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Behavioral phenotypes of genetic mouse models of autism

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Abstract

More than a hundred *de novo* single gene mutations and copy-number variants have been implicated in autism, each occurring in a small subset of cases. Mutant mouse models with syntenic mutations offer research tools to gain an understanding of the role of each gene in modulating biological and behavioral phenotypes relevant to autism. Knockout, knockin and transgenic mice incorporating risk gene mutations detected in autism spectrum disorder and comorbid neurodevelopmental disorders are now widely available. At present, autism spectrum disorder is diagnosed solely by behavioral criteria. We developed a constellation of mouse behavioral assays designed to maximize face validity to the types of social deficits and repetitive behaviors that are central to an autism diagnosis. Mouse behavioral assays for associated symptoms of autism, which include cognitive inflexibility, anxiety, hyperactivity, and unusual reactivity to sensory stimuli, are frequently included in the phenotypic analyses. Over the past 10 years, we and many other laboratories around the world have employed these and additional behavioral tests to phenotype a large number of mutant mouse models of autism. In this review, we highlight mouse models with mutations in genes that have been identified as risk genes for autism, which work through synaptic mechanisms and through the mTOR signaling pathway. Robust, replicated autism-relevant behavioral outcomes in a genetic mouse model lend credence to a causal role for specific gene contributions and downstream biological mechanisms in the etiology of autism.

Keywords

Anxiety-like; autism; cognition; genes; hyperactivity; mice; mutant models; neurodevelopmental; repetitive behavior; sensory reactivity; sociability; social behavior; vocalizations

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome with a prevalence of over 1% of the population (CDC 2014; Elsabbagh *et al.* 2012; Kim *et al.* 2011). Diagnosis by the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria is based on two categories of behavioral symptoms: (1) unusual reciprocal social interactions and impaired social communication; and (2) stereotyped and repetitive patterns of behaviors, with restricted interests and activities (American Psychiatric Association 2013; Lord & Bishop 2015). Associated symptoms, which are present in subsets of individuals with ASD, include intellectual disabilities, anxiety, seizures, hyperactivity, sleep disruption and unusual

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reactivity to sensory stimuli. Early behavioral interventions are the current standard of care and offer the best long-term outcomes at present (Lord & Jones 2013; Rogers *et al.* 2012). Intensive behavioral intervention is highly effective in teaching young children to improve their social skills and redirect their repetitive behaviors. However, even the best behavioral therapies do not work for all, are expensive, are labor- and time-intensive and are not available in many geographic regions. Understanding the causes of autism is the first step in the development of effective medical therapeutics to improve symptoms and reverse the disorder's trajectory.

Hypotheses about the genetic causes of ASD originally arose from observations of a male–female bias, 4:1 or greater, and high concordance between identical twins, 50–90%, as compared to less than 10% for non-identical twins and siblings (Fombonne 2009; Hallmayer *et al.* 2011; Miles 2011; Nordenbaek *et al.* 2014; Ritvo *et al.* 1985; Sandin *et al.* 2014; Smalley *et al.* 1988). Intensive searches for the genes causing ASD employed genome-wide association approaches in the early 2000s, progressed to analyses of copy-number variants (CNVs), and are now proceeding with exome and whole genome sequencing in thousands of individuals. Early findings quickly revealed that ASD is not a monogenic disorder. In contrast to disorders such as Huntington's disease and Fragile X syndrome, there is no one specific gene responsible for all cases of autism. Rather, a growing number of *de novo* single gene mutations and CNVs have been identified in people with autism (Alarcon *et al.* 2008; Bucan *et al.* 2009; Butler *et al.* 2005; Buxbaum *et al.* 2007; Cook & Scherer 2008; Crepel *et al.* 2014; Glessner *et al.* 2009; Iossifov *et al.* 2014; Krumm *et al.* 2015; Kumar *et al.* 2009; Lawson-Yuen *et al.* 2008; Leblond *et al.* 2014; Michaelson *et al.* 2012; Morrow 2010; Neale *et al.* 2012; O'Roak *et al.* 2011; Pinto *et al.* 2010; Szatmari *et al.* 2007; Vernes *et al.* 2008; Wang *et al.* 2009; Yuen *et al.* 2015). Mutations in common gene variants and *de novo* coding mutations may be responsible for up to 50% of ASD cases (Gaugler *et al.* 2014; Iossifov *et al.* 2014; Miles 2011). Over 100 risk genes and CNVs for ASD have been published, each one appearing in only a relatively small number of individuals (Butler *et al.* 2005; Coe *et al.* 2014; De Rubeis *et al.* 2014; Gaugler *et al.* 2014; Iossifov *et al.* 2014; Li *et al.* 2014; Parikshak *et al.* 2013; Pinto *et al.* 2014; Willsey & State 2015). Epigenetic risk factors have been implicated in ASD, including chromatin remodeling and methylation mechanisms, such as *CHD8* (Bernier *et al.* 2014; Cotney *et al.* 2015; O'Roak *et al.* 2012; Wilkinson *et al.* 2015), *HDAC* (Foley *et al.* 2012; Moldrich *et al.* 2013) and *MECP2* (Shibayama *et al.* 2004; Theoharides *et al.* 2015), Further, environmental risk factors, such as parental age (Kong *et al.* 2012) and atypical maternal autoantibodies (Braunschweig *et al.* 2013; Brimberg *et al.* 2013; Diamond *et al.* 2013; Piras *et al.* 2014), are associated with a higher incidence of ASD.

One of the most intriguing aspects regarding the genetics of ASD is the enigma of how these many risk factors converge to result in the same general cluster of symptoms diagnosed as ASD. One possibility is that there are underlying convergent downstream mechanisms which contribute to ASD symptomotology. No definitive biomarkers have yet been identified across all diagnosed cases. Rather, subsets of biological factors may define subgroups of individuals with ASD. Stratification by subgroup, either by behavioral category or biomarker, may offer the best strategy for focused clinical trials. Intensive

searches are underway to define abnormalities in neurophysiology, neuroanatomy, brain chemistry, immune markers and other key biological systems (Ecker *et al.* 2013; Jeste & Geschwind 2014; Levitt & Veenstra-VanderWeele 2015). High heterogeneity of symptoms across cases suggests that autism is actually multiple disorders, analogous to the plural concept of 'cancers', with different genetic etiologies and biological defects, to be treated with different classes of therapeutics. The concept of 'autisms' is implicit in the current use of the term ASD, implemented in the 2013 edition of the DSM-5.

Readers of *Genes, Brain and Behavior* are well aware of methods to interrogate genetic hypotheses of human disorders by targeting the homologous mutation in another species and then explicating the consequent phenotypic outcomes. Knockout (KO) and humanized knockin mice, and more recently KO rats, have been generated for many of the single gene mutations and CNVs that were identified in ASD populations and for comorbid neurodevelopmental disorders such as Fragile X and tuberous sclerosis (TSC) (Baudouin *et al.* 2012; Ey *et al.* 2011; Silverman *et al.* 2010a; Zoghbi & Bear 2012). Some of these mutant mouse models are now being employed in preclinical testing of pharmacological targets to treat the core symptoms of ASD (Silverman & Crawley 2014; Spooren *et al.* 2012; Vorstman *et al.* 2014).

As genetic mouse models emerged, our behavioral neuroscience laboratory invested in methods development to design mouse behavioral assays with high relevance to the diagnostic symptoms of autism (Crawley 2004). Because the clinical phenotype of this uniquely human disorder is complex and heterogeneous, we initiated discussions with autism clinical experts, to understand the critical symptoms that could be most meaningfully modeled in mice. Clinical researchers, including colleagues at the University of California Davis MIND Institute, Weill Cornell Medical College, University of North Carolina, University of Washington, University College London and the National Institute of Mental Health Intramural Research Program, kindly allowed us to observe diagnostic interviews and watch videotapes of children with ASD. Knowledge gained through these sessions, and from lectures and conversations with many other generous colleagues working with children, adolescents and adults with ASD, guided our thinking in the development of mouse behavioral assays that dovetail with the natural behavioral repertoire of mice. Considering the types of social approach abnormalities and inappropriate social behaviors that are common in ASD, we developed a mouse 3-chambered social approach assay (Moy *et al.* 2004; Nadler *et al.* 2004), refined methods for scoring reciprocal social interactions in juvenile and adult mice (McFarlane *et al.* 2008), adapted measures for the detection of responses to social olfactory cues (Yang & Crawley 2009), and developed call categories for ultrasonic vocalizations emitted in response to social cues during reciprocal social interactions (Scattoni *et al.* 2008, 2011). Further, we established observational scoring methods to quantify motor stereotypies and repetitive behaviors, such as self-grooming and digging, along with assembling a set of established behavioral assays relevant to anxiety, intellectual impairment, hyperactivity and sensory reactivity (McFarlane *et al.* 2008; Moy *et al.* 2008a,b; Roullet & Crawley 2011; Silverman *et al.* 2010a,b, 2012, 2013, 2015; Wohr *et al.* 2011a; Yang *et al.* 2011, 2012a, 2015), which are now widely used. A small subset of these assays is illustrated in Figure 1. This review presents examples and summaries of

ASD-relevant phenotypes discovered by our lab and many other excellent behavioral genetics labs, revealing the phenotypic consequences of targeting mutations in ASD risk genes.

A remarkable number of risk genes for ASD code for synaptic proteins. Cell adhesion proteins, including contactin-associated proteins, neuroligins and neurexins connect dendrites with axons to promote synapse formation. Postsynaptic scaffolding proteins, such as shanks and neuroligins, strengthen synapses and maintain synaptic transmission. Postsynaptic receptors, such as NMDA and metabotropic glutamate receptors, GABA receptors of varying subunit compositions, serotonin transporter and receptor subtypes, and oxytocin receptors, mediate excitatory and inhibitory synaptic signals. Sodium channels, potassium channels and downstream signaling pathways, such as the PTEN/PI3 kinase/Akt/mTOR pathway, mediate postsynaptic events and critical cellular functions. Mutations and common variants of the genes for these proteins have been identified in small numbers of individuals with autism and related disorders (Butler *et al.* 2005; Cheah *et al.* 2013; Frazier *et al.* 2014; Han *et al.* 2012; Krey *et al.* 2013; Rosander & Hallbook 2015; Tavassoli *et al.* 2014; Veenstra-VanderWeele *et al.* 2012; Weiss *et al.* 2003).

Mice with targeted mutations in many of these genes were generated by outstanding molecular genetics laboratories and generously donated to public repositories such as The Jackson Laboratory. Behavioral phenotypes have been published for some of these mutant lines. In most cases, one original publication describes the behavioral, electrophysiological, neuroanatomical, and/or biochemical phenotypes of the new mouse model of autism. In some cases, the first findings have been replicated by the same laboratory in additional publications. In a few cases, behavioral phenotypes have been replicated by other laboratories. We summarize some of the strongest findings below. Table 1 provides descriptions of gene mutations associated with human ASD. Table 2 summarizes the behavioral phenotypes in the corresponding mouse models, focusing on a subset of ASD risk genes that are involved in synaptic function and the mTOR signaling pathway. Here, we will refer to mice without any functional alleles (homozygous null) as KO mice, mice with one functional allele as heterozygous (Het) mice, mice with targeted amino acid substitutions as knockin mice, and littermate controls with both functional alleles as wildtype (WT) mice.

Mouse models of genetic risk factors for autism

The *CNTNAP2* gene, located on chromosome 7, encodes contactin-associated protein-like 2 (CASPR2), a member of the neurexin superfamily of proteins, functioning as a cell adhesion molecule and receptor (Rodenas-Cuadrado *et al.* 2014). This protein, which contains a putative PDZ binding domain, mediates interactions of neurons and glia during central nervous system development. It also is located in myelinated axons and directs potassium channel localization within differentiating neurons (Poliak *et al.* 1999, 2003). CASPR2 directly binds to the transcription factor FOXP2 (forkhead box protein P2), which has been implicated in speech and language development (Fischer & Hammerschmidt 2011; Vernes *et al.* 2008). Several mutations in the *CNTNAP2* locus, including rare, common and deletion variants, have been associated with ASD (Alarcon *et al.* 2008; Arking *et al.* 2008; Poot *et al.*

2010; Rossi *et al.* 2008; Strauss *et al.* 2006), although more recent studies indicate a limited contribution of *CNTNAP2* dysregulation to ASD (Bakkaloglu *et al.* 2008; Murdoch *et al.* 2015; Sampath *et al.* 2013). Mice lacking *Cntnap2* exhibited reduced juvenile ultrasonic vocalizations, reduced social interaction time and increased repetitive behaviors (Penagarikano *et al.* 2011). In addition to these deficits in ASD-related behaviors, *Cntnap2* KO mice also displayed abnormal neuronal cortical migration, asynchronous neuronal firing in the cortex, a reduced number of inhibitory interneurons, behavioral perseveration in a cognitive task, hyperactivity and seizures (Penagarikano *et al.* 2011).

Neuroligins are cell adhesion molecules located at the postsynaptic side of the synapse, interacting with their presynaptic partner proteins, the neurexins (Bang & Owczarek 2013). Neuroligins contribute to synaptic neurotransmission through their influence on synaptic formation and are distributed at excitatory and inhibitory synapses in an isoform-dependent manner (Hu *et al.* 2015). For example, neuroligin-1 is primarily located at excitatory synapses (Budreck *et al.* 2013; Chih *et al.* 2005; Song *et al.* 1999), while neuroligin-2 is found at inhibitory synapses (Varoqueaux *et al.* 2004); neuroligin-3 can be found at both these locations (Budreck & Scheiffele 2007). At the synapse, neuroligins bind to PSD-95, a scaffolding protein important for postsynaptic strengthening and synapse organization, particularly with ion channels and receptors, such as the glutamatergic NMDA receptor (Bolliger *et al.* 2001; Irie *et al.* 1997; Kim *et al.* 1995, 2008; Kornau *et al.* 1995; Niethammer *et al.* 1996; Shipman & Nicoll 2012). Several studies suggest that neuroligins are involved in synapse modulation and specification rather than synapse formation (Chubykin *et al.* 2007; Krueger *et al.* 2012; Varoqueaux *et al.* 2006). Neuroligin proteins encoded by X-linked genes, such as *NLGN3* and *NLGN4* which map to Xq13 and Xp22.3, respectively, have been associated with ASD in large genome-wide scans (Auranen *et al.* 2002; Glessner *et al.* 2009; Philippe *et al.* 1999), but strong associations have not been found in all studies (Vincent *et al.* 2004; Ylisaukko-oja *et al.* 2005). Using amino acid sequencing in linkage and proband case studies, deletions and frameshifts in *NLGN3* and *NLGN4* sequences have been identified in individuals with ASD (Jamain *et al.* 2003; Laumonnier *et al.* 2004; Lawson-Yuen *et al.* 2008; Marshall *et al.* 2008; Thomas *et al.* 1999; Yan *et al.* 2005).

