Advances in the understanding of cellular pathogenesis associated with Autism Spectrum Disorder

Katrina SAVORY¹, Yasir Ahmed SYED²
¹Neuroscience and Mental Health Research Institute, Hadyn Ellis Building, Cathays, Cardiff, UK
²School of Bioscience, The Sir Martin Evans Building, Museum Ave, Cardiff, UK

Received: 19-October-2019
Revised: 16-November-2019
Accepted: 20-November-2019
Online first: 22-November-2019

Review Article

Abstract

Autism Spectrum Disorders (ASD) are a group of heterogeneous neurodevelopmental disorders with an estimated worldwide prevalence of 1-2%. Although it is highly heritable, the contribution of environmental factors and risk associated genes on the aberrant brain development is not well understood. In this review, we summarise some of the key risk factors and explore ASD associated cellular pathology from the perspective of the four predominant cells in the brain; neurons, oligodendrocytes, microglia and astrocytes. Further, we discuss the contributions of the associated cellular pathology to the three common hypotheses of ASD. We highlight the major neuro-pathologies underlying ASD, however more research is needed to ensure appropriate and efficient therapies can be directed towards ASD.

Keywords: Autism spectrum disorders, Neurodevelopment, Neural lineage cells, Genetics, Risk factors.

Citation: Savory, K., Syed, YA. Advances in the understanding of cellular pathogenesis associated with Autism Spectrum Disorder. 2020 Jan 22; 2(2):96-118. Journal for ReAttach Therapy and Developmental Diversities. https://doi.org/10.26407/2019jrtdd.1.21

Copyright ©2019 Savory, K., Syed, YA. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Corresponding address:
Yasir Ahmed Syed
Neuroscience and Mental Health Research Institute, Hadyn Ellis Building, Cardiff, CF24 4HQ, UK
Tel: +44(0)2920 688 314
E-mail: syedy@cardiff.ac.uk
1. Introduction
Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders characterised by deficits in social communication and interaction, restrictive and repetitive behaviours (American Psychiatric, 2013) and can also involve sensory abnormalities (Adamson, O’Hare, & Graham, 2006; Wiggins, Robins, Bakeman, & Adamson, 2009). Symptoms associated with ASD emerge during infancy and this disorder is most commonly diagnosed in early childhood. Due to better diagnosis, the prevalence of ASD has increased over the years (Baio et al., 2018; Idring et al., 2015), with recent reports suggesting that as many as 1 in 59 have ASD (Baio et al., 2018), with an estimated prevalence of 1 in 88 in the United Kingdom (Brugha et al., 2012). The ever-changing landscape associated with diagnosis and genetics of ASD has made it difficult to estimate the true prevalence in the population. ASD is more commonly diagnosed in males, with ratios suggesting around four times as much compared to females (Scott, Baron-Cohen, Bolton, & Brayne, 2002).

This article aims to briefly review the risk factors and genetics for autism spectrum disorders and will then go on to explore the contribution of neural lineage cells to the pathogenesis of this disorder.

2. Risk Factors Associated with ASD

It is now well established that ASD is caused by aberrant brain development, however the causal links are currently unknown. Although ASD is highly heritable, environmental factors also play a key role in the aetiology of these disorders.

2.1 Prenatal risk factors

Many risk factors have been associated with ASD both during the prenatal period and early infancy. Advanced maternal age of over 35 years has been commonly associated with an increased risk of the offspring developing ASD (D. Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009; Pinborough-Zimmerman et al., 2011; K. Williams, Helm, Duncan, Peat, & Mellis, 2008), with some suggesting being over 30 years could also be a risk (Idring et al., 2014). Additionally, advanced paternal age has also been associated with increased risk (Ben Itzchak, Lahat, & Zachor, 2011). Furthermore, males are diagnosed earlier if they have older parents (Darcy-Mahoney et al., 2016).

Demographic factors also have been implicated with increased risk for ASD, where people of Caucasian ethnicity seem to be at increased risk (Pinborough-Zimmerman et al., 2011). Maternal obesity has been positively associated with an increased risk for ASD (Y.-M. Li et al., 2016). Low birth weight, defined as a newborn weighing less than 2500g (Blanc & Wardlaw, 2005) and prematurity (often associated with a low birth weight) have also been shown to contribute towards an increased risk of ASD (Ben Itzchak et al., 2011; Maramara, He, & Ming, 2014; K. Williams et al., 2008). Additionally, increased weight gain during pregnancy (D. A. Bilder et al., 2013; Windham et al., 2019) and poor nutrition (Geetha, Sukumar, Dhivyadeepa, Reddy, & Balachandar, 2019) have been linked to childhood ASD.

In addition to demographic and maternal factors, a range of obstetric complications have been associated with increased risk of ASD including fetal hypoxia (Burstyn, Wang, Yasui, Sithole, & Zwaigenbaum, 2011; Froehlich-Santino et al., 2014), high maternal blood pressure (Polo-Kantola et al., 2014) and respiratory distress (Froehlich-Santino et al., 2014).

Emerging studies looking at maternal mental health and high functioning ASD phenotypes show a positive association. Poor mental health, particularly depression and anxiety which have become increasingly prevalent during pregnancy (Heron, O’Connor, Evans, Golding, & Glover, 2004; Janssen et al., 2018; Lockwood Estrin et al., 2019), have often been associated with adverse effects on the offspring both physically and cognitively (Glynn et al., 2018; Kataja et al., 2019; Y. Liu et al., 2012; O’Connor, Heron, Golding, Beveridge, & Glover, 2002; Uguz et al., 2013). Both prenatal mental health (Hagberg, Robijn, & Jick, 2018) and the use of antidepressants, including the commonly prescribed selective serotonin reuptake inhibitors (SSRIs), during pregnancy have been associated with an increased risk of ASD (Gidaya et al., 2014; Hvid, Melbye, & Pasternak, 2013; Sujuan et al., 2017).

