interactions (Pletnikov *et al*., 1999), which are clearly ASD-related phenotypes. These BDV-infected rats also display abnormalities in postnatal hippocampus and cerebellum development (Taieb *et al*., 2001). Although BDV infection shows behavioral changes relevant to autism in offspring of affected animals, its implication and reflection to human condition is still elusive and needs to be studied further for clinical comparison, as no study directly related BDV exposure with autism in humans.

Lipopolysaccharide (LPS) is another immune activator found in the outer membrane of gram-negative bacteria that acts as an endotoxin. It is a highly immunogenic antigen that carries the ability to induce antibody responses *in vivo* (Skidmore *et al*., 1975). Although there has been no direct association between LPS and autism, peripheral blood mononuclear cells (PBMCs) of ASD patients seem to produce more TNF-α, IL-1β and IL-6 after LPS exposure, compared to controls (Jyonouchi *et al*., 2005). Interestingly, prenatally LPS-exposed mice display increased anxiety (Wang *et al*., 2010), decreased social interactions (Hava *et al*., 2006) and impaired learning and memory (Golan *et al*., 2005). In rats, gestational LPS exposure significantly decreases pre-pulse inhibition in male offspring (Romero *et al*., 2007). Other studies have found that LPS-exposed animals show increased cell density, increased excitability of pyramidal neurons and postsynaptic glutamatergic responses to NMDA-induced synaptic plasticity (Patterson, 2009). These findings from both rat and mouse studies indeed support the possibility that LPS-induced MIA can cause ASD phenotypes in offspring. More importantly, further research should be done in order to determine whether, postmortem autistic brains from individuals with a history of prenatal MIA or infection display some of the anatomical deficits observed in rodents.

Poly I:C is a double-stranded RNA that mimics viral infection and can induce MIA. Offspring of rats that have been injected with Poly I:C during pregnancy display autism-related phenotypes, including increased anxiety, stereotypic-repetitive behaviors (Patterson, 2009; Meyer *et al*., 2011), decreased social interaction and communication, impaired social preference and decreased sensorimotor coordination (Naviaux *et al*., 2013) and impaired prepulse inhibition (Patterson, 2009; Meyer *et al*., 2011). In rat and mice brains exposed to poly I:C has been found a spatially localized deficit in Purkinje cells at the lobule VII of the cerebellum, along with heterotrophic morphology and delayed migration of these cells in lobules VI and VII (Naviaux *et al*., 2013). In addition, synaptosome abnormalities were also observed, both at structural and chemical levels, including PSD malformation, downregulation of purinergic receptors and reduced phosphorylation of ERK1/2 and CAMKII (Naviaux *et al*., 2013). However, poly I:C induction in rodents have also been used to model schizophrenia (Kumamaru *et al*., 2014), so careful interpretation of results should be noted.

Overall, MIA animal models of autism could be a great tool not only in predicting the cause but also in identifying the pathophysiologic pathways involved in the disorder. This is supported by the fact that clinical epidemiologic studies can be the only practical and ethical option to identify disease-causing factors in humans. Although the type of microbial pathogens or immune activators may differ in humans to those used in animal models, the autistic effects of maternal MIA in animal models may somehow explain some pathologic mechanisms involved in human ASD. For more details on this topic, please see the works of Patterson (Patterson, 2011).

Prenatal valproate (VPA) exposure

Valproic acid (VPA) is a commonly used pharmaceutical that relieves seizures, migraine headaches and manic episodes related to bipolar disorder. However, several studies have shown that gestational VPA treatment for a life-threatening epilepsy may cause numerous defects in children, including neural tube defects (Ornoy, 2009), intellectual impairments (Moore *et al*., 2000) and cognitive-behavioral impairments (Moore *et al*., 2000), many related to the core symptoms of autism. Moreover, prenatal VPA exposure has often been associated with ASD (Christianson *et al*., 1994). The VPA animal models of ASD have thus been widely used due to their strong etiological and clinical relevance. Here, we mention notable progress and studies utilizing this model.

To investigate the possible effects of VPA on human embryos and explain its effect on brain development, rats and mice models have been widely used, although treatment dosage and injection timings vary among labs (Kataoka *et al*., 2013; Kim *et al*., 2014a). Indeed, prenatal VPA exposure to rodents does induce neural tube defects, abnormal brain mass at birth and behavioral impairments in the offspring (Kataoka *et al*., 2013; Kim *et al*., 2014a). Similar to autistic symptoms in human patients, both rats and mice that have been subjected to prenatal VPA exposure show increased stereotypic repetitive behaviors (Schneider *et al*., 2008), impaired social interactions (Kim *et al*., 2011), and decreased social preference for social novelty (Kim *et al*., 2011)

The VPA-exposed animal models also showed some common accompanying phenotypes of ASD such as increased anxiety, impaired reversal learning and fear memory processing, abnormal nesting behaviors (Schneider *et al*., 2008; Patterson, 2009), and decreased prepulse inhibition (Schneider *et al*., 2008; Patterson, 2009). In addition, our group and others have recently reported that prenatal VPA exposure at embryonic day 12 (E12) in rats recapitulates autism-related phenotypes, including deficits in social interactions (Kim *et al*., 2011) and increased seizure susceptibility, as is observed in 1/3 of ASD patients (Spence and Schneider, 2009). Interestingly, these deficits were only observed in male offspring, which is quite striking given that male preponderance is a common feature of neurodevelopmental disorders such as ASD and attention-deficit hyperactivity disorder (ADHD) (Rutter *et al*., 2003).

Physiologically, the brains of VPA-exposed rats display hyper-connectivity and hyper-plasticity in the mPFC region

(Rinaldi *et al*., 2008), along with an increased NMDA/AMPA ratio (Rinaldi *et al*., 2007). These animals also show dysregulated LTP and decreased NMDAR-mediated currents in adult mPFC, but not in early postnatal life and adolescence (Martin and Manzoni, 2014). These results demonstrate that synaptic abnormalities in the VPA animal model persist well into adulthood and suggest that an aberrant developmental switch in synaptic function of mPFC could underlie some of the ASD-related pathophysiological mechanisms. In other studies, VPA-exposed rats display abnormal neuronal migration (Kuwagata *et al*., 2009) aberrant $GABA_A$ receptor subunit expression and alterations in benzodiazepines binding, as has been observed in ASD patients (Oblak *et al*., 2011). Moreover, VPA exposure in rats reduced the expression of glutamate decarboxylase, which catalyzes the decarboxylation of glutamate to GABA and CO_2 in young neurons suggesting excitatory/inhibitory imbalance (Fukuchi *et al*., 2009). In naïve rats, GABA currents are excitatory in early development and undergo an inhibitory switch at birth, presumably through neuromodulation by oxytocin. Such shift is not observed (or is delayed) in both the VPA and fragile X models of autism, resulting in neuronal hyperexcitability and increased glutamatergic neurotransmission (Tyzio *et al*., 2014). These studies showed that lowering the intracellular chloride concentration by treating the dam with bumetanide produced long-term normalization of electrophysiological properties and behaviors in VPA offspring (Tyzio *et al*., 2014).

In vitro studies have provided additional evidence supporting the profound effects of early developmental exposure to VPA. First, cultured cells that have been treated with VPA show altered neural progenitor cell properties (Jung *et al*., 2008) and prolonged neurogenesis (Jung *et al*., 2008). In addition, VPA-exposed premature neurons and N1E-115 cell lines show enhanced expression of PSD-95 (Kim and Thayer, 2009) and increased neurite outgrowth (Yamauchi *et al*., 2008), respectively. Finally, studies have demonstrated that VPA treatment *in vitro* can increase the tissue plasminogen activator (tPA) and decrease plasminogen activator inhibitor-1 (PAI-1) activity in astrocytes but not in neurons (Cho *et al*., 2013). This led to the increased neurite outgrowth via JNK signaling, which could thus be related to the altered neural development in ASD.

A lot of progress has also been made in terms of the molecular mechanisms underlying the VPA animal model of ASD. For example, we found that the histone deacetylase inhibitor (HDACi) function of VPA prevented the apoptosis of neural progenitor cells (NPC). Mechanistically, VPA reduced the expression level of $I\kappa B\alpha$ and activated the NF-κB signaling pathway, leading to increased expression of the anti-apoptotic protein Bcl-XL (Go *et al*., 2012). In a follow-up investigation, VPA exposure at E12 enhanced Wnt1 signaling, which activated the GSK-$3\beta/\beta$ catenin pathway and lead to increased neurogenesis in the embryonic brain (Go *et al*., 2012). These processes shed light onto potential molecular pathways that could explain prolonged NPC proliferation and neuron overproduction in ASD.

In general, these studies showed that prenatal VPA exposure in rats has profound effects on neurotransmission and leads to excitatory/inhibitory imbalance, reminiscent to the human ASD condition (Kim *et al*., 2014c). We further discovered that Pax6, a transcription factor that modulates glutamatergic neuronal differentiation, was transiently increased after VPA exposure. This led to the increased sequential expression of additional transcription factors involved in the regulation of glutamatergic differentiation, including Ngn2, Tbr2 and NeuroD1. Ultimately, this series of events directed to the increased glutamatergic neurons in mature brains, marked by increased PSD-95, α-CaMKII, vGluT1 and synaptophysin expression. Conversely, there we found a slight decrease in GABAergic marker Mash1 early in development, followed by a decrease in GAD and Reelin, (Kim *et al*., 2014c), further highlighting the excitatory/inhibitory ratio shift. This imbalance was concurrent with abnormally elevated kinetic profiles of the glutamatergic NMDA, AMPA and mGluR5 pathways in the PFC of VPA-exposed young rats, through the attenuation of MeCP2 expression (Kim *et al*., 2014b), suggesting increased excitatory signaling. Intriguingly, Walcott and colleagues found that the increased neuronal excitability in young VPA-exposed rats was gradually corrected to normal levels during the adolescent period, suggesting a delay in neuronal circuit maturation, which prompts further investigation (Walcott *et al*., 2011).

As can be seen, the VPA model of autism has provided useful insights on potential mechanisms leading to ASD. Consequently, it has been also useful in the search for potential therapeutics for ASD. Our group, for example, used the VPA model to screen for drug treatments targeting known dysregulated pathways and found that NMDA receptor antagonists like MK801 and memantine, as well as the acetylcholinesterase inhibitor donepezil, normalized the social defects in the VPA-exposed animals (Kim *et al*., 2014a), in addition to bumetanide proposed by Tyzio *et al* as a therapeutic candidate (Tyzio *et al*., 2014). Overall, these studies show a great potential for using the VPA animal model of ASD in the mechanistic and therapeutic treatment exploration of ASD.