Neuroligin-1 KO mice exhibited minimal deficits in social behavior, but displayed increased grooming and spatial learning impairments, along with impaired hippocampal long-term potentiation (Blundell *et al.* 2010). Neuroligin-2 heterozygous and KO mice showed normal social interactions in social approach, but displayed increased anxiety-like behavior, decreased pain sensitivity and poor motor coordination (Blundell *et al.* 2009; Wohr *et al.* 2013). In addition, neuroligin-2 KO mice had decreased inhibitory neurotransmission, as well as decreased immunostaining of inhibitory synapse markers (Blundell *et al.* 2009; Chubykin *et al.* 2007). Neuroligin-3 knockin (R451C) mice, with an arginine to cysteine substitution at site 451, did not display robust autism-relevant behaviors, but rather had mild developmental differences, (e.g. slower righting reflexes), enhanced spatial learning acquisition and reduced acoustic startle (Chadman *et al.* 2008; Etherton *et al.* 2011; Tabuchi *et al.* 2007), suggesting that this ASD-related point mutation delayed development, altered learning and reduced sensitivity to stimuli. Neuroligin-3 knockin mice also displayed

increased inhibitory neurotransmission in the barrel cortex, increased excitatory neurotransmission and enhanced long-term potentiation in the hippocampus, increased dendritic branching in the hippocampus, as well as increased protein levels of inhibitory synaptic markers, while KO mice did not (Etherton *et al.* 2011; Tabuchi *et al.* 2007). Neuroligin-3 KO mice displayed normal sociability, but impairments in fear conditioning and olfaction, as well as hyperactivity and decreased total brain volume (Radyushkin *et al.* 2009). Characterization of *Nlgn4* KO mice revealed that loss of this neuroligin resulted in reduced sociability and ultrasonic vocalizations, as well as a reduction in total brain volume (El-Kordi *et al.* 2013; Jamain *et al.* 2008). However, phenotypic analysis of later generations of the same line of *Nlgn4* KO did not find any genotype differences in sociability, ultrasonic vocalizations, anxiety-related behaviors or general locomotor activity (Ey *et al.* 2012).

Neurexins are a class of cell adhesion proteins found on the presynaptic terminal of synapses that bind to neuroligins (Bang & Owczarek 2013). Numerous association studies have identified mutations in the *NRXN1* gene, located on chromosome 2, in intellectual disabilities and other syndromes, including several cases of autism (Ching *et al.* 2010; Feng *et al.* 2006; Glessner *et al.* 2009; Gregor *et al.* 2011; Marshall *et al.* 2008; Szatmari *et al.* 2007; Zahir *et al.* 2008). Neurexin-1α KO mice displayed increased grooming, reduced locomotor activity, reduced sensorimotor gating and increased aggression (Etherton *et al.* 2009; Grayton *et al.* 2013). Further studies are necessary to determine the exact contribution of specific neurexin and neuroligin mutations to ASD-relevant behaviors.

The *SHANK* family of genes located on chromosome 22q encodes scaffolding proteins that assist in the synaptic organization of excitatory glutamatergic neurons by binding to postsynaptic density proteins, signaling molecules, postsynaptic receptors and cytoskeletal proteins (Boeckers *et al.* 2002; Grabrucker *et al.* 2011; Lim *et al.* 1999; Naisbitt *et al.* 1999; Sheng & Kim 2000; Tu *et al.* 1999). SHANK3 can bind to neuroligins, suggesting disrupted cell adhesion may contribute to ASD (Meyer *et al.* 2004). Genetic studies have identified *de novo* and inherited mutations in *SHANK1* (Sato *et al.* 2012), *SHANK2* (Berkel *et al.* 2010, 2012; Pinto *et al.* 2010) and *SHANK3* (Boccuto *et al.* 2013; Durand *et al.* 2007; Gauthier *et al.* 2009, 2010; Marshall *et al.* 2008; Moessner *et al.* 2007). A recent meta-analysis of *SHANK* mutations has suggested that ASD severity due to *SHANK* mutations may be related to which gene is mutated, such that *SHANK3* mutations have a higher frequency and penetrance in individuals with ASD, compared to *SHANK1* and *SHANK2* (Leblond *et al.* 2014). 22q13 deletion syndrome, also known as Phelan-McDermid syndrome, is caused by a deletion on the distal part of the long arm of chromosome 22 and is associated with ASD-like behaviors, including disrupted social behavior, repetitive behaviors, motor dysfunctions, seizures and moderate to severe intellectual disability (Kolevzon *et al.* 2014; Phelan & McDermid 2012). *SHANK3* is one of the most commonly mutated genes within the Phelan-McDermid critical region and is thought to underlie most of the neural consequences of this deletion (Phelan & McDermid 2012).

While *Shank1* KO mice do not display robust autism-relevant social deficits (Silverman *et al.* 2011), *Shank1* KO mice emitted fewer ultrasonic vocalizations as pups, exhibited reduced scent marking and abnormal vocalizations as adults and had motor impairments (Silverman *et al.* 2011; Wohr *et al.* 2011b). *Shank1* KO mice also displayed dendritic spine

abnormalities, including weaker basal synaptic neurotransmission (Hung *et al.* 2008). *Shank2* KO mice had abnormalities in several ASD-relevant behaviors, including reduced sociability, as measured by fewer social contacts during same-sex interactions, and reduced preference for social novelty, as well as higher levels of repetitive behaviors (e.g. grooming and jumping) and abnormal ultrasonic vocalizations (Schmeisser *et al.* 2012; Won *et al.* 2012). In addition, *Shank2* KO mice had a reduced number of hippocampal dendritic spines and reduced glutamatergic neurotransmission in the hippocampus (Schmeisser *et al.* 2012; Won *et al.* 2012).

Mutant mice have been generated for each of the *Shank3* isoforms, with deletions in various domains of the *Shank3* gene, some of which displayed social deficits while others displayed normal sociability (Jiang & Ehlers 2013). Reduced sociability, reduced ultrasonic vocalizations and high levels of repetitive self-grooming were dependent on which isoform was deleted (Bozdagi *et al.* 2010; Drapeau *et al.* 2014; Kouser *et al.* 2013; Peca *et al.* 2011; Wang *et al.* 2011; Yang *et al.* 2012b). Reduced basal neurotransmission as well as abnormalities in neuronal morphology (e.g. neuronal hypertrophy, dendritic spine deficits) have been identified in most of these models (Bozdagi *et al.* 2010; Kouser *et al.* 2013; Peca *et al.* 2011; Wang *et al.* 2011; Yang *et al.* 2012b), underscoring the importance of the Shank proteins in maintaining normal synaptic function and neuronal structure. Therefore, several different ASD-relevant mutations in the *SHANK* gene family have been modeled in mice, and while the phenotypes differ between the specific models, it appears that complete or partial loss of Shank proteins may be detrimental to normal social behaviors and may induce high levels of repetitive behaviors in mice.

ASD risk genes in the mTOR signaling pathway

While many of the identified risk genes for ASD involve synaptic proteins, mutations in several components of the mTOR pathway are also implicated in ASD (Bourgeron 2009), suggesting that normal function of this intracellular signaling pathway is necessary for proper synaptic transmission and neuronal activity. The mTOR pathway is critical for protein synthesis, cellular proliferation and growth (Hershey *et al.* 2012; Laplante & Sabatini 2012). Activated tyrosine kinase receptors recruit and activate phosphoinositide 3-kinase (PI3K), which converts phosphatidylinositol (4,5)-biphosphate (PIP_2) to phosphatidylinositol (3, 4, 5)-triphosphate (PIP_3). PIP_3 recruits many proteins to the membrane through pleckstrin homology domains, including PDK1 and the serine/threonine kinase AKT, an important downstream effector of PIP_3. Phosphatase and tensin homolog located on chromosome 10 (PTEN) is a lipid and protein phosphatase that negatively regulates Akt activity by working in opposition to PI3K, converting PIP_3 back to PIP_2 (Maehama & Dixon 1998; Stambolic *et al.* 1998). Akt is fully activated following phosphorylation by PDK1 and mTOR complex 2 (mTORC2), one of two complexes that involves the evolutionarily conserved serine/threonine kinase, mammalian target of rapamycin (mTOR) (Bayascas & Alessi 2005; Sarbassov *et al.* 2005). Phosphorylated Akt is involved in a wide range of cellular processes, including cell proliferation, survival and growth, via a myriad of downstream signaling proteins, including TSC1 and TSC2. Activated Akt inhibits a protein complex composed of TSC1 (hamartin) and TSC2 (tuberin) through phosphorylation (Huang & Manning 2009; Tee *et al.* 2002). This disinhibits the

GTPase Rheb and actives mTOR complex 1 (mTORC1) (Sato *et al.* 2008). Once activated, mTORC1 upregulates protein synthesis by phosphorylating several key proteins, including S6 kinase 1 (S6K1), which subsequently regulates Fragile X mental retardation protein (FMRP) through phosphorylation (Narayanan *et al.* 2008). Several key proteins, such as PTEN, TSC1, TSC2 and FMRP, are strongly implicated in subsets of ASD cases, and are discussed below. However, additional components of the mTOR pathway are also under investigation for their contribution to ASD-related deficits, such as the mTOR substrate eIF4E (Gkogkas *et al.* 2013).

PTEN mutations are most often associated with a variety of hamartoma syndromes, including Cowden syndrome (Eng 2003), which are characterized by benign focal malformations. *PTEN* was identified as an ASD candidate gene after several case and prospective studies revealed an association in individuals with ASD and macrocephaly (enlarged head size) (Butler *et al.* 2005; Buxbaum *et al.* 2007; Herman *et al.* 2007; McBride *et al.* 2010; Varga *et al.* 2009). Modeling *PTEN* mutations in mice has focused on two distinct strategies: conditional KO mice, in which distinct cell types lack the gene and protein product, and heterozygous null mice that possess constitutive haploinsufficiency. Conditional KO mice with a *Pten* deletion restricted to a subset of post-mitotic hippocampal and cortical neurons exhibited deficits in social interaction, sociability and preference for social novelty as well as impaired performance in the Morris water maze and macrocephaly (Kwon *et al.* 2006; Zhou *et al.* 2009). Similarly, heterozygous KO mice with a constitutive *Pten* mutation exhibited macrocephaly and deficits in sociability (Clipperton-Allen & Page 2014), but these sociability impairments were limited to female mice in one study (Page *et al.* 2009). Additionally, Allen, Page and colleagues also showed that *Pten* heterozygous mice exhibited elevated repetitive behaviors (i.e. digging, self-grooming). To date, the results obtained with *Pten* mutant mice suggest that Pten dysfunction leads to several ASD-relevant behaviors, although more extensive behavioral characterization of the various *Pten* conditional mouse models would further elucidate this phosphatase's contribution to ASD.

Tuberous sclerosis is a genetic condition resulting from mutations in the *TSC1* or *TSC2* gene, which negatively regulate mTOR activity (Curatolo & Maria 2013). Individuals that carry mutations in either *TSC* gene have a higher than expected occurrence of ASD-like features (50%) or an ASD diagnosis (29%) (Curatolo *et al.* 2010). *Tsc1* heterozygous mice exhibited deficits in social interactions, hippocampus-dependent contextual fear conditioning, and hidden platform Morris water maze tasks (Goorden *et al.* 2007). Social deficits were not identified in *Tsc2* heterozygous mice, except when the mice were also treated prenatally with Poly I:C, a maternal immune activation model (Ehninger *et al.* 2012). However, *Tsc2* mutations did produce learning and memory deficits in Morris water maze hidden platform performance and contextual fear conditioning (Ehninger *et al.* 2008). A dominant negative *Tsc2* mutation that binds to *Tsc1* and inhibits its activity also led to reduced social interactions and a reduced preference for social novelty, although these mice exhibited normal sociability in the 3-chambered social approach task (Chevere-Torres *et al.* 2012). A specific *Tsc1* disruption limited to cerebellar Purkinje cells produced deficits in sociability, repetitive behavior and cognitive flexibility (Tsai *et al.* 2012). Similarly, *Tsc2* disruption limited to cerebellar Purkinje cells replicated deficits in sociability and social

preference, which were accompanied by increased repetitive behaviors (Reith *et al.* 2013). The study of these *Tsc1 and Tsc2* mutant mice has provided knowledge as to how these single gene mutations can model some ASD-relevant phenotypes and contribute to the overall ASD phenotype.

Fragile X syndrome (FXS) is caused by a hypermethylated CGG repeat expansion in the *FMR1* gene that leads to a drastic reduction in its protein product, FMRP. FMRP is an RNA binding protein that has been implicated in regulating protein expression (Bagni & Greenough 2005; Chen & Joseph 2015; Crawford *et al.* 2001; Kazdoba *et al.* 2014). Individuals with FXS are characterized by intellectual disability and a variety of physical abnormalities, and frequently display social dysfunction, anxiety and repetitive behaviors (Berry-Kravis *et al.* 2002; Lightbody & Reiss 2009). The diagnostic criteria for ASD commonly occur in individuals with FXS, with recent estimates ranging from 18% to 47% (Clifford *et al.* 2007; Demark *et al.* 2003; Hatton *et al.* 2006; Kaufmann *et al.* 2004; Rogers *et al.* 2001). Conversely, the proportion of FXS in the ASD population has been estimated at 3–8% (Cohen *et al.* 1991; Fombonne *et al.* 1997). The first and most widely tested mouse model of FXS is the Dutch-Belgian Consortium *Fmr1* KO mouse, which has been maintained on multiple background strains. Recent work with the *Fmr1* KO mouse has evaluated ASD-relevant phenotypes, including social deficits and repetitive behaviors. *Fmr1* KO mice on a C57BL/6 (B6) background exhibited decreased sociability in some cases (Dahlhaus & El-Husseini 2010) or decreased sniffing during a social approach test when maintained on a B6/FVB hybrid background (McNaughton *et al.* 2008). In contrast, other studies revealed normal sociability and reduced preference for social novelty in *Fmr1* KO mice maintained on FVB and B6 backgrounds (Liu & Smith 2009; Pietropaolo *et al.* 2011). In tests of direct social interaction, *Fmr1* KO mice on a B6 background showed deficits in social interaction in some studies (Mineur *et al.* 2006), but as with much of the *Fmr1* mouse behavioral literature, there are caveats to these behavioral impairments (Kazdoba *et al.* 2014). Paylor and colleagues demonstrated increased social interaction in *Fmr1* KO mice on a B6 background (Spencer *et al.* 2005, 2008). Importantly, the Paylor team presented data interpreted as higher social anxiety in these mice. *Fmr1* KO mice also exhibited elevated repetitive behaviors, another core symptom of ASD. Specifically, *Fmr1* KO mice on B6 or hybrid backgrounds had elevated levels of self-grooming, but not when they were maintained on an FVB background (McNaughton *et al.* 2008; Pietropaolo *et al.* 2011). *Fmr1* KO mice on B6 and B6 hybrid backgrounds also had higher levels of marble burying (Gholizadeh *et al.* 2014; Spencer *et al.* 2011; Veeraragavan *et al.* 2012). Intellectual disabilities which characterize FXS have been evaluated in a variety of cognitive tasks. In some reports, *Fmr1* KO mice demonstrated cognitive deficits consistent with the intellectual impairments that characterize FXS. Deficits have been observed in contextual, cued and trace fear conditioning and/or context discrimination in *Fmr1* KO mice on B6 and sighted FVB backgrounds (Auerbach *et al.* 2011; Ding *et al.* 2014; Paradee *et al.* 1999; Zhao *et al.* 2005). However, many other reports have described normal cognitive abilities in *Fmr1* KO mice maintained on B6, FVB/129 hybrid, and albino B6 backgrounds, including fear conditioning (Baker *et al.* 2010; Dobkin *et al.* 2000; Peier *et al.* 2000; Uutela *et al.* 2012; Van Dam *et al.* 2000). Similarly, spatial navigation and reversal deficits were observed during Morris water maze testing in *Fmr1* KO mice maintained on B6, albino B6 and FVB

backgrounds in some labs (Baker *et al.* 2010; D'Hooge *et al.* 1997; Kooy *et al.* 1996; The Dutch-Belgian Fragile X Consortium *et al.* 1994) but these impairments were not seen in other studies (Paradee *et al.* 1999; Uutela *et al.* 2012; Yan *et al.* 2004). Thus, although the gene and its product are absent in *Fmr1* mice, behavioral phenotypes relevant to the human syndrome and to ASD appear to be variable, with phenotypes potentially dependent on a variety of methodological and environmental factors. While genetic background is one potential factor, there does not appear to be a clear segregation of behavioral outcomes on the B6 vs. FVB backgrounds, either in the social and repetitive behavioral domains most relevant to autism, or in the cognitive domains most relevant to FXS. In contrast to the inconsistent behavioral literature on *Fmr1* mice, investigations of neuroanatomical, electrophysiological, genetic and biochemical phenotypes in *Fmr1* KO mice have allowed researchers to gain considerable insight into biological mechanisms underlying Fragile X syndrome.