2.2 Environmental risk factors

Exposure to neurotoxins, malnutrition associated with sociodemographics and medication taken in pregnancy during the critical period of development can have an accumulative effect on the risk of
developing this neurodevelopmental disorder. Studies have shown that exposure to a number of toxicants in the environment increase the risk of ASD during the prenatal period and after birth, including pesticides, air pollutants, diesel, nitrogen dioxide and living in an urban environment (Chang, Cole, & Costa, 2018; Flores-Pajot, Ofter, Do, Lavigne, & Villeneuve, 2016; Kalkbrenner, Schmidt, & Penlesky, 2014; Lauritsen et al., 2014). However, one large cohort study suggested that only exposure to a small percentage of neurotoxicants were associated with increased risk of ASD (Talbott et al., 2015).

Increasing evidence has suggested that inflammation as a result of the physiological stress response due to maternal infection and immune activation is associated with an increased risk in the offspring developing ASD (Careaga, Murai, & Bauman, 2017). Maternal infections (Atlądóttir et al., 2010; Visser et al., 2013) and influenza (Zerbo et al., 2013) during pregnancy and autoimmune diseases (Vinet et al., 2015) have been associated with increased risk and earlier diagnosis of ASD. Evidence has suggested that maternal immune activation leads to localised loss of inhibitory neurons (Shin Yim et al., 2017) and is associated with a certain profile of gut bacteria that promote inflammation (Caprioli, Pallone, & Monteleone, 2008; S. Kim et al., 2017). Gastrointestinal problems and altered gut microbiota in patients with ASD have also been reported (Finegold et al., 2002; F. Liu et al., 2019; Valicenti-McDermott et al., 2006; B. L. Williams, Homig, Parekh, & Lipkin, 2012), with one study showing a positive association between ASD severity and gastrointestinal symptoms (Adams, Johansen, Powell, Quig, & Rubin, 2011).

In addition to the gut, nutrient deficiency has also been associated with ASD. Many studies have suggested a link between vitamin D deficiency prenatally and in children with autistic traits and ASD (Bener, Khattab, & Al-Dabbagh, 2014; Bener, Khattab, Bhugra, & Hoffmann, 2017; Vinkhuyzen et al., 2018). Maternal deficiency in many other nutrients including iron, zinc and vitamin B9 have also been associated with ASD (Nutall, 2017).

3. Genetics Associated with ASD

The wide phenotypic variability of ASD along with twin studies suggest a strong association of genetics towards aetiology (Constantino et al., 2013; Ozonoff et al., 2011; Rosenberg et al., 2009). Whole exome sequencing (WES) has been a powerful tool to highlight genetic associations with Autism. One such study suggested that all de novo changes (including missense mutations and copy number variations; CNVs) account for as much as 30% of ASD diagnoses (Iossifov et al., 2014). WES has discovered 11 de novo mutations in protein-coding genes including FOXP1, GRIN2B, SCN1A and LAMC3 (ORoak et al., 2011). A further large study utilising this method looked at data from almost 12,000 ASD cases and additional controls (Satterstrom et al., 2018). This study revealed 102 risk genes for ASD, 31 of which were novel. Whole genome sequencing has also uncovered de novo mutations associated with ASD, revealing that the majority of these mutations were paternally inherited, however clustered de novo mutations (within 20kb) were mostly maternally inherited and in close proximity to CNVs (Yuen et al., 2016). Genome-wide association studies (GWAS) have been utilised to study large data sets to uncover de novo mutations, single nucleotide polymorphisms (SNPs) and CNVs associated with ASD. A recent large GWAS looking at data on 18,381 subjects with ASD and 27,969 controls highlighted five loci associated with increased risk of ASD in chromosomes 1, 7, 8 and 20 (Xia et al., 2013). Specifically, the genes linked to these loci included PTBP2 (1p21.3), SRRPK2 (7q22.3), SOX7, PINX1 (8p23.1), and NNX2-2, NNX2-4 (20p11.23), MACROD2 (20p12.1) (Grove et al., 2019), a number of which have been implicated in neurodevelopment. Additionally, SNPs in 1p13.2 including the TRIM33 gene showed links with autism. Additionally, three genes essential for neuronal function; CACNA1C, MECP2 and PTEN have also been associated with increased risk of Autism (Busch et al., 2019; J. Li et al., 2015; Wen et al., 2017).

A number of other GWAS studies have highlighted CNVs associated with an increased risk of autism. CNVs were found in over a quarter of patients with ASD in a Greek population, with the majority being deletions (Oikonomikos et al., 2016). Rare CNVs are higher in patients with ASD compared to controls (Pinto et al., 2010) with a gene enrichment analysis showing implicated genes were associated with neuronal development and function. Another study showed duplications at 1q21.1 and 15q11-13 and deletions at 16p11.2 and 22q11.21 were
associated with risk for ASD (Crespi & Crofts, 2012).

One study suggested a large number of SNPs in 5p14.1 to be associated with an increased risk of autism, however these did not reach genome-wide significance (Ma et al., 2009). A further study looking at this same region found strong associations in SNPs between the cadherin genes; CDH9 and CDH10 (K. Wang et al., 2009). A GWAS meta-analysis of patients with ASD and controls found a number of SNPs in genes at 10q24.32 showed genome-wide significance (Autism Spectrum Disorders Working Group of The Psychiatric Genomics, 2017). Genes in this implicated region are associated with a number of neurodevelopmental processes. Further, a small deletion consisting of five genes (MVP, CDIPT1, SEZ6L2, ASPHD1 and KCTD13) in the 16p11.2 region were found to be associated with ASD suggesting a minimal deletion region for ASD risk (Crepel et al., 2011).