BTBR T+Itpr3tf/J

The BTBR T+Itpr3tf/J (BTBR) mice are inbred strain mice used as an animal model of ASD, due to its natural traits that resemble ASD-phenotypes. This mouse line is derived from Black and Tan BRachyury inbred strain (BTBR), which carry mutations in a^t (nonagouti; black and tan), $Itpr3^{tf}$ (inositol 1,4,5- triphosphate receptor 3; tufted), and *T* (brachyury). Anatomically, BTBR mice exhibit the absence of the corpus callosum and a severe reduction of the hippocampal commissure (Wahlsten *et al*., 2003), as well as high circulating levels of corticosteroid, progesterone, and its $3\alpha,5\alpha$-THP metabolite (Frye and Llaneza, 2010). These mice also show altered brain connective tissue, reduced heparan sulfate levels (Blanchard *et al*., 2012), and reduced adult hippocampal neurogenesis (Stephenson *et al*., 2011). BTBR mice show decreased social behaviors (Bolivar *et al*., 2007), defects in ultrasonic vocalizations, (Wohr *et al*., 2011a), increased stereotyped repetitive behaviors (Amodeo *et al*., 2012) and repetitive self-grooming (McFarlane *et al*., 2008). Interestingly, these impairments are alleviated by acute administration of either the mGluR5 antagonist MPEP (Silverman *et al*., 2010) or the AChE inhibitor, donepezil (Karvat and Kimchi, 2014). Moreover, the SERT blocker fluoxetine enhanced the social interactions in BTBR mice (Chadman, 2011). Indeed, the autism-related phenotypes in this inbred mouse strain could be used as good models for finding therapeutic candidates for broader or idiopathic etiologies and pathophysiologies of ASD.

GENETIC MODELS

Brain-derived neurotrophic factor (BDNF)

BDNF is a secretory protein and a member of the neurotrophic factor family (Binder and Scharfman, 2004), which is widely expressed in the brain and periphery (Murer *et al*., 2001). *BDNF* has been proposed as a candidate gene for ASD susceptibility (Pardo and Eberhart, 2007) and plays a key role in the growth and differentiation of new neurons and synapses, as well as in the survival of existing neurons (Huang and Reichardt, 2001). Children with ASD were reported to possess higher BDNF levels in the blood, compared with typically-developing individuals (Bryn *et al*., 2015). Furthermore, autistic adults have been reported to have increased BDNF levels in the basal forebrain (Perry *et al*., 2001). These findings, therefore, suggest that over-expression of BDNF at various developmental time points could be associated with ASD and may be an underlying mechanism of brain overgrowth in autistic patients (Tsai, 2005). However, the role of BDNF in ASD etiology remains inconclusive, as recent work demonstrates completely opposite results, finding decreased serum BDNF levels in ASD patients (Taurines *et al*., 2014). These contradicting outcomes make BDNF a variable and perhaps unreliable biomarker for ASD; yet, it is clear that optimal levels of BDNF are essential for brain development and maintenance of normal brain function.

BDNF function has been extensively studied in mice, mainly through the use of conditional knockouts and mutants. Initial studies in these transgenics found somewhat robust behavioral phenotypes, although they were not initially attributed to autism (MacQueen *et al*., 2001). One of such phenotypes can be observed in the conditional *BDNF* knockout mouse, which displays increased locomotor activity in males and depression-like behaviors in *BDNF*$^{+/-}$ females (Monteggia *et al*., 2007). Other studies found aggressive behaviors in this model (Chan *et al*., 2006). The exact mechanism behind these deficits remains elusive, yet some studies suggest that they may be related to alterations in serotonergic signaling (Daws *et al*., 2007) and 5-HT$_{2A}$ receptor function (Chan *et al*., 2006).

To this date, only a few researchers have used the BDNF overexpression model (BDNF-tg) to investigate its possible role in ASD pathology. This could mainly be due to the fact that these mice do not display any deficits in social behavior, diminishing its face validity (Weidner *et al*., 2014). Still, the BDNF overexpression model does recapitulate some ASD-related phenotypes, including high seizure susceptibility in both males and females and other sex-specific phenotypes. For example, male BDNF-tg mice have deficits in marble burying, and display anxiety and depressive-like behaviors (Weidner *et al*., 2014). Female transgenics, on the other hand, display higher self-grooming, higher anxiety scores but no depression-like behaviors (Papaleo *et al*., 2011).

Although BDNF overexpression in animals may not well represent a monogenic ASD model, they can still be useful for studying the multifactorial aspects leading to ASD and its comorbidities, such as epilepsy (Weidner *et al*., 2014). It is also possible that neural substrates such neurotrophins and nerve growth factors, which are connected with BDNF dysregulation, may be cooperatively involved in the ASD pathophysiology.

7-dehydrocholesterol reductase (DHCR7)

DHCR7 is a ubiquitously expressed catalytic enzyme that converts 7-dehydrocholesterol to cholesterol. Defects in DHCR7 function are the main cause of Smith-Lemli-Optiz syndrome (SLOS) (Irons *et al*., 1993), which is often comorbid with autism (50%) (Tierney *et al*., 2000). SLOS patients have abnormal behavioral phenotypes including increased hyperactivity, irritability, aggression, insomnia, self-injurious behavior, repetitive and ritualistic behaviors, and impaired communication (Tierney *et al*., 2000). Interestingly, low cholesterol levels have been observed in children with idiopathic autism (Tierney *et al*., 2006).

Similar to *BDNF* homozygous knockouts, *DHCR7* null (-/-) mice have high lethality rates at birth (Fitzky *et al*., 2001); therefore, *DHCR7*$^{+/-}$ or *DHCR7* mutant mice are used as animal models. *DHCR7*$^{+/-}$ mice show low exploratory activity both in the social preference and open field tests (Moy *et al*., 2009). DHCR7 mutant mice display increased ventricular size (Correa-Cerro *et al*., 2006) and abnormalities in the hippocampus and serotonergic neurons (Waage-Baudet *et al*., 2003). Additionally, the Dhcr7-heterozygous mice show increased response to treatment with a 5-HT2A agonist, as marked by frequent head-twitch, further suggesting the involvement of the serotonergic system in the phenotypes observed in the model (Korade *et al*., 2013). These data further demonstrate the impact of cholesterol dysregulation on behavior and provide further insights onto a potential ASD mechanism that is often overlooked, as in the case of SLOS patients.

Engrailed-2 (EN2)

EN2 is a homeodomain-containing protein that regulates pattern formation during brain development (Zec *et al*., 1997). Although not consistently observed (Zhong *et al*., 2003), it has been suggested that genetic variants of EN2 are associated with ASD (Benayed *et al*., 2005; Brune *et al*., 2008), *EN2*$^{-/-}$ mice were introduced as a potential model of ASD in 2006, and were shown to have behavioral deficits in social play, aggression, spatial memory and motor coordination (Cheh *et al*., 2006). Furthermore *EN2*$^{-/-}$ mice display decreased cerebellar size and abnormal foliation patterns, similar to patients with ASD (Kuemerle *et al*., 2007). In addition, these studies found that major cell types of the olivocerebellar circuit, e.g. Purkinje, were reduced up to 30-40% (Kuemerle *et al*., 1997). This places the *EN2*$^{-/-}$ mouse in parallel to the cerebellar lesion model for ASD, as described above. Thus, even though *EN2*$^{-/-}$ mice do not fully recapitulate all of the structural abnormalities and behavioral phenotypes in ASD, it can somehow provide quality pathophysiologic insights (Kuemerle *et al*., 2007).

Fragile X mental retardation 1 (FMR1)

The *FMR1* gene encodes for fragile X mental retardation protein (FMRP) (Verheij *et al*., 1993). FMRP is an RNA-binding protein that is commonly expressed in brain, testes, and ovaries. FMRP takes part in local protein synthesis regulation in dendrites, as well as mRNA transport from nucleus to the cytoplasm (Garber *et al*., 2008). In addition, FMRP plays an essential role in synapse development (Weiler *et al*., 1997), which is vital for proper neurotransmission, learning and memory, and synaptic plasticity. Mutations in *FMR1* take the form of expanded CGG trinucleotide repeats (55-230) in the 5' gene untranslated region (5'UTR); this halts the production of FMRP and leads to a developmental condition called Fragile X Syndrome (FXS). FXS is characterized by intellectual disabilities, developmental delays, congenital malformations, seizures and autistic-like symptoms (Garber *et al*., 2008). Indeed, 10-30% of FXS patients were also diagnosed with autism (Hatton *et al*., 2006).

FMR1 knockout mice have widely been used to investigate the behavioral abnormalities and pathophysiological mechanisms underlying FXS. Interestingly, a number of studies have shown that *FMR1* knockout mice display comorbidities with autistic behaviors including decreased social interaction, increased repetitive behaviors, anxiety, hyperactivity (Bernardet and Crusio, 2006), increased seizure susceptibility (Silva and Ehninger, 2009), decreased spatial learning ability, and impaired object recognition (Brennan *et al*., 2006; Mineur *et al*., 2006). Nonetheless, some of these results are inconclusive, as McNaughton *et al*. and Spencer *et al*. reported that these mice show increased social approach and anxiety (Spencer *et al*., 2005; McNaughton *et al*., 2008), whereas Liu and Smith, and Mineur *et al*. reported decreased social approach and anxiety in *FMR1* knockout animals (Mineur *et al*., 2006; Liu and Smith, 2009). These inconclusive findings might be due to lab-specific technical differences and conditions.

Physiologically, *FMR1* knockout mice display increased dendritic spine length (Irwin *et al*., 2000), decreased mGluR5 expression (Bear *et al*., 2004) and increased mGluR-dependent LTD (Nosyreva and Huber, 2006), decreased LTP (Zhang *et al*., 2009), and an imbalance between excitation and inhibition (Silva and Ehninger, 2009). Furthermore, recent studies have demonstrated the involvement of abnormal GABAergic neurotransmission and development in the generation of autistic-related behaviors in FRX mice. For instance, it has been found that the developmental switch in GABA polarity is delayed in these mice (i.e. from depolarizing to hyperpolarizing) and that this might be due to dysregulated intracellular chloride levels, which surely contributes to abnormal brain development and can be implicated in autism pathophysiology (Tyzio *et al*., 2014).

