



# Fundamental Elements in Autism: From Neurogenesis and Neurite Growth to Synaptic Plasticity

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Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders with a high prevalence and impact on society. ASDs are characterized by deficits in both social behavior and cognitive function. There is a strong genetic basis underlying ASDs that is highly heterogeneous; however, multiple studies have highlighted the involvement of key processes, including neurogenesis, neurite growth, synaptogenesis and synaptic plasticity in the pathophysiology of neurodevelopmental disorders. In this review article, we focus on the major genes and signaling pathways implicated in ASD and discuss the cellular, molecular and functional studies that have shed light on common dysregulated pathways using *in vitro*, *in vivo* and human evidence.

## Highlights

- Autism spectrum disorder (ASD) has a prevalence of 1 in 68 children in the United States.
- ASDs are highly heterogeneous in their genetic basis.
- ASDs share common features at the cellular and molecular levels in the brain.
- Most ASD genes are implicated in neurogenesis, structural maturation, synaptogenesis and function.

**Keywords:** autism, ASD, developmental neurobiological disorders, neurogenesis, dendrite growth, neuron morphogenesis, synapse, synaptic plasticity

## INTRODUCTION

Autism spectrum disorder (ASD) comprises a heterogeneous class of neurodevelopmental disorders characterized by impaired social interactions, restrictive interests and repetitive behaviors (Landa, 2008). ASD typically presents with other mental and physical disabilities such as anxiety, attention-deficit/hyperactivity disorder (ADHD), intellectual disability (ID), epilepsy and impairments in motor coordination. In up to 25% of individuals diagnosed with ASD, an identifiable or genetic variant can be identified, providing valuable insights into the mechanisms involved in proper neurodevelopment (Huguet et al., 2013). A large number of ASD-linked genes are also associated with broad processes such as metabolism, chromatin remodeling, mRNA regulation, protein synthesis and synaptic function.

The human brain contains about 86 billion neurons making trillions of connections (Azevedo et al., 2009). Most neurons are produced in the ventricular zone (VZ) and migrate radially out into the developing neocortex, and it is estimated that about 75% of rodent, and up to 90% of human neurons use glial-guided migration (Letinic et al., 2002).

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The movement of neurons along migratory routes is guided by a number of guidance molecules that direct their movement into the cortex and the formation of an organized 6-layered structure (Marín and Rubenstein, 2001; Huang, 2009; Valiente and Marin, 2010).

After neuronal migration, neurons must undergo extensive morphological changes. Long axonal processes are extended and are required to connect to target neurons with precision, while complex dendritic arbors must grow and branch to occupy specified dendritic field volumes. These processes take place during prenatal and early postnatal periods and lay the foundations for neuronal connectivity within and across brain regions. Ultimately, with activity-dependent structural remodeling, neurons form synaptic connections and incorporate into functional neuronal networks for proper brain function. It's of no surprise that disruptions in any of these intricate processes would cause abnormalities in brain development and function, leading to neurodevelopmental disorders including ASD.

While ASD shares characteristic features at the behavioral level, its underlying causes are highly heterogeneous. Developmental dysregulation in ASD may affect processes ranging from progenitor cell proliferation and neuronal differentiation to neuron migration, axon guidance, dendrite outgrowth, synaptogenesis, synaptic function and neural circuitry.

Studies of ASD-related brain pathologies indicate that abnormal acceleration of brain growth in early childhood (Wegiel et al., 2010) accompanied with impaired neuron morphological development and brain cytoarchitecture are common features in ASDs (Bauman and Kemper, 1985; Bailey et al., 1998; van Kooten et al., 2008). Additionally, impairments in synapse formation and synaptic plasticity (Bourgeron, 2007, 2009), which ultimately lead to functional and cognitive impairments, are fundamental causative factors underlying ASD pathology.

Analysis of the Simmons Foundation Autism Research Initiative (SFARI) gene database shows that ASD causative genes display vast diversity involving up to one thousand genes (Banerjee-Basu and Packer, 2010; Abrahams et al., 2013). Additionally, a large number of rare genetic variants in protein-coding genes are causative for ASD, none of which individually account for more than 1% of the total number of ASD diagnoses. Therefore, the complexity and heterogeneity of autism genetics is a major challenge when investigating the underlying neurobiological pathways that are shared within ASD (Happé et al., 2006).

The ability to classify ASD patients according to genetics has been enhanced by the substantial amount of work done to understand ASD-linked genes, and the role of their encoded genes, in the underlying neuropathologies. For example, well known ASD-linked genes, such as neurexin, neuroligin and Shank have been well characterized for their roles in synaptic formation and function (Toro et al., 2010). Additionally, co-expression network analyses of ASD-linked genes have identified that early developmental periods when neurogenesis and synaptogenesis occur are commonly disrupted processes in ASD (Parikhshak et al., 2013). Genes involved with regulating

developmental processes such as Chromodomain Helicase DNA-binding protein 8 (*CHD8*), T-Box Brain Protein 1 (*TBR1*), and Fragile X Mental Retardation 1 (*FMR1*), have also been linked to ASD (Parikhshak et al., 2013; Willsey et al., 2013). These findings suggest that multiple processes during prenatal and early postnatal brain growth are linked to ASD, underscoring the vast heterogeneity of causative factors leading to ASD pathogenesis. ASD-risk genes, their associated disorders and the neurodevelopmental processes they affect are shown in **Table 1**.

## ALTERATIONS IN NEUROGENESIS AND NEURON MIGRATION IN ASD

### Increased Neuronal Proliferation and Macrocephaly in ASD

A growing body of literature has provided strong evidence that subsets of individuals with ASD show aberrant brain growth patterns. In patients, cerebral size may be normal at birth but display a period of increased overgrowth and a subsequent period of decline compared to unaffected control patients. An increase in neuronal numbers in prefrontal cortex has recently been observed, indicating that excess neurogenesis may be the underlying cause for an increase in cerebral size in ASD (Courchesne et al., 2011). Additionally, children diagnosed with ASD sometimes show regions of abnormal laminar positioning of cortical projection neurons (Wegiel et al., 2010). Both the development of proper lamination and the number of cortical neurons rely on temporally controlled proliferation of neural progenitors, therefore defects in neural progenitors may underlie ASD subtypes associated with overgrowth in the developing brain.

Projection neurons comprise roughly 80% of neurons in the cortex and when taking into account their dendrites, axons, myelin and synapses, they indeed could contribute to an increase in both the gray and white matter volumes in adolescents with ASD. Indeed, support for this theory has recently been shown with the comparison of neuron numbers in postmortem tissue from ASD and normal adolescents, with a surprising 67% more neurons detected in the prefrontal cortex of ASD patients (Courchesne et al., 2011). An aberrant increase in neuron numbers during prenatal neurodevelopment supports a role for a disruption of neurogenesis, which occurs mostly during gestational weeks 7–20 in humans, which coincides with the end of the embryonic period and early fetal period. Because new cell production is estimated to outnumber cell elimination by at least 100-fold in the developing brain, the role of cell death may play less of a role in macrocephaly (Rakic and Zecevic, 2000). It is important to note that programmed cell death can eliminate up to 50% of particular neuron subtypes (De Zio et al., 2005; Yamaguchi and Miura, 2015), suggesting that a shift in the balance between neuron generation and elimination could play a role in macrocephaly.

Radial glia cells must undergo a regulated series of symmetric divisions to generate more radial glia, and asymmetric divisions, to produce intermediate progenitors and post-mitotic neurons.

**TABLE 1 |** Autism spectrum disorder (ASD) genes and associated disorders.

Protein	Gene symbol	SFARI score	Associated disorders	Affected developmental processes
Astrotactin 2	<i>ASTN2</i>	3	ASD, ADHD, DD, EP, ID, OCD, SCZ	Neuron migration, Cell-Cell adhesion
Autism susceptibility candidate 2	<i>AUTS2</i>	S	ASD, ADHD, DD, EP, ID, SCZ	Neuron migration, Neurite growth
Cadherin 10	<i>CDH10</i>	4	ASD	Cell-Cell adhesion
Cadherin 13	<i>CDH13</i>	N/A	ASD	Cell-Cell adhesion
Cadherin 9	<i>CDH9</i>	4	ASD	Cell-Cell adhesion
Chromodomain helicase DNA-binding protein 8	<i>CHD8</i>	1S	ASD, DD, ID, SCZ	Cell-Cell adhesion
Contactin-associated protein-like 2	<i>CNTNAP2</i>	2S	ASD, ADHD, DD, EP, ID, OCD, SCZ, TS	Neuron migration, Synapse formation, Synaptic function
Postsynaptic density 95 KDa	<i>DLG4</i>	N/A	ASD, EP, ID, SCZ	Synaptogenesis
Distal-less homeobox 1/2	<i>DLX1/2</i>	5	ASD	Neuron migration
Fragile X mental retardation gene 1	<i>FMR1</i>	S	ASD, ADHD, DD, EP, ID	Translation, Synapse Formation, Synaptic plasticity
Gephyrin	<i>GPHN</i>	3	ASD, EP, ID, SCZ	Synaptogenesis
KIDLIA	<i>KIAA2022/NEXMIF</i>	3	ASD, ID	Neurite growth
Lissencephaly 1	<i>LIS1</i>	N/A	ASD, DD, ID, EP	Neurogenesis, Neuron migration, Intracellular transport
Methyl CpG binding protein 2	<i>MECP2</i>	S	ASD, ADHD, DD, EP, ID SCZ	Transcription, Neurite growth, Synaptogenesis, Synaptic plasticity
NudE nuclear distribution E homolog 1	<i>NDE1</i>	N/A	ASD, ADHD, DD, SCZ	Neurogenesis, Neuron migration, Intracellular transport
Neurofibromatosis 1	<i>NF1</i>	4S	ASD	Neurite growth
Neuroigin 1/2/3/4/4Y	<i>NRLG1/2/3/4/4Y</i>	N/A		Cell-Cell adhesion, Synaptogenesis
Neurexin 1/2/3	<i>NRXN1/2/3</i>	2	ASD, ADHD, BPD, DD, EP, ID, SCZ, TS	Cell-Cell adhesion, Synaptogenesis
Phosphatase and tensin homolog	<i>PTEN</i>	1S	ASD, ADHD, DD, EP, ID	Neurogenesis, Neurite growth, Translation, Synaptogenesis
Reelin	<i>RELN</i>	2	ASD, DD, EP, ID	Neuron migration, Neurite growth
Shank1/2/3	<i>SHANK1/2/3</i>	1S	ASD, BPD, DD, EP, ID, SCZ	Synaptogenesis, Synaptic plasticity
Synapsin 1/2/3	<i>SYN1/2/3</i>	4	ASD, EP, ID	Synaptogenesis, Synaptic Function
Thousand-and-one amino acid kinase 2	<i>TAOK2</i>	N/A	ASD	Neurite growth
T-Brain-1	<i>TBR1</i>	1	ASD, ADHD, DD, EP, ID	Neuron migration
Tuberous sclerosis 1	<i>TSC1</i>	S	ASD, DD, ID	Neurite growth, Synaptogenesis, Synaptic plasticity
Tuberous sclerosis 2	<i>TSC2</i>	S	ASD, DD, ID, EP	Neurite growth, Synaptogenesis, Synaptic plasticity
Ubiquitin protein ligase E3A	<i>UBE3A</i>	3S	ASD, DO, EP, ID	Neurite growth, Synaptic plasticity
WD repeat and FYVE domain containing 3	<i>WDFY3</i>	3	ASD	Neurogenesis
$\delta$ -catenin	<i>CTNND2</i>	2	ASD	Neurite growth

Summary of the genes reviewed including their associated disorders and the developmental processes they affect. The SFARI score = **1**, high confidence; **2**, strong candidate; **3**, suggestive evidence; **4**, minimal evidence; **5**, hypothesized but untested; **S**, mutations are associated with a high degree of increased risk and are frequently associated with additional features not required for an ASD diagnosis; **N/A**, not applicable; ASD, Autism Spectrum Disorder; ADHD, Attention Deficit Hyperactivity Disorder; DD, Developmental Delay; ID, Intellectual Disability; EP, Epilepsy; OCD, Obsessive Compulsive Disorder; SCZ, Schizophrenia; TS, Tourette's Syndrome.

Recently born projection neurons, principally produced via symmetric divisions of intermediate progenitor cells in the sub-ventricular zone (SVZ), will migrate in an “inside-out” fashion to establish the six layered neocortex. This mode of migration forms deeper layer neurons first, followed by later born neurons that migrate to form the outer cortical layers (Gupta et al., 2002; Nadarajah and Parnavelas, 2002; Kriegstein and Noctor, 2004). Thus, alterations in neurogenesis could lead to changes in total number neuron numbers yielded from the progenitor populations, and/or in the overall laminar structure. For example, a study identified abnormalities in lamination of the neocortex and excess neuron numbers in seven out of eight ASD cases that they examined, via magnetic resonance imaging (MRI) and postmortem histology (Hutsler et al., 2007). Cerebral dysplasia in multiple regions has been reported in ASD cases, indicative of dysregulated neurogenesis, neuronal migration

and/or maturation (Wegiel et al., 2010). Additionally, Stoner et al. (2014) identified regions of disorganized cortical lamination in ten out of the eleven ASD cases they examined. These studies have provided strong evidence to support the theory of dysregulated proliferation from neural progenitors as an underlying pathology associated with macrocephaly and cortical lamination defects in ASD. Although astrocytes are generated from the same progenitor pool as neurons, the underlying cause of macrocephaly may be largely due to increased numbers of cortical projection neurons, as an associated increase in glia cells is not observed (Courchesne et al., 2011; Morgan et al., 2014). Additionally, data suggests that the cerebral white matter, which contains glia and the myelinated projections from cortical neurons, is not increased in ASD patients with macrocephaly; however, reports do indicate delayed maturation and a compromised integrity of the white matter (Hazlett et al., 2005; Friedman et al., 2006; Bakhtiari et al.,

2012). These findings suggest that a preferential up-regulation in neuronal differentiation and proliferation play a major role in ASD.

The phosphatase and tensin homolog (*PTEN*) gene was the first gene to be clearly associated with macrocephaly in ASD (Goffin et al., 2001; Butler et al., 2005; Buxbaum et al., 2007; Varga et al., 2009). Pten was originally identified as a tumor suppressor and key negative regulator of phosphatidylinositol 3-kinase (PI3K) signaling, with Pten mutations found in multiple cancers (Zhao et al., 2004). In Pten-deficient mouse models, enhanced levels of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) lead to activation of protein kinase B (AKT) and downstream mammalian target of rapamycin (mTOR). The mTOR pathway is well known for its ability to regulate cell growth and proliferation and consistently Pten-deficient animals show neuronal over-growth, brain enlargement, seizures and premature death (Kwon et al., 2006; Ogawa et al., 2007; Garcia-Junco-Clemente and Golshani, 2014).

*CHD8* has emerged as a key ASD-linked gene. Strikingly, 80% of individuals with mutations in *CHD8* alleles display macrocephaly, which composes a much higher percentage of total macrocephaly cases in ASD patients without *CHD8* mutations (Bernier et al., 2014). Using a mouse model, Katayama et al. (2016) have shown increased brain weight, mirroring the macrocephaly observed in humans. Using transcriptome analysis of the entire brain, the authors concluded that major targets of Chd8 were genes regulated by the RE-1 silencing transcription factor (REST), which is a neuronal transcriptional repressor (Katayama et al., 2016).

WD repeat and FYVE domain containing 3 (*WDFY3*) was identified through surveys of *de novo* variants linked to ASD (Iossifov et al., 2012, 2014), which is implicated in macrocephaly and altered neural progenitor proliferation. Wdfy3 is a scaffold protein, involved in macroautophagy of large aggregation-prone proteins (Filimonenko et al., 2010). Decreased Wdfy3 expression in mice produces pronounced effects on neuronal proliferation and migration. Wdfy3 mutant mice also display macrocephaly resulting from a shift of radial glia divisions from asymmetric to symmetric (Orosco et al., 2014). This change in division ultimately produces greater numbers of neuronal progenitors and therefore brain size. Wdfy3's function in regulating cellular division is unclear, however expression studies have shown that it is up-regulated during cellular division and Wdfy3 plays a role in autophagy and regulation of proteins that control the cell cycle, ultimately resulting in a shortened cell cycle in Wdfy3 mutant mice (Orosco et al., 2014), and that additionally, because progenitor expansion and neurogenesis initiates anterolaterally and concludes posteromedially (Caviness et al., 2009), Wdfy3 mutant mice show a more pronounced affect in the anterolateral areas. This finding is in line with MRI performed in ASD adolescents, wherein temporal and frontal cortical areas showed the largest size increases (Carper et al., 2002; Hazlett et al., 2005; Schumann et al., 2010). Notably, these region-specific changes of cerebral growth could be associated with key behavioral symptoms observed in ASD. In humans,

areas such as the superior temporal sulcus and parts of the prefrontal and temporal cortex, which are key regions involved in reward and reinforcement pathways as well as social and emotional pathways are susceptible in ASD patients (Pelphrey and Carter, 2008; Redcay, 2008; Gotts et al., 2012; Gasquoin, 2014).

The association of macrocephaly with clinical phenotypes in autism has been characterized in an inconsistent manner and previous studies have indicated higher levels of cognitive function in patients with macrocephaly and ASD compared to normal controls (Courchesne and Pierce, 2005; Sacco et al., 2007). An increase in head circumference has been shown in ASD patients with special capabilities, compared to those without them (Ben-Itzhak et al., 2013a). However, additional studies have not discovered similar correlations with increased head circumferences and special abilities (Gillberg and de Souza, 2002; Ben-Itzhak and Zachor, 2007).

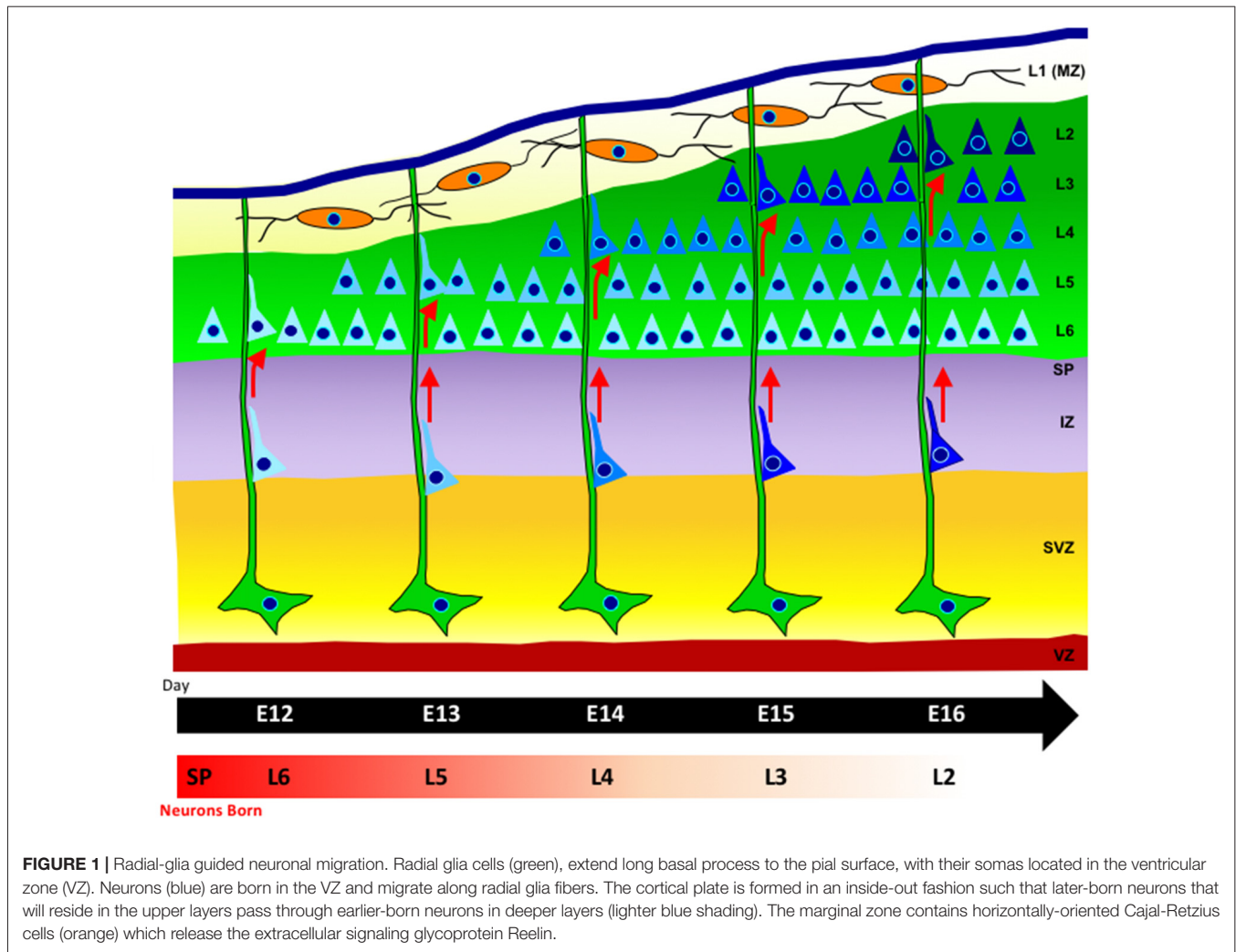
## Genes Associated with Mitotic Dysregulation of Neural Progenitors and Microcephaly in ASD

Microcephaly has not been studied as thoroughly as macrocephaly in ASD patients. The reports have indicated an increased prevalence of microcephaly in ASD, with up to 20% of cases, in comparison to 3% reported in the general population. Additionally, microcephaly is more frequent in individuals with ID and higher ASD severity (Fombonne et al., 1999; Cody et al., 2002; Miles et al., 2005; Ben-Itzhak et al., 2013b).

Autosomal recessive primary microcephaly (MCPH) is a condition that displays with significantly reduced head circumference that develops during the prenatal period (Tunca et al., 2006). The development of the forebrain is prominently affected in this form of microcephaly ultimately results in ID (Roberts et al., 2002; Bond et al., 2003). Disruption in genes encoding proteins that localize to the centrosome are known to result in MCPH (Kaindl et al., 2010), including Microcephalin 1 (*MCPH1*). *MCPH1* is a gene expressed during fetal development and mutations in *MCPH1* produce microcephaly (Jackson et al., 1998, 2002). Studies have found rare variants in the *MCPH1* gene that are linked to ASD (Ozgen et al., 2009; Neale et al., 2012), and play a role in DNA-damage repair, chromosome condensation, and the regulation of DNA damage genes (Thornton and Woods, 2009; Richards et al., 2010). Mechanistically, it has been shown that Mcph1 regulates neuroprogenitor division by coupling centrosomal maturation and mitotic spindle orientation with mitotic entry (Gruber et al., 2011).

Abnormal Spindle Primary Microcephaly (*ASPM*, *MCPH5*) is involved in orientation of the mitotic spindle, regulation of mitosis and cytokinesis (Fish et al., 2006; Passemard et al., 2009, 2016; Higgins et al., 2010). Mutant *Aspm* mice have mild microcephaly without aberrant increase in cell death, suggesting that disruptions in the proliferation of embryonic neuronal progenitor cells underlie MCPH (Pulvers et al., 2010). Additionally, *Aspm* positively regulates Wnt signaling





(Major et al., 2008), and over-expression of  $\beta$ -catenin, a positive transducer of the Wnt pathway, can rescue neurogenesis deficits in mice (Buchman et al., 2011).