A table of specific gene functions is provided for genes discussed in this section (table 1).

**Table 1**

*Physiological function of genes associated with increased risk of ASD*

| Gene     | Specific gene function                                                                                                                                                                                                 | Chromosomal location |
|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| **Neurogenesis**                                                                                                                                            |                      |
| PTBP2    | Crucial for axon development through alternative splicing (M. Zhang et al., 2019) and maturation of neurons (Q. Li et al., 2014).                                                                                            | 1p21.3               |
| EFA6     | Involved in axonal transport and regeneration (Eva, Koseki, Kanamarapudi, & Fawcett, 2017) and neuronal morphogenesis, particularly the development of dendrites (Sakagami et al., 2007; Sakagami, Matsuya, Nishimura, Suzuki, & Kondo, 2004; Sironi et al., 2009). | 10q24.32             |
| PITX3    | Required for optimal development of Mesodiencephalic dopamine neurons (Kouwenhoven, von Oerthel, & Smidt, 2017; Le, Zhang, Xie, Li, & Dani, 2015).                                                                          | 10q24.32             |
| KCTD13   | Associated with the development of cortical neurons (Gladwyn-Ng et al., 2016) and synaptic transmission (Escamilla et al., 2017).                                                                                       | 16p11.2              |
| SEZ6L2   | Seizure 6-like protein. Essential for the development of dendrites and neurites (Boonen et al., 2016; Yaguchi et al., 2017) and connectivity of synapses (Guinnessen et al., 2007). | 16p11.2              |
| MACROD2  | Expressed in hippocampal neurons during development and may be involved in neurogenesis (Ito et al., 2018), although a physiological role has yet to be identified.                                                 | 20p12.1              |
| NKX2-2   | Implicated in the development of dopamine neurons (Prakash et al., 2006), motor neurons (Clark et al., 2014; Jarrar, Dias, Ericson, Arnold, & Holz, 2015), interneurons and oligodendrocytes (Jarrar, Vauti, Arnold, & Holz, 2015; Zhu et al., 2014). | 20p11.22             |
| NKX2-4   | Involved in neurogenesis of cortical (Shen et al., 2017) and hypothalamic (Manoli & Driever, 2014) neurons.                                                                                                         | 20p11.23             |
| **Synaptogenesis**                                                                                                                                            |                      |
| CHD9     | Regulates synapses in the hippocampus (M. E. Williams et al., 2011) and has been implicated in chromatin organisation (Ooga et al., 2018).                                                                             | 5p14.1               |
| CHD10    | Involved in the regulation of E/I synapses (Smith et al., 2017).                                                                                                                                                      | 5p14.1               |
| SHANK2   | Essential for synapse development and plasticity (Ha et al., 2016; Wegener et al., 2018).                                                                                                                             | 11q13.3-q13.4        |
| **Inflammation**                                                                                                                                               |                      |
3.1. Neurexins and Neuroligins
The CNV syndrome 22q13.3 region associated with high incidences of ASD-like behaviour includes the SHANK3 gene encoding a synaptic scaffolding protein (Durand et al., 2007; Phelan & McDermid, 2012). SHANK3 binds to neuroligins (Meyer, Varoqueaux, Neeb, Oschlies, & Brose, 2004), which interact with neurexins to form glutamatergic synapses (Craig & Kang, 2007). A GWAS of the visual sensitivity phenotype associated with ASD showed a SNP in PDZK1, located at 1q21.1, was associated with increased sensitivity (Goodbourn et al., 2014). Further, PDZ domains have been shown to bind to the neuroligin NLGN1 (Meyer et al., 2004). Both neurexins and neuroligins have been associated with ASD. NLG1 and NLG4, but not NLG3 and NLG4Y have been associated with autism (Ylisaukko-oja et al., 2005) with a drosophila model of deficient Nlg2 and Nlg4 showing abnormalities in social behaviour (Cortals et al., 2017). SNPs in NRXN2 and NRXN3 have been associated with increased risk of ASD (J. Wang et al., 2018), additionally missense mutations in NRXN1 were found in two patients with ASD (Kim et al., 2008).

4. Contribution of Neural Lineage Cells in the Pathogenesis of ASD

4.1 Neurons
ASD is a disorder caused by aberrant neurodevelopment. The predominant cells in the brain, and thus most likely to be affected by adverse neurodevelopment, are neurons and glial cells. Neuronal research appears to be the main area of study in relation to ASD and a number of neuronal cells have been implicated in function, morphology, axon guidance and synaptic dysregulation, including immature neurons, pyramidal neurons located in the prefrontal cortex (PFC), mature cortical neurons, inhibitory neurons including GABAergic neurons and excitatory neurons. Macrocephaly has been associated in a number of cases of autism (Courchesne, Carper, & Akshoomoff, 2003; McBride et al., 2010) and larger brain volume in patients with autism has also been reported (Aylward, Minshew, Field, Sparks, & Singh, 2002). The cause of macrocephaly is unknown, however it may be associated with the number, maturity and morphology of neurons. One study found that children with autism had significantly more neurons in the PFC which correlated with increased brain weight (Courchesne et al., 2011). The phosphatase and tensin homolog (PTEN) gene is clearly associated with macrocephaly in ASD (Goffin, Hoefsloot, Bosgoed, Swillen, & Fryns, 2001) with a brain organoid model harbouring a deletion of this gene showing an increase in proliferation of cells leading to large sized organoids (Y. Li et al., 2017). Conversely, it has been found that larger spine densities of pyramidal neurons are associated with a smaller brain size (Hutsler & Zhang, 2010). Whilst macrocephaly is more prominently reported in ASD, microcephaly can also occur in some cases (Fombonne, Rogé, Claverie, Courty, & Kruck, 1999).