Conclusions

The summary above and in Table 2 provides descriptions of behavioral and biological phenotypes in representative genetic mouse models of ASD. The small subset of genetic mouse models included herein focuses primarily on risk genes that mediate the formation and strengthening of synapses, and postsynaptic downstream signaling through the mTOR pathway. Our selection is presented for its possible usefulness in conceptualizing a cluster of genes with potentially interrelated actions through synaptic and postsynaptic intracellular mechanisms. The appeal of this convergence concept, proposed by many autism researchers (Delorme *et al.* 2013; Geschwind & State 2015; Silverman & Crawley 2014; Spooren *et al.* 2012), includes the possibility of developing pharmacological treatments for ASD that act through impaired synaptic mechanisms, perhaps using compounds repurposed from other uses involving synaptic dysfunction. Several intriguing preclinical studies with mouse models of ASD indicate improvements in social behaviors and/or reductions in repetitive behaviors and/or amelioration of cognitive deficits after pharmacological treatments. Promising results from pharmacological interventions in mouse models of ASD and FXS include mGluR5 antagonists (Michalon *et al.* 2012; Silverman *et al.* 2012; Tian *et al.* 2015), GABA agonists (Han *et al.* 2014; Henderson *et al.* 2012; Silverman *et al.* 2015), rapamycin (Burket *et al.* 2014; Ehninger & Silva 2011; Zhou *et al.* 2009), d-cycloserine (Burket *et al.* 2013; Yadav *et al.* 2012), BDNF and ampakines (Lauterborn *et al.* 2007; Silverman *et al.* 2013), IGF-1 (Bozdagi *et al.* 2013) and oxytocin (Huang *et al.* 2014; Meziane *et al.* 2014; Modi & Young 2012; Penagarikano *et al.* 2015). Descriptions of additional mouse models of ASD are available in several other recent review articles (Ey *et al.* 2011; Kas *et al.* 2014; Silverman & Crawley 2014).

Caveats abound for the methods and interpretations of mouse behavioral phenotypes relevant to the core symptoms of autism. The first is genetic background. Just as humans with the same mutation may present with different symptoms, possibly due to protective or susceptibility genes in their genetic backgrounds, mice present with different phenotypes when a mutation is bred into different inbred strains, such as C57BL/6J, FVB/NJ and substrains of 129, each of which has its own idiosyncratic behavioral traits (Crawley *et al.* 1997). Varying behavioral phenotypes have been reported for mutant mouse models of

autism and FXS, as described above, when outcomes of the mutation were placed on divergent backgrounds and directly compared (Moy *et al.* 2009; Pietropaolo *et al.* 2011; Spencer *et al.* 2011). The second is experimental design. Employing large Ns and using WT littermates as controls are essential to avoid over-interpretations of phenotypes which were actually caused by environmental influences that affect mouse behaviors. The third is statistical analysis of behavioral data. Two-way ANOVAs are often required, in which treatment is one factor and genotype is the other factor, rather than simple *t*-tests. Stringent post-hoc tests, such as Newman-Keuls, Dunnett's and Tukey's, avoid the false positives that may be obtained from more forgiving post-hoc tests such as Fisher's LSD. Statistical comparisons must match the original experimental design. For example, our 3-chambered social approach task is not sensitive enough to compare the absolute number of seconds spent with the novel mouse across genotypes, or across drug doses. Data on social approach are correctly analyzed with a simple paired *t*-test or equivalent, which compares time with the novel mouse vs. time with the novel object within genotype only, or within a drug dose only, to provide a yes-or-no outcome measure, i.e. sociability or absence of sociability. The fourth is corroboration within the behavioral domain. Conducting two or more assays that interrogate the same behavior (e.g. at least two social tasks, or two repetitive behavior assays, or two anxiety-related tests, or several learning and memory tasks that tap into different cognitive domains) allows for stronger interpretations and generalizability of a finding within a given domain. Including relevant controls, such as open field exploration for tasks that require locomotor activity, and pain or foot shock sensitivity for fear conditioning, will ensure that a motor or sensory artifact is not the cause of a significant effect in the behavioral domain of primary interest. Large numbers of mouse behavioral assays relevant to the diagnostic and associated symptoms of ASD are available to choose from (Crawley 2012; Silverman *et al.* 2010a), along with a wealth of relevant control tests (Crawley 2007).

One additional caveat, arguably the most important, is replicability. While all scientific discoveries require replication, behavioral findings require extra attention to reproducibility because of the strong influence of the various environmental factors on mouse behaviors. Stressors, such as construction noise or rough handling, can greatly affect scores on sensitive behavioral assays for anxiety-related, social and cognitive phenotypes. These types of variable findings remain primarily anecdotal, because they are difficult to document and publish, although they are common knowledge among behavioral neuroscientists. Loss of behavioral phenotypes across breeding generations may occur due to attritional loss of the mutation or drift in background genes. Basic methodological issues, such as the age of the mice at testing, composition of the chow diet, properties of the testing equipment and testing room, social testing in single vs. mixed genotype dyads, cleaning of the equipment between subject mice, and simple random chance beyond $P < 0.05$, may create conditions that yield a positive finding that cannot be replicated. Following published procedures by expert behavioral neuroscientists can help alleviate some of these concerns. However, the best strategy to ensure high replicability is for the research team to conduct the entire experiment again in a separate cohort of mice prior to publishing. Further, to confirm the ultimate strength of a finding for the scientific community, several different laboratories should conduct essentially the same experiment with the same line of mice. When a social deficit in

a genetic mouse model of ASD is replicated across cohorts and by many labs, the strength of a finding is ensured. Highly robust, well-replicated behavioral phenotypes relevant to the symptoms of ASD in a genetic mouse model can then effectively inform our understanding of the role of that gene in the symptomotology of ASD and serve as preclinical outcome measures for therapeutic discovery.

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REFERENCES

Alarcon M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, Sebat J, Wigler M, Martin CL, Ledbetter DH, Nelson SF, Cantor RM, Geschwind DH. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. Am J Hum Genet. 2008; 82:150–159. [PubMed: 18179893]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Publishing; 2013.

Arking DE, Cutler DJ, Brune CW, Teslovich TM, West K, Ikeda M, Rea A, Guy M, Lin S, Cook EH, Chakravarti A. A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. Am J Hum Genet. 2008; 82:160–164. [PubMed: 18179894]

Auerbach BD, Osterweil EK, Bear MF. Mutations causing syndromic autism define an axis of synaptic pathophysiology. Nature. 2011; 480:63–68. [PubMed: 22113615]

Auranen M, Vanhala R, Varilo T, Ayers K, Kempas E, Ylisaukko-Oja T, Sinsheimer JS, Peltonen L, Jarvela I. A genomewide screen for autism-spectrum disorders: evidence for a major susceptibility locus on chromosome 3q25-27. Am J Hum Genet. 2002; 71:777–790. [PubMed: 12192642]

Bagni C, Greenough WT. From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. Nat Rev Neurosci. 2005; 6:376–387. [PubMed: 15861180]

Baker KB, Wray SP, Ritter R, Mason S, Lanthorn TH, Savelieva KV. Male and female Fmr1 knockout mice on C57 albino background exhibit spatial learning and memory impairments. Genes Brain Behav. 2010; 9:562–574. [PubMed: 20398059]

Bakkaloglu B, O'Roak BJ, Louvi A, Gupta AR, Abelson JF, Morgan TM, Chawarska K, Klin A, Ercan-Sencicek AG, Stillman AA, Tanriover G, Abrahams BS, Duvall JA, Robbins EM, Geschwind DH, Biederer T, Gunel M, Lifton RP, State MW. Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. Am J Hum Genet. 2008; 82:165–173. [PubMed: 18179895]

Bang ML, Owczarek S. A matter of balance: role of neurexin and neuroligin at the synapse. Neurochem Res. 2013; 38:1174–1189. [PubMed: 23559421]

Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Pun-nakkal P, Tanaka KF, Spooren W, Hen R, De Zeeuw CI, Vogt K, Scheiffele P. Shared synaptic pathophysiology in syn-dromic and nonsyndromic rodent models of autism. Science. 2012; 338:128–132. [PubMed: 22983708]

Bayascas JR, Alessi DR. Regulation of Akt/PKB Ser473 phosphorylation. Mol Cell. 2005; 18:143–145. [PubMed: 15837416]

Berkel S, Marshall CR, Weiss B, Howe J, Roeth R, Moog U, Endris V, Roberts W, Szatmari P, Pinto D, Bonin M, Riess A, Engels H, Sprengel R, Scherer SW, Rappold GA. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat Genet. 2010; 42:489–491. [PubMed: 20473310]

Berkel S, Tang W, Trevino M, Vogt M, Obenhaus HA, Gass P, Scherer SW, Sprengel R, Schratt G, Rappold GA. Inherited and de novo SHANK2 variants associated with autism spectrum disorder impair neuronal morphogenesis and physiology. Hum Mol Genet. 2012; 21:344–357. [PubMed: 21994763]

Bernier R, Golzio C, Xiong B, et al. Disruptive CHD8 mutations define a subtype of autism early in development. Cell. 2014; 158:263–276. [PubMed: 24998929]

Berry-Kravis E, Grossman AW, Crnic LS, Greenough WT. Understanding fragile X syndrome. Curr Paediatr. 2002; 12:316–324.

Blundell J, Tabuchi K, Bolliger MF, Blaiss CA, Brose N, Liu X, Sudhof TC, Powell CM. Increased anxiety-like behavior in mice lacking the inhibitory synapse cell adhesion molecule neuroligin 2. Genes Brain Behav. 2009; 8:114–126. [PubMed: 19016888]

Blundell J, Blaiss CA, Etherton MR, Espinosa F, Tabuchi K, Walz C, Bolliger MF, Sudhof TC, Powell CM. Neuroligin-1 deletion results in impaired spatial memory and increased repetitive behavior. J Neurosci. 2010; 30:2115–2129. [PubMed: 20147539]

Boccuto L, Lauri M, Sarasua SM, Skinner CD, Buccella D, Dwivedi A, Orteschi D, Collins JS, Zollino M, Visconti P, Dupont B, Tiziano D, Schroer RJ, Neri G, Stevenson RE, Gurrieri F, Schwartz CE. Prevalence of SHANK3 variants in patients with different subtypes of autism spectrum disorders. Eur J Hum Genet. 2013; 21:310–316. [PubMed: 22892527]

Boeckers TM, Bockmann J, Kreutz MR, Gundelfinger ED. ProSAP/Shank proteins - a family of higher order organizing molecules of the postsynaptic density with an emerging role in human neurological disease. J Neurochem. 2002; 81:903–910. [PubMed: 12065602]

Bolliger MF, Frei K, Winterhalter KH, Gloor SM. Identification of a novel neuroligin in humans which binds to PSD-95 and has a widespread expression. Biochem J. 2001; 356:581–588. [PubMed: 11368788]

Bourgeron T. A synaptic trek to autism. Curr Opin Neurobiol. 2009; 19:231–234. [PubMed: 19545994]

Bozdagi O, Sakurai T, Papapetrou D, Wang X, Dickstein DL, Takahashi N, Kajiwara Y, Yang M, Katz AM, Scattoni ML, Harris MJ, Saxena R, Silverman JL, Crawley JN, Zhou Q, Hof PR, Buxbaum JD. Haploinsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication. Mol Autism. 2010; 1:15. [PubMed: 21167025]

Bozdagi O, Tavassoli T, Buxbaum JD. Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay. Mol Autism. 2013; 4:9. [PubMed: 23621888]

Braunschweig D, Krakowiak P, Duncanson P, Boyce R, Hansen RL, Ashwood P, Hertz-Picciotto I, Pessah IN, Van de Water J. Autism-specific maternal autoantibodies recognize critical proteins in developing brain. Transl Psychiatry. 2013; 3:e277. [PubMed: 23838888]

Brimberg L, Sadiq A, Gregersen PK, Diamond B. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. Mol Psychiatry. 2013; 18:1171–1177. [PubMed: 23958959]

Bucan M, Abrahams BS, Wang K, et al. Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. PLoS Genet. 2009; 5:e1000536. [PubMed: 19557195]

Budreck EC, Scheiffele P. Neuroligin-3 is a neuronal adhesion protein at GABAergic and glutamatergic synapses. Eur J Neurosci. 2007; 26:1738–1748. [PubMed: 17897391]

Budreck EC, Kwon OB, Jung JH, Baudouin S, Thommen A, Kim HS, Fukazawa Y, Harada H, Tabuchi K, Shigemoto R, Scheiffele P, Kim JH. Neuroligin-1 controls synaptic abundance of NMDA-type glutamate receptors through extracellular coupling. Proc Natl Acad Sci USA. 2013; 110:725–730. [PubMed: 23269831]

Burket JA, Benson AD, Tang AH, Deutsch SI. D-Cycloserine improves sociability in the BTBR T+ Itpr3tf/J mouse model of autism spectrum disorders with altered Ras/Raf/ERK1/2 signaling. Brain Res Bull. 2013; 96:62–70. [PubMed: 23685206]

Burket JA, Benson AD, Tang AH, Deutsch SI. Rapamycin improves sociability in the BTBR T(+)Itpr3(tf)/J mouse model of autism spectrum disorders. Brain Res Bull. 2014; 100:70–75. [PubMed: 24295733]

Butler MG, Dasouki MJ, Zhou XP, Talebizadeh Z, Brown M, Takahashi TN, Miles JH, Wang CH, Stratton R, Pilarski R, Eng C. Subset of individuals with autism spectrum disorders and extreme

macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet. 2005; 42:318–321. [PubMed: 15805158]

Buxbaum JD, Cai G, Chaste P, Nygren G, Goldsmith J, Reichert J, Anckarsater H, Rastam M, Smith CJ, Silverman JM, Hollander E, Leboyer M, Gillberg C, Verloes A, Betancur C. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. Am J Med Genet B Neuropsychiatr Genet. 2007; 144B:484–491. [PubMed: 17427195]

CDC (Centers for Disease Control and Prevention) & Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. Morb Mortal Wkly Rep Surveill Summ. 2014; 63:1–21.