Some reports have also suggested a dysfunctional endocannabinoid system (ECS) in FXS as a disordered mechanism. The ECS plays a critical role in the regulation of synaptic plasticity, cognition, pain, seizure susceptibility and anxiety (Kano *et al*., 2009). On the other hand, FMRP modulates mGluR5-mediated signal transduction in glutamatergic synapses, which controls the LTD type of synaptic plasticity. Interestingly, 2-arachidonoyl-sn-glycerol (2-AG), a retrograde endocannabinoid transmitter, mediates mGluR5-dependent LTD in excitatory synapses, in the ventral striatum and PFC (Jung *et al*., 2012). The FMRP null mice exhibit increased activity of diacylglycerol lipase (DAGL), a limiting enzyme in 2-AG biosynthesis, which disrupts the GABAergic synaptic sensitivity to endocannabinoid mobilization (Maccarrone *et al*., 2010). Ultimately, this produces enhanced activation of cannabinoid receptors (CB1R and CB2R), which increases synaptic strength and excitation as a result of mGluR5-mediated 2-AG release (Maccarrone *et al*., 2010). Remarkably, modulating or blocking CB1 and CB2 receptors signaling normalizes 2-AG dysregulation and rescues the cognitive and behavioral abnormalities in FMRP null mice (Busquets-Garcia *et al*., 2013). These studies show how targeting the ECS and mGluR5 pathways can be of great therapeutic value, which certainly warrant further investigation. Overall, and based on these behavioral and neurological findings, *FMR1* knockout animal models provide useful insights on ASD pathology and the involvement of the *FMR1* gene or FMRP in the neurobiology of autism.

GABA receptor subunit beta-3 (GABRB3)

The *GABRB3* gene encodes for a major subunit of the ligand-gated GABA receptor. The gene itself is located within the 15q11-13 chromosome region. It has long been known that maternal deletion of 15q11-13, which also contains *UBE3A*, causes Angelman syndrome, which is highly comorbid with ASD (Nakao *et al*., 1994). Interestingly, down-regulation of *UBE3A* and *GABRB3* result in autism-related phenotypes in mice, similar to those caused by *MECP2* mutations in Rett syndrome (described below) (Samaco *et al*., 2005). The involvement of GABRB3 in modulating inhibitory neurotransmission is further supported by a number of clinical studies, which associate *GABRB3* polymorphisms with ASD (Buxbaum *et al*., 2002). Moreover, individuals with autism often display disruptions in GABAergic biomarkers (Blatt, 2005), including reduced expression of GABAergic receptors (Blatt *et al*., 2001) and decreased expression of GAD, the enzyme that catalyzes synthesis of GABA (Fatemi *et al*., 2002)

GABRB3 knockout (-/-) mice display many phenotypes associated with ASD. These include increased neonatal mortality, seizure susceptibility (Homanics *et al*., 1997), hyperactivity, stereotyped/circling behavior (DeLorey *et al*., 2008), deficits in learning and memory (DeLorey *et al*., 1998), and impaired social interactions, nesting ability and exploratory behaviors (DeLorey *et al*., 2008). Furthermore, GABA_A receptors in *GABRB3* null mice show a 50% reduction in GABA binding capacity, both in newborns and adults (Sinkkonen *et al*., 2003). Thus, this model has provided useful insights onto another pathological mechanism underlying Angelman syndrome or potentially ASD. Yet, additional human genetic studies must be done in order to further elucidate the role of GABRB3 in ASD (Tavassoli *et al*., 2012; Warrier *et al*., 2013).

Methyl CpG binding protein 2 (MeCP2)

MeCP2 acts mainly as a transcriptional repressor by binding to methyl groups in CpG islands of DNA (Yasui *et al*., 2007), although its role in activating gene transcription has also been observed (Chahrour *et al*., 2008). In mammals, regulation of genetic transcription by Mecp2 has been shown to be crucial for the modulation of chromatin at critical developmental time points. Human mutations in *MeCP2* cause Rett syndrome, a progressive X-linked neurodevelopmental disorder that causes mental retardation and a number of developmental deficits in females (Rett, 1966); it is thought that homozygous mutations in males result in lethality *in utero* (Rett, 1966). Historically, Rett syndrome had been initially categorized as a subtype of autism, yet more recent DSM-V criteria separate it from ASD (American Psychiatric Association, 2013).

MeCP2 knockout mice show increased anxiety (Chahrour and Zoghbi, 2007), decreased motor coordination (Guy *et al*., 2001), impaired social interactions, impaired long-term social memory, decreased nest-building ability, and impaired learning and memory (Moretti *et al*., 2006; Chahrour and Zoghbi, 2007). It has also been shown that neurons of *MeCP2*-null mice have increased gene transcription, likely mediated through enhanced histone acetylation (Guy *et al*., 2011). This is also accompanied by neurotoxicity due to excessive glutamate release from microglia (Maezawa and Jin, 2010). Moreover, *MeCP2*-null astrocytes are unable to support normal dendritic morphology in wild-type hippocampal neurons (Ballas *et al*., 2009). In addition, *MeCP2*-null neurons have abnormal dendritic and axonal development (Larimore *et al*., 2009), and *MeCP2*-deficient GABAergic neurons show reduced inhibitory quantal size and decreased expression of GAD (Chao *et al*., 2010). These findings from the *MeCP2* knockout model converge with the VPA animal model, which also shows a decreased *MeCP2* expression in a male-specific manner, leading to increased glutamatergic neurotransmission (Kim *et al*., 2014b). Collectively, this highlights the potential pathophysiological role of epigenetic dysregulation on genetic determinants of ASD.

Monoamine oxidase A (MAOA)

MAOA and its neighboring gene are regulators of the mitochondrial enzyme MAO, responsible for the oxidative deamination of monoamine neurotransmitters such as dopamine and norepinephrine. Mutations in *MAOA* cause Brunner syndrome and have been linked to antisocial behaviors, low IQ, impulsiveness and violent behaviors (Hunter, 2010). In addition, the alleles regulating the levels of *MAOA* have been correlated with autism in humans (Cohen *et al*., 2003), which is mainly driven my maternally inherited mutations in male offspring (Cohen *et al*., 2011). Moreover, clinical studies have found that variations in the number of MAOA-upstream variable number of tandem repeats (uVNTR) are associated with ASD hyperserotonemia (Hranilovic *et al*., 2008) and cortical enlargement (Davis *et al*., 2008).

Similar to the human phenotype, *MAOA*-deficient mice display aggressive behaviors (Cases *et al*., 1995), increased fear, aberrant eye-blink conditioning (Singh *et al*., 2013) and hyper-responsiveness to acoustic stimuli (Popova *et al*., 2000). In accordance with ASD, this animal model has social and communication impairments, repetitive behaviors, behavioral rigidity and motor abnormalities (Bortolato *et al*., 2013). These mice also display increased hippocampal LTP and NMDAR expression, thinning of the corpus callosum, increased dendritic arborizations in pyramidal neurons of the PFC, and disrupted microarchitecture of the cerebellum (Singh *et al*., 2013). As expected, these mice also show increased brain serotonin, dopamine and norepinephrine levels (Bortolato *et al*., 2013; Singh *et al*., 2013), which might be directly related to the manifestation of anxiety and aggressive behaviors in *MAOA*-deficient mice, albeit these phenotypes have not been well characterized in humans (Cohen *et al*., 2003). This remarkable recapitulation of the core deficits of ASD symptoms, as well as the clinically similar neuropathologic phenotypes in *MAOA*-deficient mice, makes them a plausible model wherein potential therapeutic agents could be tested, especially with monoamines as the main target.

Neurofibromin 1 (NF1)

NF1, also called neurofibromatosis-related protein, is a gene that functions as a tumor suppressor in the nervous system and plays a role in controlling the Ras signaling pathway (Cichowski and Jacks, 2001). *NF1* is part of the NMDA receptor complex (Husi *et al*., 2000), which is suggested to underlie mental retardation and learning deficits in humans (Husi *et al*., 2000). In accordance with its proposed function, mutations in *NF1* result in a life-shortening condition known as Neurofibromatosis (Rasmussen and Friedman, 2000), an autosomal dominant disorder characterized by cognitive and language deficits, poor motor skills and peripheral nerve tumors (Silva *et al*., 1997).

Interestingly, *NF1* heterozygous (+/-) mice show deficits in spatial learning in the Morris water maze (Costa *et al*., 2002; Silva *et al*., 1997), delayed acquisition of motor skills and impaired fear conditioning (Costa *et al*., 2001). In addition, cortical neurons and astrocytes of *NF1* mutant mice fail to form cortical barrels in somatosensory cortex (Lush *et al*., 2008). In human studies, however, *NF1* polymorphisms and overexpression of the gene, not deficiency, have been associated with autism (Mbarek *et al*., 1999; Marui *et al*., 2004) Thus, further study of *NF1* polymorphisms in animal models, as opposed to knock-outs or knock-downs, should be conducted in the future.

Neuroligin (NLGN) family

The *NLGN* family of genes encode for neuroligin proteins, which are cell adhesion molecules required for synaptic function (Sudhof, 2008). NLGN is found in the postsynaptic membrane and mediates synapse transmission between neurons (Jamain *et al*., 2008). Mutations of *NLGN3* and *NLGN4* are associated with X-linked intellectual disability, seizures, and autism (Jamain *et al*., 2003) In addition, an in-depth molecular genetic analysis of the *NLGN* family found an association between non-functional polymorphisms and ASD in the Finnish population. This study concluded that neuroligin mutations may cause autism only in rare cases and that variations in neuroligin alleles are not a major risk factor for autism (Ylisaukko-oja *et al*., 2005). Nonetheless, the role of several neuroligin subunits and their association with ASD have been studied in mice.

NLGN1: *NLGN1* encodes for a group of neuronal membrane-bound proteins which are involved in CNS synapse development. *NLGN1* knockout mice display impaired spatial memory and repetitive/stereotyped grooming (Blundell *et al*., 2010). The latter is thought to be related to reduced NMDA/AMPA ratios in cortico-striatal synapses (Blundell *et al*., 2010). More studies are needed in order to provide a clinical link between the autism-related phenotypes found in *NLGN1* knockout mice.