Altered morphology of neurons has been reported in many ASD cases which may be related to the symptoms of autism. One study showed patients with autism have smaller pyramidal neurons in the PFC (Jacot-Descombes et al., 2012), an area implicated in social behaviour (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). Further,
altered morphology of neurons from human cases and animal models of ASD have been found in the amygdala (Jerzy Wegiel et al., 2015) and hippocampus (Griesi-Oliveira et al., 2015); areas both associated with the anxiety and emotional-related memory features of autism (Babaev, Filetti Chatain, & Krueger-Burg, 2018; Boucher, Mayes, & Bigham, 2012; Bowler, Gaigg, & Gardiner, 2014). A less-reported symptom of ASD is deficits in face processing (Davies, Bishop, Manstead, & Tantam, 1994; Grelotti, Gauthier, & Schultz, 2002; Joseph & Tanaka, 2003). One study found that neurons in the fusiform gyrus, an essential area for face processing (Kanwisher, McDermott, & Chun, 1997), were significantly less dense and reduced in number in brains from patients with autism (van Kooten et al., 2008). Further, overexpression of SHANK2 in neurons; a gene associated with autism when defective, was associated with shorter and less neurites (Luo et al., 2019).

Mouse models are a useful tool for understanding the mechanisms by which neuronal morphology is altered in ASD and many studies have successfully recapitulated the key symptoms of autism including impaired social behaviour and repetitive behaviour. One mouse model exhibiting impaired social behaviour showed that the reduced spine pruning in pyramidal neurons found in post-mortem brains of ASD patients was likely to be caused by impaired autophagy as a result of defects in the m-TOR pathway (Tang et al., 2014).

It is not only altered morphology of neurons that has been implicated in ASD, but also deficits in migration and proliferation. Brains from patients with autism show defects in neurogenesis and migration of neurons (Jerzy Wegiel et al., 2010). Mouse models with Shank3 knockout (KO) mutations, which have been associated with autism (Boccuto et al., 2013; Durand et al., 2007; Gauthier et al., 2009), showed decreased radial glial progenitor cells and immature neurons in the hippocampus (Cope et al., 2016). A number of mouse models have shown that an increase in early neurogenesis is associated with deficits in early maturity (Orosco et al., 2014) and morphology (Arranz et al., 2019). Further, an increase in proliferation of progenitor cells has been associated with decreased mature pyramidal neurons in a mouse model of CNV syndrome 16p11.2 deletion, harbouring the MAPK3 gene (Pucilowska et al., 2015). Deficits in proliferation of cortical neurons have been shown in animal models of ASD, including a study looking at a knockdown of the autism-associated gene Chd8 in primary cortical neurons (Xu et al., 2018). A well-established rat model found that reduced proliferation was due to overexpression of a gene targeting Fzd3 and inhibiting the Wnt pathway (Yao, Huang, & He, 2019), inhibition of this pathway has also been associated with increased proliferation of neural progenitor cells through reduced transcriptional activity of β-catenin (Marchetto et al., 2017).

The identification of synaptic proteins controlling synapse formation and signalling implicated in ASD points towards synaptic malformation and dysfunction (De Rubeis et al., 2014). For example, mutations in synaptic neuroligin genes NLGN3 and NLGN4 have been associated with ASD (Jamain et al., 2003; Südhof, 2008). Mice with these deletions have been shown with synaptic defects (Gutierrez et al., 2009; C. Zhang et al., 2009). Mutations in synapsins (SYN1, SYN2, SYN3); a family of presynaptic proteins that regulate vesicle-mediated neurotransmitter release and neurites, have been found in individuals with autistic phenotypes, suggesting a potentially causative factor of ASD (Fassio et al., 2011). Primary neurons from Syn1/2/3 triple-KO mice display a significant decrease in the number of synaptic vesicles (Formasiero et al., 2012) and display impairments in social recognition tests and a decreased environmental interest; phenotypic of ASD (Greco et al., 2013; Ketzel & Gitler, 2012). The SHANK3 gene strongly associated with ASD seems to confer its pathology through synaptic dysfunction. Neurons lacking in SHANK3 are associated with fewer synapses, whereas overexpression of SHANK3 results in more mature neurons with larger spines (Betancur, Sakurai, & Buxbaum, 2009). Furthermore, single-gene mutations associated with ASD such as fragile X syndrome (FMR1), tuberous sclerosis (TSC1, TSC2), neurofibromatosis type-1 (NFI), Angelman syndrome (UBE3A), Rett syndrome (MECP2), and the PTEN hamartoma tumour syndrome seem to mediate their effect through synaptic dysregulation (Zoghbi & Bear, 2012). A recent study looking at the effect of the KO of Rnf8, linked to ASD, demonstrates a 50% increase in the number of synapses in cerebellar neurons (Vaihnegri et al., 2017). Taken together, it can be argued that synaptic
dysfunction plays a major role in the pathogenesis of ASD.