Mutations in WD Repeat Domain 62 (*WDR62*) are associated with microcephaly and other cortical abnormalities in humans (Bilgüvar et al., 2010; Yu et al., 2010). *Wdr62* deficient mice have reduced brain size due to decreased neural progenitor cell population cells show mitotic spindle instability, mitotic arrest and cell death after loss of *Wdr62* expression (Chen et al., 2014). Mutations or loss of *Wdr62* expression therefore leads to mitotic delay and death of neural progenitor cells, thereby resulting in microcephaly.

## Alterations in Neuron Migration in ASD

### Excitatory Projection Neuron Migration

The time of birth of neocortical neurons, as well as their proper movement from the proliferative zone, dictates their final position within the layers of the cerebral cortex (Angevine and Sidman, 1961). Neurons born later during neurogenesis will ultimately reach the superficial layers above earlier born

neurons, due to an “inside-out” mode of neuronal migration. Initially, multipolar neurons will migrate via cellular locomotion. As neurons continue into the neocortex, they adhere to and migrate along radial glia, which provide aid in the direction of their migration (Rakic, 1972; Hatten, 1999; Kriegstein and Noctor, 2004; Ayala et al., 2007). Neurons adopt a bipolar morphology as they move along radial glia and detach upon reaching their proper laminar position (Figure 1). Additionally, daughter neurons in different cortical layers that were generated from the same mother progenitor cell will align radially into highly connected mini-columnar structures, most likely constituting a functional unit in the brain (Gao et al., 2013).

Studies have shown that defects in neuronal migration are associated with changes in neuron density and soma size, irregular minicolumns and heterotopias (mis-localized neurons; DiCicco-Bloom et al., 2006; Uppal et al., 2014; Chen et al., 2015; Reiner et al., 2016). In humans for example, two separate studies have demonstrated evidence of aberrant cell patterning in the boundary of cortical gray-white matter, suggesting defects in neuronal migration (Hutsler et al., 2007; Avino and Hutsler,

2010). In another study, an abnormal lamination of neurons, but not glia, was detected in the cortex of adolescent ASD brain samples (Stoner et al., 2014).

Reelin is one of the best known regulators involved in neuronal migration (Folsom and Fatemi, 2013; Sekine et al., 2014). Reelin is a glycoprotein that is released from Cajal–Retzius cells in the outer marginal zone. Reelin binds to the receptors Apoer2 and Vldlr on the cell membrane of target neurons, thereby inducing tyrosine phosphorylation of the adaptor protein Dab1, which subsequently initiates signaling cascades (Forster et al., 2006; Pardo and Eberhart, 2007). Reelin is involved in the termination of migration, proper neuronal layering, as well as transition to a bipolar morphology prior to neuronal migration along radial glia. Studies using postmortem human samples suggest aberrant Reelin signaling in ASD patients (Persico et al., 2001; Bonora et al., 2003; Fatemi et al., 2005). Reelin mutations in humans produce disruptions in neuron migration and connectivity, lissencephaly and cerebellar hypoplasia (Hong et al., 2000). In the well-studied Reelin knockout (KO) mice, neuronal migration abnormalities result in an inversion of cortical layering (Falconer, 1951; D’Arcangelo et al., 1995; Hirotsune et al., 1995). Behavioral studies in Reelin KO mice show aggressive behavior, an abnormal gait, social aggression, and impairments in learning and memory (Salinger et al., 2003). T-Box Brain Protein 1 (*TBR1*) encodes a brain-specific T-box transcription factor, which plays an important role in neurodevelopment and migration and has been identified as a causative gene for ASD (Neale et al., 2012; Deriziotis et al., 2014; De Rubeis et al., 2014). *Tbr1* is involved in the differentiation of neurons from intermediate progenitors early in the development of the neocortex (Dwyer and O’Leary, 2001; Han et al., 2011; Willsey et al., 2013). *Tbr1* regulates the expression of many ASD-linked genes (Chuang et al., 2015), including the activation of Autism Susceptibility Candidate 2 (*AUTS2*), which has been identified as an ASD and ID associated gene (Bedogni et al., 2010; Srinivasan et al., 2012). Interestingly, *TBR1* KO mice do not express subplate, layer 6 or Cajal–Retzius cell markers and show a large decrease in Reelin expression, however upper cortical layers are typically normal (Hevner et al., 2001).

Multiple mutations within *AUTS2* have been identified in patients, strongly linking it as a causative factor for ASD (Sultana et al., 2002; Huang et al., 2010; Pinto et al., 2010; Talkowski et al., 2012; Cheng et al., 2013; Liu et al., 2015). The *Auts2* protein is predominantly nuclear localized and evidence suggests a role for *Auts2* in regulating gene expression during brain development (Bedogni et al., 2010; Srinivasan et al., 2012; Gao et al., 2014). Binding of *Auts2* with polycomb repressive complex 1 (PRC1) inhibits PRC1 activity leading to activation of gene transcription (Gao et al., 2014). In addition to the nuclear component, *Auts2* protein is also found in the cytoplasm, where it lays a role in regulating cortical neuronal migration and neurite growth (Hori et al., 2014).

In a cohort of Amish children, mutations within contactin-associated protein-like 2 gene (*CNTNAP2*) were found to be implicated in ASD and epilepsy (Strauss et al., 2006). *CNTNAP2* is a scaffolding protein that’s part of the Neurexin

family, whose members have previously been associated with multiple ASD-linked proteins (Jamain et al., 2003; Comoletti et al., 2004). Ectopic neurons were identified in patients with *CNTNAP2* mutations, suggesting its involvement in the regulation of neuronal migration (Strauss et al., 2006). Additionally, *CNTNAP2* mutations are linked to ADHD as well as epilepsy and seizures, conditions that are commonly co-morbid with ASD (Jackman et al., 2009; Elia et al., 2010; Mefford et al., 2010). Additionally, disruptions in *CNTNAP2* are associated with impairments in sociability and language processing (Whalley et al., 2011; Toma et al., 2013; Condro and White, 2014). *CNTNAP2* KO mice show an abnormal localization of neurons in the corpus callosum and mis-localization of the *Cux1*-positive upper layer neurons into the deeper layers, V–VI (Peñagarikano et al., 2011). *CNTNAP2* is part of a neuron-glia adhesion complex with contactin 2, therefore it may play a key role in radial glia-guided neuronal migration (Poliak et al., 1999; Denaxa et al., 2001).

Astrotactin 1 (*ASTN1*) is a neuronal cell surface antigen that regulates neuron-glia interactions that plays a major role in neuron migration (Edmondson et al., 1988; Zheng et al., 1996). *Astn1* KO mice have slower cerebellar granule cell migration, aberrant Purkinje cell morphology, decreased glia-neuron interactions and impairments in coordination compared to normal mice (Adams et al., 2002). *Astn1* interacts with *Astn2* and can regulate its expression at membrane surface, which ultimately regulates neuron-glia adhesion during migration along radial glia (Wilson et al., 2010). Genome wide association studies identified *ASTN2* as an ASD candidate gene (Lesch et al., 2008). Patients with *ASTN2* deletions are often classified with ASD or other co-morbid diagnoses such as ADHD, obsessive compulsive disorder and delayed language development (Lionel et al., 2014).

NudeE nuclear distribution E homolog (*NDE1*) is involved with the regulation of neuron proliferation, migration, and intracellular transport as part of the *Lis1/Nde/Ndel1*/cytoplasmic dynein complex (Feng et al., 2000; Kitagawa et al., 2000; Niethammer et al., 2000; Sasaki et al., 2000; McKenney et al., 2010). Lissencephaly 1 (*LIS1*) was the first gene identified with an involvement in disrupted neuron migration (Reiner et al., 1993) via its interactions with cytoplasmic dynein, *Nde1*, *Ndel1* and cytoplasmic linker protein 170 (CLIP-170; Reiner, 2000; Coquelle et al., 2002). Multiple studies have shown a major role for *Lis1* in regulating neuronal migration (Cahana et al., 2001; Tsai et al., 2007; Hippenmeyer et al., 2010) and a cross between an *Nde1* KO mouse with *Lis1* heterozygous mouse produced a severe disruption of the morphology of the VZ progenitors and radial glia, as well as a significant decrease in brain size (Pawlisz et al., 2008). This was shown to be regulated via stabilization of the dystrophin/dystroglycan glycoprotein complex (Pawlisz and Feng, 2011) and an alteration of the MAPK scaffold protein Kinase Suppressor of Ras (KSR), subsequently producing hyperactivation of MAPK/ERK pathway (Lancot et al., 2013). In support of these findings, additional studies have shown that dysregulation of the MAPK/ERK pathway affects social behavior in mice and produces ASD phenotypes,

while multiple links between ASD and hyperactivation of the Ras signaling have been reported (Levitt and Campbell, 2009; Rauen et al., 2010; Crepel et al., 2011; Faridar et al., 2014).

### Inhibitory Neuron Migration

Interneurons, which are primarily inhibitory, utilize tangential migration to migrate into the neocortex and across the plane of radial glia fibers (Lavdas et al., 1999; Marín and Rubenstein, 2001; Nery et al., 2002; Kriegstein and Noctor, 2004; Ayala et al., 2007). Upon reaching the cerebral cortex, interneurons will migrate along radial glia fibers to their final location (de Carlos et al., 1996; Wichterle et al., 2001; Polleux et al., 2002; Poluch and Juliano, 2007). Therefore, when radial glia-mediated migration becomes disrupted, interneurons will also become mis-localized.

Distal-less homeobox (*Dlx*) genes are part of the homeodomain transcription factor family which is related to the *Drosophila* distal-less (*Dll*) gene (Panganiban and Rubenstein, 2002). *Dlx1/2* are found largely in the ganglionic eminences (GE) of the developing brain and play an important role in regulating the migration of inhibitory interneurons from the medial GE into the cortex. *Dlx1* KO mice exhibit a decrease in GABAergic neurons and present with epilepsy, a commonly observed pathology in ASD patients (Cobos et al., 2005). *Dlx1/Dlx2* double KO mice show major aberrations in the migratory stream of GABAergic neurons and also an accumulation of neuronal precursor cells in the GE (Anderson et al., 1997; Ghanem et al., 2007). *Arx*, an X-linked homeobox gene and immediate downstream target of *Dlx*, may regulate *Dlx*'s role in tangential neuronal migration (Colasante et al., 2008). Patients identified with mutations in *Arx* display ID, autistic features and epilepsy (Strømme et al., 2002; Turner et al., 2002).

### ALTERATIONS IN NEURITE GROWTH AND SPINE FORMATION IN ASD

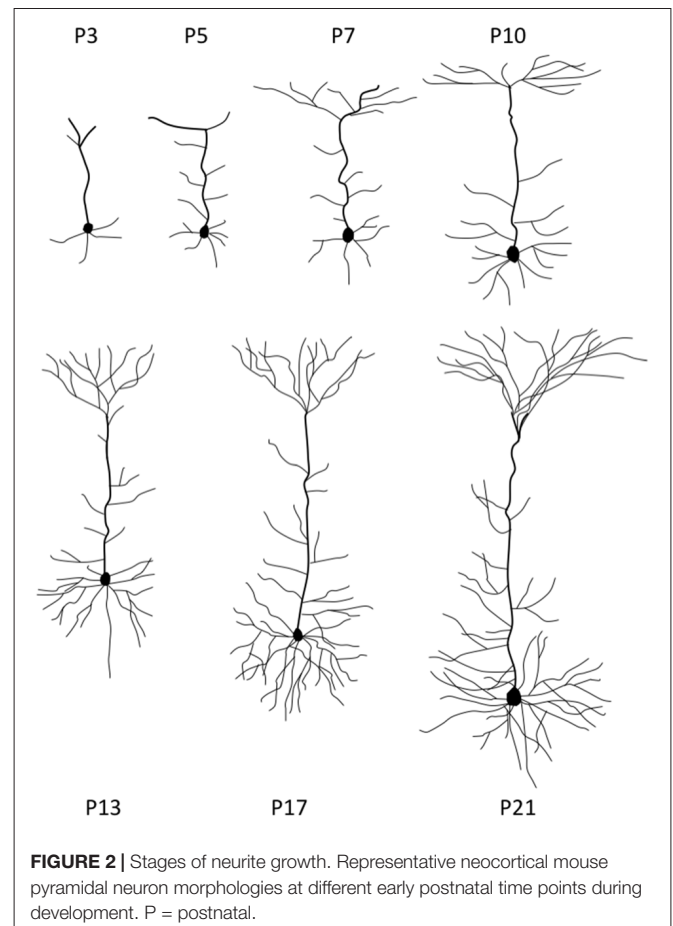
Neurons are highly specialized cells with distinct morphologies comprised of three distinct sections: the soma which contains the nucleus and the majority of the cellular organelles; a long axonal process to transmit information; and a complex dendritic arbor to receive information from neighboring neurons. The dendrites are highly branched and elaborate and therefore occupy a large area within neural tissues (Tahirovic and Bradke, 2009).

Dendrite growth can be viewed as discreet steps. After birth from neural progenitors, neurons start as a simple round soma and must first undergo cellular polarization. Neurons first adopt a multipolar morphology with the extension of minor neurites. The movement of migrating neurons is achieved through the formation, maintenance and constant transformation of microtubules in response to extracellular cues and intracellular polarity signals. During migration, the cell first extends a leading process. Stabilization of a single neurite is required for newly generated neurons to exit the multipolar stage to enter the cortical plate. This

stabilization ultimately results in formation of the leading process while the trailing process eventually develops into the future axon (Shim et al., 2008; Witte and Bradke, 2008). Next, in order to move forward, the nucleus undergoes a translocation into the stabilized leading neurite. During this process, termed nucleokinesis, the attachment of microtubules from the centrosome to the nuclear envelope exerts a traction force, pulling the nucleus into the leading neurite attached to a radial glia process (Bellion et al., 2005; Tahirovic and Bradke, 2009).

Once neurons reached their destined cortical layers, substantial dendritic outgrowth is undertaken to form dendritic arbors characteristic of a neuron subtype. At this stage, neurons are tasked with the processes of growing each branch to the correct size, initiating a new branch at the right site to complete a specific branching pattern, and directing each branch's growth into an appropriate spatial location (Tahirovic and Bradke, 2009; Jan and Jan, 2010). The early postnatal stages of neurite growth are depicted in **Figure 2**.

Dendrites are vastly different from axons in their ultimate morphology, function and developmental processes. In mammalian neurons, a notable distinction is the manner in which the microtubules are organized. Initially all neurites contain microtubules oriented with their plus-end localized distally from the soma. The neurite specified to become the axon



**FIGURE 2** | Stages of neurite growth. Representative neocortical mouse pyramidal neuron morphologies at different early postnatal time points during development. P = postnatal.

will maintain this distal plus-end orientation, while neurites that become dendrites will adopt a mixed orientation (Baas et al., 1988, 1989; Burton, 1988). Additionally, in comparison to axons, dendrites have an enrichment of cellular organelles that are transported with the aid of microtubule motors like dynein, such as Golgi outposts and mitochondria, which are utilized to supply the necessary for cellular materials required for growth (Horton and Ehlers, 2004; Horton et al., 2005; Kapitein et al., 2010).

The morphology of the dendritic arbor is largely developed early during the embryonic period; however, dendrites are highly dynamic and they maintain the overall morphology with various mechanisms into adulthood. Disruptions in dendritic growth, or breakdown of the mechanisms to maintain their morphology can be deleterious, resulting in aberrant network function. Abnormalities in neuronal connectivity between the higher-order association areas have been considered one of the major defects in ASD (Geschwind and Levitt, 2007). MRI studies have shown both large and small changes in connectivity of neuronal networks; however, the neurobiological basis for this disconnectivity remains to be fully elucidated (Casanova and Casanova, 2014; Maximo et al., 2014). A large number of autism studies have focused on dendritic development, although mostly relating to spine morphology and synaptic function, which will be discussed in detail below (Persico and Bourgeron, 2006; Kelleher and Bear, 2008; Bourgeron, 2009). However, the current body of research suggests that this is not the only morphological defect, as children with autism are frequently identified with large-scale anatomical abnormalities, suggesting dysregulation in dendritic growth and development. For example, both macrocephaly and microcephaly are identified in ASD adolescents, with 15% of ASD patients presenting with macrocephaly, while 20% display microcephaly (Lainhart et al., 1997; Fombonne et al., 1999; Cody et al., 2002; Pardo and Eberhart, 2007).

One of the proposed causes leading to macrocephaly has been suggested to be a result of increased dendrite number and size, which may be a product of excessive dendrite arborization, and/or decreased dendrite pruning (Jan and Jan, 2010). Other factors can play a role in macrocephaly, such as increased numbers of neurons and glia, however the number of dendrites may better explain certain forms of macrocephaly. Brain volumes in infants diagnosed with ASD are typically normal, however they display aberrant overgrowth as development progresses. This later onset of increased brain volume should not result from an increase in neuronal number, as the largest areas of the brain have mostly completed neurogenesis prior to birth, except for areas like the hippocampus where smaller amounts of neurogenesis occur later in life (Ming and Song, 2005; Zhao et al., 2008). The timing of increase brain size can be explained by aberrant dendrite growth and branching, which largely occurs postnatally. In humans, neurons grow and continue to elaborate their dendritic arbors, axons and form new synaptic connections until the age of five, with experience-based remodeling of synapses until 20 years of age (Stiles and Jernigan, 2010; Tau and Peterson, 2010; Pescosolido et al., 2012). Dendrites continue to extensively grow after birth, in an activity-dependent manner. Therefore,

a large contribution to the increase in brain size postnatally likely results from increased dendritic growth (Redmond et al., 2002).

Previous genetics studies have described multiple high-risk genes for autism that play roles in diverse functions, including synaptic connectivity and synapse function, dendritic and axonal growth, trafficking, transcription and translation (Volders et al., 2011; de Anda et al., 2012; Miao et al., 2013; Bakos et al., 2015). Recently, estimates have suggested that 88% of the genes that are considered to be high-risk for ASD play a role in early neurodevelopmental functions such as neurogenesis and differentiation of neuroblasts. Importantly, ~80% of these genes are involved in later phases of neurodevelopment and regulate processes involved in neurite growth and synapse formation (Casanova and Casanova, 2014).

Dendrites from an individual neuron can have a thousand or more spines, with each spine forming an excitatory synaptic connection upon maturing. Spines and synapses are produced in excess numbers during development, but synaptic numbers are later fine-tuned through activity-dependent stabilization or elimination (Changeux and Danchin, 1976). Spines are highly dynamic and undergo constant turnover and morphological plasticity with a dependency on both developmental stage and activity.

Dendritic spines are typically classified as thin, stubby and mushroom, with the latter considered more mature. Mushroom and stubby morphologies are more permanent and form strong excitatory connections (Trachtenberg et al., 2002; Kasai et al., 2003). Alternatively, thin spines are highly dynamic, shorter lasting, and form weak synaptic connections or no connection at all. Within the spine head, actin becomes enriched helps play a key role in spine formation and structural dynamics (Chazneau and Giannone, 2016). Previous studies have shown that spine formation maintenance are a major cellular processes affected in ASD (Kelleher and Bear, 2008; Bourgeron, 2009; Phillips and Pozzo-Miller, 2015). Using Golgi staining, postmortem analysis of cortical neurons from ASD brain samples showed an increase in dendritic spine density compared to normal patients (Hutsler and Zhang, 2010). Some of the high-risk autism genes implicated in dendritic growth and branching spine formation and synapse maturation are described below.

Methyl CpG binding protein 2 (*MECP2*) is an X-linked gene that codes for a protein that functions as a transcriptional repressor and an activator (Chahrouh et al., 2008). Mutations in *MeCP2* were initially linked to Rett syndrome (RTT), a neurodevelopmental condition that presents with motor and speech impairments, cognitive deficits and autism (Amir et al., 1999). RTT is typically caused by loss-of-function mutations in *MeCP2*; however, there are rare cases that are also caused by *MeCP2* duplications.

Using Golgi staining in brain slices from *MeCP2* KO mice, reductions in dendritic growth and branching have previously been reported in both apical and basal arbors of motor cortical neurons (Kishi and Macklis, 2004; Stuss et al., 2012). Additionally, to investigate *MeCP2* duplication, mice over-expressing the human *MeCP2* gene have shown excessive dendritic branching, indicating that *MeCP2* over-expression can



induce dendritic overgrowth (Jiang et al., 2013). It is possible that in subtypes of neurons MeCP2 can act as a repressor while acting as an activator in others, or it can change roles at different periods in neuronal development. For instance, MeCP2 can activate genes involved in early dendrite growth and repress genes later during dendritic remodeling. An important aspect to these findings is that MeCP2 overexpression affects the dendrites, having no impact on axon growth, suggesting a defined role for MeCP2 in dendritic development. Recent work has provided evidence for the role MeCP2 plays in dendritic development, showing that MeCP2 also regulates the expression of genes post-transcriptionally. These findings show that MeCP2 regulates microRNA (miRNA) processing via a direct interaction with DiGeorge syndrome critical region 8 (DGCR8), which plays a role in mediating the genesis of miRNAs thought to regulate dendrite morphogenesis (Gregory et al., 2004; Cheng et al., 2014).

RTT animal models also show changes in excitatory hippocampal synapse numbers. The loss of the X-linked RTT protein MeCP2 has also been shown to result in abnormal dendritic spine morphology and a decrease in spine density (Zhou et al., 2006; Chapleau et al., 2012; Stuss et al., 2012). Additionally, MeCP2 over-expression produces dendritic overgrowth in mice and these animals show a greater rate of spine turnover, with a bias toward spine removal (Jugloff et al., 2005; Jiang et al., 2013). Taken together, MeCP2, the established factor underlying RTT with autism, has a clear role in dendritic morphogenesis and synapse formation, both of which should play a major function in the cognitive impairments seen in RTT patients.

Fragile X mental retardation gene 1 (*FMR1*) is the gene underlying the disorder Fragile X syndrome (FXS), which results in ID with 15%–30% of patients also displaying ASD phenotypes (Krawczun et al., 1985; Persico and Bourgeron, 2006; Kelleher and Bear, 2008; Santoro et al., 2012). FXS is usually results from an expansion of a CGG triplet in the 5'-UTR region of the *FMR1* gene, however a few missense mutations and deletions have been identified (Santoro et al., 2012). Fragile X mental retardation protein (FMRP), the *FMR1* gene product, plays a key role in negatively regulating translation, especially local translation at the synapse (Santoro et al., 2012). In terms of FMRP's role in dendritic growth, mouse studies have shown somewhat contradictory results. In visual cortex pyramidal neurons of *FMR1* KO mice, one study has shown defects in dendritic spines, with no observable changes in dendritic morphology (Irwin et al., 2002). Conversely, multiple other studies have shown that FMRP is critical for dendritic growth and branching. In *FMR1* KO mice, visual cortex pyramidal neurons show reduced basal dendrite length and branching (Restivo et al., 2005). Using neural stem cells isolated from *FMR1* KO mice, or from postmortem tissues of FXS human fetuses, differentiated neurons showed fewer and less complex neurites with smaller somas (Castrén et al., 2005). An important caveat to these studies was that they involved loss-of-function or deletion of FMRP; however, FXS in humans is rarely caused by deletions or missense mutations in the *FMR1* gene, but rather via an expansion of the CGG triplet repeat. This

has been addressed in studies using transgenic mice with a FXS knock-in mutation consisting of 120–140 CGG repeats. Indeed, these animals display significantly impaired dendritic morphogenesis in addition to alterations in dendritic spine density and morphology (Berman et al., 2012). The studies from *Drosophila* have elucidated the mechanistic function of FMRP in dendritic growth and have shown that FMRP is involved with transportation of the mRNA for Ras-related C3 botulinum toxin substrate 1 (Rac1), a GTPase. In agreement with this, Rac1 was found to bind FMRP and affect dendrite arborization, indicating that FMRP's role in dendrite morphogenesis could in part be through its interaction with Rac1 (Lee et al., 2003). These findings strongly support a role for FMRP in dendritic arbor morphogenesis.