NLGN3: Arg451Cys (R451C) mutation of *NLGN3* has been associated with autism in humans (Comoletti *et al*., 2004). *NLGN3* mutant mice carrying the R451C mutation have been long used as a model of ASD. These mice have impaired social interactions and enhanced spatial learning, as well as enhanced synaptic inhibition in the somatosensory cortex (Etherton *et al*., 2011). However, the Etherton *et al*. study also showed an increased excitatory transmission within the hippocampal region of NLGN3 (R451C) mutant mice, but not in NLGN3 KO mice. This study concluded that NLGN3 is differentially involved in modulation of excitatory and inhibitory synaptic neurotransmission in a brain region-specific manner (Etherton *et al*., 2011). *NLGN3* mutant mice also showed deficits in ultrasonic vocalizations, impaired preference for social novelty (Jamain *et al*., 2008) and altered olfactory function (Radyushkin *et al*., 2009). However, there were no changes in time spent engaged in social interaction, pre-pulse inhibition and seizure propensity in *NLGN3* mutant mice, as compared with their wild-type controls (Radyushkin *et al*., 2009). Thus, the *NLGN3* mutant mice may only partly model autistic features and not the global ASD condition.

NLGN4: Mutations in *NLGN4* have been associated with X-linked mental retardation, autism (Jamain *et al*., 2003), and other neurodevelopmental conditions comorbid with ASD, although it has been suggested that the contribution of NLGN4 mutations to ASD is very small (Gauthier *et al*., 2005). Yet, *NLGN4* deficient mice, display impairments in social interactions and social memory (Jamain *et al*., 2008), along with reduced brain volume (Jamain *et al*., 2008). However, these mice did not display deficits in repetitive behaviors, exploratory activity, anxiety, and learning and memory (Jamain *et al*., 2008). This shows that, although NLGN4 and the rest of the NLGN subunits may not consistently represent a very strong cause for ASD, they may still contribute to the complex, connecting pathways of ASD pathophysiology.

Neurexin 1 (NRXN1)

NRXN1 is a pre-synaptic membrane cell adhesion molecule and a receptor which mediates the synaptic interaction between neurons (Li *et al*., 2006), mainly through interactions with neuroligins. Phenotypes of individuals with *NRXN1* deletion vary, and include mental retardation, language delay, schizophrenia (The International Schizophrenia Consortium, 2008; Walsh *et al*., 2008; Need *et al*., 2009), nicotine dependence (Nussbaum *et al*., 2008) and ASD (Ching *et al*., 2010). Behavioral testing of *NRXN1*α deficient mice have shown deficits in pre-pulse inhibition and nesting ability, along with increased grooming activity, and enhanced motor learning on the rota-rod test (Etherton *et al*., 2009), despite the absence of obvious social defects (Etherton *et al*., 2009). Physiologically, these mice also display alterations in excitatory synaptic transmission. As a whole, the neurexin-1 model is somewhat complex in terms of using it for the study of ASD, as many of the observed phenotypes overlap or could be associated with other disorders.

Oxytocin (OXT), oxytocin receptor (OXTR), and MAGEL2

Oxt encodes the protein precursor of oxytocin and neurophysin 1. Oxytocin is a neuromodulating hormone produced by the posterior pituitary gland. It stimulates uterine muscle contraction during childbirth and stimulates lactation. Moreover, it is known to participate in various cognitive, adaptive, cardiovascular, excretory and complex sexual functions. Recent studies have also found that oxytocin has a key role in social recognition and social interactions (Guastella *et al*., 2008; Savaskan *et al*., 2008). Such findings have produced an increasing interest in the study of oxytocin and its involvement in ASD (Gregory *et al*., 2009). Research in humans have found that oxytocin plasma levels are reduced in autistic children (Insel, 2010) and that intranasal administration of the hormone to autistic patients enhances their social interactions (Andari *et al*., 2010), reduces repetitive behaviors (Hollander *et al*., 2003) and improves emotional recognition (Guastella *et al*., 2010). Moreover, in VPA prenatal exposure and FXS animal models of autism, prenatal oxytocin treatment can rescue autistic-like behaviors in offspring, which further demonstrates the pathophysiologic involvement and therapeutic potential of this hormone in ASD (Tyzio *et al*., 2014).

In mice, *Oxt* deficiency induces impairments in social recognition (Ferguson *et al*., 2001) and decreased social odor memory in females (Kavaliers *et al*., 2003), despite normal social approach and decreased aggression (Ferguson *et al*., 2001; Winslow and Insel, 2002). Interestingly, oxytocin administration directly into the amygdala region has been shown to enhance social recognition in *Oxt* knockout mice (Winslow and Insel, 2002), similar to what is observed when oxytocin is administered to autistic individuals (Andari *et al*., 2010).

In recent studies, common polymorphisms in the oxytocin receptor gene (*Oxtr*) have also revealed an association with ASD (Jacob *et al*., 2007; Gregory *et al*., 2009). Moreover, a number of *Oxtr* SNPs were associated with autism in various ethnic populations, encouraging further exploration to define its role in ASD (Wu *et al*., 2005; Jacob *et al*., 2007; Liu *et al*., 2010). However, a study discouraged the association of common *Oxtr* variation with autism in mixed Caucasian populations (Tansey *et al*., 2010) but later meta-analysis studies with one of the largest population ever investigated for *Oxtr* polymorphisms, showed positive correlations with autism (LoParo and Waldman, 2015). Additional studies further support these later findings by finding a positive correlation between *Oxtr* polymorphisms and social recognition skills, thus suggesting *Oxtr* SNPs as predictors of social impairments in both typically developing individuals and in children with ASD (Parker *et al*., 2014).

Accordingly, conditional Oxtr knockout mice, display deficits in social memory and defective ultrasonic vocalizations (Lee *et al*., 2008), but are devoid of stereotyped/repetitive behavior phenotypes (Pobbe *et al*., 2012). In addition, *Oxtr*-null mice display increased aggression and high seizure susceptibility (Sala *et al*., 2011). These mice also have a decreased ratio of GABAergic presynapses to the total number of presynapses in hippocampal neurons (Sala *et al*., 2011), suggesting that alterations in the oxytocin system or aberrant oxytocin receptor function can have profound effects in the overall excitatory/inhibitory balance in the brain.

Additional evidence supporting the role of oxytocin in ASD comes from studies using the Magel2 mouse model. *MAGEL2* is a paternally imprinted gene that has been recently identified as an autism risk gene and has been associated with Prader-Willi Syndrome (PWS) (Boccaccio *et al*., 1999; Schaaf *et al*., 2013). PWS results from large deletions in chromosome 15q11-q13 and is characterized by intellectual disabilities, repetitive behaviors, and hyperphagia-induced obesity. Interestingly, individuals with PWS have high comorbidity with ASD (>30%) (Dykens *et al*., 2011). In congruence with ASD, the *Magel2*-deficient mice showed abnormalities in social recognition and interaction, as well as learning difficulties in adults (Meziane *et al*., 2015). More importantly, at birth, these mice have reduced production of oxytocin in the hypothalamus, which causes decreased suckling behavior and leads to a 50% mortality rate (Schaller *et al*., 2010). Interestingly, a single postnatal injection or a one-week-long administration of oxytocin after birth improved suckling, prevented mortality as well as the development of behavioral impairments in adulthood (Schaller *et al*., 2010; Meziane *et al*., 2015), suggesting a mechanistic link between oxytocin and Magel2. Thus, additional studies exploring the relationship between Magel2 and oxytocin will be beneficial for supporting the potential of oxytocin as a therapeutic treatment for ASD.

Phosphatase and tensin homolog (PTEN)

PTEN is a tumor suppressor protein involved in cell cycle arrest and apoptosis through negative regulation of the AKT/PKB signaling pathway (Chu and Tarnawski, 2004). A number of genetic variants in *PTEN* have been observed in ASD patients with macrocephalic phenotypes (Butler *et al*., 2005), which stimulated the study of a *PTEN* transgenic mouse model. Given that *PTEN*-null mice die during embryogenesis (Di Cristofano *et al*., 1998), conditional knockout mice are used to investigate the role of *PTEN* in development and autism pathogenesis. *PTEN* mutant mice display abnormal social interactions, hyperactivity, excessive responses to external stimuli and decreased prepulse inhibition (Ogawa *et al*., 2007); they also develop macrocephaly and neuronal hypertrophy in the CNS, similar to human patients (Kwon *et al*., 2006). A recent study suggested that PTEN deficiency *in vivo* increases the net excitatory drive onto granule neurons, enlarges the neuronal size, and increases the density of dendritic spines (Luikart *et al*., 2011). Further studies have shown that deletion of PTEN leads to increased cell proliferation (Gregorian *et al*., 2009; Bonaguidi *et al*., 2011). These findings all agree with the role of PTEN as a regulator of neural stem cell proliferation and lineage specification (Zhou and Parada, 2012). Lastly, PTEN may also interact and synergize with other signaling pathways, such as the PI3K/AKT and TSC/mTORC1 pathway, that contribute to the complex pathogenesis of the global ASD condition (Zhou and Parada, 2012).

Reelin (RELN)

Reelin is a secreted extracellular matrix (ECM) protein that is important for ECM development and plays an essential role in the migration and proper positioning of cortical neurons (D'Arcangelo, 2005). In adult brains, Reelin is actively involved in synaptic regulation, formation of dendrites and modulation of cognitive function (Rogers *et al*., 2011). In the hippocampus, Reelin accumulation is essential for NMDA subunit receptor maturation and NR2B surface mobility, which ultimately leads to mature excitatory synapses (Groc *et al*., 2007). In addition to NMDA receptor regulation in cortical neurons, Reelin mediates tyrosine phosphorylation and increases calcium influx, which is physiologically involved in learning and memory (Chen *et al*., 2005). Down-regulation of Reelin in cortical GABAergic interneurons has been frequently observed in schizophrenia, bipolar disorders and autism (Ognibene *et al*., 2007). Furthermore, mutations in 7q22-23, consisting of longer triplet repeats in the 5'UTR of *RELN* gene locus, have been observed in autistic patients (Gillberg, 1998; Yan *et al*., 2000).

Mice used to model the effects of *RELN* mutations, known as *Reeler* (rl/rl) mice, display cortical disorganization in various brain regions, including cortex, cerebellum, hippocampus, subcortical regions, and spinal cord (Martin, 1981; Goffinet, 1983; Yip *et al*., 2000; D'Arcangelo, 2005). Decreased density of striatal GABAergic interneurons were also found (Marrone *et al*., 2006). Behaviorally, Reeler mice showed increased seizure susceptibility (Patrylo *et al*., 2006) and decreased ultrasonic vocalizations (Ognibene *et al*., 2007).