The excitatory-inhibitory (E/I) balance theory of autism has become increasingly of interest in recent years in an attempt to explain the wide range of symptoms and common pathologies associated with ASD including repetitive behaviours, hyperactivity, anxiety and epilepsy (Rubenstein & Merzenich, 2003). Evidence from human patients has shown increased formation of excitatory synapses associated with increased IL-6 in the cerebellum of patients (Horigen Wei et al., 2011). A mixture of results have been found from studies using human induced pluripotent stem cells (hiPCSs) derived from ASD patients. Glutamate is the most abundant excitatory neurotransmitter in the brain (Fonnum, 1984) and decreased levels have been shown along with a reduction in synapses of neural progenitor cells (Marchetto et al., 2017) and mature neurons (Russo et al., 2018). Further, an increase in GABAergic neurons; responsible for the secretion of the main inhibitory neurotransmitter in the brain, has been found in neural progenitor cells (Marchetto et al., 2017) and telencephalic organoids (Mariani et al., 2015).

The well-established Shank3 KO model has shown impaired morphology of inhibitory neurons with longer dendrites, but decreased spine and postsynaptic density (Peça et al., 2011) and down-regulation of a sub-type of inhibitory neuron (Filice, Vörckel, Sungur, Wöhr, & Schwaller, 2016), however another study showed that activity in both inhibitory and excitatory neurons was reduced (Huang et al., 2019). Further, mouse models have shown a decrease in a type of positive inhibitory interneuron (Pucilowska et al., 2015) and overproduction of excitatory neurons (Fang et al., 2014) in upper layers of the cortex.

The discrepancy between these findings could be explained by the different types of inhibitory and excitatory neurons in the brain. The Me2C mouse model of autism that displays ASD-like symptoms including impaired social interaction showed a decrease in excitatory transmission and increase in inhibitory transmission in cortical neurons (Harrington et al., 2016). Further, a mouse model of autism involving the Ih2 KO, associated with deficits in motor and cognitive function (Giza et al., 2010), showed increased excitability through enhanced neurotransmission from NMDA receptors (Soda et al., 2019). Another potential explanation is that the number of neurons do not always directly relate to the amount of inhibitory or excitatory neurotransmitter release, for example, a heterozygous KO of Dyrk1a shows ASD like-behaviours and increased number of both excitatory and inhibitory neurons, but only a significant increase in excitatory synapses (Arranz et al., 2019). Overall, these findings suggest a predominancy excitatory E/I balance could be a factor in the clinical phenotypes associated with ASD.

4.2. Oligodendrocytes

Oligodendrocytes are the only myelin-forming cells of the mammalian central nervous system. In humans, half of the brain is composed of white matter, which is predominantly made of myelin, and is 500% more abundant in comparison to mice (K. Zhang & Sejnowski, 2000). Oligodendrocyte pathology has been found in patients with ASD. Adults with ASD show significantly lower numbers of oligodendrocytes (Morgan, Barger, Amaral, & Schumann, 2014). Further, pathology has been found in the PFC; an area associated with social behaviour (Finkay et al., 2015; Franklin et al., 2017; Pirone et al., 2018) and increased expression of oligodendrocyte markers have been found in the hippocampus and PFC, but are significantly decreased in density in part of the hippocampus (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Brains from adult autistic patients have a lower amount of myelinated thin axons but an increase of medium thickness axons in the lateral PFC (Trutzer, Garcia-Cabezas, & Zikopoulos, 2019) and increased myelination in the medial PFC (Carmody & Lewis, 2010). This evidence could explain some of the social abnormalities seen in ASD.

A number of genes and SNPs implicated in autism have been associated with oligodendrocytes. SNPs in the DUSP15 and CD38 genes; involved in oligodendrocyte differentiation and development, have been found in children with autism (van Tilborg et al., 2018; Munesue et al., 2010; Hattori et al., 2017) and clearance of degraded myelin is also associated with CD38 (Roboon et al., 2019). Chromatin remodelers including CHD7 and CHD8 have been linked to ASD (Jiang et al., 2013; Xu et al., 2018). Loss-of-function Chld7 is associated with reduced number of oligodendrocyte progenitor cells (OPCs) through apoptosis (Marie et al., 2018).
Further, this gene has downstream effects on many genes involved in cell survival, proliferation and apoptosis [54]. Gene expression studies have also shown increased expression of genes associated with oligodendrocytes in the cerebellum from patients with autism including MBP, MAG, OLG1, OLG2 (Zeidán-Chuliá et al., 2016). Although contrasting results have been found in the BTBR mouse model of autism (H. Wei et al., 2016). Prenatal hypoxia and inflammation are risks factors for ASD. One mouse model using both hypoxia and inflammation to cause diffuse white matter injury showed autism-like behaviour in the mice. Further, they showed impaired maturation of oligodendrocytes and delayed myelination (van Tilborg et al., 2018). This study supports the notion that presence of inflammation contributes towards abberant myelination during neurodevelopment. Abnormal myelination has further been confirmed in two other mouse models of ASD showing both deficits in deposition and thickness of the myelin sheath (Graciarena, Seiffe, Nait-Oumesmar, & Depino, 2019; H. Lee, Thacker, Sarn, Dutta, & Eng, 2019), with the latter showing decreased myelination in areas associated with social behaviour, potentially a result of impaired maturation of OPCs. On the contrary, another study looking into the effect of developmental myelination in a mouse model of Timothy syndrome, in which a gain-of-function mutation in the α1 subunit of the L-type calcium channel Cav1.2 gives rise to an ASD phenotype, was associated with an increase in the number of mature oligodendrocytes and myelination (Cheli et al., 2018). A recent study looking into the effect of Cyp1: a critical gene in 15q11.2 deletion syndrome, demonstrate that deletion of this gene resulted in a decrease in the myelination in the corpus callosum and interfered with the learning abilit of rats (Silva et al., 2019). Taken together, dysregulation in oligodendrocyte differentiation and developmental myelination play an important role towards the pathogenic mechanisms of ASD.