Chadman KK, Gong S, Scattoni ML, Boltuck SE, Gandhy SU, Heintz N, Crawley JN. Minimal aberrant behavioral phenotypes of neuroligin-3 R451C knockin mice. Autism Res. 2008; 1:147–158. [PubMed: 19360662]

Cheah CS, Westenbroek RE, Roden WH, Kalume F, Oakley JC, Jansen LA, Catterall WA. Correlations in timing of sodium channel expression, epilepsy, and sudden death in Dravet syndrome. Channels (Austin). 2013; 7:468–472. [PubMed: 23965409]

Chen E, Joseph S. Fragile X mental retardation protein: a paradigm for translational control by RNA-binding proteins. Biochimie. 2015; 114:147–154. [PubMed: 25701550]

Chevere-Torres I, Maki JM, Santini E, Klann E. Impaired social interactions and motor learning skills in tuberous sclerosis complex model mice expressing a dominant/negative form of tuberin. Neurobiol Dis. 2012; 45:156–164. [PubMed: 21827857]

Chih B, Engelman H, Scheiffele P. Control of excitatory and inhibitory synapse formation by neuroligins. Science. 2005; 307:1324–1328. [PubMed: 15681343]

Ching MS, Shen Y, Tan WH, et al. Deletions of NRXN1 (neurexin-1) predispose to a wide spectrum of developmental disorders. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B:937–947. [PubMed: 20468056]

Chubykin AA, Atasoy D, Etherton MR, Brose N, Kavalali ET, Gibson JR, Sudhof TC. Activity-dependent validation of excitatory versus inhibitory synapses by neuroligin-1 versus neuroligin-2. Neuron. 2007; 54:919–931. [PubMed: 17582332]

Clifford S, Dissanayake C, Bui QM, Huggins R, Taylor AK, Loesch DZ. Autism spectrum phenotype in males and females with fragile X full mutation and premutation. J Autism Dev Disord. 2007; 37:738–747. [PubMed: 17031449]

Clipperton-Allen AE, Page DT. Pten haploinsufficient mice show broad brain overgrowth but selective impairments in autism-relevant behavioral tests. Hum Mol Genet. 2014; 23:3490–3505. [PubMed: 24497577]

Clipperton-Allen AE, Page DT. Decreased aggression and increased repetitive behavior in Pten haploinsufficient mice. Genes Brain Behav. 2015; 14:145–157. [PubMed: 25561290]

Coe BP, Witherspoon K, Rosenfeld JA, et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet. 2014; 46:1063–1071. [PubMed: 25217958]

Cohen IL, Sudhalter V, Pfadt A, Jenkins EC, Brown WT, Vietze PM. Why are autism and the fragile-X syndrome associated? Conceptual and methodological issues. Am J Hum Genet. 1991; 48:195–202. [PubMed: 1990832]

Cook EH Jr, Scherer SW. Copy-number variations associated with neuropsychiatric conditions. Nature. 2008; 455:919–923. [PubMed: 18923514]

Cotney J, Muhle RA, Sanders SJ, Liu L, Willsey AJ, Niu W, Liu W, Klei L, Lei J, Yin J, Reilly SK, Tebbenkamp AT, Bichsel C, Pletikos M, Sestan N, Roeder K, State MW, Devlin B, Noonan JP. The autism-associated chromatin modifier CHD8 regulates other autism risk genes during human neurodevelopment. Nat Commun. 2015; 6:6404. [PubMed: 25752243]

Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: Human genome epidemiology review. Genet Med. 2001; 3:359–371. [PubMed: 11545690]

Crawley JN. Designing mouse behavioral tasks relevant to autistic-like behaviors. Ment Retard Dev Disabil Res Rev. 2004; 10:248–258. [PubMed: 15666335]

Crawley, JN. What's Wrong With My Mouse?: Behavioral Phenotyping of Transgenic and Knockout Mice. Hoboken, NJ: John Wiley & Sons, Inc; 2007.

Crawley JN. Translational animal models of autism and neu-rodevelopmental disorders. Dialogues Clin Neurosci. 2012; 14:293–305. [PubMed: 23226954]

Crawley JN, Belknap JK, Collins A, Crabbe JC, Frankel W, Henderson N, Hitzemann RJ, Maxson SC, Miner LL, Silva AJ, Wehner JM, Wynshaw-Boris A, Paylor R. Behavioral phenotypes of inbred mouse strains: implications and recommendations for molecular studies. Psychopharmacology (Berl). 1997; 132:107–124. [PubMed: 9266608]

Crepel A, De Wolf V, Brison N, Ceulemans B, Walleghem D, Peuteman G, Lambrechts D, Steyaert J, Noens I, Devriendt K, Peeters H. Association of CDH11 with non-syndromic ASD. Am J Med Genet B Neuropsychiatr Genet. 2014; 165B:391–398. [PubMed: 24839052]

Curatolo P, Maria BL. Tuberous sclerosis. Handb Clin Neurol. 2013; 111:323–331. [PubMed: 23622183]

Curatolo P, Napolioni V, Moavero R. Autism spectrum disorders in tuberous sclerosis: pathogenetic pathways and implications for treatment. J Child Neurol. 2010; 25:873–880. [PubMed: 20207609]

Dahlhaus R, El-Husseini A. Altered neuroligin expression is involved in social deficits in a mouse model of the fragile X syndrome. Behav Brain Res. 2010; 208:96–105. [PubMed: 19932134]

De Rubeis S, He X, Goldberg AP, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature. 2014; 515:209–215. [PubMed: 25363760]

Delorme R, Ey E, Toro R, Leboyer M, Gillberg C, Bourgeron T. Progress toward treatments for synaptic defects in autism. Nat Med. 2013; 19:685–694. [PubMed: 23744158]

Demark JL, Feldman MA, Holden JJ. Behavioral relationship between autism and fragile x syndrome. Am J Ment Retard. 2003; 108:314–326. [PubMed: 12901707]

D'Hooge R, Nagels G, Franck F, Bakker CE, Reyniers E, Storm K, Kooy RF, Oostra BA, Willems PJ, De Deyn PP. Mildly impaired water maze performance in male Fmr1 knockout mice. Neuroscience. 1997; 76:367–376. [PubMed: 9015322]

Diamond B, Honig G, Mader S, Brimberg L, Volpe BT. Brain-reactive antibodies and disease. Annu Rev Immunol. 2013; 31:345–385. [PubMed: 23516983]

Ding Q, Sethna F, Wang H. Behavioral analysis of male and female Fmr1 knockout mice on C57BL/6 background. Behav Brain Res. 2014; 271:72–78. [PubMed: 24886775]

Dobkin C, Rabe A, Dumas R, El Idrissi A, Haubenstock H, Brown WT. Fmr1 knockout mouse has a distinctive strain-specific learning impairment. Neuroscience10. 2000; 0:423–429.

Drapeau E, Dorr NP, Elder GA, Buxbaum JD. Absence of strong strain effects in behavioral analyses of Shank3-deficient mice. Dis Model Mech. 2014; 7:667–681. [PubMed: 24652766]

Durand CM, Betancur C, Boeckers TM, et al. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet. 2007; 39:25–27. [PubMed: 17173049]

Ecker C, Spooren W, Murphy D. Developing new pharmacotherapies for autism. J Intern Med. 2013; 274:308–320. [PubMed: 23865950]

Ehninger D, Silva AJ. Rapamycin for treating tuberous sclerosis and autism spectrum disorders. Trends Mol Med. 2011; 17:78–87. [PubMed: 21115397]

Ehninger D, Han S, Shilyansky C, Zhou Y, Li W, Kwiatkowski DJ, Ramesh V, Silva AJ. Reversal of learning deficits in a Tsc2+/− mouse model of tuberous sclerosis. Nat Med. 2008; 14:843–848. [PubMed: 18568033]

Ehninger D, Sano Y, de Vries PJ, Dies K, Franz D, Geschwind DH, Kaur M, Lee YS, Li W, Lowe JK, Nakagawa JA, Sahin M, Smith K, Whittemore V, Silva AJ. Gestational immune activation and Tsc2 haploinsufficiency cooperate to disrupt fetal survival and may perturb social behavior in adult mice. Mol Psychiatry. 2012; 17:62–70. [PubMed: 21079609]

El-Kordi A, Winkler D, Hammerschmidt K, Kastner A, Krueger D, Ronnenberg A, Ritter C, Jatho J, Radyushkin K, Bourgeron T, Fischer J, Brose N, Ehrenreich H. Development of an autism severity score for mice using Nlgn4 null mutants as a construct-valid model of heritable monogenic autism. Behav Brain Res. 2013; 251:41–49. [PubMed: 23183221]

Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, Montiel-Nava C, Patel V, Paula CS, Wang C, Yasamy MT, Fombonne E. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012; 5:160–179. [PubMed: 22495912]

Eng C. PTEN: one gene, many syndromes. Hum Mutat. 2003; 22:183–198. [PubMed: 12938083]

Etherton MR, Blaiss CA, Powell CM, Sudhof TC. Mouse neurexin-1alpha deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments. Proc Natl Acad Sci USA. 2009; 106:17998–18003. [PubMed: 19822762]

Etherton M, Foldy C, Sharma M, Tabuchi K, Liu X, Shamloo M, Malenka RC, Sudhof TC. Autism-linked neuroligin-3 R451C mutation differentially alters hippocampal and cortical synaptic function. Proc Natl Acad Sci USA. 2011; 108:13764–13769. [PubMed: 21808020]

Ey E, Leblond CS, Bourgeron T. Behavioral profiles of mouse models for autism spectrum disorders. Autism Res. 2011; 4:5–16. [PubMed: 21328568]

Ey E, Yang M, Katz AM, Woldeyohannes L, Silverman JL, Leblond CS, Faure P, Torquet N, Le Sourd AM, Bourgeron T, Crawley JN. Absence of deficits in social behaviors and ultrasonic vocalizations in later generations of mice lacking neuroligin4. Genes Brain Behav. 2012; 11:928–941. [PubMed: 22989184]

Feng J, Schroer R, Yan J, Song W, Yang C, Bockholt A, Cook EH Jr, Skinner C, Schwartz CE, Sommer SS. High frequency of neurexin 1beta signal peptide structural variants in patients with autism. Neurosci Lett. 2006; 409:10–13. [PubMed: 17034946]

Fischer J, Hammerschmidt K. Ultrasonic vocalizations in mouse models for speech and socio-cognitive disorders: insights into the evolution of vocal communication. Genes Brain Behav. 2011; 10:17–27. [PubMed: 20579107]

Foley AG, Gannon S, Rombach-Mullan N, Prendergast A, Barry C, Cassidy AW, Regan CM. Class I histone deacetylase inhibition ameliorates social cognition and cell adhesion molecule plasticity deficits in a rodent model of autism spectrum disorder. Neuropharmacology. 2012; 63:750–760. [PubMed: 22683514]

Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009; 65:591–598. [PubMed: 19218885]

Fombonne E, Du Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a French epidemiological survey. J Am Acad Child Adolesc Psychiatry. 1997; 36:1561–1569. [PubMed: 9394941]

Frazier TW, Embacher R, Tilot AK, Koenig K, Mester J, Eng C. Molecular and phenotypic abnormalities in individuals with germline heterozygous PTEN mutations and autism. Mol Psychiatry. 2014; 20:1132–1138. [PubMed: 25288137]

Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, Mahajan M, Manaa D, Pawitan Y, Reichert J, Ripke S, Sandin S, Sklar P, Svantesson O, Reichenberg A, Hultman CM, Devlin B, Roeder K, Buxbaum JD. Most genetic risk for autism resides with common variation. Nat Genet. 2014; 46:881–885. [PubMed: 25038753]

Gauthier J, Spiegelman D, Piton A, Lafreniere RG, Laurent S, St-Onge J, Lapointe L, Hamdan FF, Cossette P, Mot-tron L, Fombonne E, Joober R, Marineau C, Drapeau P, Rouleau GA. Novel de novo SHANK3 mutation in autistic patients. Am J Med Genet B Neuropsychiatr Genet. 2009; 150B:421–424. [PubMed: 18615476]

Gauthier J, Champagne N, Lafreniere RG, et al. De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. Proc Natl Acad Sci USA. 2010; 107:7863–7868. [PubMed: 20385823]

Geschwind DH, State MW. Gene hunting in autism spectrum disorder: on the path to precision medicine. Lancet Neurol. 2015 http://dx.doi.org/10.1016/S1474-4422(15)00044-7.

Gholizadeh S, Arsenault J, Xuan IC, Pacey LK, Hampson DR. Reduced phenotypic severity following adeno-associated virus-mediated Fmr1 gene delivery in fragile X mice. Neuropsychopharmacology. 2014; 39:3100–3111. [PubMed: 24998620]

Gkogkas CG, Khoutorsky A, Ran I, Rampakakis E, Nevarko T, Weatherill DB, Vasuta C, Yee S, Truitt M, Dallaire P, Major F, Lasko P, Ruggero D, Nader K, Lacaille JC, Sonenberg N. Autism-related deficits via dysregulated eIF4E-dependent translational control. Nature. 2013; 493:371–377. [PubMed: 23172145]

Glessner JT, Wang K, Cai G, et al. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature. 2009; 459:569–573. [PubMed: 19404257]

Goorden SM, van Woerden GM, van der Weerd L, Cheadle JP, Elgersma Y. Cognitive deficits in Tsc1+/− mice in the absence of cerebral lesions and seizures. Ann Neurol. 2007; 62:648–655. [PubMed: 18067135]

Grabrucker AM, Schmeisser MJ, Schoen M, Boeckers TM. Postsynaptic ProSAP/Shank scaffolds in the cross-hair of synaptopathies. Trends Cell Biol. 2011; 21:594–603. [PubMed: 21840719]

Grayton HM, Missler M, Collier DA, Fernandes C. Altered social behaviours in neurexin 1alpha knockout mice resemble core symptoms in neurodevelopmental disorders. PLoS One. 2013; 8:e67114. [PubMed: 23840597]

Gregor A, Albrecht B, Bader I, et al. Expanding the clinical spectrum associated with defects in CNTNAP2 and NRXN1. BMC Med Genet. 2011; 12:106. [PubMed: 21827697]

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C, Grether JK, Risch N. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatr y. 2011; 68:1095–1102.

Han S, Tai C, Westenbroek RE, Yu FH, Cheah CS, Potter GB, Rubenstein JL, Scheuer T, de la Iglesia HO, Catter-all WA. Autistic-like behaviour in Scn1a+/− mice and rescue by enhanced GABA-mediated neurotransmission. Nature. 2012; 489:385–390. [PubMed: 22914087]

Han S, Tai C, Jones CJ, Scheuer T, Catterall WA. Enhancement of inhibitory neurotransmission by GABAA receptors having alpha2,3-subunits ameliorates behavioral deficits in a mouse model of autism. Neuron. 2014; 81:1282–1289. [PubMed: 24656250]

Hatton DD, Sideris J, Skinner M, Mankowski J, Bailey DB Jr, Roberts J, Mirrett P. Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. Am J Med Genet A. 2006; 140a:1804–1813. [PubMed: 16700053]

Henderson C, Wijetunge L, Kinoshita MN, Shumway M, Hammond RS, Postma FR, Brynczka C, Rush R, Thomas A, Pay-lor R, Warren ST, Vanderklish PW, Kind PC, Carpenter RL, Bear MF, Healy AM. Reversal of disease-related pathologies in the fragile X mouse model by selective activation of GABAB receptors with arbaclofen. Sci Transl Med. 2012; 4:152ra128.