In previous reports, heterozygous *Reeler* mutant (+/rl) mice had shown indistinguishable features in anatomy (Stanfield and Cowan, 1979) and behavior (Muroga *et al*., 1982) from normal (+/+) mice. However, later studies reported that +/rl mice displayed abnormalities in anatomical (Smalheiser *et al*., 2000; Liu *et al*., 2001) and behavioral (Tueting *et al*., 1999) phenotypes, resembling those of human schizophrenia patients. *Reeler* mutant mice also showed deficits in pre-pulse inhibition and decreased exploration in the elevated plus maze test (Tueting *et al*., 1999). Other studies, such as those of Salinger *et al*., reported that +/rl mice have normal social aggressive behaviors (Salinger *et al*., 2003), whereas Podhoma *et al* found no behavioral abnormalities in the model (Podhorna and Didriksen, 2004). Recently, Iafrati and colleagues developed the juvenile reelin-haploinsufficient heterozygous reeler mice (HRM), which exhibited a reduction in dendritic spine density and abnormal LTP in the prefrontal cortex, as well as deficits in fear memory formation (Iafrati *et al*., 2014). Overall, studies in Reeler mice have resulted in conflicting and inconsistent findings of behavioral phenotypes. Whether +/rl mice are suitable as animal models for schizophrenia and/or autism requires further investigation.

Serotonin transporter (SERT, *SLC6A4*)

The serotonin transporter (5-HTT, SERT) removes serotonin from the synaptic cleft back into the presynaptic terminal and has a general role in the termination and recycling of serotonin during neurotransmission. Hyperserotonemia is one of the most consistent findings in ASD patients (Hranilovic *et al*., 2008). However, there is conflicting evidence regarding the involvement of SERT in ASD, especially from a genetics standpoint. Only one study found a significant association between SERT polymorphism (*SLC6A4* variants) and autism hyperserotonemia, which failed to replicate in other studies (Betancur *et al*., 2002; Huang and Santangelo, 2008). It is also difficult to determine whether hyperserotonemia in autism is related to serotonin activity and re-uptake (Prasad *et al*., 2009).

In preclinical studies, the *5-HTT* knockout mice showed decreased exploratory behavior, increased anxiety-like behaviors (Holmes *et al*., 2003), elevated sensitivity to stress (Jiang *et al*., 2009) and reduced social interactions (Kalueff *et al*., 2007). In the brains of *5-HTT* knockout mice, altered cortical thickness and cell density (Altamura *et al*., 2007) as well as altered hypothalamic-pituitary-adrenal (HPA) axis signaling (Jiang *et al*., 2009) were observed. Genetic variations in the SERT gene, including Gly56Ala, Ile425Leu, Ile425Val, Phe465Leu, Leu550Val, and Lys605Asn, enhance the serotonin re-uptake activity of SERT proteins (Prasad *et al*., 2009). Currently, no strong association between SERT polymorphisms and ASD has been found, despite the consistent occurrence of hyperserotonemia in autism; thus, the involvement of SERT variation is yet to be established. As a result, further research is needed both at the clinical and animal model level. It is important nonetheless, to acknowledge the fact that SERT animal models may not be uniquely reflecting autism-related phenotypes, as there may be some association between the gene and other disorders, such as obsessive-compulsive disorder (Veenstra-Vanderweele *et al*., 2009). Thus, careful interpretation of results when using this animal model is needed.

SH3 and multiple ankyrin repeat domains protein (SHANK)

SHANKs are postsynaptic scaffold proteins that interact with neurotransmitter receptors, ion channels, and other membrane proteins. SHANKs play a key role in synapse formation and dendritic spine maturation during brain development. Shank genes have long been implicated in ASD and Shank dysregulation supports the synaptic dysfunction hypothesis in ASD pathophysiology (Jiang and Ehlers, 2013). Nevertheless, the molecular diversity of *SHANK* genes and their heterogeneity in both the human and mouse genome poses a great challenge in using *Shank* mutant models, as described below.

SHANK1: Hung and colleagues reported that *SHANK1*$^{-/-}$ mice showed increased anxiety-like behavior, impaired contextual fear memory and enhanced spatial learning (Hung *et al*., 2008). Another study also reported reduced ultrasonic vocalizations and decreased scent marking behaviors in

SHANK1$^{-/-}$ mice (Wohr *et al*., 2011b). However, Silverman and colleagues observed that although null mutant mice showed some degree of motor disability and anxiety, they did not display other autism-related deficits, especially in terms of reciprocal social interactions (Silverman *et al*., 2011). This study, therefore, raised the notion that *SHANK1*$^{-/-}$ mice may not be appropriate for modeling autism-related social deficits, but could be useful in understanding alterations in motor function. Further neurobiological studies showed that *SHANK1*$^{-/-}$ mice displayed alterations in the composition of postsynaptic density proteins, reduced size of dendritic spines and weaker basal synaptic transmission (Hung *et al*., 2008). The involvement of *SHANK1* gene in autism etiology has not been ruled out since a previous study found a male-heritable *SHANK1* microdeletion in ASD patients (Sato *et al*., 2012).

SHANK2: Mutations in the *SHANK2* gene have been reported in ASD patients (Berkel *et al*., 2010; Leblond *et al*., 2012). Furthermore, heritable *SHANK2* variants, particularly T1127M and R462X, are known to affect spine volume and result in smaller SHANK2 cluster sizes (Berkel *et al*., 2012). Rodent overexpression of the R462X variant results in a more severe phenotype of defective dendritic branching and decreased postsynaptic clustering (Berkel *et al*., 2012). In animal models, *ProSAP1/Shank2*$^{-/-}$ mutant mice displayed fewer dendritic spines and lower basal synaptic transmission along with increased NMDA-mediated excitatory currents (Schmeisser *et al*., 2012). These mutant mice display autism-related behavioral phenotypes, including repetitive grooming, hyperactivity, and impaired vocal and social behaviors (Schmeisser *et al*., 2012). Won *et al*. confirmed and further found that *Shank2*$^{-/-}$ mutant mice exhibited decreased social interactions, impaired ultrasonic vocalizations, and repetitive jumping behavior. However, in contrast to the previous study, these mutant mice showed decreased NMDA receptor function (Won *et al*., 2012). Based on these mechanistic findings, Won *et al*.'s study also tested therapeutic candidates for ASD and found that D-cycloserine (a partial agonist of NMDA receptor) normalized the function of NMDAR and enhanced social interactions in *Shank2*$^{-/-}$ mutant mice (Won *et al*., 2012). It is likely that the opposing NMDA function findings in these studies are related to the fact that they use different exon mutation sites in each model, which could result in slightly different protein disruptions. Yet, and as a whole, these results provide useful insights in the importance of maintaining a normal range of NMDA function in the brain, as both over- and under- regulation of NMDA transmission could result in abnormal behavioral phenotypes.

SHANK3: Mutations in *SHANK3*, such as those observed in microdeletions of 22q13, have been implicated in ASD etiology. Recent studies reported that *SHANK3* genes are lost or rearranged in ASD patients and are associated with developmental delays, dysmorphic features and autistic behaviors (Manning *et al*., 2004). Moreover, heterozygous mutations of SHANK3 may cause ASD in a gene-dosage-dependent manner (Durand *et al*., 2007). *SHANK3* mutant mice have been recently proposed as a model of ASD and have provided great insights on the pathological mechanisms that could underlie the disorder. For example, *SHANK3B*$^{-/-}$ mice display repetitive grooming and deficits in social interactions, along with cortico-striatal circuit alterations and striatal synaptic defects (Peca *et al*., 2011). In another study, these mice showed deficits in glutamatergic synaptic transmission and hippocampal LTP, yet only displayed mild social deficits in juvenile but not adult age (Yang *et al*., 2012). In addition, increased self-grooming, decreased ultrasonic vocalizations, and decreased reversal learning were observed only in some cohorts, suggesting variable phenotypic severity in SHANK3 mutant mice (Yang *et al*., 2012). Yet another investigation revealed decreased excitatory postsynaptic currents (EPSCs) in pyramidal neurons of the hippocampal CA1 region, highlighting a reduced basal neurotransmission in these animals in an AMPAR-mediated manner (Bozdagi *et al*., 2010). The GluR1-immunoreactive puncta of the stratum radiatum was also quantitatively reduced, along with impaired LTP but not LTD (Bozdagi *et al*., 2010). Behaviorally, these mice displayed reduced social sniffing and ultrasonic vocalizations in the presence of a female mouse (Bozdagi *et al*., 2010).

Although the Shank3 mouse model data is very compelling, human studies still suggest that not all genetic mutations and alterations in *SHANK3* directly lead to ASD, thus careful interpretations should be given. This was suggested by a clinical study, where a child with autism showed a rare genetic variant in Shank3, consisting of a 1-bp insertion in exon 11; although this mutation was of high penetrance, it was not attributed a strong etiological relationship to the ASD phenotype (Kolevzon *et al*., 2011). Lastly, it is important to note that the phenotypic consequences of Shank3 dysfunction can be rather complex and require careful interpretation since similar mutations can be associated to both ASD and schizophrenia (Gauthier *et al*., 2010).

Tuberous sclerosis complex protein (TSC) 1 or 2

Mutations of *TSC1* or *TSC2* cause the Tuberous sclerosis complex (TSC) disorder. *TSC1* encodes hamartin and *TSC2* encodes tuberin. TSC1/TSC2 act as tumor growth suppressors and are involved in cell proliferation and differentiation. TSC patients have a high prevalence of autism, ranging from 20 to 60% (Bolton *et al*., 2002; Curatolo *et al*., 2004). TSC1/TSC2 mutations are associated with neurological deficits including cognitive dysfunction, epilepsy, and autism (DiMario, 2004; Goorden *et al*., 2007).

Mutant mice that lack TSC1 in astrocytes showed significant brain pathologies and seizure vulnerability (Uhlmann *et al*., 2002). Furthermore, neuronal loss of TSC1 induced cortical hyperexcitability and seizure susceptibility in mice (Meikle *et al*., 2007). Sparse deletion of *TSC1* in CA1 hippocampal neurons led to enhanced AMPAR and NMDAR-mediated EPSCs, as well as an increase in spontaneous EPSC frequency, and absent mGluR-LTD in the hippocampus (Bateup *et al*., 2011). *TSC1* conditional knockout in neural progenitor cells resulted in increased brain size and elevated mToRC1 signaling, as well as decreased mToRC2 signaling in mice (Carson *et al*., 2011). More importantly, hetero- or homozygous loss of TSC in mice induced abnormal social interactions, repetitive behaviors, and impaired vocalizations, coupled with decreased Purkinje neurons (Tsai *et al*., 2012). Overall, these studies suggest that conditional or complete *TSC1* deficiency leads to an elevation in glutamatergic or excitatory synaptic activity, and once again implies dysregulation of mToR signaling in the pathophysiology of ASD.