4.3. Microglia

Microglia are the immune cells of the brain and are capable of producing and reacting to a range of immune responses by secreting cytokines (Hanisch, 2002). Brains from autistic patients show increased size, density, number and activity of microglia in the PFC (Morgan et al., 2010; Tetreault et al., 2012). Animal models focusing on neurodevelopment have shown abnormal microglial morphology and decreased density in the PFC (Sanagi et al., 2019). Additionally, a mouse model of 15q11-q13 duplication showed decreased amount of a microglia marker in the amygdala in early postnatal mice (Shigemori, Sakai, Takumi, Itoh, & Suzuki, 2015). TREM2, an immune receptor known to regulate the level of neurons by activation of microglia, has been shown to be downregulated in the autistic brain (Filipello et al., 2018). The study demonstrated that Trem2 KO mice display altered sociability and was associated with repetitive behaviour. It is plausible that either deficient or too many microglia along with abnormal morphology cause some of the social and anxiety features of ASD.

Microglia activation is another event associated with ASD. Active microglia is commonly seen as a sign of inflammation in the central nervous system (Dheen & Charanjit Kaur and Eng-Ang, 2007). Brains from autistic patients show increased activation of microglia along with pro inflammatory markers in both brain and cerebrospinal fluid (Patel, Tsilioni, Leeman, & Theoharides, 2016; Suzuki et al., 2013; Vargas et al., 2005). Increased neurotensin has been found in some children with autism and this peptide was shown to activate microglia through stimulation of the mTOR pathway (Patel et al., 2016). Further, rodents injected with a drug that increased microglial activation showed ASD-like behaviour (Zerrate et al., 2007). The glutamate receptor mGluR5: shown to decrease microglial activation (Loane, Stoica, Pajoohesh-Ganji, Bymes, & Faden, 2009), has been shown to be significantly decreased in the brains of patients with autism accompanied by increase in pro-inflammatory markers (Chana et al., 2015). Research has shown that inflammation has an adverse effect on neurodevelopment (van der Burg et al., 2015). Together, these studies suggest that, at least in part, there is an inflammatory pathology in ASD.

Microglia may also have a role in the physical development of neurons. Evidence from brains of patients with autism have shown microglia exist in a much closer proximity to neurons in patients (Morgan et al., 2012). Whilst the phenotypical result of this interaction is unknown, research in other areas have shown microglia become close in
proximity to neurons when motor neurons are degenerating in a model of motor neuron disease (Toedebusch et al., 2018). Other studies have shown prolonged microglial-neuronal contact after damage, in particular with the synapses (Wake, Moorhouse, Jinno, Kohsaka, & Nabekura, 2009). This may be an attempt of synaptic pruning: an essential mechanism of neurodevelopment (Paolicelli et al., 2011), to counterbalance the increased neurogenesis seen in autism. On the other hand, it may suggest defective microglia activation in ASD. It has been shown that the communication between neurons and microglia and deficits in synaptic pruning results in impaired social behaviour and repetitive behaviours (Zhan et al., 2014); key features of autism. Another animal model of autism (Atg7 deficient) shows an increase in the number and density of dendritic spines and increased immature synapses as a result of deficits in synaptic pruning by microglia (H. J. Kim et al., 2017). Research has also shown that brains of patients with autism have significantly higher expression of markers of microglia but neuronal markers are significantly decreased in the PFC (Edmonson, Ziets, & Rennert, 2014). This could suggest i) microglia are attempting to play a therapeutic role for defective neurons, ii) microglia themselves are defective and are causing neuronal harm, potentially through dysfunctional synaptic pruning. Furthermore, maternal immune activation; one of the risk factors for ASD, may potentially mediate its effect through microglial activation, which opens up an opportunity for immunomodulatory treatment options to rescue some of the associated phenotypes of ASD.

4.4. Astrocytes

Astrocytes are an integral part of the tripartite synapse (Eroglu & Barres, 2010) and play a key role in the regulatory control of synaptic function and plasticity, (Tewari & Parpura, 2016) which in turn play a key role in social behaviour and cognitive functions. Astrocytes have been less implicated in ASD compared to the three other major types of brain cells reviewed here (neurons, oligodendrocytes and microglia). This may be due to a reduced involvement in these disorders or a lack of research into the link between astrocytes and ASD. Research has shown contrasting results in regards to astrocytes and ASD. In the cerebellum, one study reported increased GFAP (Laurence & Fatemi, 2005); a major marker of astrocytes, whereas another study showed a decrease of the astrocytic marker AQP4 (Fatemi, Folsom, Reutiman, & Lee, 2008) in brains of patients with autism. One explanation for these findings is the timing at which astrocytes may be more active during development. Earlier in development GFAP has been shown to be significantly increased, whilst expression decreased postnatally in the cerebellum (Vargas et al., 2005). This study further showed that whilst expression was decreased, there was an increase in protein, suggestive of post transcriptional modifications.