Herman GE, Butter E, Enrile B, Pastore M, Prior TW, Som-mer A. Increasing knowledge of PTEN germline mutations: two additional patients with autism and macrocephaly. Am J Med Genet A. 2007; 143a:589–593. [PubMed: 17286265]

Hershey JW, Sonenberg N, Mathews MB. Principles of translational control: an overview. Cold Spring Harb Perspect Biol. 2012; 4:a011528. [PubMed: 23209153]

Hu X, Luo JH, Xu J. The interplay between synaptic activity and neuroligin function in the CNS. Biomed Res Int. 2015; 2015:498957. [PubMed: 25839034]

Huang J, Manning BD. A complex interplay between Akt, TSC2, and the two mTOR complexes. Biochem Soc Trans. 2009; 37:217–222. [PubMed: 19143635]

Huang H, Michetti C, Busnelli M, Manago F, Sannino S, Scheg-gia D, Giancardo L, Sona D, Murino V, Chini B, Scattoni ML, Papaleo F. Chronic and acute intranasal oxytocin produce divergent social effects in mice. Neuropsychopharmacology. 2014; 39:1102–1114. [PubMed: 24190025]

Hung AY, Futai K, Sala C, Valtschanoff JG, Ryu J, Woodworth MA, Kidd FL, Sung CC, Miyakawa T, Bear MF, Weinberg RJ, Sheng M. Smaller dendritic spines, weaker synaptic transmission, but enhanced spatial learning in mice lacking Shank1. J Neurosci. 2008; 28:1697–1708. [PubMed: 18272690]

Iossifov I, O'Roak BJ, Sanders SJ, et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014; 515:216–221. [PubMed: 25363768]

Irie M, Hata Y, Takeuchi M, Ichtchenko K, Toyoda A, Hirao K, Takai Y, Rosahl TW, Sudhof TC. Binding of neuroligins to PSD-95. Science. 1997; 277:1511–1515. [PubMed: 9278515]

Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. Nat Genet. 2003; 34:27–29. [PubMed: 12669065]

Jamain S, Radyushkin K, Hammerschmidt K, Granon S, Boretius S, Varoqueaux F, Ramanantsoa N, Gallego J, Ronnenberg A, Winter D, Frahm J, Fischer J, Bourgeron T, Ehrenreich H, Brose N. Reduced social interaction and ultrasonic communication in a mouse model of monogenic heritable autism. Proc Natl Acad Sci USA. 2008; 105:1710–1715. [PubMed: 18227507]

Jeste SS, Geschwind DH. Disentangling the heterogeneity of autism spectrum disorder through genetic findings. Nat Rev Neurol. 2014; 10:74–81. [PubMed: 24468882]

Jiang YH, Ehlers MD. Modeling autism by SHANK gene mutations in mice. Neuron. 2013; 78:8–27. [PubMed: 23583105]

Kas MJ, Glennon JC, Buitelaar J, Ey E, Biemans B, Crawley J, Ring RH, Lajonchere C, Esclassan F, Talpos J, Noldus LP, Burbach JP, Steckler T. Assessing behavioural and cognitive domains of autism spectrum disorders in rodents: current status and future perspectives. Psychopharmacology (Berl). 2014; 231:1125–1146. [PubMed: 24048469]

Kaufmann WE, Cortell R, Kau AS, Bukelis I, Tierney E, Gray RM, Cox C, Capone GT, Stanard P. Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. Am J Med Genet A. 2004; 129a:225–234. [PubMed: 15326621]

Kazdoba TM, Leach PT, Silverman JL, Crawley JN. Modeling fragile X syndrome in the Fmr1 knockout mouse. Intractable Rare Dis Res. 2014; 3:118–133. [PubMed: 25606362]

Kim E, Niethammer M, Rothschild A, Jan YN, Sheng M. Clustering of Shaker-type K+ channels by interaction with a family of membrane-associated guanylate kinases. Nature. 1995; 378:85–88. [PubMed: 7477295]

Kim J, Jung SY, Lee YK, Park S, Choi JS, Lee CJ, Kim HS, Choi YB, Scheiffele P, Bailey CH, Kandel ER, Kim JH. Neuroligin-1 is required for normal expression of LTP and associative fear memory in the amygdala of adult animals. Proc Natl Acad Sci USA. 2008; 105:9087–9092. [PubMed: 18579781]

Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, Cheon KA, Kim SJ, Kim YK, Lee H, Song DH, Grinker RR. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry. 2011; 168:904–912. [PubMed: 21558103]

Kolevzon A, Angarita B, Bush L, Wang AT, Frank Y, Yang A, Rapaport R, Saland J, Srivastava S, Farrell C, Edelmann LJ, Buxbaum JD. Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring. J Neurodev Disord. 2014; 6:39. [PubMed: 25784960]

Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, Gudjonsson SA, Sigurdsson A, Jonasdottir A, Wong WS, Sigurdsson G, Walters GB, Steinberg S, Helgason H, Thorleifsson G, Gudbjartsson DF, Helgason A, Magnusson OT, Thorsteinsdottir U, Stefansson K. Rate of de novo mutations and the importance of father's age to disease risk. Nature. 2012; 488:471–475. [PubMed: 22914163]

Kooy RF, D'Hooge R, Reyniers E, Bakker CE, Nagels G, De Boulle K, Storm K, Clincke G, De Deyn PP, Oostra BA, Willems PJ. Transgenic mouse model for the fragile X syndrome. Am J Med Genet. 1996; 64:241–245. [PubMed: 8844056]

Kornau HC, Schenker LT, Kennedy MB, Seeburg PH. Domain interaction between NMDA receptor subunits and the postsynaptic density protein PSD-95. Science. 1995; 269:1737–1740. [PubMed: 7569905]

Kouser M, Speed HE, Dewey CM, Reimers JM, Widman AJ, Gupta N, Liu S, Jaramillo TC, Bangash M, Xiao B, Worley PF, Powell CM. Loss of predominant Shank3 isoforms results in hippocampus-dependent impairments in behavior and synaptic transmission. J Neurosci. 2013; 33:18448–18468. [PubMed: 24259569]

Krey JF, Pasca SP, Shcheglovitov A, Yazawa M, Schwemberger R, Rasmusson R, Dolmetsch RE. Timothy syndrome is associated with activity-dependent dendritic retraction in rodent and human neurons. Nat Neurosci. 2013; 16:201–209. [PubMed: 23313911]

Krueger DD, Tuffy LP, Papadopoulos T, Brose N. The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. Curr Opin Neurobiol. 2012; 22:412–422. [PubMed: 22424845]

Krumm N, Turner TN, Baker C, Vives L, Mohajeri K, Wither-spoon K, Raja A, Coe BP, Stessman HA, He ZX, Leal SM, Bernier R, Eichler EE. Excess of rare, inherited truncating mutations in autism. Nat Genet. 2015; 47:582–588. [PubMed: 25961944]

Kumar RA, Marshall CR, Badner JA, Babatz TD, Mukamel Z, Aldinger KA, Sudi J, Brune CW, Goh G, Karamohamed S, Sutcliffe JS, Cook EH, Geschwind DH, Dobyns WB, Scherer SW, Christian SL. Association and mutation analyses of 16p11.2 autism candidate genes. PLoS One. 2009; 4:e4582. [PubMed: 19242545]

Kwon CH, Luikart BW, Powell CM, Zhou J, Matheny SA, Zhang W, Li Y, Baker SJ, Parada LF. Pten regulates neuronal arborization and social interaction in mice. Neuron. 2006; 50:377–388. [PubMed: 16675393]

Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012; 149:274–293. [PubMed: 22500797]

Laumonnier F, Bonnet-Brilhault F, Gomot M, Blanc R, David A, Moizard MP, Raynaud M, Ronce N, Lemonnier E, Calvas P, Laudier B, Chelly J, Fryns JP, Ropers HH, Hamel BC, Andres C, Barthelemy C, Moraine C, Briault S. X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. Am J Hum Genet. 2004; 74:552–557. [PubMed: 14963808]

Lauterborn JC, Rex CS, Kramar E, Chen LY, Pandyarajan V, Lynch G, Gall CM. Brain-derived neurotrophic factor rescues synaptic plasticity in a mouse model of fragile X syndrome. J Neurosci. 2007; 27:10685–10694. [PubMed: 17913902]

Lawson-Yuen A, Saldivar JS, Sommer S, Picker J. Familial deletion within NLGN4 associated with autism and Tourette syndrome. Eur J Hum Genet. 2008; 16:614–618. [PubMed: 18231125]

Leblond CS, Nava C, Polge A, et al. Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: a gradient of severity in cognitive impairments. PLoS Genet. 2014; 10:e1004580. [PubMed: 25188300]

Levitt P, Veenstra-VanderWeele J. Neurodevelopment and the origins of brain disorders. Neuropsychopharmacology. 2015; 40:1–3. [PubMed: 25482168]

Li J, Shi M, Ma Z, Zhao S, Euskirchen G, Ziskin J, Urban A, Hallmayer J, Snyder M. Integrated systems analysis reveals a molecular network underlying autism spectrum disorders. Mol Syst Biol. 2014; 10:774. [PubMed: 25549968]

Lightbody AA, Reiss AL. Gene, brain, and behavior relationships in fragile X syndrome: evidence from neuroimaging studies. Dev Disabil Res Rev. 2009; 15:343–352. [PubMed: 20014368]

Lim S, Naisbitt S, Yoon J, Hwang JI, Suh PG, Sheng M, Kim E. Characterization of the Shank family of synaptic proteins. Multiple genes, alternative splicing, and differential expression in brain and development. J Biol Chem. 1999; 274:29510–29518. [PubMed: 10506216]

Liu ZH, Smith CB. Dissociation of social and nonsocial anxiety in a mouse model of fragile X syndrome. Neurosci Lett. 2009; 454:62–66. [PubMed: 19429055]

Lord C, Bishop SL. Recent advances in autism research as reflected in DSM-5 criteria for autism spectrum disorder. Annu Rev Clin Psychol. 2015; 11:53–70. [PubMed: 25581244]

Lord C, Jones RM. New strategies and findings for behavioral interventions in autism spectrum disorders. Ann N Y Acad Sci. 2013; 1304:70–76. [PubMed: 24279894]

Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem. 1998; 273:13375–13378. [PubMed: 9593664]

Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in autism spectrum disorder. Am J Hum Genet. 2008; 82:477–488. [PubMed: 18252227]

McBride KL, Varga EA, Pastore MT, Prior TW, Manickam K, Atkin JF, Herman GE. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. Autism Res. 2010; 3:137–141. [PubMed: 20533527]

McFarlane HG, Kusek GK, Yang M, Phoenix JL, Bolivar VJ, Crawley JN. Autism-like behavioral phenotypes in BTBR T+tf/J mice. Genes Brain Behav. 2008; 7:152–163. [PubMed: 17559418]

McNaughton CH, Moon J, Strawderman MS, Maclean KN, Evans J, Strupp BJ. Evidence for social anxiety and impaired social cognition in a mouse model of fragile X syndrome. Behav Neurosci. 2008; 122:293–300. [PubMed: 18410169]

Meyer G, Varoqueaux F, Neeb A, Oschlies M, Brose N. The complexity of PDZ domain-mediated interactions at gluta-matergic synapses: a case study on neuroligin. Neuropharmacol-ogy. 2004; 47:724–733.

Meziane H, Schaller F, Bauer S, Villard C, Matarazzo V, Riet F, Guillon G, Lafitte D, Desarmenien MG, Tauber M, Mus-catelli F. An early postnatal oxytocin treatment prevents social and learning deficits in adult mice deficient for Magel2, a gene involved in Prader-Willi syndrome and autism. Biol Psychiatry. 2014; 78:85–94. [PubMed: 25599930]

Michaelson JJ, Shi Y, Gujral M, et al. Whole-genome sequencing in autism identifies hot spots for de novo germline mutation. Cell. 2012; 151:1431–1442. [PubMed: 23260136]

Michalon A, Sidorov M, Ballard TM, Ozmen L, Spooren W, Wettstein JG, Jaeschke G, Bear MF, Lindemann L. Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. Neuron. 2012; 74:49–56. [PubMed: 22500629]

Miles JH. Autism spectrum disorders--a genetics review. Genet Med. 2011; 13:278–294. [PubMed: 21358411]

Mineur YS, Huynh LX, Crusio WE. Social behavior deficits in the Fmr1 mutant mouse. Behav Brain Res. 2006; 168:172–175. [PubMed: 16343653]

Modi ME, Young LJ. The oxytocin system in drug discovery for autism: animal models and novel therapeutic strategies. Horm Behav. 2012; 61:340–350. [PubMed: 22206823]

Moessner R, Marshall CR, Sutcliffe JS, Skaug J, Pinto D, Vincent J, Zwaigenbaum L, Fernandez B, Roberts W, Szatmari P, Scherer SW. Contribution of SHANK3 mutations to autism spectrum disorder. Am J Hum Genet. 2007; 81:1289–1297. [PubMed: 17999366]

Moldrich RX, Leanage G, She D, Dolan-Evans E, Nelson M, Reza N, Reutens DC. Inhibition of histone deacetylase in utero causes sociability deficits in postnatal mice. Behav Brain Res. 2013; 257:253–264. [PubMed: 24103642]

Morrow EM. Genomic copy number variation in disorders of cognitive development. J Am Acad Child Adolesc Psychiatry. 2010; 49:1091–1104. [PubMed: 20970697]

Moy SS, Nadler JJ, Perez A, Barbaro RP, Johns JM, Mag-nuson TR, Piven J, Crawley JN. Sociability and preference for social novelty in five inbred strains: an approach to assess autistic-like behavior in mice. Genes Brain Behav. 2004; 3:287–302. [PubMed: 15344922]

Moy SS, Nadler JJ, Poe MD, Nonneman RJ, Young NB, Koller BH, Crawley JN, Duncan GE, Bodfish JW. Development of a mouse test for repetitive, restricted behaviors: relevance to autism. Behav Brain Res. 2008a; 188:178–194. [PubMed: 18068825]

Moy SS, Nadler JJ, Young NB, Nonneman RJ, Segall SK, Andrade GM, Crawley JN, Magnuson TR. Social approach and repetitive behavior in eleven inbred mouse strains. Behav Brain Res. 2008b; 191:118–129. [PubMed: 18440079]

Moy SS, Nadler JJ, Young NB, Nonneman RJ, Grossman AW, Murphy DL, D'Ercole AJ, Crawley JN, Magnuson TR, Lauder JM. Social approach in genetically engineered mouse lines relevant to autism. Genes Brain Behav. 2009; 8:129–142. [PubMed: 19016890]