FMRP is localized within dendrites and in addition to abnormal dendritic growth and branching, brains from FXS patients display an immature synaptic phenotype (Rudelli et al., 1985). FXS patients have an increased spine density on both apical and basal dendrites in neocortex and more spines characterized by an immature morphology. Additionally, Golgi studies from human FXS patients reveal a significant increase in long spines with less shorter spines compared to controls in multiple cortical areas (Hinton et al., 1991; Irwin et al., 2001). In *FMR1* KO mouse models, spine phenotypes correlate with those observed in humans with FXS as these mice have an increase in longer spines and a corresponding decrease in shorter spines. Additionally, dendritic spines in FXS mice display a more immature morphology with fewer mushroom and stubby spines present (Irwin et al., 2001, 2002; McKinney et al., 2005). In addition, changes in synaptic proteins such as postsynaptic density-95 kDa (PSD-95) have been observed in FXS (Ifrim et al., 2015).

Although FMRP's role in impaired spine formation and morphology in FXS has not been completely elucidated, FMRP has been identified to interact with multiple proteins that are linked to dendritic and spine regulation. Cytoplasmic FMRP-interacting protein 1 (CYFIP1), a binding partner of FMRP, is a protein that has recently generated interest as its genetic locus is chr15q11.2, a susceptibility area in ASD. When bound to FMRP, CYFIP1 can inhibit translation and regulates actin dynamics. This can therefore regulate the growth and removal, as well as the labiality and morphology of spines (De Rubeis et al., 2013). A down-regulation of CYFIP1 mRNA has been detected in subgroups of FXS patients with ASD (Nowicki et al., 2007). Conversely, over-expression of CYFIP1 results in higher dendritic complexity *in vitro*, while neurons that are haploinsufficient for CYFIP1 show decreased dendritic complexity and an increase in the relative levels of immature to mature dendritic spines (Pathania et al., 2014).

Pten is a phosphatase that de-phosphorylates PIP3, which serves to inhibit PI3K/AKT/mTOR signaling (Kwon et al., 2006; Ogawa et al., 2007; Garcia-Junco-Clemente and Golshani, 2014). Mice lacking Pten selectively in the central nervous system show an increase in activation of the AKT/mTOR/S6K pathway, an increase in neuron size, macrocephaly, as well as decreased and disorganized dendritic and axonal growth

(Kwon et al., 2006). Pten KO during early development, as well as in adult mice disrupts neuron morphogenesis, suggesting that Pten plays an important role in dendritic growth and maintenance in adulthood in addition to its function during early neurodevelopment (Kwon et al., 2006; Chow et al., 2009). Therefore, Pten, a protein with a clear link to autism, has a definitive role in dendrite morphogenesis.

*TSC1* and *TSC2* are tumor-suppressing genes that have been linked to brain tumors in tuberous sclerosis complex (TSC; Huang and Manning, 2008). However, their involvement in neurodevelopmental disorders including epilepsy, autism and ID has become increasingly studied (Kwiatkowski and Manning, 2005; Persico and Bourgeron, 2006). In pheochromocytoma 12 (PC12) cells, an inducible neuron-like cell line, transfection of *TSC1* antisense oligonucleotides was shown to increase neurite outgrowth through RhoA activation, while knockdown of *Tsc2* decreased neurite growth (Florice et al., 2007). In another study, overexpression of *Tsc1/Tsc2* was found to impair axon formation. Knockdown of *Tsc1/Tsc2* *in vitro* induced multiple axons, while genetic deletion *in vivo* in the mouse induced ectopic axons (Choi et al., 2008). There is strong evidence that TSC genes are linked to ASD risk and play a major role in neurite growth, therefore it will be important to further elucidate their mechanistic role in neuron morphogenesis and ASD in future research.

Mammalian target of rapamycin (mTOR is a serine/threonine kinase that regulates cellular growth and is induced by growth factors and environmental cues (Laplante and Sabatini, 2012). Via regulation of the cytoskeleton, mTOR plays an important function in regulating dendritic outgrowth, and proteins known to inhibit mTOR signaling have been associated with aberrant dendrite and spine development in ASD (Thomanetz et al., 2013; Skalecka et al., 2016), including Pten and *Tsc 1/2* (Weston et al., 2014). Pten serves to inhibit the PI3K/AKT/mTOR signaling pathway, thereby affecting growth and protein translation, and Pten mutations have been discovered in multiple individuals diagnosed with ASD. Additionally, mice carrying PTEN mutations or genetic deletions show impaired social interactions and increased sensory responses. Loss of Pten produces an increase in dendritic growth, synaptic connectivity and disorganized dendritic and axonal processes (Kwon et al., 2006; Orloff et al., 2013). Conversely, knockdown of Pten in the amygdala decreases spine density, with an increase in mushroom spines and decrease in thin protrusions (Haws et al., 2014). Additionally, it has been previously shown that the TSC pathway plays an important role in regulating synaptic function, and in hippocampal neurons, loss of *Tsc 2* expression produces an expansion of neuronal somas as well as spines (Tavazoie et al., 2005). These findings provide strong evidence that mTOR, and its interacting proteins, are involved in regulating both dendritic and spine development in ASD.

Neurofibromatosis is a condition in which tumors grow in the nervous system. Mutations in Neurofibromatosis-1 (*NF1*) produce neurofibromas and between 30% and 65% of children with *NF1* mutations display learning disabilities and display significantly higher rates of autism, suggesting

a causal relationship to autism (Rosser and Packer, 2003; Garg et al., 2013). Neurofibromin, the protein product of the *NF1* gene, is a GTPase activating protein that negatively regulates the Ras signaling pathway (Costa and Silva, 2003). *NF1* conditional KO mice display impaired dendritic morphogenesis and Golgi staining from *NF1* KO mouse brains reveals shorter apical dendrites in pyramidal neurons. *NF1*'s function in dendrite morphogenesis has been shown to act through cAMP/PKA/Rho/ROCK signaling (Brown et al., 2012). RhoA plays a major role in actin dynamics and neurite growth and branching. With the inhibition of RhoA, an increase in the branching of neuronal processes is observed, and with the activation of RhoA, a decrease in the length and complexity of processes is observed (Li et al., 2000; Nakayama et al., 2000; Wong et al., 2000).

Loss of expression of *KIAA2022/KIDLIA* was previously identified by our group and others as the causative protein for severe ID and autistic behavior in multiple families (Cantagrel et al., 2004, 2009; Ishikawa et al., 2012; Van Maldergem et al., 2013; Charzewska et al., 2015; Kuroda et al., 2015). Clinical examinations of patients with *KIDLIA* mutations or a loss of expression, display enlarged ventricles, Virchow-Robin spaces, a thin corpus callosum and small cerebellar vermis. Additionally, strabismus has been observed in patients, with some dysmorphic features including a round face during early postnatal periods, febrile seizures, severely impaired or no language, stereotypical hand movements and delayed acquisition of motor milestones (Cantagrel et al., 2004, 2009). Interestingly, a patient with decreased expression of *KIDLIA* had only mild cognitive deficits with a significant delay in language acquisition as well as repetitive and stereotyped behaviors, indicating that the effects may be gene-dosage dependent (Van Maldergem et al., 2013).

With shRNA-mediated knockdown of *KIDLIA* in rat hippocampal neurons in culture, significant impairments in dendritic growth and branching are observed (Van Maldergem et al., 2013; Gilbert and Man, 2016). Mechanistically, we've recently reported that loss of *KIDLIA* significantly impairs actin dynamics and produces an aberrant increase in total and membrane-localized N-cadherin. N-cadherin was found to bind much greater levels of  $\delta$ -catenin, thereby releasing the latter's inhibition on downstream RhoA (Gilbert et al., 2016). Additionally, microcephaly has been reported in human patients with a loss of *KIDLIA* expression (Cantagrel et al., 2004; Van Maldergem et al., 2013; Kuroda et al., 2015). These findings suggest that the regulation of neuronal morphogenesis through dendrite growth and synapse formation are major underlying factors contributing to the cognitive impairments observed in patients with genetic deletions or functional mutations in *KIDLIA*.

Ubiquitin protein ligase E3A (*UBE3A*) is the causative gene for Angelman syndrome, a developmental disorder characterized by language impairments, ataxia, ID and hyperactivity (Williams et al., 2006). Individuals identified with Angelman syndrome are often co-diagnosed with autism (Steffenburg et al., 1996; Peters et al., 2004). In addition, *Ube3A* over-expression leads

to autism in humans and in animal models (Bucan et al., 2009; Smith et al., 2011; Noor et al., 2015). *UBE3A* is an imprinted gene that encodes an E3 ubiquitin ligase, that typically expresses from both maternal and paternal alleles in most tissues, but is only expressed from the maternal allele in brain (Mabb et al., 2011). Previous studies have shown that Ube3A is required for normal dendritic morphogenesis in the mouse (Miao et al., 2013) and shRNA-mediated knockdown of Ube3A *in vivo* impairs dendritic growth cortical pyramidal neurons in the mouse (Miao et al., 2013). Additionally, studies in *Drosophila* strongly support a role for Ube3A in dendritic growth and branching. Both over-expression and loss of the Ube3A *Drosophila* homolog have been shown to result in decreased dendrite branching in larval sensory neurons (Lu et al., 2009). These studies suggest that Ube3A plays a significant role in dendrite growth and support that dysregulated neuron morphogenesis may underlie developmental disorders like Angelman syndrome and ASD.

Thousand-and-one amino acid kinase 2 (*TAOK2*) belongs to the family of MAP kinase kinase kinases (MAPKKK) and is located in chromosome 16, an area associated with increased ASD-risk (Weiss et al., 2008) and schizophrenia (McCarthy et al., 2009). Both Taok1 and Taok2 activate mitogen-activated protein kinase (MAPK) pathways via JNK and p38 which results in regulation of gene transcription (Chen and Cobb, 2001; Chen et al., 2003). Additionally, FMRP regulates Taok2 mRNA (Darnell et al., 2011), the protein underlying FXS, providing an additional link to its involvement in neurodevelopmental disorders. A recent study *in vivo* has shown that knockdown or overexpression of Taok2 showed opposing effects on basal dendrite development in the neocortex (de Anda et al., 2012). Specifically, primary dendrite numbers were reduced after Taok2 knockdown, while the number of primary dendrite numbers was increased with over-expression. Additionally, this effect was preferential for the basal dendrites on basal dendrites, as Taok2 knockdown produced no changes in apical dendrite morphology on the same neurons. The role of Taok2 on dendrite growth was dependent on interactions with Neuropilin 1, a membrane receptor that binds Semaphorin 3A, which leads to initiation of the JNK cascade (de Anda et al., 2012). Interestingly, this finding shows that Taok2 expression selectively affects specific dendritic areas, i.e., the basal dendrites, providing evidence that specialized molecular pathways are used for the formation of different dendritic areas.

Reelin, as discussed previously for its role in neuron migration, seems to also play a significant function in dendrite arborization in hippocampal and cortical neurons (Niu et al., 2004; Jossin and Goffinet, 2007; MacLaurin et al., 2007; Chameau et al., 2009; Hoe et al., 2009; Matsuki et al., 2010). Reelin, and its downstream signaling pathway through Vldlr/Apoer2-Dab1, serves to promote dendrite development. Reeler mice contain a loss-of-function mutation in *RELN*, and display decreased dendrite branching in the hippocampus (Niu et al., 2004). Additionally, Reelin has also been shown to affect cortical dendritic growth *in vivo* (Hoe et al., 2009) and Reelin application

to Reelin KO mouse brain slices can promote dendritic growth (Nichols and Olson, 2010). The role of alterations in neurite growth and branching and the associated ASD-linked genes, are described in detail later.

## ALTERATIONS IN SYNAPTIC COMPONENTS IN ASD

Synapses are highly specialized structures required for signal transduction and plasticity within neuronal networks, making up the functional contact sites between neurons. A synapse is composed of the axon terminal, the presynapse, a synaptic cleft which contains adhesion proteins and the extracellular matrix, and the postsynaptic density with receptors on a target neuron's dendrites. The presynapse contains mitochondria and is characterized by a pool of synaptic vesicles filled with neurotransmitters. Action potentials arriving at the axon terminal mediate calcium influx, which causes the vesicles to fuse with specialized regions of the plasma membrane called active zones to release their content into the synaptic cleft. A precise coupling between the electrical stimulus (action potential) and release of neurotransmitter is crucial for proper signal transmission to the postsynaptic neuron. The postsynapse is characterized by the presence of receptors that bind neurotransmitters released from the presynapse, which initiates signaling cascades that ultimately propagate the electrical signal in postsynaptic neuron. Receptors are clustered in a region called the postsynaptic density (PSD) in the excitatory synapse.

Synapses are classified as excitatory and inhibitory, depending on whether they use glutamate or  $\gamma$ -aminobutyric acid (GABA) as their main neurotransmitter, respectively. Additionally, the formation and structure of excitatory and inhibitory synapses is uniquely different. Whereas excitatory synapses made on dendritic spines, inhibitory synapses are formed directly on the dendritic shaft. Additionally, both excitatory and inhibitory synapses have distinct proteomic profiles to specialize each synapse with the appropriate receptors and signaling molecules. Synaptic dysfunctions, whether they arise from functional mutations in pre- or postsynaptic proteins, are a common underlying pathology in ASD and are discussed in detail below.

### Presynaptic Proteins Linked to ASD

Neurexins (*NRXN*) are synaptic adhesion proteins that localize to the membrane of the presynapse and bind Neuroligins (NLGNs), which are localized on the postsynaptic membrane. There are three genes within the NRXN family (*NRXN1*, *NRXN2*, and *NRXN3*) with multiple mutations or copy number variations having been identified in NRXN family members in ASD diagnoses (Feng et al., 2006; Autism Genome Project Consortium et al., 2007; Bremer et al., 2011; Yangngam et al., 2014). *NRXN1* mutations have also been identified in multiple neuropsychiatric disorders, including Tourette syndrome, schizophrenia, ADHD and bipolar disorder (Stone et al., 2008; Guilmatre et al., 2009; Zhang et al., 2009; Sundaram et al., 2010; Lionel et al., 2011).



*NRXN1* $\alpha$  KO mice exhibit reduced excitatory synaptic strength, with a decrease in the input–output relationship of evoked postsynaptic potentials and miniature excitatory postsynaptic current (mEPSC) frequency (Etherton et al., 2009). In behavioral tests, *NRXN1* KO mice display an increase in grooming behavior, however no change in spatial learning or social behavior (Etherton et al., 2009). In  $\alpha$ -*NRXN* triple KO mice, where *NRXN1* $\alpha/2\alpha/3\alpha$  were deleted, synapse formation was normal but  $\alpha$ -Nrxns were required to couple  $Ca^{2+}$  channels to vesicle exocytosis (Missler et al., 2003).

The synapsins (*SYN*) are a family of presynaptic proteins involved in vesicle-mediated neurotransmitter release and neurite outgrowth (Rosahl et al., 1995). In mammals, the synapsin family of proteins contains three members (synapsin 1, synapsin 2, and synapsin 3). Primary neuron cultures from *SYN1/2/3* triple KO mice display severely altered synaptic vesicle localization and a significant decrease in the number of synaptic vesicles (Fornasiero et al., 2012). Additionally, mutations in *SYN1* (A51G, A550T, Q555X and T567A) have been identified in a family with epilepsy and autistic phenotypes, suggesting its link as a causative factor for ASD (Fassio et al., 2011). Additionally, the nonsense mutation, Q555X, reduces CaMKII and MAPK/ERK activity, which regulates synaptic vesicle trafficking and neurite growth, and the A550T and T567A missense mutations have been shown to impair synapsin localization to the presynapse (Fassio et al., 2011).

In synapsin KO mice, studies have shown behavioral deficits in social novelty and avoidance behavior in social approach as well as epileptic activity, all of which are typical in ASD (Greco et al., 2013; Ketzef and Gitler, 2014). *SYN1/3* double KO mice show an impairment in social transmission of food preference, while *SYN1/2* double KO mice have a decrease in environmental interest. Additionally, *SYN2* KO mice have impairments in social recognition tests and display an increase in repetitive self grooming (Greco et al., 2013). These findings suggest that synapsins play an important role in the underlying pathology leading to behavioral phenotypes typical in ASD.

## Postsynaptic Proteins Linked to ASD

Neuroigins (*NLGN*) are cell adhesion proteins that localize to the postsynaptic membrane and play an integral function in synapse formation via binding their presynaptic partners, *NRXNs*. In humans *NLGN* family is composed of *five* genes (*NLGN1/2/3/4/4Y*). The large extracellular domain of Nlgns have a high sequence similarity to acetylcholinesterase and is required to bind to  $\beta$ -Nrxn during synapse formation (Dean and Dresbach, 2006). Nlgns-1, -3 and -4 are localized to excitatory synapses, while *Nlgn2* is found at inhibitory synapses (Missler et al., 2003). Previous studies have shown that overexpression of *Nlgn1* can increase excitatory synaptic strength and the synaptic NMDAR/AMPA ratio both *in vitro* and *in vivo* (Schnell et al., 2012). Conversely, *Nlgn2* overexpression increases inhibitory synaptic strength. Additionally, *Nlgn1* expression can promote

synapse maturity but does not induce synapse formation of glutamatergic synapses (Chubykin et al., 2007; Schnell et al., 2012).

The Shank family are scaffolding proteins localized to the postsynapse and interact with NMDA receptors as well as Nlgn-Nrxn complexes. The Shank protein can interact with multiple important postsynaptic proteins including the actin cytoskeleton via ankyrin repeats,  $Ca^{2+}$  signaling via calpain/calmodulin and the glutamate receptor-interacting protein (GRIP) through its SH3 domain (Lim et al., 1999; Yoo et al., 2014). *SHANK1*, *SHANK2* and *SHANK3* comprise the Shank family of proteins and they are found throughout the brain, however each isoform varies in its distribution.

*SHANK3* was the first gene in the Shank family of synaptic scaffolding proteins to be linked to ASD. During spine formation, *Shank3* is an important scaffolding protein and loss of *Shank3 in vitro* results in a decrease in both the length and density of spines. Conversely, over-expression of *Shank3* results in more mature and larger spines (Betancur et al., 2009). *SHANK3* resides on chromosome 22q13.3, and ASD-linked region with deletions linked to Phelan-McDermid syndrome. This syndrome is characterized by developmental delay, severely impaired language, ASD and ID (Phelan, 2008).

Transgenic mice harboring various *SHANK* mutations or deletions have elucidated Shank's in synapse formation, function and its role in ASD. Transgenic mice with genetic KO of the longest isoform of *SHANK3*, have been shown to recapitulate the phenotypes observed from *SHANK3* mutations in humans. Although social impairments in these mice have varied, they have all shown increased repetitive grooming, a behavior typical in ASD mouse models (Bozdagi et al., 2010; Peça et al., 2011; Wang et al., 2011; Yang et al., 2012).

Postsynaptic density protein-95 (PSD-95, *DLG4*) is an important postsynaptic scaffolding protein that localizes to excitatory synapses. PSD-95 is composed of three PDZ domains that target it to the postsynapse, an SH3 domain, and a guanylate kinase domain on its C-terminal. Nlgn, NMDARs and potassium channels all interact with the PDZ domains on PSD-95. PSD-95 localizes to spine heads in excitatory synapses and has been shown to promote synapse stabilization. The E3 ubiquitin ligase, murine double minute-2 (*Mdm2*) ubiquitinates PSD-95 and subsequently binds with protocadherin-10 (*Pcdh10*), sending it to the proteasome to be degraded. *Pcdh10* is an ASD-linked gene (Morrow et al., 2008) and its expression is regulated via the interaction of myocyte enhancer factor-2 (MEF2) and FMRP (Tsai N. P. et al., 2012). Additionally, in FMRP KO neurons, dysregulated *Mdm2* prevents MEF2-induced PSD-95 ubiquitination and synapse elimination (Tsai N. P. et al., 2012), providing evidence for altered activity-dependent synapse elimination in an ASD model. PSD-95 KO mice (*DLG4* KO) show multiple behavioral and molecular abnormalities that are linked to ASD pathology. *DLG4* KO mice display impaired communication and social interactions, decreased motor coordination, as well as



increased anxiety and repetitive behaviors. Additionally, *DLG4* KO mice display defects in dendritic spine morphology in the amygdala and aberrant expression of multiple synapse-related genes in the forebrain (Feyder et al., 2010).

Gephyrin is a key postsynaptic scaffolding protein in inhibitory synapses. Gephyrin's three major domains include a N-terminal G-domain, a C-terminal E-domain, with a large linker region connecting the two domains. Gephyrin interacts with glycine receptors with high affinity and the  $\alpha$  and  $\beta$  subunits of the GABA<sub>A</sub> receptor. Nlgn2 binds to gephyrin via a cytoplasmic motif region and activates collybistin, and the Nlgn2/gephyrin/collybistin complex is necessary for clustering of inhibitory receptors (Poulopoulos et al., 2009). In gephyrin KO mice, there is a decrease in GABA<sub>A</sub> and glycine receptor clustering, whereas glutamate receptor localization remains normal (Kneussel et al., 1999; Grosskreutz et al., 2003).

Rare exonic deletions within the gephyrin (*GPHN*) gene have been reported in subsets of patients with ASD (Lionel et al., 2013). A *de novo* 273 kb deletion in *GPHN* displayed developmental delay, cyclical seizures, repetitive behaviors increased anxiety and obsessive compulsive disorders, in one family (Lionel et al., 2013).

### Adhesion Complexes Involved in ASD

CNTNAP2 is a member of the Nrnx superfamily and plays an important role regulating the clustering of potassium channels and neuron-glia interactions. CNTNAP2 was first linked to ASD Amish children presenting with developmental disorders, seizures, and impaired language were found to have a homozygous mutation in CNTNAP2 (Strauss et al., 2006). After genetic deletion of CNTNAP2, mice show significantly decreased numbers of dendritic spines as well as a decrease in the GluA1 subunit of AMPARs. Additionally, an aggregation of GluA1 was observed in the cytoplasm, suggesting that synaptic deficits may be in part due to a trafficking problem (Varea et al., 2015). CNTNAP2 KO mice show common ASD behavioral phenotypes, including repetitive movements as well as social deficits (Peñagarikano et al., 2011).