Brains of patients with autism have shown an increase in FMRP in astrocytes, a protein essential for normal cognitive function (Santos, Kanellopoulos, & Baghi, 2014), but a decrease in neurons combined with neuronal deficits in the cerebral cortex (Jarek Wegiel et al., 2018). This may suggest that astrocytes are less affected by ASD and may not represent an area where pathology is evident. In support of this, typical astrocyte morphology was seen in the dorsolateral PFC from patients with autism (T. T. Lee et al., 2017) and a mouse model inducible KO of Glit1; the glutamate transporter secreted by astrocytes, did not show deficits in social behaviour (Aida et al., 2015). On the other hand, one study showed Fmr1 astrocyte KO mice had reduced expression of the excitatory protein Glit1 in astrocytes and impaired glutamate uptake, leading to increased extracellular glutamate and was associated with increased activity of pyramidal neurons (Higashimori et al., 2016). iPSC astrocytes from Rett syndrome patients seem to have accelerated differentiation (Andoh-Noda et al., 2015). When wild-type neurons were cultured in conditioned media obtained from these astrocytes it led to an alteration in neural connectivity (E. C. Williams et al., 2014). Altogether, this research suggests that defective astrocytes contribute towards impaired neuronal health and the pathology of ASD. A summary of ASD risk factors and the contribution of neural lineage cells towards the pathology of ASD is given in figure 1.

Advances in the understanding of cellular pathogenesis associated with Autism Spectrum Disorder
Figure 1: Contribution of the risk factors to the cellular pathologies and hypotheses associated with ASD.

Diagram of risk factors, hypotheses of ASD and which neural lineage cells may be linked to these hypotheses. The solid arrows denote hypotheses with strong links to the relevant neural lineage cells. The dotted arrow shows a potential link between the hypothesis and neural lineage cells.

4.5. Brain organoids
Organoids are becoming increasingly popular ways to study structure and function of neural cells. There are a number of advantages of using 3D cellular model organoids over the widely-used 2D neural cultures. Organoids are much better models as they are able to replicate the development of the neocortex (Camp et al., 2015) and are improved models to test drugs for treatment due to their more complex structure and organisation (Ranga, Gjorevski, & Lutolf, 2014); better to recapitulate brain pathology over 2D models. Currently, due to the relative novelty of this cellular model, very little research on cerebral organoids and ASD have been conducted. Of the research published it has been shown that heterozygous knockouts of the CHD8 gene replicate results of 2D cell culture in regards to differentially expressed genes associated with CHD8 and autism (P. Wang et al., 2015; P. Wang et al., 2017). One other study looking at overproduction of FOXG1 in patient-derived organoids showed an overproduction of GABAergic inhibitory neurons (Mariani et al., 2015). Whilst this gene is not directly linked to autism, it has been associated with Rett Syndrome (Ariani et al., 2008), which involves a number of autistic-like features. Further, brain organoids are potential models to recapitulate morphological phenotypes of ASD, as discussed, the PTEN mutation leads to large sized organoids (Y. Li et al., 2017); consistent with the macrocephaly phenotype of this gene mutation.

5. Clinical Implications and Future Perspectives
To make a difference in the lives of subjects with ASD, it is essential to provide a better diagnosis and an effective treatment. The therapies that are available for ASD vary widely for very young children and toddlers. While social and adaptive therapies have been recommended for young children, behavioural therapies have proven to be effective for adults. Due to the complex genetics associated with ASD, it is crucial to define and
investigate the impact of genetics on brain development and cellular pathogenesis such as impaired neural maturation and neuroinflammation. This information will serve as a basis for the development of effective therapies that can alleviate some of the symptoms. Furthermore, developing and refining the human cellular models that can identify a clear neurobiological process is crucial, as to develop a platform for the screening of drugs.

Conflict of Interests
The authors declare no conflict of interest.

References
Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal Flora and Gastrointestinal Status in Children with Autism - Comparisons to Typical Children and Correlation with Autism Severity. *BMC gastroenterology*, 11, 22-22. doi:10.1186/1471-230X-11-22

Adamsen, A., O'Hare, A., & Graham, C. (2006). Impairments in Sensory Modulation in Children with Autism Spectrum Disorder. *British Journal of Occupational Therapy*, 69(8), 357-364. doi:10.1177/0308022606090803

Aida, T., Yoshida, J., Nomura, M., Tanimura, A., Iino, Y., Sorna, M., . . . Tanaka, K. (2015). Astroglial glutamate transporter deficiency increases synaptic excitability and leads to pathological repetitive behaviors in mice. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*, 40(7), 1569-1579. doi:10.1038/npp.2015.26

American Psychiatric, A. (2013). Diagnostic and statistical manual of mental disorders. *BMC Med*, 17, 133-137.

Anderson, S. W., Bechera, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neuroscience*, 2(11), 1032-1037. doi:10.1038/14833

Andoh-Noda, T., Akamatsu, W., Miyake, K., Matsumoto, T., Yamaguchi, R., Sanosaka, T., . . . Nakashima, K. (2015). Differentiation of multipotent neural stem cells derived from Rett syndrome patients is biased toward the astrocytic lineage. *Molecular brain*, 8(1), 31.

Ariani, F., Hayek, G., Rondinella, D., Artuso, R., Mencarelli, M. A., Spanhol-Rosseto, A., . . . Ricciardi, S. (2008). FOXG1 is responsible for the congenital variant of Rett syndrome. *The American Journal of Human Genetics*, 83(1), 89-93.