Interestingly, *TSC2*$^{w/-}$ mice showed no significant brain pathology (Onda *et al*., 2002), yet a recent study suggested that heterozygous TSC (+/-) mutant mice with maternal immune activation by poly I:C leads to impaired social interactions in offspring (Ehninger *et al*., 2012). In other studies, TSC$^{+/-}$ mice displayed alterations in ultrasonic vocalizations (Young *et al*., 2010) while mice expressing a dominant negative form of tuberin showed impaired social interactions (Chevere-Torres *et al*., 2012). Moreover, selective deletion of *TSC2* in Purkinje cells increased Purkinje cell size and induced ER oxidative stress, which eventually led to cellular apoptosis in these neurons (Reith *et al*., 2011). Interestingly, such phenotypes were rescued by treatment with the mToRC1 inhibitor rapamycin (Reith *et al*., 2011). Concurrent with these studies, Tsc2$^{+/-}$ mice exhibit mToR-dependent upregulation of GluN2C-containing NMDARs, and display seizure symptoms early in life (Lozovaya *et al*., 2014) and deficient mGluR-LTD in the hippocampus (Auerbach *et al*., 2011). More recently, Tang *et al*. showed that Tsc2$^{+/-}$ mice have impaired social behaviors, in which their brain exhibit upregulated mToR activity and abnormal postnatal dendritic pruning mediated by inactivation of normal autophagy (Tang *et al*., 2014).

Although there is a considerable prevalence of ASD in TSC, and mouse models show compelling evidence supporting the role of TSC1/TSC2 in autism etiology, the exact neurobiological mechanism by which this occurs is still poorly understood (Numis *et al*., 2011). Some would suggest persistent seizures or epilepsy in early development as the main driver of autistic behavioral phenotypes in TSC (Curatolo *et al*., 2004; Numis *et al*., 2011). Yet, it is worthy of noting that gene-environment interactions (e.g. maternal immune activation) could play a major role in precipitating the development autism symptomatology and could provide novel implications for ASD pathophysiology and etiology (Ehninger *et al*., 2012). In this way, animal models of TSC could help uncover unknown biological pathways associated with ASD, especially in terms of how early disruptions in brain activity (e.g. seizures), genes, and environmental factors lead to the disorder.

Ubiquitin-protein ligase E3A (UBE3A)

UBE3A gene encodes the E6AP ubiquitin-protein ligase (E6AP) protein, which mediates ubiquitin-dependent protein degradation. As mentioned above, mutations of *UBE3A* and *GABRB3*, both located in chromosome 15q11-13, cause Angelman syndrome (AS) (Wagstaff *et al*., 1991). *UBE3A* regulates excitatory synapse development by ubiquitin-dependent degradation of Arc, a synaptic protein that promotes AMPA receptor internalization (Greer *et al*., 2010). Interestingly, preclinical studies have found that increased gene dosage of *UBE3A* leads to reduced glutamate synaptic transmission in mice and result in autism-related behaviors (Smith *et al*., 2011). Furthermore, maternal deletion of *UBE3A* increases the emission of ultrasonic vocalizations (Jiang *et al*., 2010) and seizure susceptibility in offspring mice (Miura *et al*., 2002). On the other hand, *UBE3A* knockout in mice leads to Arc accumulation in neurons, which weakens synaptic function through the excessive internalization of AMPA receptors (Greer *et al*., 2010). These findings could mean that UBE3A mutations, more specifically implicated in AS, may also have a specific role in ASD etiology. This is supported by a clinical study in Italian patients with autism, which found a potential role of UBE3A in ASD pathogenesis (Guffanti *et al*., 2011). Another clinical study highlighted the phenotypic overlap between AS and ASD, as autistic phenotypes were observed in some children with AS (Peters *et al*., 2004). Indeed, the UBE3A mouse models present good candidates for studying ASD pathogenesis, as the gene seems to partake in complex signaling pathways that exacerbate autism symptomatology in syndromes such as AS.

Arginine Vasopressin (AVP) and its receptor (AVPR1A)

AVP is a pituitary hormone that mainly functions as an antidiuretic by stimulating water reabsorption in the collecting ducts of nephrons. It also plays a contributive role in peripheral vasoconstriction, smooth muscle contraction during parturition and lactation, cognition, tolerance, adaptation, cardiovascular regulation and complex sexual and maternal behaviors; indeed, it functions very similarly to oxytocin. The AVP receptor, AVPR1A, belongs to the G-protein coupled receptor family (along with V2R and OXT receptors) and works by activating the phosphatidylinositol-calcium second messenger system. When activated, AVPR1A leads to cell proliferation and contraction, glycogenolysis, the release of coagulation factors and platelet aggregation. Interestingly, the *AVPR1A* gene has been associated with ASD (Wassink *et al*., 2004; Yirmiya *et al*., 2006).

With regards to ASD, the study of the Brattleboro rat could reveal useful insights on the effect of AVP alterations in producing autism-related phenotypes. The Brattleboro rat is an inbred strain that does not synthesize vasopressin due to a homozygous frameshift mutation in the AVP gene (Schmale *et al*., 1989). This rat strain was found to have decreased social recognition (Engelmann and Landgraf, 1994) and no cardiovascular response to social isolation (Gardiner and Bennett, 1983). Similarly, vasopressin receptor 1a (*V1aR*) knockout mice also show defects in social recognition, social interactions, anxiety (Bielsky *et al*., 2005; Insel, 2010), social aggression, social motivation, social memory (Wersinger *et al*., 2004; Caldwell *et al*., 2008), and ultrasonic vocalizations (Scattoni *et al*., 2008). Interestingly, studies in humans have found a significant association between autism and heritable genetic defects in *AVPR1a* (Wassink *et al*., 2004), including transmission disequilibrium within the *AVR* intronic microsatellite region (Yirmiya *et al*., 2006). These findings, together with the known role of *AVPR1a* in social skill formation, suggest a link between vasopressin dysregulation and development of autism, thus warranting the use of AVP mouse models for the elucidation of ASD-related mechanistic insights.

Contactin-associated protein-like 2 (CNTNAP2)

The *CNTNAP2* gene encodes contactin associated protein-like 2 (Caspr2) protein, which is part of the neurexin family and, therefore, plays a key role in cell adhesion. During the early nervous system development, Caspr2 mediates neuron-glia interactions and helps in localizing potassium channels in developing axons (Poliak *et al*., 1999). The transcription factor forkhead box protein P2 (FOXP2), involved in speech and language development, regulates and directly binds to CNTNAP2 (Fisher and Scharff, 2009). Recessive-truncating mutations in CNTNAP2 cause Cortical Dysplasia Focal Epilepsy (CDFE) syndrome, which is highly comorbid with ASD (70%) (Strauss *et al*., 2006). Additionally, many other mutations within the CNTNAP2 gene have been identified in a number of ASD patients (Alarcón *et al*., 2008; Arking *et al*., 2008).

Interestingly, *Cntnap2*$^{-/-}$ mice exhibit the three core symptoms of ASD, including decreased social interactions, reduced vocalizations, and repetitive behaviors, as well as hyperactivity and epileptic seizures (Peñagarikano *et al*., 2011). Moreover, these knockout mice show abnormal neuronal migration and decreased neuronal synchrony, concurrent with a reduction in the total number of GABAergic interneurons (Peñagarikano *et al*., 2011). This study found that risperidone treatment rescued the repetitive behaviors of these mice. More recently, the same group found that the oxytocin system is defective in these mice and that both acute and chronic administration of the hormone rescued the social behavioral phenotypes (Peñagarikano *et al*., 2015). In other recent studies, *Cntnap2*$^{-/-}$ mice display impairments in auditory processing, and their hippocampus show reduction of evoked IPSC in the perisomatic part of the CA1 region while the excitatory inputs were barely affected (Truong *et al*., 2015). These findings further elucidate the roles of *Cntnap2* gene in language development and synaptic function which are commonly affected in ASD.

In the Australian population common genetic variants in the *CNTNAP2* gene were found, one of which was carried by a boy with autism and speech delays, confirming the gene's involvement in language development and ASD (Whitehouse *et al*., 2011). Another study found that polymorphisms in *CNTNAP2* were correlated with autism and impaired frontal lobe connectivity (Scott-Van Zeeland *et al*., 2010). In a population study of Chinese families with autism, a number *CNTNAP2* SNPs were identified and significantly correlated with increased ASD risk (Li *et al*., 2010). However, not all *CNTNAP2* variants are necessarily implicated in ASD, which may limit and complicate the use of knockout mice (Sampath *et al*., 2013). Nevertheless, the known and important roles of CNTNAP2 in brain and language development may help in elucidating the pathophysiologic mechanisms of ASD in a subset of patients.

Eukaryotic translation initiation factor 4E (eIF4E)

The *eIF4E* gene is found in the chromosome 4q locus and encodes a component of the eukaryotic translation initiation factor 4F complex. The encoded protein recognizes the 7-methylguanosine cap structure found at the 5' end of mRNA. eIF4E acts as a downstream effector in the mToR, PTEN and FMRP pathways and functions as a promoter of translational initiation of target mRNAs such as neuroligins, by recruiting ribosomes to mRNA. Patients with ASD have been found to carry variants within the eIF4E gene promoter and mToR-mediated eIF4A hyperactivation has been observed in autistic FXS patients (Szatmari *et al*., 2007; Hoeffer *et al*., 2013).

In mice with direct eIF4E overexpression, or indirect overexpression through knockout of eIF4E repressor 4E-BP2 (eukaryotic translation initiation factor 4E-binding protein 2), impaired social interactions, communication deficits, and repetitive behaviors were observed (Gkogkas *et al*., 2013; Santini *et al*., 2013). In line with these autistic behaviors, these mice also display synaptic abnormalities in the mPFC, striatum and hippocampus, including increased excitatory to inhibitory ratios and an increase in eIF4E-dependent neuroligins expression (Gkogkas *et al*., 2013). These alterations were partly due to an increase in cap-dependent translation (Santini *et al*., 2013), which could be a promising pathophysiological target with implications for therapeutic treatment of ASD. The clear causal relationship between a known genetic defect and direct neurobehavioral abnormalities validates the use of the eIF4E animal model and makes it of high clinical relevance. In addition, eIF4E's causal relationship to synaptic development and plasticity in mice supports the involvement of excitation/inhibition imbalance in ASD.