Cadherins (*CDH*) are transmembrane proteins that function in cell-cell adhesion and play roles in neuron migration, dendritic growth, spine morphology, synaptogenesis and synapse remodeling (Tan et al., 2010; Redies et al., 2012; Bian et al., 2015; Egusa et al., 2016; Gilbert et al., 2016). In genome-wide association studies, common variants in *CDH9* and *CDH10* genes on chromosome 5p14.1 have been identified to link with ASD (Wang et al., 2009). Additionally, deletions within 16q23 in *CDH13* have also been identified in ASD patients (Sanders et al., 2011). Neural cadherin (N-cadherin) is a calcium dependent cell-cell adhesion glycoprotein that plays important roles in neurodevelopment (Garcia-Castro et al., 2000).  $\delta$ -catenin, a neuron specific member of the p120 family of catenins, is a known interactor of the cytoplasmic juxtamembrane region of N-cadherin (Lu et al., 1999). The  $\delta$ -catenin gene, *CTNND2*, is candidate gene in ASD and functions within a protein network

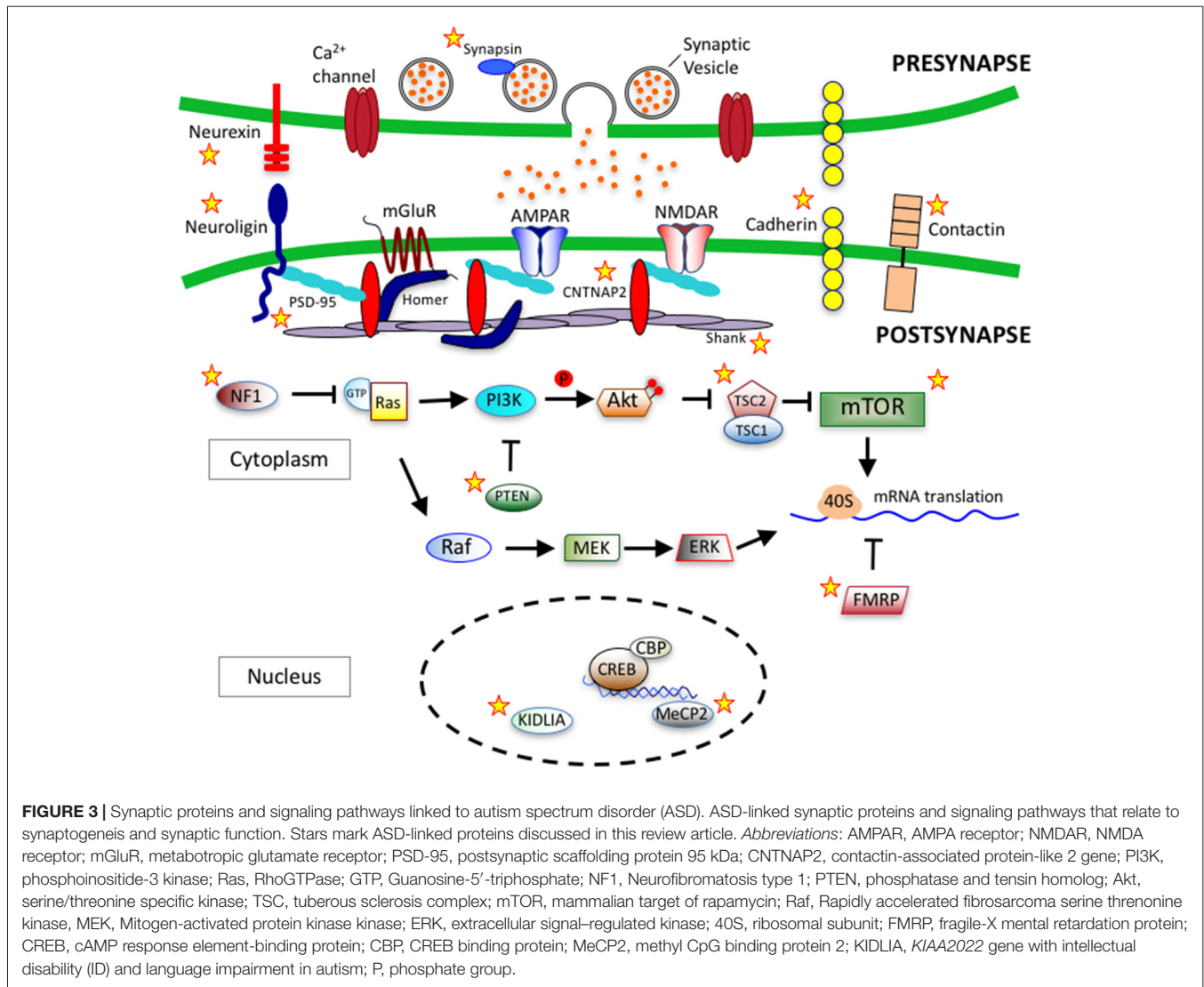
that has a major role dendritic and spine growth and dynamics (Bian et al., 2015; Turner et al., 2015; Yuan et al., 2015). Over-expression of  $\delta$ -catenin induces dendritic and spine growth in primary neuron cultures (Martinez et al., 2003; Arikath et al., 2009), while knockdown of  $\delta$ -catenin serves to impair dendritic growth (Elia et al., 2006; Arikath et al., 2008). **Figure 3** depicts key synaptic proteins and signaling pathways linked to ASD.

### DYSREGULATION OF SYNAPTIC PLASTICITY AND NEURONAL ACTIVITY IN ASD

Based on the different ASD-linked pathways discussed previously, it can be inferred that changes in synaptic plasticity via altered synaptic strength and/or number, may be an underlying pathology in ASD patients and mouse models. Interestingly, many ASD-linked mutation results in altered gene transcription and protein synthesis of synaptic related transcripts, effects which can also be observed with changes in neuronal activity (Kelleher and Bear, 2008; Akins et al., 2009; Darnell et al., 2011; Qiu et al., 2012; Gilbert and Man, 2014).

Initial findings from *FMR1* mutant mice, the mouse model of FXS, did not show impairments in LTP using a standard HFS paradigm (Godfraind et al., 1996; Li et al., 2002). However, using a low threshold stimulation protocol, LTP induction was reduced in multiple brain areas, including the hippocampus and somatosensory cortex (Larson et al., 2005; Zhao et al., 2005; Lauterborn et al., 2007). Additionally, mGluR-LTP was impaired in the basolateral amygdala and visual cortex (Wilson and Cox, 2007; Suvrathan et al., 2010). These findings provide evidence that different brain regions or synapse-specific deficits occur in mice with loss of FMRP. The most prominent change in synaptic plasticity has been observed with enhanced mGluR-LTD the cerebellum and in CA1 of the hippocampus (Huber et al., 2002; Koekkoek et al., 2005). An enhancement of LTD in the CA1 region has led to the theory that synaptic loss of FMRP produces increased signaling through mGluRs (Huber et al., 2002; Bear et al., 2004; Osterweil et al., 2010). Additionally, genetic reduction, or mGluR5 inhibition, rescues behavioral deficits in *FMR1* mice (Dolen et al., 2007; Michalon et al., 2012). These rescue experiments therefore suggest the ability to reverse some of the impairments in FXS patients. The different impairments in synaptic function found across various brain regions in *FMR1* mice provide evidence of a correlation between impaired synaptic plasticity and behavioral deficits in ASD. These studies also provide evidence that the *FMR1* KO mouse may be a good model to explore the pathophysiology of ASD and investigate possible treatment strategies (Bhakar et al., 2012).

Synaptic plasticity has been studied in great detail in the *UBE3A* maternally deficient mice, the Angelman syndrome mouse model. In the CA1, HFS-LTP is reduced in transgenic mice and the reduction in CA1 LTP could be rescued with stronger stimulation protocols (Weeber et al., 2003).



These findings indicate that Ube3a's role in synaptic plasticity may be as a modulator of LTP, not necessarily required for LTP induction. In the same study, a reduction in calmodulin-dependent protein kinase II (CaMKII) activity was observed in transgenic mice, and genetic reduction of CaMKII's inhibitory autophosphorylation rescued deficits in LTP and learning and memory tasks in transgenic animals (van Woerden et al., 2007). These findings provide evidence that altered CaMKII activity mediates the impairment in synaptic plasticity in *UBE3A* deficient mice; however, it remains to be elucidated how loss of *UBE3A* alters the activity of CaMKII.

Both of the *TSC1* or *TSC2* KO mice are embryonic lethal; however, mice harboring *TSC1* or *TSC2* heterozygous mutations display synaptic dysfunction and cognitive impairments (Kobayashi et al., 2001; von der Brélie et al., 2006; Ehninger et al., 2008). In *TSC2* heterozygous rats, LFS-LTD was decreased and L-LTP was enhanced

in the CA1 of the hippocampus; however, E-LTP was unaffected (von der Brélie et al., 2006; Ehninger et al., 2008), suggesting changes in protein synthesis pathways necessary for L-LTP expression. Additionally, in *TSC2* heterozygous mice, mGluR-LTD was decreased but LFS-LTD was unchanged (Auerbach et al., 2011). A reduction in mGluR-LTD in *TSC2* heterozygous animals opposes what is observed in the *FMRI* KO mice; however, mGluR-LTD in both animals don't show sensitivity to protein synthesis inhibitors (Auerbach et al., 2011). An additional study using mice with a specific deletion of *TSC1* in cerebellar Purkinje cells displayed deficits in social interactions, an increase repetitive behavior as well as defects in ultrasonic vocalizations. These animals however were not investigated for changes in synaptic plasticity in the cerebellum (Tsai P. T. et al., 2012). These findings suggest that impaired synaptic plasticity is a major pathology in *TSC* mouse models of autism, underlying the observed deficits in

social interaction in both in *TSC1* and *TSC2* heterozygous animals.

In *MECP2* KO mice, reductions in LTP and LFS-LTD in CA1 of the hippocampus have been reported. It's interesting to note that younger mice (~3–5 weeks of age) show no impairments in synaptic plasticity, indicating that impaired synaptic plasticity correlates with the delayed deficits observed in human RTT patients (Chen et al., 2001; Asaka et al., 2006). A mouse model containing a truncation of MeCP2 (MeCP2308/Y) showed a reduction in LTP as well as paired-pulse stimulation, but no changes in mGluR-LTD (Shahbazian et al., 2002; Weng et al., 2011). Interestingly, another study has shown that impaired LTP in CA1 of the hippocampus could be rescued by genetically reintroducing MeCP2 (Guy et al., 2007; Weng et al., 2011).

Shank proteins regulate levels and modulate the signaling of both metabotropic and ionotropic glutamate receptors at the synapse, and synaptic plasticity has been studied in multiple Shank3 mouse models (Tu et al., 1999; Uchino et al., 2006). Investigation of mEPSCs, paired pulse ratio (PPF and PPD), input/output curves and population spikes have indicated different abnormalities in synaptic transmission in hippocampal CA1 synapses of mice with different Shank3 mutations (Wang et al., 2011). Additionally, hippocampal LTP is reduced in the CA1 of the hippocampus in subsets of mice with Shank3 truncations, as well as LFS- LTD and mGluR-LTD (Bozdagi et al., 2010; Bangash et al., 2011; Wang et al., 2011).

It has been hypothesized that disruptions in neuronal circuits involved with language and social behavior in subtypes of autism may be caused by unbalanced high levels of excitation, or disproportionately weak inhibition (Rubenstein and Merzenich, 2003; Gao and Penzes, 2015). With a more excitable cortex, the brain would have wide-ranging abnormalities in perception, memory, cognition and motor control, and would be highly susceptible to epilepsy (Rubenstein and Merzenich, 2003). In support of this theory, a decrease in glutamate decarboxylase 67 (*GAD67*) mRNA in autistic cerebellar Purkinje cells has been identified in human autism samples (Yip et al., 2007). Additionally, another study has shown a decrease in GABAergic inhibition in autism patient samples (Hussman, 2001), indicating that decreased GABAergic inhibition may disrupt the excitation/inhibition balance within neuronal networks in autism.

As a novel form of synaptic regulation opposing the Hebbian type plasticity, homeostatic synaptic plasticity (HSP) is a negative feedback response that serves to compensate for changes in network activity (Turrigiano et al., 1998; Hou et al., 2008, 2011, 2015; Yu and Goda, 2009; Pozo and Goda, 2010; Wang et al., 2012; Gilbert et al., 2016). In response to global decreases or increases in network activity from a homeostatic set-point, synaptic strengths are scaled up or down, respectively (Turrigiano et al., 1998). HSP may be important for maintaining network activity homeostasis and avoiding potential epileptogenic states and sleep may be necessary for synaptic homeostasis (Tononi and Cirelli, 2003; Kuhn et al., 2016). The studies in *Drosophila* for

example, have shown that the size and number of synapses decrease after sleep and increase within a few hours of waking (Gilestro et al., 2009). Interestingly, Nlgns regulate levels of glutamatergic and GABAergic currents after sleep deprivation, indicating they play an important role in this sleep-dependent HSP (Huber et al., 2004; Gilestro et al., 2009; El Helou et al., 2013) and Nlgn defects could result in disturbances in sleep and circadian rhythms, a common disorder found in ASD patients (Bourgeron, 2007). FMRP, the RNA-binding protein involved with regulating dendritic protein translation, has also been shown to be required for increases in synaptic strength after neuronal activity blockade or application of retinoic acid in the mouse hippocampus, indicating that some symptoms of FXS may be due to impaired HSP (Soden and Chen, 2010). Release of brain-derived neurotrophic factor (BDNF) from postsynaptic neurons has previously been identified to be required for a retrograde homeostatic up-regulation of presynaptic function. Increased BDNF levels in ASD patient blood samples has been observed as well as higher plasma levels of serotonin and N-acetylserotonin (NAS), a potent agonist of the BDNF receptor tyrosine receptor kinase B (TrkB; Jang et al., 2010; Halepoto et al., 2014; Kasarpalkar et al., 2014; Pagan et al., 2014). Excess levels of NAS could therefore increase TrkB-induced PI3K signaling, resulting in increased protein translation, similar to findings observed with mutations in components of the mTOR pathway.

## FINAL CONCLUSIONS

ASD is diagnosed at the behavioral level with the presentation of its core phenotypes of impaired social interactions, restrictive interests and repetitive behaviors. Although the etiological factors of ASD are highly heterogeneous, recent research has strongly pointed to common cellular events that are impaired in ASD, including neurogenesis, morphogenesis, synapse maturation and synaptic plasticity. In this regard, loss-, or gain-, of-function mutations in single genes that are causative for ASD have given researchers unique opportunities to make important mechanistic insights. A common theme emerging within the field is that in the developing brain, alterations in dendritic growth, synapse formation and synaptic function result in neuronal network dysfunction, ultimately leading to complex social and cognitive dysfunction. Further elucidation into these pathways, as well as advancements in gene therapies and targeted drugs to modulate these processes, could provide exciting and promising new therapies for the treatment of ASDs.

## AUTHOR CONTRIBUTIONS

JG and H-YM wrote and edited the manuscript.

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## REFERENCES

- Abrahams, B. S., Arking, D. E., Campbell, D. B., Mefford, H. C., Morrow, E. M., Weiss, L. A., et al. (2013). SFARI Gene 2.0: a community-driven knowledgebase for the autism spectrum disorders (ASDs). *Mol. Autism* 4:36. doi: 10.1186/2040-2392-4-36
- Adams, N. C., Tomoda, T., Cooper, M., Dietz, G., and Hatten, M. E. (2002). Mice that lack astrotactin have slowed neuronal migration. *Development* 129, 965–972.
- Akins, M. R., Berk-Rauch, H. E., and Fallon, J. R. (2009). Presynaptic translation: stepping out of the postsynaptic shadow. *Front. Neural Circuits* 3:17. doi: 10.3389/neuro.04.017.2009
- Amir, R. E., Van den Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., and Zoghbi, H. Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat. Genet.* 23, 185–188. doi: 10.1038/13810
- Anderson, S. A., Eisenstat, D. D., Shi, L., and Rubenstein, J. L. (1997). Interneuron migration from basal forebrain to neocortex: dependence on *Dlx* genes. *Science* 278, 474–476. doi: 10.1126/science.278.5337.474
- Angevine, J. B. Jr., and Sidman, R. L. (1961). Autoradiographic study of cell migration during histogenesis of cerebral cortex in the mouse. *Nature* 192, 766–768. doi: 10.1038/192766b0
- Arikath, J., Israely, I., Tao, Y., Mei, L., Liu, X., and Reichardt, L. F. (2008). Erbin controls dendritic morphogenesis by regulating localization of delta-catenin. *J. Neurosci.* 28, 7047–7056. doi: 10.1523/JNEUROSCI.0451-08.2008
- Arikath, J., Peng, I. F., Ng, Y. G., Israely, I., Liu, X., Ullian, E. M., et al. (2009). Delta-catenin regulates spine and synapse morphogenesis and function in hippocampal neurons during development. *J. Neurosci.* 29, 5435–5442. doi: 10.1523/JNEUROSCI.0835-09.2009
- Asaka, Y., Jugloff, D. G., Zhang, L., Eubanks, J. H., and Fitzsimonds, R. M. (2006). Hippocampal synaptic plasticity is impaired in the *Mecp2*-null mouse model of Rett syndrome. *Neurobiol. Dis.* 21, 217–227. doi: 10.1016/j.nbd.2005.07.005
- Auerbach, B. D., Osterweil, E. K., and Bear, M. F. (2011). Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature* 480, 63–68. doi: 10.1038/nature10658
- Autism Genome Project Consortium, Szatmari, P., Paterson, A. D., Zwaigenbaum, L., Roberts, W., Brian, J., et al. (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat. Genet.* 39, 319–328. doi: 10.1038/ng1985
- Avino, T. A., and Hutslar, J. J. (2010). Abnormal cell patterning at the cortical gray-white matter boundary in autism spectrum disorders. *Brain Res.* 1360, 138–146. doi: 10.1016/j.brainres.2010.08.091
- Ayala, R., Shu, T., and Tsai, L. H. (2007). Trekking across the brain: the journey of neuronal migration. *Cell* 128, 29–43. doi: 10.1016/j.cell.2006.12.021
- Azevedo, F. A., Carvalho, L. R., Grinberg, L. T., Farfel, J. M., Ferretti, R. E., Leite, R. E., et al. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J. Comp. Neurol.* 513, 532–541. doi: 10.1002/cne.21974
- Baas, P. W., Black, M. M., and Banker, G. A. (1989). Changes in microtubule polarity orientation during the development of hippocampal neurons in culture. *J. Cell Biol.* 109, 3085–3094. doi: 10.1083/jcb.109.6.3085
- Baas, P. W., Deitch, J. S., Black, M. M., and Banker, G. A. (1988). Polarity orientation of microtubules in hippocampal neurons: uniformity in the axon and nonuniformity in the dendrite. *Proc. Natl. Acad. Sci. U S A* 85, 8335–8339. doi: 10.1073/pnas.85.21.8335
- Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M., et al. (1998). A clinicopathological study of autism. *Brain* 121, 889–905. doi: 10.1093/brain/121.5.889
- Bakhtiar, R., Zürcher, N. R., Rogier, O., Russo, B., Hippolyte, L., Granziera, C., et al. (2012). Differences in white matter reflect atypical developmental trajectory in autism: a Tract-based Spatial Statistics study. *Neuroimage Clin.* 1, 48–56. doi: 10.1016/j.nicl.2012.09.001
- Bakos, J., Bacova, Z., Grant, S. G., Castejon, A. M., and Ostatnikova, D. (2015). Are molecules involved in neuritegenesis and axon guidance related to autism pathogenesis? *Neuromolecular Med.* 17, 297–304. doi: 10.1007/s12017-015-8357-7
- Banerjee-Basu, S., and Packer, A. (2010). SFARI Gene: an evolving database for the autism research community. *Dis. Model. Mech.* 3, 133–135. doi: 10.1242/dmm.005439
- Bangash, M. A., Park, J. M., Melnikova, T., Wang, D., Jeon, S. K., Lee, D., et al. (2011). Enhanced polyubiquitination of Shank3 and NMDA receptor in a mouse model of autism. *Cell* 145, 758–772. doi: 10.1016/j.cell.2011.03.052
- Bauman, M., and Kemper, T. L. (1985). Histoanatomic observations of the brain in early infantile autism. *Neurology* 35, 866–874. doi: 10.1212/WNL.35.6.866
- Bear, M. F., Huber, K. M., and Warren, S. T. (2004). The mGluR theory of fragile X mental retardation. *Trends Neurosci.* 27, 370–377. doi: 10.1016/j.tins.2004.04.009
- Bedogni, F., Hodge, R. D., Nelson, B. R., Frederick, E. A., Shiba, N., Daza, R. A., et al. (2010). Autism susceptibility candidate 2 (*Auts2*) encodes a nuclear protein expressed in developing brain regions implicated in autism neuropathology. *Gene Expr. Patterns* 10, 9–15. doi: 10.1016/j.gep.2009.11.005
- Bellion, A., Baudoin, J. P., Alvarez, C., Bornens, M., and Metin, C. (2005). Nucleokinesis in tangentially migrating neurons comprises two alternating phases: forward migration of the Golgi/centrosome associated with centrosome splitting and myosin contraction at the rear. *J. Neurosci.* 25, 5691–5699. doi: 10.1523/JNEUROSCI.1030-05.2005
- Ben-Itzhak, E., Aviva, B., and Zachor, D. A. (2013a). Are special abilities in autism spectrum disorder associated with a distinct clinical presentation? *Res. Autism Spec. Dis.* 7, 1122–1128. doi: 10.1016/j.rasd.2013.05.003
- Ben-Itzhak, E., Ben-Shachar, S., and Zachor, D. A. (2013b). Specific neurological phenotypes in autism spectrum disorders are associated with sex representation. *Autism Res.* 6, 596–604. doi: 10.1002/aur.1319
- Ben-Itzhak, E., and Zachor, D. A. (2007). The effects of intellectual functioning and autism severity on outcome of early behavioral intervention for children with autism. *Res. Dev. Disabil.* 28, 287–303. doi: 10.1016/j.ridd.2006.03.002
- Berman, R. F., Murray, K. D., Arque, G., Hunsaker, M. R., and Wenzel, H. J. (2012). Abnormal dendrite and spine morphology in primary visual cortex in the CGG knock-in mouse model of the fragile X premutation. *Epilepsia* 53, 150–160. doi: 10.1111/j.1528-1167.2012.03486.x
- Bernier, R., Golzio, C., Xiong, B., Stessman, H. A., Coe, B. P., Penn, O., et al. (2014). Disruptive *CHD8* mutations define a subtype of autism early in development. *Cell* 158, 263–276. doi: 10.1016/j.cell.2014.06.017
- Betanour, C., Sakurai, T., and Buxbaum, J. D. (2009). The emerging role of synaptic cell-adhesion pathways in the pathogenesis of autism spectrum disorders. *Trends Neurosci.* 32, 402–412. doi: 10.1016/j.tins.2009.04.003
- Bhakar, A. L., Dölen, G., and Bear, M. F. (2012). The pathophysiology of fragile X (and what it teaches us about synapses). *Annu. Rev. Neurosci.* 35, 417–443. doi: 10.1146/annurev-neuro-060909-153138
- Bian, W. J., Miao, W. Y., He, S. J., Qiu, Z., and Yu, X. (2015). Coordinated spine pruning and maturation mediated by inter-spine competition for cadherin/catenin complexes. *Cell* 162, 808–822. doi: 10.1016/j.cell.2015.07.018
- Bilgüvar, K., Öztürk, A. K., Louvi, A., Kwan, K. Y., Choi, M., Tatli, B., et al. (2010). Whole-exome sequencing identifies recessive *WDR62* mutations in severe brain malformations. *Nature* 467, 207–210. doi: 10.1038/nature09327
- Bond, J., Scott, S., Hampshire, D. J., Springell, K., Corry, P., Abramowicz, M. J., et al. (2003). Protein-truncating mutations in *ASPM* cause variable reduction in brain size. *Am. J. Hum. Genet.* 73, 1170–1177. doi: 10.1086/379085
- Bonora, E., Beyer, K. S., Lamb, J. A., Parr, J. R., Klauk, S. M., Benner, A., et al. (2003). Analysis of reelin as a candidate gene for autism. *Mol. Psychiatry* 8, 885–892. doi: 10.1038/sj.mp.4001310
- Bourgeron, T. (2007). The possible interplay of synaptic and clock genes in autism spectrum disorders. *Cold Spring Harb. Symp. Quant. Biol.* 72, 645–654. doi: 10.1101/sqb.2007.72.020
- Bourgeron, T. (2009). A synaptic trek to autism. *Curr. Opin. Neurobiol.* 19, 231–234. doi: 10.1016/j.conb.2009.06.003
- Bozdagi, O., Sakurai, T., Papapetrou, D., Wang, X., Dickstein, D. L., Takahashi, N., et al. (2010). Haploinsufficiency of the autism-associated *Shank3* gene leads to deficits in synaptic function, social interaction and social communication. *Mol. Autism* 1:15. doi: 10.1186/2040-2392-1-15
- Bremer, A., Giacobini, M., Eriksson, M., Gustavsson, P., Nordin, V., Fernell, E., et al. (2011). Copy number variation characteristics in subpopulations of patients with autism spectrum disorders. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 156, 115–124. doi: 10.1002/ajmg.b.31142