Murdoch JD, Gupta AR, Sanders SJ, Walker MF, Keaney J, Fernandez TV, Murtha MT, Anyanwu S, Ober GT, Raubeson MJ, DiLullo NM, Villa N, Waqar Z, Sullivan C, Gonzalez L, Willsey AJ, Choe SY, Neale BM, Daly MJ, State MW. No evidence for association of autism with rare heterozygous point mutations in contactin-associated protein-like 2 (CNTNAP2), or in other contactin-associated proteins or contactins. PLoS Genet. 2015; 11:e1004852. [PubMed: 25621974]

Nadler JJ, Moy SS, Dold G, Trang D, Simmons N, Perez A, Young NB, Barbaro RP, Piven J, Magnuson TR, Crawley JN. Automated apparatus for quantitation of social approach behaviors in mice. Genes Brain Behav. 2004; 3:303–314. [PubMed: 15344923]

Naisbitt S, Kim E, Tu JC, Xiao B, Sala C, Valtschanoff J, Weinberg RJ, Worley PF, Sheng M. Shank, a novel family of postsynaptic density proteins that binds to the NMDA receptor/PSD-95/GKAP complex and cortactin. Neuron. 1999; 23:569–582. [PubMed: 10433268]

Narayanan U, Nalavadi V, Nakamoto M, Thomas G, Ceman S, Bassell GJ, Warren ST. S6K1 phosphorylates and regulates fragile X mental retardation protein (FMRP) with the neuronal protein synthesis-dependent mammalian target of rapamycin (mTOR) signaling cascade. J Biol Chem. 2008; 283:18478–18482. [PubMed: 18474609]

Neale BM, Kou Y, Liu L, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature. 2012; 485:242–245. [PubMed: 22495311]

Niethammer M, Kim E, Sheng M. Interaction between the C terminus of NMDA receptor subunits and multiple members of the PSD-95 family of membrane-associated guanylate kinases. J Neurosci. 1996; 16:2157–2163. [PubMed: 8601796]

Nordenbaek C, Jorgensen M, Kyvik KO, Bilenberg N. A Danish population-based twin study on autism spectrum disorders. Eur Child Adolesc Psychiatry. 2014; 23:35–43. [PubMed: 23661220]

Ogawa S, Kwon CH, Zhou J, Koovakkattu D, Parada LF, Sinton CM. A seizure-prone phenotype is associated with altered free-running rhythm in Pten mutant mice. Brain Res. 2007; 1168:112–123. [PubMed: 17706614]

O'Roak BJ, Deriziotis P, Lee C, Vives L, Schwartz JJ, Girirajan S, Karakoc E, Mackenzie AP, Ng SB, Baker C, Rieder MJ, Nickerson DA, Bernier R, Fisher SE, Shendure J, Eichler EE. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 2011; 43:585–589. [PubMed: 21572417]

O'Roak BJ, Vives L, Fu W, et al. Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science. 2012; 338:1619–1622. [PubMed: 23160955]

Page DT, Kuti OJ, Prestia C, Sur M. Haploinsufficiency for Pten and Serotonin transporter cooperatively influences brain size and social behavior. Proc Natl Acad Sci USA. 2009; 106:1989–1994. [PubMed: 19208814]

Paradee W, Melikian HE, Rasmussen DL, Kenneson A, Conn PJ, Warren ST. Fragile X mouse: strain effects of knockout phenotype and evidence suggesting deficient amygdala function. Neuroscience. 1999; 94:185–192. [PubMed: 10613508]

Parikshak NN, Luo R, Zhang A, Won H, Lowe JK, Chandran V, Horvath S, Geschwind DH. Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. Cell. 2013; 155:1008–1021. [PubMed: 24267887]

Peca J, Feliciano C, Ting JT, Wang W, Wells MF, Venkatraman TN, Lascola CD, Fu Z, Feng G. Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. Nature. 2011; 472:437–442. [PubMed: 21423165]

Peier AM, McIlwain KL, Kenneson A, Warren ST, Paylor R, Nelson DL. (Over)correction of FMR1 deficiency with YAC transgenics: behavioral and physical features. Hum Mol Genet. 2000; 9:1145–1159. [PubMed: 10767339]

Penagarikano O, Abrahams BS, Herman EI, Winden KD, Gdalyahu A, Dong H, Sonnenblick LI, Gruver R, Almajano J, Bragin A, Golshani P, Trachtenberg JT, Peles E, Geschwind DH. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. Cell. 2011; 147:235–246. [PubMed: 21962519]

Penagarikano O, Lazaro MT, Lu XH, Gordon A, Dong H, Lam HA, Peles E, Maidment NT, Murphy NP, Yang XW, Golshani P, Geschwind DH. Exogenous and evoked oxytocin restores social behavior in the Cntnap2 mouse model of autism. Sci Transl Med. 2015; 7:271ra278.

Phelan K, McDermid HE. The 22q13.3 deletion syndrome (Phelan-McDermid Syndrome). Mol Syndromol. 2012; 2:186–201. [PubMed: 22670140]

Philippe A, Martinez M, Guilloud-Bataille M, Gillberg C, Rastam M, Sponheim E, Coleman M, Zappella M, Aschauer H, Van Maldergem L, Penet C, Feingold J, Brice A, Leboyer M. Genome-wide scan for autism susceptibility genes. Paris Autism Research International Sibpair Study. Hum Mol Genet. 1999; 8:805–812. [PubMed: 10196369]

Pietropaolo S, Guilleminot A, Martin B, D'Amato FR, Cru-sio WE. Genetic-background modulation of core and variable autistic-like symptoms in Fmr1 knock-out mice. PLoS One. 2011; 6:e17073. [PubMed: 21364941]

Pinto D, Pagnamenta AT, Klei L, et al. Functional impact of global rare copy number variation in autism spectrum disorders. Nature. 2010; 466:368–372. [PubMed: 20531469]

Pinto D, Delaby E, Merico D, et al. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. Am J Hum Genet. 2014; 94:677–694. [PubMed: 24768552]

Piras IS, Haapanen L, Napolioni V, Sacco R, Van de Water J, Persico AM. Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in Italian children with Autism Spectrum Disorder. Brain Behav Immun. 2014; 38:91–99. [PubMed: 24389156]

Poliak S, Gollan L, Martinez R, Custer A, Einheber S, Salzer JL, Trimmer JS, Shrager P, Peles E. Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K+ channels. Neuron. 1999; 24:1037–1047. [PubMed: 10624965]

Poliak S, Salomon D, Elhanany H, Sabanay H, Kiernan B, Pevny L, Stewart CL, Xu X, Chiu SY, Shrager P, Furley AJ, Peles E. Juxtaparanodal clustering of Shaker-like K+ channels in myelinated axons depends on Caspr2 and TAG-1. J Cell Biol. 2003; 162:1149–1160. [PubMed: 12963709]

Poot M, Beyer V, Schwaab I, Damatova N, Van't Slot R, Prothero J, Holder SE, Haaf T. Disruption of CNTNAP2 and additional structural genome changes in a boy with speech delay and autism spectrum disorder. Neurogenetics. 2010; 11:81–89. [PubMed: 19582487]

Radyushkin K, Hammerschmidt K, Boretius S, Varoqueaux F, El-Kordi A, Ronnenberg A, Winter D, Frahm J, Fischer J, Brose N, Ehrenreich H. Neuroligin-3-deficient mice: model of a monogenic heritable form of autism with an olfactory deficit. Genes Brain Behav. 2009; 8:416–425. [PubMed: 19243448]

Reith RM, McKenna J, Wu H, Hashmi SS, Cho SH, Dash PK, Gambello MJ. Loss of Tsc2 in Purkinje cells is associated with autistic-like behavior in a mouse model of tuberous sclerosis complex. Neurobiol Dis. 2013; 51:93–103. [PubMed: 23123587]

Ritvo ER, Freeman BJ, Mason-Brothers A, Mo A, Ritvo AM. Concordance for the syndrome of autism in 40 pairs of afflicted twins. Am J Psychiatry. 1985; 142:74–77. [PubMed: 4038442]

Rodenas-Cuadrado P, Ho J, Vernes SC. Shining a light on CNTNAP2: complex functions to complex disorders. Eur J Hum Genet. 2014; 22:171–178. [PubMed: 23714751]

Rogers SJ, Wehner DE, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. J Dev Behav Pediatr. 2001; 22:409–417. [PubMed: 11773805]

Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, Guo M, Dawson G. Effects of a brief Early Start Denver model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. J Am Acad Child Adolesc Psychiatry. 2012; 51:1052–1065. [PubMed: 23021480]

Rosander C, Hallbook T. Dravet syndrome in Sweden: a population-based study. Dev Med Child Neurol. 2015; 57:628–633.

Rossi E, Verri AP, Patricelli MG, Destefani V, Ricca I, Vetro A, Ciccone R, Giorda R, Toniolo D, Maraschio P, Zuffardi O. A 12 Mb deletion at 7q33-q35 associated with autism spectrum disorders and primary amenorrhea. Eur J Med Genet. 2008; 51:631–638. [PubMed: 18675947]

Roullet FI, Crawley JN. Mouse models of autism: testing hypotheses about molecular mechanisms. Curr Top Behav Neurosci. 2011; 7:187–212. [PubMed: 21225409]

Sampath S, Bhat S, Gupta S, O'Connor A, West AB, Arking DE, Chakravarti A. Defining the contribution of CNTNAP2 to autism susceptibility. PLoS One. 2013; 8:e77906. [PubMed: 24147096]

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA. 2014; 311:1770–1777. [PubMed: 24794370]

Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005; 307:1098–1101. [PubMed: 15718470]

Sato T, Umetsu A, Tamanoi F. Characterization of the Rheb-mTOR signaling pathway in mammalian cells: constitutive active mutants of Rheb and mTOR. Methods Enzymol. 2008; 438:307–320. [PubMed: 18413257]

Sato D, Lionel AC, Leblond CS, et al. SHANK1 deletions in males with autism spectrum disorder. Am J Hum Genet. 2012; 90:879–887. [PubMed: 22503632]

Scattoni ML, Gandhy SU, Ricceri L, Crawley JN. Unusual repertoire of vocalizations in the BTBR T +tf/J mouse model of autism. PLoS One. 2008; 3:e3067. [PubMed: 18728777]

Scattoni ML, Ricceri L, Crawley JN. Unusual repertoire of vocalizations in adult BTBR T+tf/J mice during three types of social encounters. Genes Brain Behav. 2011; 10:44–56. [PubMed: 20618443]

Schmeisser MJ, Ey E, Wegener S, et al. Autistic-like behaviours and hyperactivity in mice lacking ProSAP1/Shank2. Nature. 2012; 486:256–260. [PubMed: 22699619]

Sheng M, Kim E. The Shank family of scaffold proteins. J Cell Sci. 2000; 113(Pt 11):1851–1856. [PubMed: 10806096]

Shibayama A, Cook EH Jr, Feng J, Glanzmann C, Yan J, Craddock N, Jones IR, Goldman D, Heston LL, Sommer SS. MECP2 structural and 3′-UTR variants in schizophrenia, autism and other psychiatric diseases: a possible association with autism. Am J Med Genet B Neuropsychiatr Genet. 2004; 128B:50–53. [PubMed: 15211631]

Shipman SL, Nicoll RA. Dimerization of postsynaptic neuroligin drives synaptic assembly via transsynaptic clustering of neurexin. Proc Natl Acad Sci USA. 2012; 109:19432–19437. [PubMed: 23129658]

Silverman JL, Crawley JN. The promising trajectory of autism therapeutics discovery. Drug Discov Today. 2014; 19:838–844. [PubMed: 24362109]

Silverman JL, Yang M, Lord C, Crawley JN. Behavioural phenotyping assays for mouse models of autism. Nat Rev Neurosci. 2010a; 11:490–502. [PubMed: 20559336]

Silverman JL, Yang M, Turner SM, Katz AM, Bell DB, Koenig JI, Crawley JN. Low stress reactivity and neuroendocrine factors in the BTBR T+tf/J mouse model of autism. Neu-roscience. 2010b; 171:1197–1208.

Silverman JL, Turner SM, Barkan CL, Tolu SS, Saxena R, Hung AY, Sheng M, Crawley JN. Sociability and motor functions in Shank1 mutant mice. Brain Res. 2011; 1380:120–137. [PubMed: 20868654]

Silverman JL, Smith DG, Rizzo SJ, Karras MN, Turner SM, Tolu SS, Bryce DK, Smith DL, Fonseca K, Ring RH, Crawley JN. Negative allosteric modulation of the mGluR5 receptor reduces repetitive behaviors and rescues social deficits in mouse models of autism. Sci Transl Med. 2012; 4:131ra151.

Silverman JL, Oliver CF, Karras MN, Gastrell PT, Crawley JN. AMPAKINE enhancement of social interaction in the BTBR mouse model of autism. Neuropharmacology. 2013; 64:268–282. [PubMed: 22801296]

Silverman JL, Pride MC, Hayes JE, Puhger KR, Butler-Struben HM, Baker S, Crawley JN. GABA receptor agonist R-baclofen reverses social deficits and reduces repetitive behavior in two mouse models of autism. Neuropsychopharmacology. 2015; 40:2228–2239. [PubMed: 25754761]

Smalley SL, Asarnow RF, Spence MA. Autism and genetics. A decade of research. Arch Gen Psychiatr y. 1988; 45:953–961.