DISCUSSION

Frequency of use and general applicability of ASD animal models

A number of ASD animal models have been established, proposed and utilized to investigate the pathways of abnormal development leading to ASD. Notably, prenatal VPA exposure and monogenetic defects in *FMR1*, *MeCP2*, *NLGNs*, and *Oxt* have been most substantially studied. Moreover, the maternal immune activation (MIA) model and the prenatal VPA exposure model have both consistently recapitulated general autistic symptoms and phenotypes. Particularly, VPA exposure produced various autistic symptoms and phenotypes in rodents, such as macrocephaly, seizure susceptibility, GABAergic defects, and male-specificity. In the genetic models, knockout of *FMR1* or *GABRB3* leads to impaired social interactions, repetitive behaviors, increased excitatory neurotransmission, and seizure susceptibility. However, only a handful of studies on the neurobiological defects of *GABRB3* knockout mice has been reported. These genetic models were inspired by studies that showed a strong association between the genes and ASD. Recently, *SHANK3* mutant mice have emerged as a compelling model of ASD, and most studies have focused in understanding the underlying synaptic abnormalities. Indeed, animal models have played an essential role in the molecular and neurobiological exploration of various autism etiologies and have led to the testing and discovery of many therapeutic candidates. These studies highlight the incredible utility of animal models, despite the clear evolutionary separation and evident differences in brain structure, function, and complexity.

Imbalance between excitation and inhibition in ASD animal models

The brain of ASD patients show specific and notable features that include increased prevalence of macrocephaly (Fidler *et al*., 2000; Hardan *et al*., 2001; Gillberg and de Souza, 2002), reduced GABAergic signaling (Blatt *et al*., 2001; Oblak *et al*., 2011) and increased glutamatergic signaling (Shinohe *et al*., 2006). Moreover, it has also been reported that ASD patients have abnormalities in cortical minicolumn organization (Casanova *et al*., 2002) and synaptic development (Geschwind and Levitt, 2007; Hutsler and Zhang, 2010). In addition, some of the most prominent anatomical features of autistic brains include increased number of neurons (Casanova *et al*., 2006), reduced number of Purkinje cells in the cerebellum (Rout and Dhossche, 2008) and reduced GABAergic neurons and markers (Fatemi *et al*., 2009). These features are reminiscent of imbalanced excitation and inhibition in the autistic brain, which has been recently proposed as a major cause of ASD symptomatology. Along these lines, a number of studies have suggested that an increase in the ratio of excitatory versus inhibitory neurotransmission is consistent across various autism etiologies (Dani *et al*., 2005). For example, the expression of GABA_A receptor subunits (Samaco *et al*., 2005) and GAD proteins (Fatemi *et al*., 2002) are decreased in the brain of autistic patients. Disrupted inhibitory architecture in the brain of ASD patients were also reported (Casanova *et al*., 2003).

Converging evidence supporting the role of imbalanced excitatory/inhibitory neurotransmission in ASD has also been found in a number of animal models. For example, prenatal VPA exposed-rats have increased excitation and hypercon-

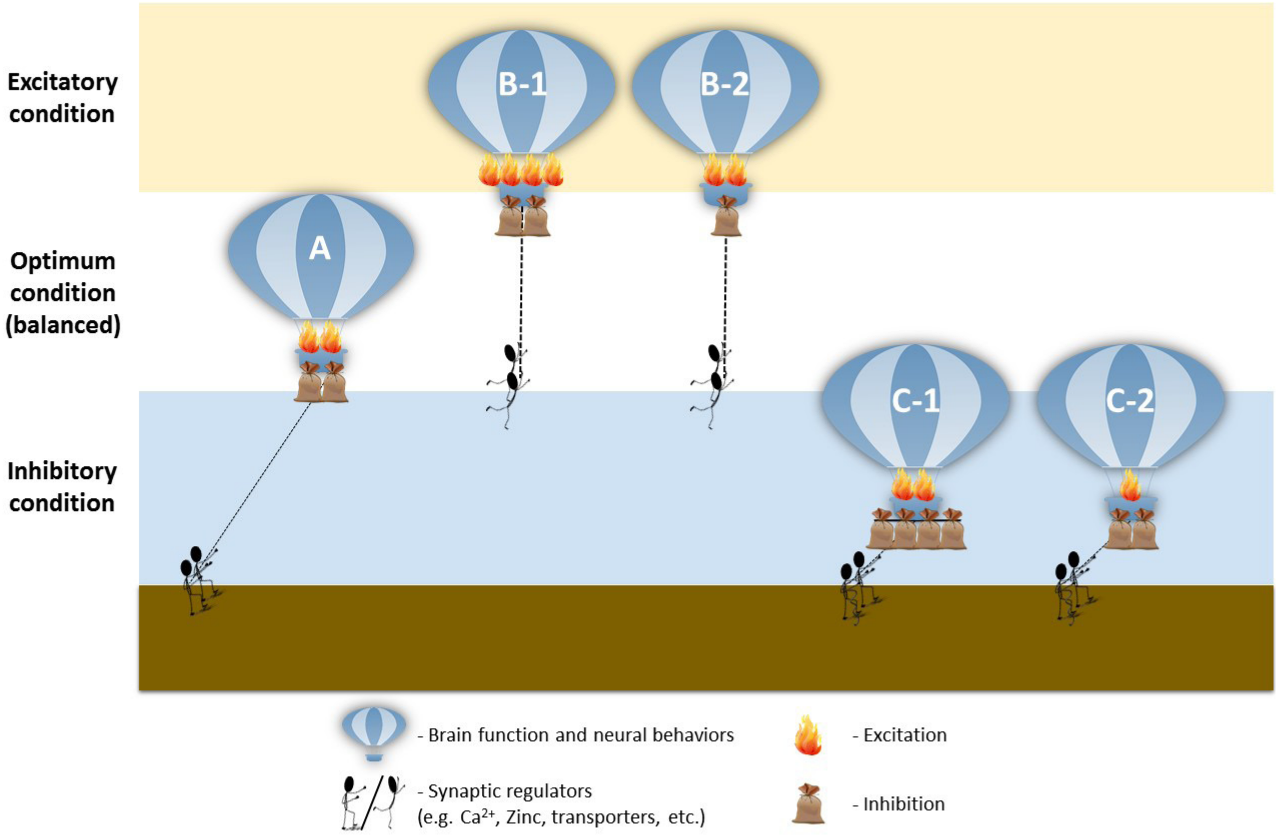

Fig. 1. Excitatory/Inhibitory Imbalance in ASD. (A) Normal/optimum condition (balanced excitation, inhibition and synaptic regulation). (B) Hyper-excitatory condition due to increased excitation from a variety of genetic and/or environmental factors (B-1, i.e. FMR1, MeCP2, NLGN3, PTEN, SAHNK2 and PTEN genetic knockout/mutations; LPS and VPA prenatal exposures) or decreased-inhibitory regulators (B-2, i.e. CNTNAP2, GABRB3, MeCP2, RELN genetic knockout/mutations; prenatal VPA exposure) affecting synaptic strength; synaptic regulators could be normal. (C) Hyper-inhibitory condition due to increased inhibition from genetic or environmental factors (C-1, for example, NLGN3 mutation) and decreased excitation inducers (C-2, i.e. SHANK2 & UBE3A genetic knockout/mutations).

nectivity in the brain, as well as NMDA receptor over-expression (Rinaldi *et al*., 2007, 2008). Moreover, the prenatal LPS-exposed models show pyramidal neuron hyperexcitability, increased postsynaptic glutamatergic activity, and reduced NMDA-induced synaptic plasticity (Lante *et al*., 2008; Patterson, 2009). In addition, reduction of mGluR5 expression in the brain of *FMR1* knockout mice was also associated with an increased excitatory/inhibitory ratio (Silva and Ehninger, 2009). *MeCP2* knockout mice, on the other hand, showed defects in GABAergic neuron function, as demonstrated by reduced inhibitory quantal size and decreased GAD expression (Chao *et al*., 2010). In addition, these mice display excessive glutamate release by microglia (Maezawa and Jin, 2010). Interestingly, in the VPA prenatal exposure animal model, MeCP2 expression was attenuated and glutamatergic transmission was increased, reflected by the upregulation of NMDA, AMPA and mGlu receptors and postsynaptic proteins (Kim *et al*., 2014b). In the *Oxtr*-null mice, a decreased ratio of GABAergic synapse versus the total presynapse was observed (Sala *et al*., 2011), while, in *PTEN* mutant mice, the net excitatory drive was increased (Luikart *et al*., 2011). In *Reeler* mice, decreased density of striatal GABAergic interneurons was shown (Marrone *et al*., 2006). More recently, eIF4E's causal role in synaptic development and plasticity has provided additional evidence supporting the E/I imbalance hypothesis of ASD pathogenesis (Santini *et al*., 2013). Both human and animal studies have demonstrated that the overall anatomical sites and neurotransmission phenotypes related to ASD, especially in terms of E/I imbalance, could vary depending on the etiologic factors involved. Many of the studies included in this review suggest either "too much excitation" or "too little inhibition" and vice versa, as the culprits for the altered E/I ratios in the animal models, which mostly result in common, although not identical, behavioral phenotypes. By carefully comparing the data obtained from the various animal models of ASD, we can obtain an idea of how and why the seemingly diverse neurobiological changes caused by each etiologic factor induce similar behavioral phenotypes. Furthermore, the data gathered from