- Brown, J. A., Diggs-Andrews, K. A., Gianino, S. M., and Gutmann, D. H. (2012). Neurofibromatosis-1 heterozygosity impairs CNS neuronal morphology in a cAMP/PKA/ROCK-dependent manner. *Mol. Cell. Neurosci.* 49, 13–22. doi: 10.1016/j.mcn.2011.08.008
- Bucan, M., Abrahams, B. S., Wang, K., Glessner, J. T., Herman, E. I., Sonnenblick, L. I., et al. (2009). Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. *PLoS Genet.* 5:e1000536. doi: 10.1371/journal.pgen.1000536
- Buchman, J. J., Durak, O., and Tsai, L. H. (2011). ASPM regulates Wnt signaling pathway activity in the developing brain. *Genes Dev.* 25, 1909–1914. doi: 10.1101/gad.16830211
- Burton, P. R. (1988). Dendrites of mitral cell neurons contain microtubules of opposite polarity. *Brain Res.* 473, 107–115. doi: 10.1016/0006-8993(88)90321-6
- Butler, M. G., Dasouki, M. J., Zhou, X. P., Talebizadeh, Z., Brown, M., Takahashi, T. N., et al. (2005). Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J. Med. Genet.* 42, 318–321. doi: 10.1136/jmg.2004.024646
- Buxbaum, J. D., Cai, G., Chaste, P., Nygren, G., Goldsmith, J., Reichert, J., et al. (2007). Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 144B, 484–491. doi: 10.1002/ajmg.b.30493
- Cahana, A., Escamez, T., Nowakowski, R. S., Hayes, N. L., Giacobini, M., von Holst, A., et al. (2001). Targeted mutagenesis of Lis1 disrupts cortical development and LIS1 homodimerization. *Proc. Natl. Acad. Sci. U S A* 98, 6429–6434. doi: 10.1073/pnas.101122598
- Cantagrel, V., Haddad, M. R., Ciofi, P., Andrieu, D., Lossi, A. M., Maldergem, L., et al. (2009). Spatiotemporal expression in mouse brain of Kiaa2022, a gene disrupted in two patients with severe mental retardation. *Gene Expr. Patterns* 9, 423–429. doi: 10.1016/j.gep.2009.06.001
- Cantagrel, V., Lossi, A. M., Boulanger, S., Depetris, D., Mattei, M. G., Gecz, J., et al. (2004). Disruption of a new X linked gene highly expressed in brain in a family with two mentally retarded males. *J. Med. Genet.* 41, 736–742. doi: 10.1136/jmg.2004.021626
- Carper, R. A., Moses, P., Tighe, Z. D., and Courchesne, E. (2002). Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage* 16, 1038–1051. doi: 10.1006/nimg.2002.1099
- Casanova, E. L., and Casanova, M. F. (2014). Genetics studies indicate that neural induction and early neuronal maturation are disturbed in autism. *Front. Cell. Neurosci.* 8:397. doi: 10.3389/fncel.2014.00397
- Castrén, M., Tervonen, T., Kärkkäinen, V., Heinonen, S., Castrén, E., Larsson, K., et al. (2005). Altered differentiation of neural stem cells in fragile X syndrome. *Proc. Natl. Acad. Sci. U S A* 102, 17834–17839. doi: 10.1073/pnas.0508995102
- Caviness, V. S. Jr., Nowakowski, R. S., and Bhide, P. G. (2009). Neocortical neurogenesis: morphogenetic gradients and beyond. *Trends Neurosci.* 32, 443–450. doi: 10.1016/j.tins.2009.05.003
- Chahrouh, M., Jung, S. Y., Shaw, C., Zhou, X., Wong, S. T., Qin, J., et al. (2008). Mecp2, a key contributor to neurological disease, activates and represses transcription. *Science* 320, 1224–1229. doi: 10.1126/science.1153252
- Chameau, P., Inta, D., Vitalis, T., Monyer, H., Wadman, W. J., and van Hooft, J. A. (2009). The N-terminal region of reelin regulates postnatal dendritic maturation of cortical pyramidal neurons. *Proc. Natl. Acad. Sci. U S A* 106, 7227–7232. doi: 10.1073/pnas.0810764106
- Changeux, J. P., and Danchin, A. (1976). Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature* 264, 705–712. doi: 10.1038/264705a0
- Chapleau, C. A., Boggio, E. M., Calfa, G., Percy, A. K., Giustetto, M., and Pozzo-Miller, L. (2012). Hippocampal CA1 pyramidal neurons of Mecp2 mutant mice show a dendritic spine phenotype only in the presymptomatic stage. *Neural Plast.* 2012:976164. doi: 10.1155/2012/976164
- Charzewska, A., Rzońca, S., Janeczko, M., Nawara, M., Smyk, M., Bal, J., et al. (2015). A duplication of the whole KIAA2022 gene validates the gene role in the pathogenesis of intellectual disability and autism. *Clin. Genet.* 88, 297–299. doi: 10.1111/cge.12528
- Chazeau, A., and Giannone, G. (2016). Organization and dynamics of the actin cytoskeleton during dendritic spine morphological remodeling. *Cell. Mol. Life Sci.* 73, 3053–3073. doi: 10.1007/s00018-016-2214-1
- Chen, R. Z., Akbarian, S., Tudor, M., and Jaenisch, R. (2001). Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. *Nat. Genet.* 27, 327–331. doi: 10.1038/85906
- Chen, Z., and Cobb, M. H. (2001). Regulation of stress-responsive mitogen-activated protein (MAP) kinase pathways by TAO2. *J. Biol. Chem.* 276, 16070–16075. doi: 10.1074/jbc.M100681200
- Chen, J. A., Penagarikano, O., Belgard, T. G., Swarup, V., and Geschwind, D. H. (2015). The emerging picture of autism spectrum disorder: genetics and pathology. *Annu. Rev. Pathol.* 10, 111–144. doi: 10.1146/annurev-pathol-012414-040405
- Chen, Z., Raman, M., Chen, L., Lee, S. F., Gilman, A. G., and Cobb, M. H. (2003). TAO (thousand-and-one amino acid) protein kinases mediate signaling from carbachol to p38 mitogen-activated protein kinase and ternary complex factors. *J. Biol. Chem.* 278, 22278–22283. doi: 10.1074/jbc.M301173200
- Chen, J. F., Zhang, Y., Wilde, J., Hansen, K. C., Lai, F., and Niswander, L. (2014). Microcephaly disease gene Wdr62 regulates mitotic progression of embryonic neural stem cells and brain size. *Nat. Commun.* 5:3885. doi: 10.1038/ncomms4885
- Cheng, Y., Quinn, J. F., and Weiss, L. A. (2013). An eQTL mapping approach reveals that rare variants in the SEMA5A regulatory network impact autism risk. *Hum. Mol. Genet.* 22, 2960–2972. doi: 10.1093/hmg/ddt150
- Cheng, T. L., Wang, Z., Liao, Q., Zhu, Y., Zhou, W. H., Xu, W., et al. (2014). Mecp2 suppresses nuclear microRNA processing and dendritic growth by regulating the DGCR8/Drosha complex. *Dev. Cell* 28, 547–560. doi: 10.1016/j.devcel.2014.01.032
- Choi, Y. J., Di Nardo, A., Kramvis, I., Meikle, L., Kwiatkowski, D. J., Sahin, M., et al. (2008). Tuberous sclerosis complex proteins control axon formation. *Genes Dev.* 22, 2485–2495. doi: 10.1101/gad.1685008
- Chow, D. K., Groszer, M., Pribadi, M., Machniki, M., Carmichael, S. T., Liu, X., et al. (2009). Laminar and compartmental regulation of dendritic growth in mature cortex. *Nat. Neurosci.* 12, 116–118. doi: 10.1038/nn.2255
- Chuang, H. C., Huang, T. N., and Hsueh, Y. P. (2015). T-brain-1—A potential master regulator in autism spectrum disorders. *Autism Res.* 8, 412–426. doi: 10.1002/aur.1456
- Chubykin, A. A., Atasoy, D., Etherton, M. R., Brose, N., Kavalali, E. T., Gibson, J. R., et al. (2007). Activity-dependent validation of excitatory versus inhibitory synapses by neuroligin-1 versus neuroligin-2. *Neuron* 54, 919–931. doi: 10.1016/j.neuron.2007.05.029
- Cobos, I., Calcagnotto, M. E., Vilaythong, A. J., Thwin, M. T., Noebels, J. L., Baraban, S. C., et al. (2005). Mice lacking Dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. *Nat. Neurosci.* 8, 1059–1068. doi: 10.1038/nn1499
- Cody, H., Pelphey, K., and Piven, J. (2002). Structural and functional magnetic resonance imaging of autism. *Int. J. Dev. Neurosci.* 20, 421–438. doi: 10.1016/S0736-5748(02)00053-9
- Colasante, G., Collombat, P., Raimondi, V., Bonanomi, D., Ferrai, C., Maira, M., et al. (2008). Arx is a direct target of Dlx2 and thereby contributes to the tangential migration of GABAergic interneurons. *J. Neurosci.* 28, 10674–10686. doi: 10.1523/JNEUROSCI.1283-08.2008
- Comoletti, D., De Jaco, A., Jennings, L. L., Flynn, R. E., Gaietta, G., Tsigelny, I., et al. (2004). The Arg451Cys-neuroligin-3 mutation associated with autism reveals a defect in protein processing. *J. Neurosci.* 24, 4889–4893. doi: 10.1523/JNEUROSCI.0468-04.2004
- Condro, M. C., and White, S. A. (2014). Distribution of language-related Cntnbp2 protein in neural circuits critical for vocal learning. *J. Comp. Neurol.* 522, 169–185. doi: 10.1002/cne.23394
- Coquelle, F. M., Caspi, M., Cordelieres, F. P., Dompierre, J. P., Dujardin, D. L., Koifman, C., et al. (2002). LIS1, CLIP-170's key to the dynein/dynactin pathway. *Mol. Cell. Biol.* 22, 3089–3102. doi: 10.1128/mcb.22.9.3089-3102.2002
- Costa, R. M., and Silva, A. J. (2003). Mouse models of neurofibromatosis type I: bridging the GAP. *Trends Mol. Med.* 9, 19–23. doi: 10.1016/s1471-4914(02)00008-4
- Courchesne, E., Mouton, P. R., Calhoun, M. E., Semendeferi, K., Ahrens-Barbeau, C., Hallet, M. J., et al. (2011). Neuron number and size in prefrontal cortex of children with autism. *JAMA* 306, 2001–2010. doi: 10.1001/jama.2011.1638

- Courchesne, E., and Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr. Opin. Neurobiol.* 15, 225–230. doi: 10.1016/j.conb.2005.03.001
- Crepel, A., Steyaert, J., De la Marche, W., De Wolf, V., Fryns, J. P., Noens, I., et al. (2011). Narrowing the critical deletion region for autism spectrum disorders on 16p11.2. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 156, 243–245. doi: 10.1002/ajmg.b.31163
- D'Arcangelo, G., Miao, G. G., Chen, S. C., Soares, H. D., Morgan, J. I., and Curran, T. (1995). A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. *Nature* 374, 719–723. doi: 10.1038/374719a0
- Darnell, J. C., Van Driesche, S. J., Zhang, C., Hung, K. Y., Mele, A., Fraser, C. E., et al. (2011). FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. *Cell* 146, 247–261. doi: 10.1016/j.cell.2011.06.013
- de Anda, F. C., Rosario, A. L., Durak, O., Tran, T., Graff, J., Meletis, K., et al. (2012). Autism spectrum disorder susceptibility gene *TAOK2* affects basal dendrite formation in the neocortex. *Nat. Neurosci.* 15, 1022–1031. doi: 10.1038/nn.3141
- de Carlos, J. A., López-Mascaraque, L., and Valverde, F. (1996). Dynamics of cell migration from the lateral ganglionic eminence in the rat. *J. Neurosci.* 16, 6146–6156.
- De Rubeis, S., He, X., Goldberg, A. P., Poultney, C. S., Samocha, K., Cicek, A. E., et al. (2014). Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* 515, 209–215. doi: 10.1038/nature13772
- De Rubeis, S., Pasciuto, E., Li, K. W., Fernandez, E., Di Marino, D., Buzzi, A., et al. (2013). CYFIP1 coordinates mRNA translation and cytoskeleton remodeling to ensure proper dendritic spine formation. *Neuron* 79, 1169–1182. doi: 10.1016/j.neuron.2013.06.039
- De Zio, D., Giunta, L., Corvaro, M., Ferraro, E., and Cecconi, F. (2005). Expanding roles of programmed cell death in mammalian neurodevelopment. *Semin. Cell Dev. Biol.* 16, 281–294. doi: 10.1016/j.semcdb.2004.12.003
- Dean, C., and Dresbach, T. (2006). Neuroligins and neuexins: linking cell adhesion, synapse formation and cognitive function. *Trends Neurosci.* 29, 21–29. doi: 10.1016/j.tins.2005.11.003
- Denaxa, M., Chan, C. H., Schachner, M., Parnavelas, J. G., and Karagozeos, D. (2001). The adhesion molecule TAG-1 mediates the migration of cortical interneurons from the ganglionic eminence along the corticofugal fiber system. *Development* 128, 4635–4644.
- Deriziotis, P., O'Roak, B. J., Graham, S. A., Estruch, S. B., Dimitropoulou, D., Bernier, R. A., et al. (2014). *De novo* TBR1 mutations in sporadic autism disrupt protein functions. *Nat. Commun.* 5:4954. doi: 10.1038/ncomms5954
- DiCicco-Bloom, E., Lord, C., Zwaigenbaum, L., Courchesne, E., Dager, S., Schmitz, C., et al. (2006). The developmental neurobiology of autism spectrum disorder. *J. Neurosci.* 26, 6897–6906. doi: 10.1523/JNEUROSCI.1712-06.2006
- Dolen, G., Osterweil, E., Rao, B. S., Smith, G. B., Auerbach, B. D., Chattarji, S., et al. (2007). Correction of fragile X syndrome in mice. *Neuron* 56, 955–962. doi: 10.1016/j.neuron.2007.12.001
- Dwyer, N. D., and O'Leary, D. D. (2001). Tbr1 conducts the orchestration of early cortical development. *Neuron* 29, 309–311. doi: 10.1016/s0896-6273(01)00202-1
- Edmondson, J. C., Liem, R. K., Kuster, J. E., and Hatten, M. E. (1988). Astrotactin: a novel neuronal cell surface antigen that mediates neuron-astroglial interactions in cerebellar microcultures. *J. Cell Biol.* 106, 505–517. doi: 10.1083/jcb.106.2.505
- Egusa, S. F., Inoue, Y. U., Asami, J., Terakawa, Y. W., Hoshino, M., and Inoue, T. (2016). Classic cadherin expressions balance postnatal neuronal positioning and dendrite dynamics to elaborate the specific cytoarchitecture of the mouse cortical area. *Neurosci. Res.* 105, 49–64. doi: 10.1016/j.neures.2015.09.006
- Ehninger, D., Han, S., Shilyansky, C., Zhou, Y., Li, W., Kwiatkowski, D. J., et al. (2008). Reversal of learning deficits in a *Tsc2*<sup>+/-</sup> mouse model of tuberous sclerosis. *Nat. Med.* 14, 843–848. doi: 10.1038/nm1788
- El Helou, J., Belanger-Nelson, E., Freyburger, M., Dorsaz, S., Curie, T., La Spada, F., et al. (2013). Neuroligin-1 links neuronal activity to sleep-wake regulation. *Proc. Natl. Acad. Sci. U S A* 110, 9974–9979. doi: 10.1073/pnas.1221381110
- Elia, J., Gai, X., Xie, H. M., Perin, J. C., Geiger, E., Glessner, J. T., et al. (2010). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Mol. Psychiatry* 15, 637–646. doi: 10.1038/mp.2009.57
- Elia, L., Yamamoto, M., Zang, K., and Reichardt, L. (2006). p120 catenin regulates dendritic spine and synapse development through Rho-family GTPases and cadherins. *Neuron* 51, 43–56. doi: 10.1016/j.neuron.2006.05.018
- Etherton, M. R., Blaiss, C. A., Powell, C. M., and Südhof, T. C. (2009). Mouse neuexin-1alpha deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments. *Proc. Natl. Acad. Sci. U S A* 106, 17998–18003. doi: 10.1073/pnas.0910297106
- Falconer, D. S. (1951). Two new mutants, 'trembler' and 'reeler', with neurological actions in the house mouse (*Mus musculus* L.). *J. Genet.* 50, 192–201. doi: 10.1007/bf02996215
- Faridar, A., Jones-Davis, D., Rider, E., Li, J., Gobius, I., Morcom, L., et al. (2014). Mapk/Erk activation in an animal model of social deficits shows a possible link to autism. *Mol. Autism* 5:57. doi: 10.1186/2040-2392-5-57
- Fassio, A., Patry, L., Congia, S., Onofri, F., Piton, A., Gauthier, J., et al. (2011). SYN1 loss-of-function mutations in autism and partial epilepsy cause impaired synaptic function. *Hum. Mol. Genet.* 20, 2297–2307. doi: 10.1093/hmg/ddr122
- Fatemi, S. H., Snow, A. V., Stary, J. M., Araghi-Niknam, M., Reutiman, T. J., Lee, S., et al. (2005). Reelin signaling is impaired in autism. *Biol. Psychiatry* 57, 777–787. doi: 10.1016/j.biopsych.2004.12.018
- Feng, Y., Olson, E. C., Stukenberg, P. T., Flanagan, L. A., Kirschner, M. W., and Walsh, C. A. (2000). LIS1 regulates CNS lamination by interacting with mNudE, a central component of the centrosome. *Neuron* 28, 665–679. doi: 10.1016/s0896-6273(00)00145-8
- Feng, J., Schroer, R., Yan, J., Song, W., Yang, C., Bockholt, A., et al. (2006). High frequency of neuexin 1β signal peptide structural variants in patients with autism. *Neurosci. Lett.* 409, 10–13. doi: 10.1016/j.neulet.2006.08.017
- Feyder, M., Karlsson, R. M., Mathur, P., Lyman, M., Bock, R., Momenan, R., et al. (2010). Association of mouse Dlg4 (PSD-95) gene deletion and human DLG4 gene variation with phenotypes relevant to autism spectrum disorders and Williams' syndrome. *Am. J. Psychiatry* 167, 1508–1517. doi: 10.1176/appi.ajp.2010.10040484
- Filimonenko, M., Isakson, P., Finley, K. D., Anderson, M., Jeong, H., Melia, T. J., et al. (2010). The selective macroautophagic degradation of aggregated proteins requires the PI3P-binding protein Alf<sub>y</sub>. *Mol. Cell* 38, 265–279. doi: 10.1016/j.molcel.2010.04.007
- Fish, J. L., Kosodo, Y., Enard, W., Pääbo, S., and Huttner, W. B. (2006). Aspm specifically maintains symmetric proliferative divisions of neuroepithelial cells. *Proc. Natl. Acad. Sci. U S A* 103, 10438–10443. doi: 10.1073/pnas.0604066103
- Florice, F., Higaki, K., Maki, H., Nanba, E., Ninomiya, H., and Ohno, K. (2007). Antisense suppression of TSC1 gene product, hamartin, enhances neurite outgrowth in NGF-treated PC12h cells. *Brain Dev.* 29, 502–509. doi: 10.1016/j.braindev.2007.01.007
- Folsom, T. D., and Fatemi, S. H. (2013). The involvement of Reelin in neurodevelopmental disorders. *Neuropharmacology* 68, 122–135. doi: 10.1016/j.neuropharm.2012.08.015
- Fombonne, E., Roge, B., Claverie, J., Courty, S., and Fremolle, J. (1999). Microcephaly and macrocephaly in autism. *J. Autism Dev. Disord.* 29, 113–119. doi: 10.1023/A:1023036509476
- Fornasiero, E. F., Raimondi, A., Guarnieri, F. C., Orlando, M., Fesce, R., Benfenati, F., et al. (2012). Synapsins contribute to the dynamic spatial organization of synaptic vesicles in an activity-dependent manner. *J. Neurosci.* 32, 12214–12227. doi: 10.1523/JNEUROSCI.1554-12.2012
- Forster, E., Jossin, Y., Zhao, S., Chai, X., Frotscher, M., and Goffinet, A. M. (2006). Recent progress in understanding the role of Reelin in radial neuronal migration, with specific emphasis on the dentate gyrus. *Eur. J. Neurosci.* 23, 901–909. doi: 10.1111/j.1460-9568.2006.04612.x
- Friedman, S. D., Shaw, D. W., Artru, A. A., Dawson, G., Petropoulos, H., and Dager, S. R. (2006). Gray and white matter brain chemistry in young children with autism. *Arch. Gen. Psychiatry* 63, 786–794. doi: 10.1001/archpsyc.63.7.786
- Gao, Z., Lee, P., Stafford, J. M., von Schimmelmann, M., Schaefer, A., and Reinberg, D. (2014). An AUTS2-Polycomb complex activates gene expression in the CNS. *Nature* 516, 349–354. doi: 10.1038/nature13921
- Gao, R., and Penzes, P. (2015). Common mechanisms of excitatory and inhibitory imbalance in schizophrenia and autism spectrum disorders. *Curr. Mol. Med.* 15, 146–167. doi: 10.2174/1566524015666150303003028