Song JY, Ichtchenko K, Sudhof TC, Brose N. Neuroligin 1 is a postsynaptic cell-adhesion molecule of excitatory synapses. Proc Natl Acad Sci USA. 1999; 96:1100–1105. [PubMed: 9927700]

Spencer CM, Alekseyenko O, Serysheva E, Yuva-Paylor LA, Paylor R. Altered anxiety-related and social behaviors in the Fmr1 knockout mouse model of fragile X syndrome. Genes Brain Behav. 2005; 4:420–430. [PubMed: 16176388]

Spencer CM, Graham DF, Yuva-Paylor LA, Nelson DL, Paylor R. Social behavior in Fmr1 knockout mice carrying a human FMR1 transgene. Behav Neurosci. 2008; 122:710–715. [PubMed: 18513141]

Spencer CM, Alekseyenko O, Hamilton SM, Thomas AM, Serysheva E, Yuva-Paylor LA, Paylor R. Modifying behavioral phenotypes in Fmr1KO mice: genetic background differences reveal autistic-like responses. Autism Res. 2011; 4:40–56. [PubMed: 21268289]

Spooren W, Lindemann L, Ghosh A, Santarelli L. Synapse dysfunction in autism: a molecular medicine approach to drug discovery in neurodevelopmental disorders. Trends Pharmacol Sci. 2012; 33:669–684. [PubMed: 23084458]

Stambolic V, Suzuki A, de la Pompa JL, Brothers GM, Mirtsos C, Sasaki T, Ruland J, Penninger JM, Siderovski DP, Mak TW. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell. 1998; 95:29–39. [PubMed: 9778245]

Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, Stephan DA, Morton DH. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med. 2006; 354:1370–1377. [PubMed: 16571880]

Szatmari P, Paterson AD, Zwaigenbaum L, et al. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet. 2007; 39:319–328. [PubMed: 17322880]

Tabuchi K, Blundell J, Etherton MR, Hammer RE, Liu X, Powell CM, Sudhof TC. A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science. 2007; 318:71–76. [PubMed: 17823315]

Tavassoli T, Kolevzon A, Wang AT, Curchack-Lichtin J, Halpern D, Schwartz L, Soffes S, Bush L, Grodberg D, Cai G, Buxbaum JD. De novo SCN2A splice site mutation in a boy with Autism spectrum disorder. BMC Med Genet. 2014; 15:35. [PubMed: 24650168]

Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ, Cantley LC, Blenis J. Tuberous sclerosis complex-1 and −2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc Natl Acad Sci USA. 2002; 99:13571–13576. [PubMed: 12271141]

Bakker CE, Verheij C, Willemsen R, van der Helm R, Oerlemans F, Vermey M, Bygrave A, Hoogeveen A, Oostra BA, Reyniers E, De Boule K, D'Hooge R, Cras P, van Velzen D, Nagels G, Martin J-J, De Deyn PP, Darby JK, Willems PJ. The Dutch-Belgian Fragile X Consortium. Fmr1 knockout mice: a model to study fragile X mental retardation. Cell. 1994; 78:23–33. [PubMed: 8033209]

Theoharides TC, Athanassiou M, Panagiotidou S, Doyle R. Dysregulated brain immunity and neurotrophin signaling in Rett syndrome and autism spectrum disorders. J Neuroimmunol. 2015; 279:33–38. [PubMed: 25669997]

Thomas NS, Sharp AJ, Browne CE, Skuse D, Hardie C, Dennis NR. Xp deletions associated with autism in three females. Hum Genet. 1999; 104:43–48. [PubMed: 10071191]

Tian D, Stoppel LJ, Heynen AJ, Lindemann L, Jaeschke G, Mills AA, Bear MF. Contribution of mGluR5 to pathophysiology in a mouse model of human chromosome 16p11.2 microdeletion. Nat Neurosci. 2015; 18:182–184. [PubMed: 25581360]

Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, Steinberg J, Crawley JN, Regehr WG, Sahin M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. Nature. 2012; 488:647–651. [PubMed: 22763451]

Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, Doan A, Aakalu VK, Lanahan AA, Sheng M, Worley PF. Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. Neuron. 1999; 23:583–592. [PubMed: 10433269]

Uutela M, Lindholm J, Louhivuori V, Wei H, Louhivuori LM, Pertovaara A, Akerman K, Castren E, Castren ML. Reduction of BDNF expression in Fmr1 knockout mice worsens cognitive deficits but improves hyperactivity and sensorimotor deficits. Genes Brain Behav. 2012; 11:513–523. [PubMed: 22435671]

Van Dam D, D'Hooge R, Hauben E, Reyniers E, Gantois I, Bakker CE, Oostra BA, Kooy RF, De Deyn PP. Spatial learning, contextual fear conditioning and conditioned emotional response in Fmr1 knockout mice. Behav Brain Res. 2000; 117:127–136. [PubMed: 11099766]

Varga EA, Pastore M, Prior T, Herman GE, McBride KL. The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. Genet Med. 2009; 11:111–117. [PubMed: 19265751]

Varoqueaux F, Jamain S, Brose N. Neuroligin 2 is exclusively localized to inhibitory synapses. Eur J Cell Biol. 2004; 83:449–456. [PubMed: 15540461]

Varoqueaux F, Aramuni G, Rawson RL, Mohrmann R, Missler M, Gottmann K, Zhang W, Sudhof TC, Brose N. Neuroligins determine synapse maturation and function. Neuron. 2006; 51:741–754. [PubMed: 16982420]

Veenstra-VanderWeele J, Muller CL, Iwamoto H, Sauer JE, Owens WA, Shah CR, Cohen J, Mannangatti P, Jessen T, Thompson BJ, Ye R, Kerr TM, Carneiro AM, Craw-ley JN, Sanders-Bush E, McMahon DG, Ramamoorthy S, Daws LC, Sutcliffe JS, Blakely RD. Autism gene variant causes hyperserotonemia, serotonin receptor hypersensitivity, social impairment and repetitive behavior. Proc Natl Acad Sci USA. 2012; 109:5469–5474. [PubMed: 22431635]

Veeraragavan S, Graham D, Bui N, Yuva-Paylor LA, Wess J, Paylor R. Genetic reduction of muscarinic M4 receptor modulates analgesic response and acoustic startle response in a mouse model of fragile X syndrome (FXS). Behav Brain Res. 2012; 228:1–8. [PubMed: 22123412]

Vernes SC, Newbury DF, Abrahams BS, Winchester L, Nicod J, Groszer M, Alarcon M, Oliver PL, Davies KE, Geschwind DH, Monaco AP, Fisher SE. A functional genetic link between distinct developmental language disorders. N Engl J Med. 2008; 359:2337–2345. [PubMed: 18987363]

Vincent JB, Kolozsvari D, Roberts WS, Bolton PF, Gurling HM, Scherer SW. Mutation screening of X-chromosomal neuroligin genes: no mutations in 196 autism probands. Am J Med Genet B Neuropsychiatr Genet. 2004; 129B:82–84. [PubMed: 15274046]

Vorstman JA, Spooren W, Persico AM, Collier DA, Aigner S, Jagasia R, Glennon JC, Buitelaar JK. Using genetic findings in autism for the development of new pharmaceutical compounds. Psychopharmacology (Berl). 2014; 231:1063–1078. [PubMed: 24292384]

Wang K, Zhang H, Ma D, et al. Common genetic variants on 5p14.1 associate with autism spectrum disorders. Nature. 2009; 459:528–533. [PubMed: 19404256]

Wang X, McCoy PA, Rodriguiz RM, Pan Y, Je HS, Roberts AC, Kim CJ, Berrios J, Colvin JS, Bousquet-Moore D, Lorenzo I, Wu G, Weinberg RJ, Ehlers MD, Philpot BD, Beaudet AL, Wetsel WC, Jiang YH. Synaptic dysfunction and abnormal behaviors in mice lacking major isoforms of Shank3. Hum Mol Genet. 2011; 20:3093–3108. [PubMed: 21558424]

Weiss LA, Escayg A, Kearney JA, Trudeau M, MacDonald BT, Mori M, Reichert J, Buxbaum JD, Meisler MH. Sodium channels SCN1A, SCN2A and SCN3A in familial autism. Mol Psychiatry. 2003; 8:186–194. [PubMed: 12610651]

Wilkinson B, Grepo N, Thompson BL, Kim J, Wang K, Evgrafov OV, Lu W, Knowles JA, Campbell DB. The autism-associated gene chromodomain helicase DNA-binding protein 8 (CHD8) regulates noncoding RNAs and autism-related genes. Transl Psychiatry. 2015; 5:e568. [PubMed: 25989142]

Willsey AJ, State MW. Autism spectrum disorders: from genes to neurobiology. Curr Opin Neurobiol. 2015; 30:92–99. [PubMed: 25464374]

Wohr M, Roullet FI, Crawley JN. Reduced scent marking and ultrasonic vocalizations in the BTBR T +tf/J mouse model of autism. Genes Brain Behav. 2011a; 10:35–43. [PubMed: 20345893]

Wohr M, Roullet FI, Hung AY, Sheng M, Crawley JN. Communication impairments in mice lacking Shank1: reduced levels of ultrasonic vocalizations and scent marking behavior. PLoS One. 2011b; 6:e20631. [PubMed: 21695253]

Wohr M, Silverman JL, Scattoni ML, Turner SM, Harris MJ, Saxena R, Crawley JN. Developmental delays and reduced pup ultrasonic vocalizations but normal sociability in mice lacking the postsynaptic cell adhesion protein neuroligin2. Behav Brain Res. 2013; 251:50–64. [PubMed: 22820233]

Won H, Lee HR, Gee HY, Mah W, Kim JI, Lee J, Ha S, Chung C, Jung ES, Cho YS, Park SG, Lee JS, Lee K, Kim D, Bae YC, Kaang BK, Lee MG, Kim E. Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function. Nature. 2012; 486:261–265. [PubMed: 22699620]

Yadav R, Gupta SC, Hillman BG, Bhatt JM, Stairs DJ, Dravid SM. Deletion of glutamate delta-1 receptor in mouse leads to aberrant emotional and social behaviors. PLoS One. 2012; 7:e32969. [PubMed: 22412961]

Yan QJ, Asafo-Adjei PK, Arnold HM, Brown RE, Bauchwitz RP. A phenotypic and molecular characterization of the fmr1-tm1Cgr fragile X mouse. Genes Brain Behav. 2004; 3:337–359. [PubMed: 15544577]

Yan J, Oliveira G, Coutinho A, Yang C, Feng J, Katz C, Sram J, Bockholt A, Jones IR, Craddock N, Cook EH Jr, Vicente A, Sommer SS. Analysis of the neuroligin 3 and 4 genes in autism and other neuropsychiatric patients. Mol Psychiatry. 2005; 10:329–332. [PubMed: 15622415]

Yang M, Crawley JN. Simple behavioral assessment of mouse olfaction. Current Protocols in Neuroscience. 2009:8–24. [PubMed: 19575470]

Yang M, Silverman JL, Crawley JN. Automated three-chambered social approach task for mice. Current Protocols in Neuroscience. 2011:8–26.

Yang M, Abrams DN, Zhang JY, Weber MD, Katz AM, Clarke AM, Silverman JL, Crawley JN. Low sociability in BTBR T+tf/J mice is independent of partner strain. Physiol Behav. 2012a; 107:649–662. [PubMed: 22245067]

Yang M, Bozdagi O, Scattoni ML, Wohr M, Roullet FI, Katz AM, Abrams DN, Kalikhman D, Simon H, Woldeyohannes L, Zhang JY, Harris MJ, Saxena R, Silverman JL, Buxbaum JD, Crawley JN. Reduced excitatory neurotransmission and mild autism-relevant phenotypes in adolescent Shank3 null mutant mice. J Neurosci. 2012b; 32:6525–6541. [PubMed: 22573675]

Yang M, Mahrt EJ, Lewis F, Foley G, Portmann T, Dolmetsch RE, Portfors CV, Crawley JN. 16p11.2 deletion syndrome mice display sensory and ultrasonic vocalization deficits during social interactions. Autism Res. 2015

Ylisaukko-oja T, Rehnstrom K, Auranen M, Vanhala R, Alen R, Kempas E, Ellonen P, Turunen JA, Makkonen I, Riikonen R, Nieminen-von Wendt T, von Wendt L, Peltonen L, Jarvela I. Analysis of four neuroligin genes as candidates for autism. Eur J Hum Genet. 2005; 13:1285–1292. [PubMed: 16077734]

Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Med. 2015; 21:185–191. [PubMed: 25621899]

Zahir FR, Baross A, Delaney AD, Eydoux P, Fernandes ND, Pugh T, Marra MA, Friedman JM. A patient with vertebral, cognitive and behavioural abnormalities and a de novo deletion of NRXN1alpha. J Med Genet. 2008; 45:239–243. [PubMed: 18057082]

Zhao MG, Toyoda H, Ko SW, Ding HK, Wu LJ, Zhuo M. Deficits in trace fear memory and long-term potentiation in a mouse model for fragile X syndrome. J Neurosci. 2005; 25:7385–7392. [PubMed: 16093389]

Zhou J, Blundell J, Ogawa S, Kwon CH, Zhang W, Sinton C, Powell CM, Parada LF. Pharmacological inhibition of mTORC1 suppresses anatomical, cellular, and behavioral abnormalities in neural-specific Pten knock-out mice. J Neurosci. 2009; 29:1773–1783. [PubMed: 19211884]

Zoghbi HY, Bear MF. Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. Cold Spring Harb Perspect Biol. 2012; 4:a009886. [PubMed: 22258914]

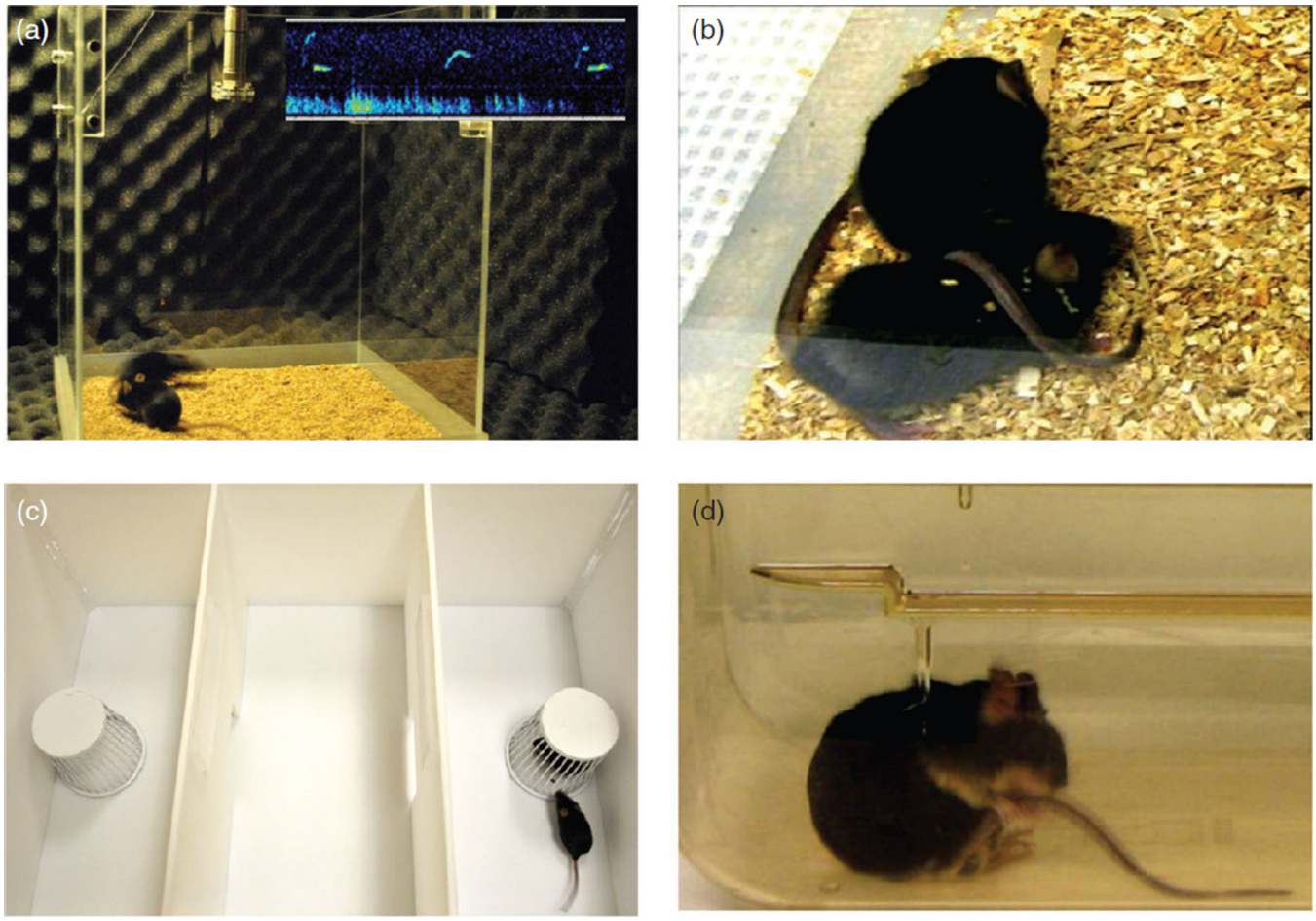

Figure 1. Examples of rodent behavioral assays with face validity to the diagnostic symptoms of autism

(a) Two mice interacting in a Noldus Phenotyper 3000 reciprocal social interaction chamber equipped with an Avisoft ultrasonic microphone. The inset shows representative ultrasonic vocalizations recorded during adult male–female social interaction. (b) Close-up of two mice displaying ‘crawl over and under’ during the reciprocal social interaction test session. (c) 3-Chambered social approach apparatus offers automated scoring of time spent with a novel social partner vs. time spent with a novel object. (d) BTBR mouse engaged in repetitive self-grooming. Photos by Jane Hayes, Michael Pride, Jill Silverman and Mu Yang, MIND Institute, University of California Davis School of Medicine.