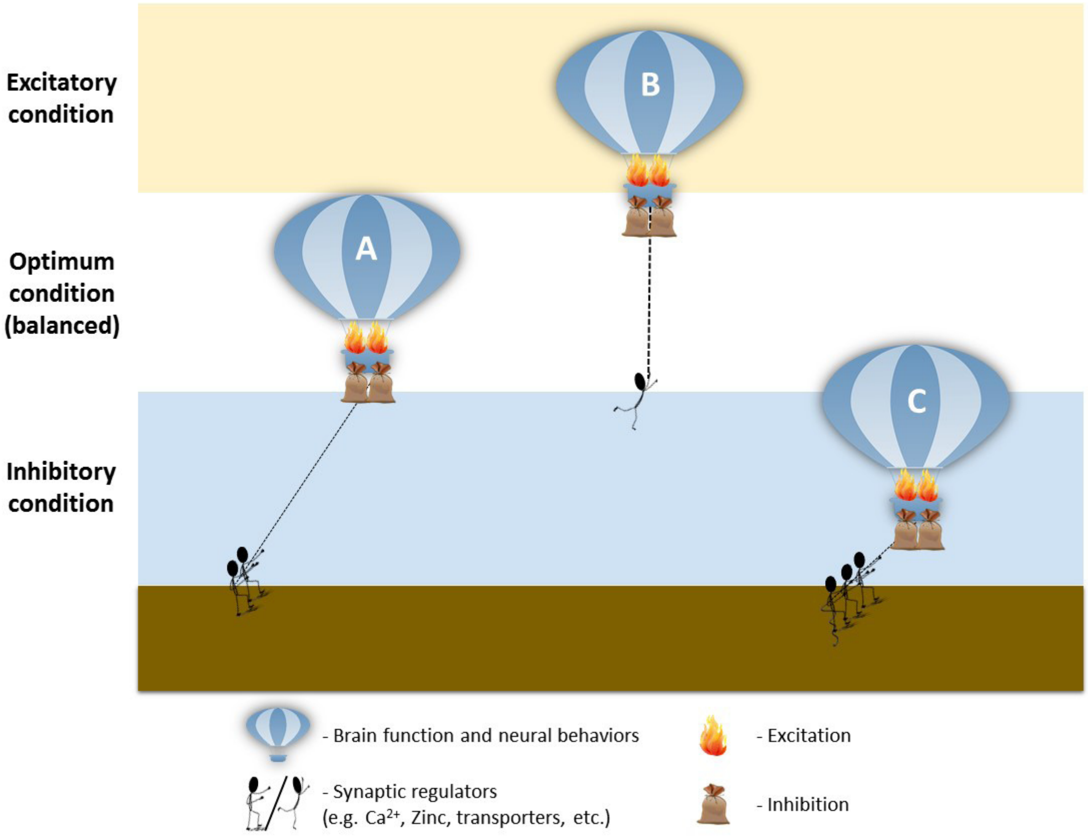

Fig. 2. Altered synaptic regulators in ASD leading to E-I imbalance. (A) Normal/optimum condition (balanced excitation, inhibition, and synaptic regulation). (B) Hyper-excitatory condition due to altered synaptic regulators. Even with the normal synaptic structure and numbers, dysregulation of synaptic modulators such as altered intracellular calcium level either by genetic or environmental factors may render the brain to more excitable states. (C) Hyper-inhibitory condition due to altered synaptic regulators, for example, reduced intracellular calcium level. With the altered synaptic regulators function, otherwise harmless weak stimuli (either genetic or environmental) may contribute to the manifestation of autistic phenotypes, which explains various types of gene (environmental) x gene (environmental) interaction. Alternatively, innate differences in the synaptic modulator functions between male and female may explain the gender-skewed prevalence of ASD.

all of these models may help us find multiple levels of convergence in terms of signaling pathways, receptor and neurotransmitter systems, and specific neuronal circuits involved in the pathophysiologic mechanisms of ASD.

Alterations in the function of postsynaptic proteins, which mediate synapse formation and maturation, can be also notably related to the defects in excitatory neurotransmission. For example, genetic abnormalities in neuroligins and neurexins result in decreased excitatory activity and altered NMDA/AMPA ratios in multiple animal models (Etherton *et al*., 2009; Blundell *et al*., 2010). In addition, defects in the SHANK genes also led to impaired NMDA receptor function and mGluR5-dependent synaptic transmission (Verpelli *et al*., 2011). This suggests that the study of a subset of these animal models can provide useful information about the specific implications of synaptic dysregulation in the pathophysiology of ASD.

Altogether, our current knowledge from animal models, in combination with clinical findings in ASD, suggests that aberrations in E/I activity are likely involved in the disorder pathogenesis. This leads to the conclusion that optimal levels of excitation and inhibition are essential in the maintenance of proper synaptic function and prevent the precipitation of aberrant behavioral phenotypes (Fig. 1). As schematically represented in our hot air balloon conceptualization, maintaining the optimal range of neurobehavioral activity requires adequate balance of excitation (as represented by the hot air regulated by the activity of gas burners) and inhibition (as represented by weights regulated by sand bags); alterations in either direction will cause a drift into pathologic neurobehavioral phenotypes. One important aspect of this model is the role that synaptic activity modulators have in the overall E/I state, as they become key determinants of whether or not autistic behaviors arise, in a way that might involve the metaplastic regulation of LTP and LTD (Abraham, 2008; Turrigiano, 2012). For examples, the innate properties of neural circuits, as well as the homeostatic maintenance of intracellular calcium concentration and the expression level of other neuromodulators, may differentially determine the final behavioral outcome. These, together with an interplay between genetic and/or environmental factors, will ultimately regulate and determine synapse quantity and structure (Fig. 2 as represented by persons grabbing the safety line of the hot air balloon). This model also predicts that stimuli affecting the long-term activity and expression of synaptic modulators may result in long-term hyper- or hypo-sensitivity, and is analogous to how gene *x* gene or gene *x* environmental interactions contribute to specific phenotypes (see below).

Opposing neurotransmission profiles with similar behavior symptoms in animal models

As can be appreciated from the numerous studies described above, most of them found similar behavioral phenotypes in their models, yet somewhat opposing neurotransmission profiles. One good example is the *Shank2*$^{-/-}$ mutant mice, where Schmeisser *et al*. (2012) found heightened NMDAR excitatory currents in the model, whereas Won *et al*. (2012) discovered a decreased NMDA receptor function. Nevertheless, both studies found repetitive grooming, hyperactivity, impaired vocalizations and social behaviors in *Shank2*$^{-/-}$ mutant mice. A similar phenomenon was also observed in models showing abnormalities in the serotonergic system. For example, rats exposed to prenatal VPA displayed low serotonin levels in the hippocampus at postnatal day 50 (Dufour-Rainfray *et al*., 2010) as well as the abnormal migration of 5-HT$^+$ neurons (Kuwagata *et al*., 2009). *BDNF*$^{-/+}$ and *DHCR7* mutant mice further showed serotonergic transmission defects (Rios *et al*., 2006; Daws *et al*., 2007). On the other hand, *MAOA* deficient mice displayed elevated levels of serotonin and other monoamines in the brain (Bortolato *et al*., 2013; Singh *et al*., 2013). Interestingly, all of these models express similar aggressive and social deficit behaviors (although varied in locomotor activity), despite the opposing serotonin phenotypes. As such, this demonstrates an obvious variability across the various animal models, where opposing neurophysiological phenotypes can overlap with common behavioral symptoms. These conflicting results can perhaps be resolved by employing a more careful comparison of the various animal models and the clinical presentation within each corresponding etiological subgroup, be it at the molecular, behavioral, and physiological level. Nonetheless, this might be a challenging task given the heterogeneity of ASD. This, therefore, calls for a more individualized approach in the treatment of ASD patients. This approach will also be beneficial for future patient stratification and subgroup classification, which may aid in devising a group or patient-specific treatment based on specific autistic features and range in the spectrum.

Interactions between environment and genetics

Although a number of genetic models have been reported for ASD, most, if not all of them, only share a part of the core symptoms of the disorder. Moreover, single gene knockout models usually correspond to specific syndromes that can be distinguished from ASD. Thus, although ASD-like symptoms occur in a number of single-gene disorders such as tuberous sclerosis, Angelman syndrome, phenylketonuria, Joubert syndrome, Mőbius syndrome and fragile X syndrome, more than 90% of ASD cases are not related to any of these (Geschwind, 2011). Indeed, the etiological heterogeneity of ASD further hinders the identification of causative genes (Bill and Geschwind, 2009). Twin studies showed that ASD is highly heritable, with monozygotic twins showing 60-90% concordance and dizygotic twins showing <5% concordance (Steffenburg *et al*., 1989; Bailey *et al*., 1995). However, recent studies have shown that monozygotic twins do not always display complete heritability (100% concordance) and attribute this in part to environmental factors, which could either aggravate or even protect against ASD (Croen *et al*., 2005; Hallmayer *et al*., 2011). Moreover, it was suggested that at least 40% of ASD cases are likely spawned by environmental causes (Hertz-Picciotto *et al*., 2006). Based on these reports, the role of the environment should not be ignored as it might have a substantial impact in the development of ASD (Bill and Geschwind, 2009). In addition, the prevalence of ASD has remarkably increased over the years, (Hertz-Picciotto *et al*., 2006) from 4-5 per 10,000 births in 1990s (Fombonne, 1999) to 4-6 per 1000 births in early 2000s (Chakrabarti and Fombonne, 2005) and to 14.7 per 1000 children (US) in 2010 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014). It is thought that, perhaps, environmental factors could be contributing to the rise in ASD prevalence over time. One good example that used animal models to explore this hypothesis was the work of Ehninger *et al*., as described above, which demonstrated that MIA (through poly I:C treatment) in TSC mutant mice potentiated the social impairments in the offspring (Ehninger *et al*., 2012). Indeed, this experimental design provides new insights to potentially harmonize the involvement of genetics and environment in the development of ASD. Along with the increasing awareness about the co-contributions of environmental and genetic factors in the development and rise of ASD diagnoses (Arndt *et al*., 2005; Bello, 2007; Kolevzon *et al*., 2007), other animal models suitable for the study of gene-environmental interactions (G×E) in ASD are eagerly anticipated. In this regard, our group is now actively investigating the effects of combined environmental (VPA exposure) and genetic mutations in animal brain development and autism-related phenotypes.

CONCLUSION AND FUTURE DIRECTION

While the prevalence of ASD has increased over the years, the number of proposed etiologic factors including genetic, epigenetic and environmental factors has also grown. Moreover, theories about the pathophysiologic mechanisms and pathways underlying the disorder have greatly diversified. As much as it is beneficial and essential to dig deeper into the neurobiological events underlying the phenotypes in ASD, animal studies require careful interpretation, especially due to the increasing evidence of ASD comorbidity and phenotype overlap with other disorders. Animal models provide an important role in completing the puzzle of how each etiologic factor contributes to ASD pathophysiology. It is evident that every specific etiologic condition being modeled in ASD holds a uniquely different set of behavioral and neurobiological phenotypes. This nonetheless, will likely foment the development of therapeutic strategies targeted towards the specific symptoms and neuronal abnormalities observed. Scientists and medical practitioners should, therefore, collaborate and create a database or open resource for mining the possible environmental or genetic causes that can be assessed in every autistic family and individual, in combination with potential case-specific therapeutic treatments. From there, more applicable and effective therapies could be given to autistic patients with a clearly identified etiology. Patient- and etiology-specific approaches may be the ultimate solution to treat the complex and heterogeneous disorder that is ASD.

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