- Gao, P., Sultan, K. T., Zhang, X. J., and Shi, S. H. (2013). Lineage-dependent circuit assembly in the neocortex. *Development* 140, 2645–2655. doi: 10.1242/dev.087668
- Garcia-Castro, M. I., Vielmetter, E., and Bronner-Fraser, M. (2000). N-Cadherin, a cell adhesion molecule involved in establishment of embryonic left-right asymmetry. *Science* 288, 1047–1051. doi: 10.1126/science.288.5468.1047
- Garcia-Junco-Clemente, P., and Golshani, P. (2014). PTEN: a master regulator of neuronal structure, function, and plasticity. *Commun. Integr. Biol.* 7:e28358. doi: 10.4161/cib.28358
- Garg, S., Lehtonen, A., Huson, S. M., Emsley, R., Trump, D., Evans, D. G., et al. (2013). Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. *Dev. Med. Child Neurol.* 55, 139–145. doi: 10.1111/dmcn.12043
- Gasquoine, P. G. (2014). Contributions of the insula to cognition and emotion. *Neuropsychol. Rev.* 24, 77–87. doi: 10.1007/s11065-014-9246-9
- Geschwind, D., and Levitt, P. (2007). Autism spectrum disorders: developmental disconnection syndromes. *Curr. Opin. Neurobiol.* 17, 103–111. doi: 10.1016/j.conb.2007.01.009
- Ghanem, N., Yu, M., Long, J., Hatch, G., Rubenstein, J. L., and Ekker, M. (2007). Distinct cis-regulatory elements from the *Dlx1/Dlx2* locus mark different progenitor cell populations in the ganglionic eminences and different subtypes of adult cortical interneurons. *J. Neurosci.* 27, 5012–5022. doi: 10.1523/JNEUROSCI.4725-06.2007
- Gilbert, J., and Man, H. Y. (2014). Translational dysregulation in autism. *Cell Dev. Biol.* 3:e124. doi: 10.4172/2168-9296.1000e124
- Gilbert, J., and Man, H. Y. (2016). The X-linked autism protein KIAA2022/KIDLIA regulates neurite outgrowth via N-cadherin and delta-catenin signaling. *eNeuro* 3:ENEURO.0238-16.2016. doi: 10.1523/ENEURO.0238-16.2016
- Gilbert, J., Shu, S., Yang, X., Lu, Y., Zhu, L. Q., and Man, H. Y. (2016).  $\beta$ -Amyloid triggers aberrant over-scaling of homeostatic synaptic plasticity. *Acta Neuropathol. Commun.* 4:131. doi: 10.1186/s40478-017-0423-y
- Gilastro, G. F., Tononi, G., and Cirelli, C. (2009). Widespread changes in synaptic markers as a function of sleep and wakefulness in *Drosophila*. *Science* 324, 109–112. doi: 10.1126/science.1166673
- Gillberg, C., and de Souza, L. (2002). Head circumference in autism, Asperger syndrome and ADHD: a comparative study. *Dev. Med. Child Neurol.* 44, 296–300. doi: 10.1017/s0012162201002110
- Godfraind, J. M., Reyniers, E., De Boule, K., D'Hooge, R., De Deyn, P. P., Bakker, C. E., et al. (1996). Long-term potentiation in the hippocampus of fragile X knockout mice. *Am. J. Med. Genet.* 64, 246–251. doi: 10.1002/(SICI)1096-8628(19960809)64:2<246::AID-AJMG2>3.0.CO;2-S
- Goffin, A., Hoefsloot, L. H., Bosgoed, E., Swillen, A., and Fryns, J. P. (2001). PTEN mutation in a family with Cowden syndrome and autism. *Am. J. Med. Genet.* 105, 521–524. doi: 10.1002/ajmg.1477
- Gotts, S. J., Simmons, W. K., Milbury, L. A., Wallace, G. L., Cox, R. W., and Martin, A. (2012). Fractionation of social brain circuits in autism spectrum disorders. *Brain* 135, 2711–2725. doi: 10.1093/brain/aww160
- Greco, B., Manago, F., Tucci, V., Kao, H. T., Valtorta, F., and Benfenati, F. (2013). Autism-related behavioral abnormalities in synapsin knockout mice. *Behav. Brain Res.* 251, 65–74. doi: 10.1016/j.bbr.2012.12.015
- Gregory, R. I., Yan, K. P., Amuthan, G., Chendrimada, T., Doratotaj, B., Cooch, N., et al. (2004). The Microprocessor complex mediates the genesis of microRNAs. *Nature* 432, 235–240. doi: 10.1038/nature03120
- Grosskreutz, Y., Betz, H., and Kneussel, M. (2003). Rescue of molybdenum cofactor biosynthesis in gephyrin-deficient mice by a *Cnx1* transgene. *Biochem. Biophys. Res. Commun.* 301, 450–455. doi: 10.1016/s0006-291x(02)03062-0
- Gruber, R., Zhou, Z., Sukchev, M., Joerss, T., Frappart, P. O., and Wang, Z. Q. (2011). MCPH1 regulates the neuroprogenitor division mode by coupling the centrosomal cycle with mitotic entry through the Chk1-Cdc25 pathway. *Nat. Cell Biol.* 13, 1325–1334. doi: 10.1038/ncb2342
- Guilmatre, A., Dubourg, C., Mosca, A. L., Legallie, S., Goldenberg, A., Drouin-Garraud, V., et al. (2009). Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. *Arch. Gen. Psychiatry* 66, 947–956. doi: 10.1001/archgenpsychiatry.2009.80
- Gupta, A., Tsai, L. H., and Wynshaw-Boris, A. (2002). Life is a journey: a genetic look at neocortical development. *Nat. Rev. Genet.* 3, 342–355. doi: 10.1038/nrg799
- Guy, J., Gan, J., Selfridge, J., Cobb, S., and Bird, A. (2007). Reversal of neurological defects in a mouse model of Rett syndrome. *Science* 315, 1143–1147. doi: 10.1126/science.1138389
- Halepoto, D. M., Bashir, S., and A L-Ayadhi, L. (2014). Possible role of brain-derived neurotrophic factor (BDNF) in autism spectrum disorder: current status. *J. Coll. Physicians Surg. Pak.* 24, 274–278.
- Han, W., Kwan, K. Y., Shim, S., Lam, M. M., Shin, Y., Xu, X., et al. (2011). TBRI directly represses *Fezf2* to control the laminar origin and development of the corticospinal tract. *Proc. Natl. Acad. Sci. U S A* 108, 3041–3046. doi: 10.1073/pnas.1016723108
- Happe, F., Ronald, A., and Plomin, R. (2006). Time to give up on a single explanation for autism. *Nat. Neurosci.* 9, 1218–1220. doi: 10.1038/nn1770
- Hatten, M. E. (1999). Central nervous system neuronal migration. *Annu. Rev. Neurosci.* 22, 511–539. doi: 10.1146/annurev.neuro.22.1.511
- Haws, M. E., Jaramillo, T. C., Espinosa, F., Widman, A. J., Stuber, G. D., Sparta, D. R., et al. (2014). PTEN knockdown alters dendritic spine/protrusion morphology, not density. *J. Comp. Neurol.* 522, 1171–1190. doi: 10.1002/cne.23488
- Hazlett, H. C., Poe, M., Gerig, G., Smith, R. G., Provenzale, J., Ross, A., et al. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. *Arch. Gen. Psychiatry* 62, 1366–1376. doi: 10.1001/archpsyc.62.12.1366
- Hevner, R. F., Shi, L., Justice, N., Hsueh, Y., Sheng, M., Smiga, S., et al. (2001). *Tbr1* regulates differentiation of the preplate and layer 6. *Neuron* 29, 353–366. doi: 10.1016/s0896-6273(01)00211-2
- Higgins, J., Midgley, C., Bergh, A. M., Bell, S. M., Askham, J. M., Roberts, E., et al. (2010). Human ASPM participates in spindle organisation, spindle orientation and cytokinesis. *BMC Cell Biol.* 11:85. doi: 10.1186/1471-2121-11-85
- Hinton, V. J., Brown, W. T., Wisniewski, K., and Rudelli, R. D. (1991). Analysis of neocortex in three males with the fragile X syndrome. *Am. J. Med. Genet.* 41, 289–294. doi: 10.1002/ajmg.1320410306
- Hippenmeyer, S., Youn, Y. H., Moon, H. M., Miyamichi, K., Zong, H., Wynshaw-Boris, A., et al. (2010). Genetic mosaic dissection of *Lis1* and *Ndel1* in neuronal migration. *Neuron* 68, 695–709. doi: 10.1016/j.neuron.2010.09.027
- Hirotsune, S., Takahara, T., Sasaki, N., Hirose, K., Yoshiki, A., Ohashi, T., et al. (1995). The reeler gene encodes a protein with an EGF-like motif expressed by pioneer neurons. *Nat. Genet.* 10, 77–83. doi: 10.1038/ng0595-77
- Hoe, H. S., Lee, K. J., Carney, R. S., Lee, J., Markova, A., Lee, J. Y., et al. (2009). Interaction of reelin with amyloid precursor protein promotes neurite outgrowth. *J. Neurosci.* 29, 7459–7473. doi: 10.1523/JNEUROSCI.4872-08.2009
- Hong, S. E., Shugart, Y. Y., Huang, D. T., Shahwan, S. A., Grant, P. E., Hourihane, J. O., et al. (2000). Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human *RELN* mutations. *Nat. Genet.* 26, 93–96. doi: 10.1038/79246
- Hori, K., Nagai, T., Shan, W., Sakamoto, A., Taya, S., Hashimoto, R., et al. (2014). Cytoskeletal regulation by *AUTS2* in neuronal migration and neuritogenesis. *Cell Rep.* 9, 2166–2179. doi: 10.1016/j.celrep.2014.11.045
- Horton, A. C., and Ehlers, M. D. (2004). Secretory trafficking in neuronal dendrites. *Nat. Cell Biol.* 6, 585–591. doi: 10.1038/ncb0704-585
- Horton, A., Rácz, B., Monson, E., Lin, A., Weinberg, R., and Ehlers, M. (2005). Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. *Neuron* 48, 757–771. doi: 10.1016/j.neuron.2005.11.005
- Hou, Q., Gilbert, J., and Man, H. Y. (2011). Homeostatic regulation of AMPA receptor trafficking and degradation by light-controlled single-synaptic activation. *Neuron* 72, 806–818. doi: 10.1016/j.neuron.2011.10.011
- Hou, Q., Ruan, H., Gilbert, J., Wang, G., Ma, Q., Yao, W. D., et al. (2015). MicroRNA miR124 is required for the expression of homeostatic synaptic plasticity. *Nat. Commun.* 6:10045. doi: 10.1038/ncomms10045
- Hou, Q., Zhang, D., Jarzylo, L., Haganir, R. L., and Man, H. Y. (2008). Homeostatic regulation of AMPA receptor expression at single hippocampal synapses. *Proc. Natl. Acad. Sci. U S A* 105, 775–780. doi: 10.1073/pnas.0706447105
- Huang, Z. (2009). Molecular regulation of neuronal migration during neocortical development. *Mol. Cell. Neurosci.* 42, 11–22. doi: 10.1016/j.mcn.2009.06.003



- Huang, J., and Manning, B. D. (2008). The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. *Biochem. J.* 412, 179–190. doi: 10.1042/BJ20080281
- Huang, X. L., Zou, Y. S., Maher, T. A., Newton, S., and Milunsky, J. M. (2010). A *de novo* balanced translocation breakpoint truncating the autism susceptibility candidate 2 (AUTS2) gene in a patient with autism. *Am. J. Med. Genet. A* 152A, 2112–2114. doi: 10.1002/ajmg.a.33497
- Huber, K. M., Gallagher, S. M., Warren, S. T., and Bear, M. F. (2002). Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc. Natl. Acad. Sci. U S A* 99, 7746–7750. doi: 10.1073/pnas.122205699
- Huber, R., Ghilardi, M. F., Massimini, M., and Tononi, G. (2004). Local sleep and learning. *Nature* 430, 78–81. doi: 10.1038/nature02663
- Huguet, G., Ey, E., and Bourgeron, T. (2013). The genetic landscapes of autism spectrum disorders. *Annu. Rev. Genomics Hum. Genet.* 14, 191–213. doi: 10.1146/annurev-genom-091212-153431
- Hussman, J. P. (2001). Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *J. Autism Dev. Disord.* 31, 247–248. doi: 10.1023/A:1010715619091
- Hutsler, J. J., Love, T., and Zhang, H. (2007). Histological and magnetic resonance imaging assessment of cortical layering and thickness in autism spectrum disorders. *Biol. Psychiatry* 61, 449–457. doi: 10.1016/j.biopsych.2006.01.015
- Hutsler, J. J., and Zhang, H. (2010). Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Res.* 1309, 83–94. doi: 10.1016/j.brainres.2009.09.120
- Ifrim, M. F., Williams, K. R., and Bassell, G. J. (2015). Single-molecule imaging of PSD-95 mRNA translation in dendrites and its dysregulation in a mouse model of Fragile X syndrome. *J. Neurosci.* 35, 7116–7130. doi: 10.1523/JNEUROSCI.2802-14.2015
- Iossifov, I., O’Roak, B. J., Sanders, S. J., Ronemus, M., Krumm, N., Levy, D., et al. (2014). The contribution of *de novo* coding mutations to autism spectrum disorder. *Nature* 515, 216–221. doi: 10.1038/nature13908
- Iossifov, I., Ronemus, M., Levy, D., Wang, Z., Hakker, I., Rosenbaum, J., et al. (2012). *De novo* gene disruptions in children on the autistic spectrum. *Neuron* 74, 285–299. doi: 10.1016/j.neuron.2012.04.009
- Irwin, S. A., Idupulapati, M., Gilbert, M. E., Harris, J. B., Chakravarti, A. B., Rogers, E. J., et al. (2002). Dendritic spine and dendritic field characteristics of layer V pyramidal neurons in the visual cortex of fragile-X knockout mice. *Am. J. Med. Genet.* 111, 140–146. doi: 10.1002/ajmg.10500
- Irwin, S. A., Patel, B., Idupulapati, M., Harris, J. B., Crisostomo, R. A., Larsen, B. P., et al. (2001). Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: a quantitative examination. *Am. J. Med. Genet.* 98, 161–167. doi: 10.1002/1096-8628(20010115)98:2<161::AID-AJMG1025>3.3.CO;2-2
- Ishikawa, T., Miyata, S., Koyama, Y., Yoshikawa, K., Hattori, T., Kumamoto, N., et al. (2012). Transient expression of Xpn, an XLMR protein related to neurite extension, during brain development and participation in neurite outgrowth. *Neuroscience* 214, 181–191. doi: 10.1016/j.neuroscience.2012.04.030
- Jackman, C., Horn, N. D., Molleston, J. P., and Sokol, D. K. (2009). Gene associated with seizures, autism and hepatomegaly in an Amish girl. *Pediatr. Neurol.* 40, 310–313. doi: 10.1016/j.pediatrneurol.2008.10.013
- Jackson, A. P., Eastwood, H., Bell, S. M., Adu, J., Toomes, C., Carr, I. M., et al. (2002). Identification of microcephalin, a protein implicated in determining the size of the human brain. *Am. J. Hum. Genet.* 71, 136–142. doi: 10.1086/341283
- Jackson, A. P., McHale, D. P., Campbell, D. A., Jafri, H., Rashid, Y., Mannan, J., et al. (1998). Primary autosomal recessive microcephaly (MCPH1) maps to chromosome 8p22-pter. *Am. J. Hum. Genet.* 63, 541–546. doi: 10.1086/301966
- Jamain, S., Quach, H., Betancur, C., Råstam, M., Colineaux, C., Gillberg, I., et al. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat. Genet.* 34, 27–29. doi: 10.1038/ng1136
- Jan, Y. N., and Jan, L. Y. (2010). Branching out: mechanisms of dendritic arborization. *Nat. Rev. Neurosci.* 11, 316–328. doi: 10.1038/nrn2836
- Jang, S. W., Liu, X., Pradoldej, S., Tosini, G., Chang, Q., Iuvone, P. M., et al. (2010). N-acetylserotonin activates TrkB receptor in a circadian rhythm. *Proc. Natl. Acad. Sci. U S A* 107, 3876–3881. doi: 10.1073/pnas.0912531107
- Jiang, M., Ash, R. T., Baker, S. A., Suter, B., Ferguson, A., Park, J., et al. (2013). Dendritic arborization and spine dynamics are abnormal in the mouse model of MECP2 duplication syndrome. *J. Neurosci.* 33, 19518–19533. doi: 10.1523/JNEUROSCI.1745-13.2013
- Jossin, Y., and Goffinet, A. M. (2007). Reelin signals through phosphatidylinositol 3-kinase and Akt to control cortical development and through mTor to regulate dendritic growth. *Mol. Cell. Biol.* 27, 7113–7124. doi: 10.1128/mcb.00928-07
- Jugloff, D. G., Jung, B. P., Purushotham, D., Logan, R., and Eubanks, J. H. (2005). Increased dendritic complexity and axonal length in cultured mouse cortical neurons overexpressing methyl-CpG-binding protein MeCP2. *Neurobiol. Dis.* 19, 18–27. doi: 10.1016/j.nbd.2004.11.002
- Kaindl, A. M., Passemard, S., Kumar, P., Kraemer, N., Issa, L., Zwirner, A., et al. (2010). Many roads lead to primary autosomal recessive microcephaly. *Prog. Neurobiol.* 90, 363–383. doi: 10.1016/j.pneurobio.2009.11.002
- Kapitein, L. C., Schlager, M. A., Kuijpers, M., Wulf, P. S., van Spronsen, M., MacKintosh, F. C., et al. (2010). Mixed microtubules steer dynein-driven cargo transport into dendrites. *Curr. Biol.* 20, 290–299. doi: 10.1016/j.cub.2009.12.052
- Kasai, H., Matsuzaki, M., Noguchi, J., Yasumatsu, N., and Nakahara, H. (2003). Structure-stability-function relationships of dendritic spines. *Trends Neurosci.* 26, 360–368. doi: 10.1016/s0166-2236(03)00162-0
- Kasarpalkar, N. J., Kothari, S. T., and Dave, U. P. (2014). Brain-derived neurotrophic factor in children with autism spectrum disorder. *Ann. Neurosci.* 21, 129–133. doi: 10.5214/ans.0972.7531.210403
- Katayama, Y., Nishiyama, M., Shoji, H., Ohkawa, Y., Kawamura, A., Sato, T., et al. (2016). CHD8 haploinsufficiency results in autistic-like phenotypes in mice. *Nature* 537, 675–679. doi: 10.1038/nature19357
- Kelleher, R., and Bear, M. (2008). The autistic neuron: troubled translation? *Cell* 135, 401–406. doi: 10.1016/j.cell.2008.10.017
- Ketzel, M., and Gitler, D. (2014). Epileptic synapsin triple knockout mice exhibit progressive long-term aberrant plasticity in the entorhinal cortex. *Cereb. Cortex* 24, 996–1008. doi: 10.1093/cercor/bhs384
- Kishi, N., and Macklis, J. D. (2004). MECP2 is progressively expressed in post-migratory neurons and is involved in neuronal maturation rather than cell fate decisions. *Mol. Cell. Neurosci.* 27, 306–321. doi: 10.1016/j.mcn.2004.07.006
- Kitagawa, M., Umez, M., Aoki, J., Koizumi, H., Arai, H., and Inoue, K. (2000). Direct association of LIS1, the lissencephaly gene product, with a mammalian homologue of a fungal nuclear distribution protein, rNUDE. *FEBS Lett.* 479, 57–62. doi: 10.1016/s0014-5793(00)01856-1
- Kneussel, M., Brandstatter, J. H., Laube, B., Stahl, S., Muller, U., and Betz, H. (1999). Loss of postsynaptic GABA<sub>A</sub> receptor clustering in gephyrin-deficient mice. *J. Neurosci.* 19, 9289–9297.
- Kobayashi, T., Minowa, O., Sugitani, Y., Takai, S., Mitani, H., Kobayashi, E., et al. (2001). A germ-line Tsc1 mutation causes tumor development and embryonic lethality that are similar, but not identical to, those caused by Tsc2 mutation in mice. *Proc. Natl. Acad. Sci. U S A* 98, 8762–8767. doi: 10.1073/pnas.151033798
- Koekkoek, S. K., Yamaguchi, K., Milojkovic, B. A., Dortland, B. R., Ruigrok, T. J., Maex, R., et al. (2005). Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile X syndrome. *Neuron* 47, 339–352. doi: 10.1016/j.neuron.2005.07.005
- Krawczun, M. S., Jenkins, E. C., and Brown, W. T. (1985). Analysis of the fragile-X chromosome: localization and detection of the fragile site in high resolution preparations. *Hum. Genet.* 69, 209–211. doi: 10.1007/bf00293026
- Kriegstein, A. R., and Noctor, S. C. (2004). Patterns of neuronal migration in the embryonic cortex. *Trends Neurosci.* 27, 392–399. doi: 10.1016/j.tins.2004.05.001
- Kuhn, M., Wolf, E., Maier, J. G., Mainberger, F., Feige, B., Schmid, H., et al. (2016). Sleep recalibrates homeostatic and associative synaptic plasticity in the human cortex. *Nat. Commun.* 7:12455. doi: 10.1038/ncomms12455
- Kuroda, Y., Ohashi, I., Naruto, T., Ida, K., Enomoto, Y., Saito, T., et al. (2015). Delineation of the KIAA2022 mutation phenotype: two patients with X-linked intellectual disability and distinctive features. *Am. J. Med. Genet. A* 167, 1349–1353. doi: 10.1002/ajmg.a.37002
- Kwiatkowski, D. J., and Manning, B. D. (2005). Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. *Hum. Mol. Genet.* 14, R251–R258. doi: 10.1093/hmg/ddi260
- Kwon, C.-H., Luikart, B., Powell, C., Zhou, J., Matheny, S., Zhang, W., et al. (2006). Pten regulates neuronal arborization and social interaction in mice. *Neuron* 50, 377–388. doi: 10.1016/j.neuron.2006.03.023