Table 1

Examples of autism risk genes identified by human genetic studies

Gene	Identification method	Investigated population	Reference for genetic study
CNTNAP2			
Association with ASD	Linkage study	Old Order Amish families (4 children and 6 parents) with an autosomal recessive founder (null mutation)	Strauss *et al.* (2006)
	Linkage, association and gene expression studies	172 parent–child trios from the Autism Genetic Resource Exchange (AGRE) resource	Alarcon *et al.* (2008)
	Genome-wide linkage study, family based-association mapping	National Institute of Mental Health Autism Genetics Initiative Repository; Stage I: 72 muliplex families (148 affected, 292 controls); Stage II: 1295 parent–child trios (145 mulitplex families with 303 affected children)	Arking *et al.* (2008)
	Cytogenetics	34 year old female	Rossi *et al.* (2008)
	Cytogenetics	11 year old male	Poot *et al.* (2010)
Limited association with ASD	Cytogenetics, linkage and resequencing	635 ASD cases and 942 controls	Bakkaloglu *et al.* (2008)
	Genetic association analyses; transmission disequilibrium test	186 multiplex (408 trios) and 323 simplex families with ASD from the AGRE resource	Sampath *et al.* (2013)
No association with ASD	Next generation sequencing	2704 ASD cases, 2747 controls	Murdoch *et al.* (2015)
NLGN1			
Association with ASD	Whole genome copy number variant study	859 ASD cases, 1409 controls; 1336 ASD cases, 1110 controls	Glessner *et al.* (2009)
Limited association with ASD	Mutation analysis, linkage analysis, association analysis	30 ASD cases; 19 families with 41 ASD cases; 100 families with 122 ASD cases	Ylisaukko-oja *et al.* (2005)
NLGN3			
Association with ASD	Amino acid sequencing, linkage study	36 ASD sibling pairs, 122 ASD trios, 350 unrelated controls	Jamain *et al.* (2003)
Limited association with ASD	Mutation analysis, linkage analysis, association analysis	30 ASD cases; 19 families with 41 ASD cases; 100 families with 122 ASD cases	Ylisaukko-oja *et al.* (2005)
NLGN4			
Association with ASD	Cytogenetic analysis, fluorescence in situ hybridization (FISH)	8 females, 3 with ASD	Thomas *et al.* (1999)
	Amino acid sequencing, linkage study	36 ASD sibling pairs, 122 ASD trios, 350 unrelated controls	Jamain *et al.* (2003)
	Linkage analysis and gene sequencing	10 members of a French family with ASD and intellectual disability, 200 controls	Laumonnier *et al.* (2004)
	Direct sequencing and mutation analysis	148 unrelated ASD cases, 48 ADHD and bipolar cases, 288 unaffected controls	Yan *et al.* (2005)
	Chromosome analysis	Family with 1 ASD proband, 96 controls	Lawson-Yuen *et al.* (2008)
	Single nucleotide polymorphism microarrays and karyotyping	427 unrelated ASD families	Marshall *et al.* (2008)

Gene	Identification method	Investigated population	Reference for genetic study
Limited association with ASD	Mutation analysis, linkage analysis, association analysis	30 ASD cases; 19 families with 41 ASD cases; 100 families with 122 ASD cases	Ylisaukko-oja *et al.* (2005)
No association with ASD	PCR genetic screen, denaturing high performance liquid chromatography	196 ASD cases from 183 multiplex and 13 simplex families	Vincent *et al.* (2004)
NRXN1			
	Gene scanning and sequencing	103 Caucasian ASD cases, 61 Afro-American ASD cases, 535 Caucasian controls	Feng *et al.* (2006)
	Linkage study, using comparative analysis of hybridization intensities	1496 multiplex ASD families (at least 2 affected individuals) (7917 family members)	Szatmari *et al.* (2007)
	Single nucleotide polymorphism microarrays and karyotyping	427 unrelated ASD families	Marshall *et al.* (2008)
	Cytogenic analysis	1 ASD case study	Zahir *et al.* (2008)
	Whole genome CNV study	859 ASD cases, 1409 controls; 1336 ASD cases, 1110 controls	Glessner *et al.* (2009)
	Comparative genomic hybridization microarrays	3540 cases with developmental disorders, ASD, intellectual disability	Ching *et al.* (2010)
SHANK1			
	Microarray	1158 Canadian and 456 European ASD cases, 15122 controls	Sato *et al.* (2012)
	Meta-analysis of copy-number and coding-sequence variants	5657 ASD cases, 19163 controls; 76 0 – 214 7 ASD cases, 492–1090 controls depending on the *SHANK* gene	LeBlond *et al.* (2014)
SHANK2			
	Genome-wide microarray scan; DNA sequencing	396 ASD cases, 184 individuals with intellectual disability, 659 unaffected controls	Berkel *et al.* (2010)
	Dense genotyping arrays	996 European ASD cases, 1287 matched controls	Pinto *et al.* (2010)
	Meta-analysis of copy-number and coding-sequence variants	5657 ASD cases, 19, 163 controls; 76 0 – 214 7 ASD cases, 492–1090 controls depending on the *SHANK* gene	LeBlond *et al.* (2014)
SHANK3			
	FISH analysis; direct sequencing	226 families with at least 1 ASD child, 270 controls	Durand *et al.* (2007)
	DNA sequencing and microarray-based comparative intensity analysis	400 Canadian ASD cases; HapMap collection was used for comparison	Moessner *et al.* (2007)
	Single nucleotide polymorphism microarrays and karyotyping	427 unrelated ASD families	Marshall *et al.* (2008)
	Gene sequencing	427 ASD cases, 190 controls	Gauthier *et al.* (2009)
	Denaturing high performance liquid chromatography, direct sequencing, multiplex ligation-dependent probe amplification, array comparative genomic hybridization	3 cohorts: 133 American ASD cases; 88 Italian ASD cases; 104 American ASD cases; 560 American controls and 422 Italian controls	Boccuto *et al.* (2013)
	Meta-analysis of copy-number	5657 ASD cases, 19, 163 controls;	LeBlond *et al.* (2014)

Gene	Identification method	Investigated population	Reference for genetic study
	and coding-sequence variants	76 0 – 2147 ASD cases, 492–1090 controls depending on the *SHANK* gene	
PTEN			
	Direct DNA sequencing	18 ASD cases with macrocephaly	Butler *et al.* (2005)
	Direct DNA sequencing, multiplex ligation-dependent probe amplification	88 ASD cases with macrocephaly	Buxbaum *et al.* (2007)
	Direct DNA sequencing	2 ASD cases with macrocephaly	Herman *et al.* (2007)
	Direct DNA Sequencing	114 cases of ASD, developmental delay or macrocephaly	Varga *et al.* (2009)
	Direct DNA sequencing	93 cases of ASD or developmental delays with macrocephaly	McBride *et al.* (2010)

Table 2

Examples of genetic mouse models of autism

Mouse model	Mouse phenotype	Reference
Cntnap2 knockout mouse	• Reduced social interactions • Increased repetitive behaviors • Reduced juvenile ultrasonic vocalizations • Hyperactivity • Seizures • Abnormal cortical migration • Asynchronous neurotransmission • Reduced number of interneurons	Penagarikano *et al.* (2011)
Neuroligin-1 knockout mouse	• Minimally impaired social approach • Repetitive behavior • Spatial learning deficits • Impaired hippocampal long term potentiation • Reduced NMDA/AMPA glutamate receptor ratio at cortico-striatal synapses	Blundell *et al.* (2010)
Neuroligin-2* knockout mouse	• Increased anxiety-like behavior • Decreased pain sensitivity • Decreased motor coordination • Reduced exploratory activity • Developmental milestone delays • Reduced ultrasonic pup vocalizations • Decreased inhibitory synaptic puncta, with no change in overall synapse number • Reduced inhibitory synaptic neurotransmission	Chubykin *et al.* (2007), Blundell *et al.* (2009) and Wohr *et al.* (2013)
Neuroligin-3* knockout mouse	• Reduced fear conditioning • Olfactory impairments • Hyperactivity • Decreased total brain volume	Radyushkin *et al.* (2009)
Neuroligin-3* knockin mouse (R451C substitution)	• Enhanced water maze spatial learning acquisition • Increased protein levels of inhibitory synaptic markers • Increased inhibitory neurotransmission in the somatosensory barrel cortex • Increase in AMPA-mediated excitatory neurotransmission and enhanced long-term potentiation in the hippocampus • Increased dendritic branching in the hippocampus	Tabuchi *et al.* (2007) and Etherton *et al.* (2011)
Neuroligin-3* knockin mouse (R451C substitution)	• Reduced ultrasonic vocalizations in pups • Reduced acoustic startle to high decibel tones	Chadman *et al.* (2008)

Mouse model	Mouse phenotype	Reference
	• Minor developmental differences in growth and righting reflexes	
Nlgn4 knockout mouse (gene trap insertion downstream of exon I)	• Reduced social interaction time • Impaired social approach and social novelty recognition • Reduced ultrasonic vocalizations • Reduced volume of total brain, cerebellum and brain stem	Jamain *et al.* (2008) and El-Kordi *et al.* (2013)
*Nlgn4** knockout mouse (gene trap insertion downstream of exon I)	• No genotype differences in ultrasonic vocalizations, anxiety-related behaviors or locomotor activity	Ey *et al.* (2012)
Neurexin 1α* knockout mouse	• Increased grooming • Decreased prepulse inhibition • Reduced excitatory synaptic neurotransmission	Etherton *et al.* (2009)
Neurexin 1α* knockout mouse	• Reduced exploratory activity in novel environments • Increased aggressive behaviors • Mild increases in anxiety-like behavior	Grayton *et al.* (2013)
*Shank1** knockout mouse (targeted replacement of PDZ domain (exons XIV and XV))	• Anxiety-like phenotype • Impaired contextual fear memory • Enhanced spatial learning • Impaired long term memory retention • Reduced dendritic spine size and smaller postsynaptic densities • Weaker basal synaptic neurotransmission	Hung *et al.* (2008)
*Shank1** knockout mouse (targeted replacement of PDZ domain (exons XIV and XV))	• Mild anxiety-like phenotype • Reduced exploratory locomotion	Silverman *et al.* (2011)
*Shank1** knockout mouse (targeted replacement of PDZ domain (exons XIV and XV))	• Reduced pup ultrasonic vocalizations • Reduced male scent marking and abnormal ultrasonic vocalizations in response to female pheromones	Wohr *et al.* (2011b)
Shank2 knockout mouse (lacking all Shank2 isoforms)	• Fewer social contacts during same-sex interactions • Reduced social novelty recognition • Repetitive grooming • Abnormal ultrasonic vocalizations • Hyperactivity • Increased anxiety-like behavior • Reduced dendritic spines • Impaired glutamatergic neurotransmission	Schmeisser *et al.* (2012)
Shank2 knockout mouse (exon VI and VII microdeletion and a	• Reduced home-cage social interaction • Reduced social preference	Won *et al.* (2012)

Mouse model	Mouse phenotype	Reference
frameshift for both *Shank* splice variants)	• Repetitive jumping • Reduced ultrasonic vocalizations • Impaired spatial learning • Decreased glutamatergic NMDA receptor function	
*Shank3A** heterozygous mouse (ankyrin repeat domain deletion (exon IV-IX))	• Reduced social sniffing in male–female reciprocal social interactions • Reduced ultrasonic vocalizations • Reduced long term potentiation • Transient dendritic spine expansion during long term potentiation • Reduced basal AMPA neurotransmission	Bozdagi *et al.* (2010)
*Shank3A** heterozygous and knockout mice (ankyrin repeat domain deletion (exon IV-IX))	• Reduction of select parameters (e.g. sniffing, following, front approach and push-crawl) in juvenile reciprocal social interaction in male heterozygous and knockout mice • Increased repetitive grooming in male heterozygous and knockout mice • Impaired novel object recognition in knockout mice • Mild motor learning deficits in knockout mice • Lower pain sensitivity in knockout mice (C57BL/6 background) • Impaired synaptic transmission, induction and long-term potenti-ation in knockout mice	Yang *et al.* (2012b) and Drapeau *et al.* (2014)
Shank3A knockout mouse (ankyrin repeat domain deletion (exon IV-IX))	• Reduced social interaction time • Repetitive behaviors • Aberrant ultrasonic vocalizations • Reduced activity and motor learning in males • Impaired acquisition in Morris water maze • Reduced postsynaptic protein and glutamate receptor protein levels • Longer dendritic spines • Reduced long term potentiation	Wang *et al.* (2011)
*Shank3A** knockout mouse (ankyrin repeat domain deletion)	• Reduced preference for social novelty	Peca *et al.* (2011)
Shank3B knockout mouse (PDZ domain deletion)	• Reduced social interaction and social novelty recognition • Self-injurious repetitive grooming • Increased anxiety-like behavior • Reduced postsynaptic proteins and glutamate receptor protein levels • Neuronal hypertrophy and reduction in dendritic spines • Increased caudate volume • Reduced neurotransmission in corticostriatal circuits	Peca *et al.* (2011)
*Shank3** knockout mouse (exon 21 deletion, including the Homer binding domain)	• Increased repetitive grooming in older knockout mice • Impaired spatial learning	Kouser *et al.* (2013)

Mouse model	Mouse phenotype	Reference
	• Avoidance of inanimate objects • Impaired motor coordination • Increased pain sensitivity • Decreased excitatory neurotransmission and reduced long-term potentiation • Increased mGluR5 receptor levels in synaptic fractions	
Nse-Cre Pten conditional knockout mouse (*Pten* deletion restricted to subsets of postmitotic cortical and hippocampal neurons)	• Decreased social interaction with juvenile mice • Reduced sociability and preference for social novelty • Spatial learning deficits • Reduced exploratory activity in the center of the open field • Increased startle responses and reduced sensorimotor gating • Spontaneous seizures • Macrocephaly, including hippocampal dentate gyrus enlargement • Hippocampal granule cell and cortical neuron hypertrophy	Kwon *et al.* (2006), Ogawa *et al.* (2007) and Zhou *et al.* (2009)
Pten heterozygous mouse	• Reduced sociability and preference for social novelty • Increased repetitive behavior • Decreased aggression and reduced social investigation in the resident-intruder test • Reduced sensorimotor gating • Increased depression-like behavior in male heterozygous mice • Macrocephaly and higher brain mass	Page *et al.* (2009); Clipperton-Allen and Page (2014) and Clipperton-Allen and Page (2015)

The asterisk (*) following the name of a mouse model indicates that its social behaviors were normal, using assays with high face validity to the types of social deficits which characterize autism.