- Lainhart, J. E., Piven, J., Wzorek, M., Landa, R., Santangelo, S. L., Coon, H., et al. (1997). Macrocephaly in children and adults with autism. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 282–290. doi: 10.1097/00004583-199702000-00019
- Lancot, A. A., Peng, C. Y., Pawlisz, A. S., Joksimovic, M., and Feng, Y. (2013). Spatially dependent dynamic MAPK modulation by the Nde1-Lis1-Brap complex patterns mammalian CNS. *Dev. Cell* 25, 241–255. doi: 10.1016/j.devcel.2013.04.006
- Landa, R. J. (2008). Diagnosis of autism spectrum disorders in the first 3 years of life. *Nat. Clin. Pract. Neurol.* 4, 138–147. doi: 10.1038/ncpneu0731
- Laplante, M., and Sabatini, D. M. (2012). mTOR signaling in growth control and disease. *Cell* 149, 274–293. doi: 10.1016/j.cell.2012.03.017
- Larson, J., Jessen, R. E., Kim, D., Fine, A. K., and du Hoffmann, J. (2005). Age-dependent and selective impairment of long-term potentiation in the anterior piriform cortex of mice lacking the fragile X mental retardation protein. *J. Neurosci.* 25, 9460–9469. doi: 10.1523/jneurosci.2638-05.2005
- Lauterborn, J. C., Rex, C. S., Kramár, E., Chen, L. Y., Pandeyarajan, V., Lynch, G., et al. (2007). Brain-derived neurotrophic factor rescues synaptic plasticity in a mouse model of fragile X syndrome. *J. Neurosci.* 27, 10685–10694. doi: 10.1523/jneurosci.2624-07.2007
- Lavdas, A. A., Grigoriou, M., Pachnis, V., and Parnavelas, J. G. (1999). The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex. *J. Neurosci.* 19, 7881–7888.
- Lee, A., Li, W., Xu, K., Bogert, B. A., Su, K., and Gao, F. B. (2003). Control of dendritic development by the *Drosophila* fragile X-related gene involves the small GTPase Rac1. *Development* 130, 5543–5552. doi: 10.1242/dev.00792
- Lesch, K. P., Timmesfeld, N., Renner, T. J., Halperin, R., Roser, C., Nguyen, T. T., et al. (2008). Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. *J. Neural Transm.* 115, 1573–1585. doi: 10.1007/s00702-008-0119-3
- Letinic, K., Zoncu, R., and Rakic, P. (2002). Origin of GABAergic neurons in the human neocortex. *Nature* 417, 645–649. doi: 10.1038/nature00779
- Levitt, P., and Campbell, D. B. (2009). The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders. *J. Clin. Invest.* 119, 747–754. doi: 10.1172/jci37934
- Li, J., Pelletier, M. R., Perez Velazquez, J. L., and Carlen, P. L. (2002). Reduced cortical synaptic plasticity and GluR1 expression associated with fragile X mental retardation protein deficiency. *Mol. Cell. Neurosci.* 19, 138–151. doi: 10.1006/mcne.2001.1085
- Li, Z., Van Aelst, L., and Cline, H. T. (2000). Rho GTPases regulate distinct aspects of dendritic arbor growth in *Xenopus* central neurons *in vivo*. *Nat. Neurosci.* 3, 217–225. doi: 10.1038/72920
- Lim, S., Naisbitt, S., Yoon, J., Hwang, J. I., Suh, P. G., Sheng, M., et al. (1999). Characterization of the Shank family of synaptic proteins. Multiple genes, alternative splicing, and differential expression in brain and development. *J. Biol. Chem.* 274, 29510–29518. doi: 10.1074/jbc.274.41.29510
- Lionel, A. C., Crosbie, J., Barbosa, N., Goodale, T., Thiruvahindrapuram, B., Rickaby, J., et al. (2011). Rare copy number variation discovery and cross-disorder comparisons identify risk genes for ADHD. *Sci. Transl. Med.* 3:95ra75. doi: 10.1126/scitranslmed.3002464
- Lionel, A. C., Tammimies, K., Vaags, A. K., Rosenfeld, J. A., Ahn, J. W., Merico, D., et al. (2014). Disruption of the ASTN2/TRIM32 locus at 9q33.1 is a risk factor in males for autism spectrum disorders, ADHD and other neurodevelopmental phenotypes. *Hum. Mol. Genet.* 23, 2752–2768. doi: 10.1093/hmg/ddt669
- Lionel, A. C., Vaags, A. K., Sato, D., Gazzellone, M. J., Mitchell, E. B., Chen, H. Y., et al. (2013). Rare exonic deletions implicate the synaptic organizer Gephyrin (GPHN) in risk for autism, schizophrenia and seizures. *Hum. Mol. Genet.* 22, 2055–2066. doi: 10.1093/hmg/ddt056
- Liu, Y., Zhao, D., Dong, R., Yang, X., Zhang, Y., Tammimies, K., et al. (2015). *De novo* exon 1 deletion of AUTS2 gene in a patient with autism spectrum disorder and developmental delay: a case report and a brief literature review. *Am. J. Med. Genet. A* 167, 1381–1385. doi: 10.1002/ajmg.a.37050
- Lu, Q., Paredes, M., Medina, M., and Zhou, J. (1999).  $\Delta$ -Catenin, an adhesive junction-associated protein which promotes cell scattering. *J. Cell Biol.* 144, 519–532.
- Lu, Y., Wang, F., Li, Y., Ferris, J., Lee, J. A., and Gao, F. B. (2009). The *Drosophila* homologue of the Angelman syndrome ubiquitin ligase regulates the formation of terminal dendritic branches. *Hum. Mol. Genet.* 18, 454–462. doi: 10.1093/hmg/ddn373
- Mabb, A. M., Judson, M. C., Zylka, M. J., and Philpot, B. D. (2011). Angelman syndrome: insights into genomic imprinting and neurodevelopmental phenotypes. *Trends Neurosci.* 34, 293–303. doi: 10.1016/j.tins.2011.04.001
- MacLaurin, S. A., Krucker, T., and Fish, K. N. (2007). Hippocampal dendritic arbor growth *in vitro*: regulation by Reelin-Disabled-1 signaling. *Brain Res.* 1172, 1–9. doi: 10.1016/j.brainres.2007.07.035
- Major, M. B., Roberts, B. S., Berndt, J. D., Marine, S., Anastas, J., Chung, N., et al. (2008). New regulators of Wnt/ $\beta$ -catenin signaling revealed by integrative molecular screening. *Sci. Signal.* 1:ra12. doi: 10.1126/scisignal.2000037
- Marín, O., and Rubenstein, J. L. (2001). A long, remarkable journey: tangential migration in the telencephalon. *Nat. Rev. Neurosci.* 2, 780–790. doi: 10.1038/35097509
- Martinez, M., Ochiishi, T., Majewski, M., and Kosik, K. S. (2003). Dual regulation of neuronal morphogenesis by a  $\delta$ -catenin-cortactin complex and Rho. *J. Cell Biol.* 162, 99–111. doi: 10.1083/jcb.200211025
- Matsuki, T., Matthews, R. T., Cooper, J. A., van der Brug, M. P., Cookson, M. R., Hardy, J. A., et al. (2010). Reelin and stk25 have opposing roles in neuronal polarization and dendritic Golgi deployment. *Cell* 143, 826–836. doi: 10.1016/j.cell.2010.10.029
- Maximo, J. O., Cadena, E. J., and Kana, R. K. (2014). The implications of brain connectivity in the neuropsychology of autism. *Neuropsychol. Rev.* 24, 16–31. doi: 10.1007/s11065-014-9250-0
- McCarthy, S. E., Makarov, V., Kirov, G., Addington, A. M., McClellan, J., Yoon, S., et al. (2009). Microduplications of 16p11.2 are associated with schizophrenia. *Nat. Genet.* 41, 1223–1227. doi: 10.1038/ng.474
- McKenney, R. J., Vershini, M., Kunwar, A., Vallee, R. B., and Gross, S. P. (2010). LIS1 and NudE induce a persistent dynein force-producing state. *Cell* 141, 304–314. doi: 10.1016/j.cell.2010.02.035
- McKinney, B. C., Grossman, A. W., Elisseeu, N. M., and Greenough, W. T. (2005). Dendritic spine abnormalities in the occipital cortex of C57BL/6 Fmr1 knockout mice. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 136B, 98–102. doi: 10.1002/ajmg.b.30183
- Mefford, H. C., Muhle, H., Ostertag, P., von Spiczak, S., Buysse, K., Baker, C., et al. (2010). Genome-wide copy number variation in epilepsy: novel susceptibility loci in idiopathic generalized and focal epilepsies. *PLoS Genet.* 6:e1000962. doi: 10.1371/journal.pgen.1000962
- Miao, S., Chen, R., Ye, J., Tan, G. H., Li, S., Zhang, J., et al. (2013). The Angelman syndrome protein Ube3a is required for polarized dendrite morphogenesis in pyramidal neurons. *J. Neurosci.* 33, 327–333. doi: 10.1523/jneurosci.2509-12.2013
- Michalon, A., Sidorov, M., Ballard, T. M., Ozmen, L., Spooren, W., Wettstein, J. G., et al. (2012). Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. *Neuron* 74, 49–56. doi: 10.1016/j.neuron.2012.03.009
- Miles, J. H., Takahashi, T. N., Bagby, S., Sahota, P. K., Vaslow, D. F., Wang, C. H., et al. (2005). Essential versus complex autism: definition of fundamental prognostic subtypes. *Am. J. Med. Genet. A* 135, 171–180. doi: 10.1002/ajmg.a.30590
- Ming, G. L., and Song, H. (2005). Adult neurogenesis in the mammalian central nervous system. *Annu. Rev. Neurosci.* 28, 223–250. doi: 10.1146/annurev.neuro.28.051804.101459
- Missler, M., Zhang, W., Rohlmann, A., Kattenstroth, G., Hammer, R. E., Gottmann, K., et al. (2003).  $\alpha$ -neurexins couple  $Ca^{2+}$  channels to synaptic vesicle exocytosis. *Nature* 423, 939–948. doi: 10.1038/nature01755
- Morgan, J. T., Barger, N., Amaral, D. G., and Schumann, C. M. (2014). Stereological study of amygdala glial populations in adolescents and adults with autism spectrum disorder. *PLoS One* 9:e110356. doi: 10.1371/journal.pone.0110356
- Morrow, E. M., Yoo, S. Y., Flavell, S. W., Kim, T. K., Lin, Y., Hill, R. S., et al. (2008). Identifying autism loci and genes by tracing recent shared ancestry. *Science* 321, 218–223. doi: 10.1126/science.1157657
- Nadarajah, B., and Parnavelas, J. G. (2002). Modes of neuronal migration in the developing cerebral cortex. *Nat. Rev. Neurosci.* 3, 423–432. doi: 10.1038/nrn845
- Nakayama, A. Y., Harms, M. B., and Luo, L. (2000). Small GTPases Rac and Rho in the maintenance of dendritic spines and branches in hippocampal pyramidal neurons. *J. Neurosci.* 20, 5329–5338.
- Neale, B. M., Kou, Y., Liu, L., Ma'ayan, A., Samocha, K. E., Sabo, A., et al. (2012). Patterns and rates of exonic *de novo* mutations in autism spectrum disorders. *Nature* 485, 242–245. doi: 10.1038/nature11011

- Nery, S., Fishell, G., and Corbin, J. G. (2002). The caudal ganglionic eminence is a source of distinct cortical and subcortical cell populations. *Nat. Neurosci.* 5, 1279–1287. doi: 10.1038/nn971
- Nichols, A. J., and Olson, E. C. (2010). Reelin promotes neuronal orientation and dendritogenesis during preplate splitting. *Cereb. Cortex* 20, 2213–2223. doi: 10.1093/cercor/bhp303
- Niethammer, M., Smith, D. S., Ayala, R., Peng, J., Ko, J., Lee, M. S., et al. (2000). NUDEL is a novel Cdk5 substrate that associates with LIS1 and cytoplasmic dynein. *Neuron* 28, 697–711. doi: 10.1016/s0896-6273(00)00147-1
- Niu, S., Renfro, A., Quattrocchi, C. C., Sheldon, M., and D'Arcangelo, G. (2004). Reelin promotes hippocampal dendrite development through the VLDLR/ApoER2-Dab1 pathway. *Neuron* 41, 71–84. doi: 10.1016/s0896-6273(03)00819-5
- Noor, A., Dupuis, L., Mittal, K., Lionel, A. C., Marshall, C. R., Scherer, S. W., et al. (2015). 15q11.2 Duplication encompassing only the UBE3A gene is associated with developmental delay and neuropsychiatric phenotypes. *Hum. Mutat.* 36, 689–693. doi: 10.1002/humu.22800
- Nowicki, S. T., Tassone, F., Ono, M. Y., Ferranti, J., Croquette, M. F., Goodlin-Jones, B., et al. (2007). The Prader-Willi phenotype of fragile X syndrome. *J. Dev. Behav. Pediatr.* 28, 133–138. doi: 10.1097/01.DBP.0000267563.18952.c9
- Ogawa, S., Kwon, C. H., Zhou, J., Koovakkattu, D., Parada, L. F., and Sinton, C. M. (2007). A seizure-prone phenotype is associated with altered free-running rhythm in Pten mutant mice. *Brain Res.* 1168, 112–123. doi: 10.1016/j.brainres.2007.06.074
- Orloff, M. S., He, X., Peterson, C., Chen, F., Chen, J. L., Mester, J. L., et al. (2013). Germline PIK3CA and AKT1 mutations in Cowden and Cowden-like syndromes. *Am. J. Hum. Genet.* 92, 76–80. doi: 10.1016/j.ajhg.2012.10.021
- Orosco, L. A., Ross, A. P., Cates, S. L., Scott, S. E., Wu, D., Sohn, J., et al. (2014). Loss of Wdfy3 in mice alters cerebral cortical neurogenesis reflecting aspects of the autism pathology. *Nat. Commun.* 5:4692. doi: 10.1038/ncomms5692
- Osterweil, E. K., Krueger, D. D., Reinhold, K., and Bear, M. F. (2010). Hypersensitivity to mGluR5 and ERK1/2 leads to excessive protein synthesis in the hippocampus of a mouse model of fragile X syndrome. *J. Neurosci.* 30, 15616–15627. doi: 10.1523/jneurosci.3888-10.2010
- Ozgen, H. M., van Daalen, E., Bolton, P. F., Maloney, V. K., Huang, S., Cresswell, L., et al. (2009). Copy number changes of the microcephalin 1 gene (MCPH1) in patients with autism spectrum disorders. *Clin. Genet.* 76, 348–356. doi: 10.1111/j.1399-0004.2009.01254.x
- Pagan, C., Delorme, R., Callebort, J., Goubran-Botros, H., Amsellem, F., Drouot, X., et al. (2014). The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectrum disorders. *Transl. Psychiatry* 4:e479. doi: 10.1038/tp.2014.120
- Panganiban, G., and Rubenstein, J. L. (2002). Developmental functions of the Distal-less/Dlx homeobox genes. *Development* 129, 4371–4386.
- Pardo, C. A., and Eberhart, C. G. (2007). The neurobiology of autism. *Brain Pathol.* 17, 434–447. doi: 10.1111/j.1750-3639.2007.00102.x
- Parikshak, N. N., Luo, R., Zhang, A., Won, H., Lowe, J. K., Chandran, V., et al. (2013). Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. *Cell* 155, 1008–1021. doi: 10.1016/j.cell.2013.10.031
- Passemar, S., Titomanlio, L., Elmaleh, M., Afenjar, A., Alessandri, J. L., Andria, G., et al. (2009). Expanding the clinical and neuroradiologic phenotype of primary microcephaly due to ASPM mutations. *Neurology* 73, 962–969. doi: 10.1212/wnl.0b013e3181b8799a
- Passemar, S., Verloes, A., Billette de Villemeur, T., Boespflug-Tanguy, O., Hernandez, K., Laurent, M., et al. (2016). Abnormal spindle-like microcephaly-associated (ASPM) mutations strongly disrupt neocortical structure but spare the hippocampus and long-term memory. *Cortex* 74, 158–176. doi: 10.1016/j.cortex.2015.10.010
- Pathania, M., Davenport, E. C., Muir, J., Sheehan, D. F., López-Doménech, G., and Kittler, J. T. (2014). The autism and schizophrenia associated gene CYFIP1 is critical for the maintenance of dendritic complexity and the stabilization of mature spines. *Transl. Psychiatry* 4:e374. doi: 10.1038/tp.2014.36
- Pawlisz, A. S., and Feng, Y. (2011). Three-dimensional regulation of radial glial functions by Lis1-Nde1 and dystrophin glycoprotein complexes. *PLoS Biol.* 9:e1001172. doi: 10.1371/journal.pbio.1001172
- Pawlisz, A. S., Mutch, C., Wynshaw-Boris, A., Chenn, A., Walsh, C. A., and Feng, Y. (2008). Lis1-Nde1-dependent neuronal fate control determines cerebral cortical size and lamination. *Hum. Mol. Genet.* 17, 2441–2455. doi: 10.1093/hmg/ddn144
- Peça, J., Feliciano, C., Ting, J. T., Wang, W., Wells, M. F., Venkatraman, T. N., et al. (2011). Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. *Nature* 472, 437–442. doi: 10.1038/nature09965
- Pelphrey, K. A., and Carter, E. J. (2008). Brain mechanisms for social perception: lessons from autism and typical development. *Ann. N Y Acad. Sci.* 1145, 283–299. doi: 10.1196/annals.1416.007
- Peñarikano, O., Abrahams, B. S., Herman, E. I., Winden, K. D., Gdalyahu, A., Dong, H., et al. (2011). Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* 147, 235–246. doi: 10.1016/j.cell.2011.08.040
- Persico, A., and Bourgeron, T. (2006). Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci.* 29, 349–358. doi: 10.1016/j.tins.2006.05.010
- Persico, A. M., D'Agruma, L., Maiorano, N., Totaro, A., Militerni, R., Bravaccio, C., et al. (2001). Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder. *Mol. Psychiatry* 6, 150–159. doi: 10.1038/sj.mp.40.00850
- Pescosolido, M. F., Yang, U., Sabbagh, M., and Morrow, E. M. (2012). Lighting a path: genetic studies pinpoint neurodevelopmental mechanisms in autism and related disorders. *Dialogues Clin. Neurosci.* 14, 239–252.
- Peters, S. U., Beaudet, A. L., Madduri, N., and Bacino, C. A. (2004). Autism in Angelman syndrome: implications for autism research. *Clin. Genet.* 66, 530–536. doi: 10.1111/j.1399-0004.2004.00362.x
- Phelan, M. C. (2008). Deletion 22q13.3 syndrome. *Orphanet J. Rare Dis.* 3:14. doi: 10.1186/1750-1172-3-14
- Phillips, M., and Pozzo-Miller, L. (2015). Dendritic spine dysgenesis in autism related disorders. *Neurosci. Lett.* 601, 30–40. doi: 10.1016/j.neulet.2015.01.011
- Pinto, D., Pagnamenta, A. T., Klei, L., Anney, R., Merico, D., Regan, R., et al. (2010). Functional impact of global rare copy number variation in autism spectrum disorders. *Nature* 466, 368–372. doi: 10.1038/nature09146
- Poliak, S., Gollan, L., Martinez, R., Custer, A., Einheber, S., Salzer, J. L., et al. (1999). Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K<sup>+</sup> channels. *Neuron* 24, 1037–1047. doi: 10.1016/s0896-6273(00)81049-1
- Polleux, F., Whitford, K. L., Dijkhuizen, P. A., Vitalis, T., and Ghosh, A. (2002). Control of cortical interneuron migration by neurotrophins and PI3-kinase signaling. *Development* 129, 3147–3160.
- Poluch, S., and Juliano, S. L. (2007). A normal radial glial scaffold is necessary for migration of interneurons during neocortical development. *Glia* 55, 822–830. doi: 10.1002/glia.20488
- Pouloupoulos, A., Aramuni, G., Meyer, G., Soykan, T., Hoon, M., Papadopoulos, T., et al. (2009). Neuroligin 2 drives postsynaptic assembly at perisomatic inhibitory synapses through gephyrin and collyistin. *Neuron* 63, 628–642. doi: 10.1016/j.neuron.2009.08.023
- Pozo, K., and Goda, Y. (2010). Unraveling mechanisms of homeostatic synaptic plasticity. *Neuron* 66, 337–351. doi: 10.1016/j.neuron.2010.04.028
- Pulvers, J. N., Bryk, J., Fish, J. L., Wilsch-Bräuninger, M., Arai, Y., Schreier, D., et al. (2010). Mutations in mouse Aspm (abnormal spindle-like microcephaly associated) cause not only microcephaly but also major defects in the germline. *Proc. Natl. Acad. Sci. U S A* 107, 16595–16600. doi: 10.1073/pnas.1010494107
- Qiu, Z., Sylwestrak, E. L., Lieberman, D. N., Zhang, Y., Liu, X. Y., and Ghosh, A. (2012). The Rett syndrome protein MeCP2 regulates synaptic scaling. *J. Neurosci.* 32, 989–994. doi: 10.1523/jneurosci.0175-11.2012
- Rakic, P. (1972). Mode of cell migration to the superficial layers of fetal monkey neocortex. *J. Comp. Neurol.* 145, 61–83. doi: 10.1002/cne.9014.50105
- Rakic, S., and Zecevic, N. (2000). Programmed cell death in the developing human telencephalon. *Eur. J. Neurosci.* 12, 2721–2734. doi: 10.1046/j.1460-9568.2000.00153.x
- Rauen, K. A., Schoyer, L., McCormick, F., Lin, A. E., Allanson, J. E., Stevenson, D. A., et al. (2010). Proceedings from the 2009 genetic syndromes of the Ras/MAPK pathway: from bedside to bench and back. *Am. J. Med. Genet. A* 152A, 4–24. doi: 10.1002/ajmg.a.33183

- Redcay, E. (2008). The superior temporal sulcus performs a common function for social and speech perception: implications for the emergence of autism. *Neurosci. Biobehav. Rev.* 32, 123–142. doi: 10.1016/j.neubiorev.2007.06.004
- Redies, C., Hertel, N., and Hubner, C. A. (2012). Cadherins and neuropsychiatric disorders. *Brain Res.* 1470, 130–144. doi: 10.1016/j.brainres.2012.06.020
- Redmond, L., Kashani, A. H., and Ghosh, A. (2002). Calcium regulation of dendritic growth via CaM kinase IV and CREB-mediated transcription. *Neuron* 34, 999–1010. doi: 10.1016/s0896-6273(02)00737-7
- Reiner, O. (2000). LIS1. Let's interact sometimes... (part 1). *Neuron* 28, 633–636. doi: 10.1016/S0896-6273(00)00142-2
- Reiner, O., Carrozzo, R., Shen, Y., Wehnert, M., Faustinella, F., Dobyns, W. B., et al. (1993). Isolation of a Miller-Dieker lissencephaly gene containing G protein  $\beta$ -subunit-like repeats. *Nature* 364, 717–721. doi: 10.1136/jmg.30.11.972-c
- Reiner, O., Karzbrun, E., Kshirsagar, A., and Kaibuchi, K. (2016). Regulation of neuronal migration, an emerging topic in autism spectrum disorders. *J. Neurochem.* 136, 440–456. doi: 10.1111/jnc.13403
- Restivo, L., Ferrari, F., Passino, E., Sgobio, C., Bock, J., Oostra, B. A., et al. (2005). Enriched environment promotes behavioral and morphological recovery in a mouse model for the fragile X syndrome. *Proc. Natl. Acad. Sci. U S A* 102, 11557–11562. doi: 10.1073/pnas.0504984102
- Richards, M. W., Leung, J. W., Roe, S. M., Li, K., Chen, J., and Bayliss, R. (2010). A pocket on the surface of the N-terminal BRCT domain of Mcph1 is required to prevent abnormal chromosome condensation. *J. Mol. Biol.* 395, 908–915. doi: 10.1016/j.jmb.2009.11.029
- Roberts, E., Hampshire, D. J., Pattison, L., Springell, K., Jafri, H., Corry, P., et al. (2002). Autosomal recessive primary microcephaly: an analysis of locus heterogeneity and phenotypic variation. *J. Med. Genet.* 39, 718–721. doi: 10.1136/jmg.39.10.718
- Rosahl, T. W., Spillane, D., Missler, M., Herz, J., Selig, D. K., Wolff, J. R., et al. (1995). Essential functions of synapsins I and II in synaptic vesicle regulation. *Nature* 375, 488–493. doi: 10.1038/375488a0
- Rosser, T. L., and Packer, R. J. (2003). Neurocognitive dysfunction in children with neurofibromatosis type 1. *Curr. Neurol. Neurosci. Rep.* 3, 129–136. doi: 10.1007/s11910-003-0064-3
- Rubenstein, J. L., and Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav.* 2, 255–267. doi: 10.1034/j.1601-183x.2003.00037.x
- Rudelli, R. D., Brown, W. T., Wisniewski, K., Jenkins, E. C., Laure-Kamionowska, M., Connell, F., et al. (1985). Adult fragile X syndrome. Clinico-neuropathologic findings. *Acta Neuropathol.* 67, 289–295. doi: 10.1007/bf00687814
- Sacco, R., Militerni, R., Frolli, A., Bravaccio, C., Gritti, A., Elia, M., et al. (2007). Clinical, morphological, and biochemical correlates of head circumference in autism. *Biol. Psychiatry* 62, 1038–1047. doi: 10.1016/j.biopsych.2007.04.039
- Salinger, W. L., Ladrow, P., and Wheeler, C. (2003). Behavioral phenotype of the reeler mutant mouse: effects of RELN gene dosage and social isolation. *Behav. Neurosci.* 117, 1257–1275. doi: 10.1037/0735-7044.117.6.1257
- Sanders, S. J., Ercan-Sencicek, A. G., Hus, V., Luo, R., Murtha, M. T., Moreno-DeLuca, D., et al. (2011). Multiple recurrent *de novo* CNVs, including duplications of the 7Q12.23 Williams syndrome region, are strongly associated with autism. *Neuron* 70, 863–885. doi: 10.1016/j.neuron.2011.05.002
- Santorio, M. R., Bray, S. M., and Warren, S. T. (2012). Molecular mechanisms of fragile X syndrome: a twenty-year perspective. *Annu. Rev. Pathol.* 7, 219–245. doi: 10.1146/annurev-pathol-011811-132457
- Sasaki, S., Shionoya, A., Ishida, M., Gambello, M. J., Yingling, J., Wynshaw-Boris, A., et al. (2000). A LIS1/NUDEL/cytoplasmic dynein heavy chain complex in the developing and adult nervous system. *Neuron* 28, 681–696. doi: 10.1016/s0896-6273(00)00146-x
- Schnell, E., Bensen, A. L., Washburn, E. K., and Westbrook, G. L. (2012). Neuroligin-1 overexpression in newborn granule cells *in vivo*. *PLoS One* 7:e48045. doi: 10.1371/journal.pone.0048045
- Schumann, C. M., Bloss, C. S., Barnes, C. C., Wideman, G. M., Carper, R. A., Akshoomoff, N., et al. (2010). Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J. Neurosci.* 30, 4419–4427. doi: 10.1523/jneurosci.5714-09.2010
- Sekine, K., Kubo, K., and Nakajima, K. (2014). How does Reelin control neuronal migration and layer formation in the developing mammalian neocortex? *Neurosci. Res.* 86, 50–58. doi: 10.1016/j.neures.2014.06.004
- Shahbazian, M., Young, J., Yuva-Paylor, L., Spencer, C., Antalffy, B., Noebels, J., et al. (2002). Mice with truncated MeCP2 recapitulate many Rett syndrome features and display hyperacetylation of histone H3. *Neuron* 35, 243–254. doi: 10.1016/s0896-6273(02)00768-7
- Shim, S. Y., Wang, J., Asada, N., Neumayer, G., Tran, H. C., Ishiguro, K., et al. (2008). Protein 600 is a microtubule/endoplasmic reticulum-associated protein in CNS neurons. *J. Neurosci.* 28, 3604–3614. doi: 10.1523/jneurosci.5278-07.2008
- Skalecka, A., Liszewska, E., Bilinski, R., Gkogkas, C., Khouutorsky, A., Malik, A. R., et al. (2016). mTOR kinase is needed for the development and stabilization of dendritic arbors in newly born olfactory bulb neurons. *Dev. Neurobiol.* 76, 1308–1327. doi: 10.1002/dneu.22392
- Smith, S. E., Zhou, Y. D., Zhang, G., Jin, Z., Stoppel, D. C., and Anderson, M. P. (2011). Increased gene dosage of *Ube3a* results in autism traits and decreased glutamate synaptic transmission in mice. *Sci. Transl. Med.* 3:103ra97. doi: 10.1126/scitranslmed.3002627
- Soden, M. E., and Chen, L. (2010). Fragile X protein FMRP is required for homeostatic plasticity and regulation of synaptic strength by retinoic acid. *J. Neurosci.* 30, 16910–16921. doi: 10.1523/jneurosci.3660-10.2010
- Srinivasan, K., Leone, D. P., Bateson, R. K., Dobрева, G., Kohwi, Y., Kohwi-Shigematsu, T., et al. (2012). A network of genetic repression and depression specifies projection fates in the developing neocortex. *Proc. Natl. Acad. Sci. U S A* 109, 19071–19078. doi: 10.1073/pnas.1216793109
- Steffenburg, S., Gillberg, C. L., Steffenburg, U., and Kyllerman, M. (1996). Autism in Angelman syndrome: a population-based study. *Pediatr. Neurol.* 14, 131–136. doi: 10.1016/0887-8994(96)00011-2
- Stiles, J., and Jernigan, T. L. (2010). The basics of brain development. *Neuropsychol. Rev.* 20, 327–348. doi: 10.1007/s11065-010-9148-4
- Stoner, R., Chow, M. L., Boyle, M. P., Sunkin, S. M., Mouton, P. R., Roy, S., et al. (2014). Patches of disorganization in the neocortex of children with autism. *N Engl J. Med.* 370, 1209–1219. doi: 10.1056/NEJMoa1307491
- Stone, J. L., O'Donovan, M. C., Gurling, H., Kirov, G. K., Blackwood, D. H. R., Corvin, A., et al. (2008). Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 455, 237–241. doi: 10.1038/nature07239
- Strauss, K. A., Puffenberger, E. G., Huentelman, M. J., Gottlieb, S., Dobrin, S. E., Parod, J. M., et al. (2006). Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J. Med.* 354, 1370–1377. doi: 10.1056/NEJMoa052773
- Stromme, P., Mangelsdorf, M. E., Scheffer, I. E., and Gecz, J. (2002). Infantile spasms, dystonia, and other X-linked phenotypes caused by mutations in Aristaless related homeobox gene, ARX. *Brain Dev.* 24, 266–268. doi: 10.1016/s0387-7604(02)00079-7
- Stuss, D. P., Boyd, J. D., Levin, D. B., and Delaney, K. R. (2012). MeCP2 mutation results in compartment-specific reductions in dendritic branching and spine density in layer 5 motor cortical neurons of YFP-H mice. *PLoS One* 7:e31896. doi: 10.1371/journal.pone.0031896
- Sultana, R., Yu, C. E., Yu, J., Munson, J., Chen, D., Hua, W., et al. (2002). Identification of a novel gene on chromosome 7q11.2 interrupted by a translocation breakpoint in a pair of autistic twins. *Genomics* 80, 129–134. doi: 10.1006/geno.2002.6810
- Sundaram, S. K., Huq, A. M., Wilson, B. J., and Chugani, H. T. (2010). Tourette syndrome is associated with recurrent exonic copy number variants. *Neurology* 74, 1583–1590. doi: 10.1212/wnl.0b013e3181e0f147
- Suvrathan, A., Hoeffler, C. A., Wong, H., Klann, E., and Chattarji, S. (2010). Characterization and reversal of synaptic defects in the amygdala in a mouse model of fragile X syndrome. *Proc. Natl. Acad. Sci. U S A* 107, 11591–11596. doi: 10.1073/pnas.1002262107
- Tahirovic, S., and Bradke, F. (2009). Neuronal polarity. *Cold Spring Harb. Perspect. Biol.* 1:a001644. doi: 10.1101/cshperspect.a001644
- Talkowski, M. E., Rosenfeld, J. A., Blumenthal, I., Pillalamarri, V., Chiang, C., Heilbut, A., et al. (2012). Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries. *Cell* 149, 525–537. doi: 10.1016/j.cell.2012.03.028



- Tan, Z.-J., Peng, Y., Song, H.-L., Zheng, J.-J., and Yu, X. (2010). N-cadherin-dependent neuron-neuron interaction is required for the maintenance of activity-induced dendrite growth. *Proc. Natl. Acad. Sci. U S A* 107, 9873–9878. doi: 10.1073/pnas.1003480107
- Tau, G. Z., and Peterson, B. S. (2010). Normal development of brain circuits. *Neuropsychopharmacology* 35, 147–168. doi: 10.1038/npp.2009.115
- Tavazoie, S. F., Alvarez, V. A., Ridenour, D. A., Kwiatkowski, D. J., and Sabatini, B. L. (2005). Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. *Nat. Neurosci.* 8, 1727–1734. doi: 10.1038/nn1566
- Thomanetz, V., Angliker, N., Cloetta, D., Lustenberger, R. M., Schweighauser, M., Oliveri, F., et al. (2013). Ablation of the mTORC2 component rictor in brain or Purkinje cells affects size and neuron morphology. *J. Cell Biol.* 201, 293–308. doi: 10.1083/jcb.201205030
- Thornton, G. K., and Woods, C. G. (2009). Primary microcephaly: do all roads lead to Rome? *Trends Genet.* 25, 501–510. doi: 10.1016/j.tig.2009.09.011
- Toma, C., Hervás, A., Torrico, B., Balmaña, N., Salgado, M., Maristany, M., et al. (2013). Analysis of two language-related genes in autism: a case-control association study of FOXP2 and CNTNAP2. *Psychiatr. Genet.* 23, 82–85. doi: 10.1097/ypg.0b013e32835d6fc6
- Tononi, G., and Cirelli, C. (2003). Sleep and synaptic homeostasis: a hypothesis. *Brain Res. Bull.* 62, 143–150. doi: 10.1016/j.brainresbull.2003.09.004
- Toro, R., Konyukh, M., Delorme, R., Leblond, C., Chaste, P., Fauchereau, F., et al. (2010). Key role for gene dosage and synaptic homeostasis in autism spectrum disorders. *Trends Genet.* 26, 363–372. doi: 10.1016/j.tig.2010.05.007
- Trachtenberg, J. T., Chen, B. E., Knott, G. W., Feng, G., Sanes, J. R., Welker, E., et al. (2002). Long-term *in vivo* imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* 420, 788–794. doi: 10.1038/nature01273
- Tsai, J. W., Bremner, K. H., and Vallee, R. B. (2007). Dual subcellular roles for LIS1 and dynein in radial neuronal migration in live brain tissue. *Nat. Neurosci.* 10, 970–979. doi: 10.1038/nn1934
- Tsai, P. T., Hull, C., Chu, Y., Greene-Colozzi, E., Sadowski, A. R., Leech, J. M., et al. (2012). Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature* 488, 647–651. doi: 10.1038/nature11310
- Tsai, N. P., Wilkerson, J. R., Guo, W., Maksimova, M. A., DeMartino, G. N., Cowan, C. W., et al. (2012). Multiple autism-linked genes mediate synapse elimination via proteasomal degradation of a synaptic scaffold PSD-95. *Cell* 151, 1581–1594. doi: 10.1016/j.cell.2012.11.040
- Tu, J. C., Xiao, B., Naisbitt, S., Yuan, J. P., Petralia, R. S., Brakeman, P., et al. (1999). Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron* 23, 583–592. doi: 10.1016/s0896-6273(00)80810-7
- Tunca, Y., Vurucu, S., Parma, J., Akin, R., Désir, J., Baser, I., et al. (2006). Prenatal diagnosis of primary microcephaly in two consanguineous families by confrontation of morphometry with DNA data. *Prenat. Diagn.* 26, 449–453. doi: 10.1002/pd.1434
- Turner, G., Partington, M., Kerr, B., Mangelsdorf, M., and Gecz, J. (2002). Variable expression of mental retardation, autism, seizures, and dystonic hand movements in two families with an identical ARX gene mutation. *Am. J. Med. Genet.* 112, 405–411. doi: 10.1002/ajmg.10714
- Turner, T. N., Sharma, K., Oh, E. C., Liu, Y. P., Collins, R. L., Sosa, M. X., et al. (2015). Loss of delta-catenin function in severe autism. *Nature* 520, 51–56. doi: 10.1038/nature14186
- Turrigiano, G. G., Leslie, K. R., Desai, N. S., Rutherford, L. C., and Nelson, S. B. (1998). Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391, 892–896. doi: 10.1038/36103
- Uchino, S., Wada, H., Honda, S., Nakamura, Y., Ondo, Y., Uchiyama, T., et al. (2006). Direct interaction of post-synaptic density-95/Dlg/ZO-1 domain-containing synaptic molecule Shank3 with GluR1  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor. *J. Neurochem.* 97, 1203–1214. doi: 10.1111/j.1471-4159.2006.03831.x
- Uppal, N., Wicinski, B., Buxbaum, J. D., Heinsen, H., Schmitz, C., and Hof, P. R. (2014). Neuropathology of the anterior midcingulate cortex in young children with autism. *J. Neuropathol. Exp. Neurol.* 73, 891–902. doi: 10.1097/nen.000000000000108
- Valiente, M., and Marin, O. (2010). Neuronal migration mechanisms in development and disease. *Curr. Opin. Neurobiol.* 20, 68–78. doi: 10.1016/j.conb.2009.12.003
- van Kooten, I. A., Palmen, S. J., von Cappeln, P., Steinbusch, H. W., Korr, H., Heinsen, H., et al. (2008). Neurons in the fusiform gyrus are fewer and smaller in autism. *Brain* 131, 987–999. doi: 10.1093/brain/awn033
- Van Maldergem, L., Hou, Q., Kalscheuer, V. M., Rio, M., Doco-Fenzy, M., Medeira, A., et al. (2013). Loss of function of KIAA2022 causes mild to severe intellectual disability with an autism spectrum disorder and impairs neurite outgrowth. *Hum. Mol. Genet.* 22, 3306–3314. doi: 10.1093/hmg/ddt187
- van Woerden, G. M., Harris, K. D., Hojjati, M. R., Gustin, R. M., Qiu, S., de Avila Freire, R., et al. (2007). Rescue of neurological deficits in a mouse model for Angelman syndrome by reduction of  $\alpha$ CaMKII inhibitory phosphorylation. *Nat. Neurosci.* 10, 280–282. doi: 10.1038/nn1845
- Varea, O., Martin-de-Saavedra, M. D., Kopeikina, K. J., Schurmann, B., Fleming, H. J., Fawcett-Patel, J. M., et al. (2015). Synaptic abnormalities and cytoplasmic glutamate receptor aggregates in contactin associated protein-like 2/Caspr2 knockout neurons. *Proc. Natl. Acad. Sci. U S A* 112, 6176–6181. doi: 10.1073/pnas.1423205112
- Varga, E. A., Pastore, M., Prior, T., Herman, G. E., and McBride, K. L. (2009). The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. *Genet. Med.* 11, 111–117. doi: 10.1097/gim.0b013e31818fd762
- Volders, K., Nuytens, K., and Creemers, J. W. (2011). The autism candidate gene Neurobeachin encodes a scaffolding protein implicated in membrane trafficking and signaling. *Curr. Mol. Med.* 11, 204–217. doi: 10.2174/156652411795243432
- von der Brellie, C., Waltereit, R., Zhang, L., Beck, H., and Kirschstein, T. (2006). Impaired synaptic plasticity in a rat model of tuberous sclerosis. *Eur. J. Neurosci.* 23, 686–692. doi: 10.1111/j.1460-9568.2006.04594.x
- Wang, G., Gilbert, J., and Man, H. Y. (2012). AMPA receptor trafficking in homeostatic synaptic plasticity: functional molecules and signaling cascades. *Neural Plast.* 2012:825364. doi: 10.1155/2012/825364
- Wang, X., McCoy, P. A., Rodriguiz, R. M., Pan, Y., Je, H. S., Roberts, A. C., et al. (2011). Synaptic dysfunction and abnormal behaviors in mice lacking major isoforms of Shank3. *Hum. Mol. Genet.* 20, 3093–3108. doi: 10.1093/hmg/ddr212
- Wang, K., Zhang, H., Ma, D., Bucan, M., Glessner, J. T., Abrahams, B. S., et al. (2009). Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* 459, 528–533. doi: 10.1038/nature07999
- Weeber, E. J., Jiang, Y. H., Elgersma, Y., Varga, A. W., Carrasquillo, Y., Brown, S. E., et al. (2003). Derangements of hippocampal calcium/calmodulin-dependent protein kinase II in a mouse model for Angelman mental retardation syndrome. *J. Neurosci.* 23, 2634–2644.
- Wegiel, J., Kuchna, I., Nowicki, K., Imaki, H., Wegiel, J., Marchi, E., et al. (2010). The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol.* 119, 755–770. doi: 10.1007/s00401-010-0655-4
- Weiss, L. A., Shen, Y., Korn, J. M., Arking, D. E., Miller, D. T., Fossdal, R., et al. (2008). Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J. Med.* 358, 667–675. doi: 10.1056/NEJMoa075974
- Weng, S. M., McLeod, F., Bailey, M. E., and Cobb, S. R. (2011). Synaptic plasticity deficits in an experimental model of rett syndrome: long-term potentiation saturation and its pharmacological reversal. *Neurosci* 180, 314–321. doi: 10.1016/j.neuroscience.2011.01.061
- Weston, M. C., Chen, H., and Swann, J. W. (2014). Loss of mTOR repressors Tsc1 or Pten has divergent effects on excitatory and inhibitory synaptic transmission in single hippocampal neuron cultures. *Front. Mol. Neurosci.* 7:1. doi: 10.3389/fnfmol.2014.00001
- Whalley, H. C., O'Connell, G., Sussmann, J. E., Peel, A., Stanfield, A. C., Hayiou-Thomas, M. E., et al. (2011). Genetic variation in CNTNAP2 alters brain function during linguistic processing in healthy individuals. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 156B, 941–948. doi: 10.1002/ajmg.b.31241
- Wichterle, H., Turnbull, D. H., Nery, S., Fishell, G., and Alvarez-Buylla, A. (2001). *in utero* fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain. *Development* 128, 3759–3771.
- Williams, C. A., Beaudet, A. L., Clayton-Smith, J., Knoll, J. H., Kyllerman, M., Laan, L. A., et al. (2006). Angelman syndrome 2005: updated consensus for

- diagnostic criteria. *Am. J. Med. Genet. A* 140, 413–418. doi: 10.1002/ajmg.a.31074
- Willsey, A. J., Sanders, S. J., Li, M., Dong, S., Tebbenkamp, A. T., Muhle, R. A., et al. (2013). Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. *Cell* 155, 997–1007. doi: 10.1016/j.cell.2013.10.020
- Wilson, B. M., and Cox, C. L. (2007). Absence of metabotropic glutamate receptor-mediated plasticity in the neocortex of fragile X mice. *Proc. Natl. Acad. Sci. U S A* 104, 2454–2459. doi: 10.1073/pnas.0610875104
- Wilson, P. M., Fryer, R. H., Fang, Y., and Hatten, M. E. (2010). Astn2, a novel member of the astrotactin gene family, regulates the trafficking of ASTN1 during glial-guided neuronal migration. *J. Neurosci.* 30, 8529–8540. doi: 10.1523/JNEUROSCI.0032-10.2010
- Witte, H., and Bradke, F. (2008). The role of the cytoskeleton during neuronal polarization. *Curr. Opin. Neurobiol.* 18, 479–487. doi: 10.1016/j.conb.2008.09.019
- Wong, W. T., Faulkner-Jones, B. E., Sanes, J. R., and Wong, R. O. (2000). Rapid dendritic remodeling in the developing retina: dependence on neurotransmission and reciprocal regulation by Rac and Rho. *J. Neurosci.* 20, 5024–5036.
- Yamaguchi, Y., and Miura, M. (2015). Programmed cell death in neurodevelopment. *Dev. Cell* 32, 478–490. doi: 10.1016/j.devcel.2015.01.019
- Yang, M., Bozdagi, O., Scattoni, M. L., Wöhr, M., Roulet, F. I., Katz, A. M., et al. (2012). Reduced excitatory neurotransmission and mild autism-relevant phenotypes in adolescent Shank3 null mutant mice. *J. Neurosci.* 32, 6525–6541. doi: 10.1523/JNEUROSCI.6107-11.2012
- Yangngam, S., Plong-On, O., Sripo, T., Roongpraiwan, R., Hansakunachai, T., Wirojanan, J., et al. (2014). Mutation screening of the neurexin 1 gene in thai patients with intellectual disability and autism spectrum disorder. *Genet. Test. Mol. Biomarkers* 18, 510–515. doi: 10.1089/gtmb.2014.0003
- Yip, J., Soghomonian, J. J., and Blatt, G. J. (2007). Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta Neuropathol.* 113, 559–568. doi: 10.1007/s00401-006-0176-3
- Yoo, J., Bakes, J., Bradley, C., Collingridge, G. L., and Kaang, B. K. (2014). Shank mutant mice as an animal model of autism. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369:20130143. doi: 10.1098/rstb.2013.0143
- Yu, L., and Goda, Y. (2009). Dendritic signalling and homeostatic adaptation. *Curr. Opin. Neurobiol.* 19, 327–335. doi: 10.1016/j.conb.2009.07.002
- Yu, T. W., Mochida, G. H., Tischfield, D. J., Sgaier, S. K., Flores-Sarnat, L., Sergi, C. M., et al. (2010). Mutations in WDR62, encoding a centrosome-associated protein, cause microcephaly with simplified gyri and abnormal cortical architecture. *Nat. Genet.* 42, 1015–1020. doi: 10.1038/ng.683
- Yuan, L., Seong, E., Beuscher, J. L., and Arikath, J. (2015). Delta-catenin regulates spine architecture via cadherin and PDZ-dependent interactions. *J. Biol. Chem.* 290, 10947–10957. doi: 10.1074/jbc.m114.632679
- Zhang, D., Cheng, L., Qian, Y., Alliey-Rodriguez, N., Kelsoe, J. R., Greenwood, T., et al. (2009). Singleton deletions throughout the genome increase risk of bipolar disorder. *Mol. Psychiatry* 14, 376–380. doi: 10.1038/mp.2008.144
- Zhao, C., Deng, W., and Gage, F. H. (2008). Mechanisms and functional implications of adult neurogenesis. *Cell* 132, 645–660. doi: 10.1016/j.cell.2008.01.033
- Zhao, H., Dupont, J., Yakar, S., Karas, M., and LeRoith, D. (2004). PTEN inhibits cell proliferation and induces apoptosis by downregulating cell surface IGF-IR expression in prostate cancer cells. *Oncogene* 23, 786–794. doi: 10.1038/sj.onc.1207162
- Zhao, M. G., Toyoda, H., Ko, S. W., Ding, H. K., Wu, L. J., and Zhuo, M. (2005). Deficits in trace fear memory and long-term potentiation in a mouse model for fragile X syndrome. *J. Neurosci.* 25, 7385–7392. doi: 10.1523/JNEUROSCI.1520-05.2005
- Zheng, C., Heintz, N., and Hatten, M. E. (1996). CNS gene encoding astrotactin, which supports neuronal migration along glial fibers. *Science* 272, 417–419. doi: 10.1126/science.272.5260.417
- Zhou, Z., Hong, E. J., Cohen, S., Zhao, W. N., Ho, H. Y., Schmidt, L., et al. (2006). Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth and spine maturation. *Neuron* 52, 255–269. doi: 10.1016/j.neuron.2006.09.037

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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