Arranz, J., Balducci, E., Arató, K., Sánchez-Elezepuru, G., Najar, S., Parras, A., . . . Arbonés, M. L. (2019). Impaired development of neocortical circuits contributes to the neurological alterations in DYRK1A haplosufficiency syndrome. *Neurobiology of Disease*, 127, 210-222. doi:https://doi.org/10.1016/j.nbd.2019.02.022

Atladóttir, H. Ó., Thorsen, P., Østergaard, L., Schendel, D. E., Lemcke, S., Abdallah, M., & Parner, E. T. (2010). Maternal Infection Researching Hospitalization During Pregnancy and Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, 40(12), 1423-1430. doi:10.1007/s10803-010-1006-y

Autism Spectrum Disorders Working Group of The Psychiatric Genomics, C. (2017). Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Molecular autism*, 8, 21-21. doi:10.1186/s12276-017-0137-9

Ayward, E. H., Minshew, N. J., Field, K., Sparks, B. F., & Singh, N. (2002). Effects of age on brain volume and head circumference in autism. *Neurology*, 59(2), 175. doi:10.1212/WNL.59.2.175

Babaei, O., Piletti Chatain, C., & Knueger-Burg, D. (2018). Inhibition in the amygdala anxiety circuitry. *Experimental & molecular medicine*, 50(4), 18-18. doi:10.1038/jemm.2018.0063-8

Baio, J., Wiggins, L., Christensen, D. L., Maenner, M. J., Daniels, J., Warren, Z., . . . Dowling, N. F. (2018). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002)*, 67(6), 1-23. doi:10.15585/mmwr.ss6706a1

Ben Itzhak, E., Lahut, E., & Zachor, D. A. (2011). Advanced parental ages and low birth weight in autism spectrum disorders—Rates and effect on functioning. *Research in Developmental Disabilities*, 32(5), 1776-1781. doi:https://doi.org/10.1016/j.ridd.2011.03.004

Ben, J., Jiang, B., Wang, D., Liu, Q., Zhang, Y., Qi, Y., . . . Zhang, Y. (2019). Major vault protein suppresses obesity and atherosclerosis through inhibiting IKK–NF-κB signaling mediated inflammation. *Nature communications*, 10(1), 1801.

Bener, A., Khattab, A. O., & Al-Dabbagh, M. M. (2014). Is high prevalence of Vitamin D deficiency evidence for autism disorder?: In a highly endogamous population. *Journal of pediatric...
Brugha, T., Cooper, S. A., McManus, S., Purdon, S.,
Boucher, M., Staudt, C., Gilis, F., Oorschot, V.,
Boccuto, L., Lauri, M., Sarasua, S. M., Skinner, C. D.,
Blanc, A. K., & Wardlaw, T. (2005). Monitoring multiple features in memory by
Buchanan, D. A., Bak, B., Betancur, C., Sakurai, T., & Buxbaum, J. D. (2009). The
Bener, A., Khattab, A. O., Bhugra, D., & Hoffmann, G. F. (2017). Iron and vitamin D levels among
Bucella, D., Dwivedi, A., . . . Schwartz, C. E. (2013). Prevalence of SHANK3 variants in
Burstyn, I., Wang, X., Yasui, Y., Sithole, F., & Zwaigenbaum, L. (2011). Autism spectrum
disorders and fetal hypoxia in a population-based cohort: accounting for missing exposures via
Estimation-Maximization algorithm. *BMC Medical Research Methodology, 11*, 2-2.
doi:10.1186/1471-2288-11-2
Busch, R. M., Srivastava, S., Hogue, O., Frazier, T. W.,
Klaas, P., Hardan, A., . . . Eng, C. (2019). Neurobehavioral phenotype of autism spectrum disorder associated with germine heterozygous
mutations in PTEN. *Translational psychiatry, 9*(1), 1-9.
Camp, J. G., Bashsha, F., Florio, M., Kanton, S., Gerber, T.,
Wilsch-Bruininger, M., . . . Lancaster, M. (2015). Human cerebral organoids recapitulate
gene expression programs of fetal neocortex development. *Proceedings of the National Academy of Sciences, 112*(51), 15672-15677.
Caprioni, F., Pallone, F., & Monteleone, G. (2008). Th17 immune response in IBD: A new pathogenic mechanism. *Journal of Crohn's and Colitis, 2*(4),
291-295. doi:10.1016/j.crohns.2008.05.004
Caragea, M., Murri, T., & Bauman, M. D. (2017). Maternal Immune Activation and Autism Spectrum Disorder: From Rodents to Nonhuman and Human Primates. *Biological Psychiatry, 81*(5), 391-401. doi:https://doi.org/10.1016/j.biopsych.2016.10.020
Carney, D. P., & Lewis, M. (2010). Regional white matter development in children with autism spectrum disorders. *Developmental Psychobiology, 52*(8), 755-763. doi:10.1002/dev.20471
Chana, G., Laskaris, L., Pantelis, C., Gillett, P., Testa, R.,
Zantomio, D., . . . Skafidas, E. (2015). Decreased expression of mGluR5 within the dorsolateral prefrontal cortex in autism and increased microglial number in mGluR5 knockout mice: Pathophysiological and neurobehavioral implications. *Brain, Behavior, and Immunity, 49*, 197-205. doi:https://doi.org/10.1016/j.bbi.2015.05.009
Chang, Y.-C., Cole, T. B., & Costa, L. G. (2018). Prenatal and early-life diesel exhaust exposure causes autism-like behavioral changes in mice. *Particle and fibre toxicology, 15*(1), 18-18. doi:10.1186/s12989-018-0254-4
Cheli, V. T., Santiago Gonzalez, D. A., Zamora, N. N.,
Lama, T. N., Spreuer, V., Rasmussen, R. L., . . .
Paez, P. M. (2018). Enhanced oligodendrocyte maturation and myelination in a mouse model of Timothy syndrome. *Glia, 66*(11), 2324-2339.
Clark, J. K., O’Keefe, A., Mastracci, T. L., Sussel, L., Matise, M. P., & Kucenas, S. (2014). Mammalian Nkx2.2+ perineurial glia are essential for motor nerve development. Developmental Dynamics, 243(9), 1116-1129.

Constantino, J. N., Todorov, A., Hilton, C., Law, P., Zhang, Y., Molloy, E., . . . Geschwind, D. (2013). Autism recurrence in half siblings: strong support for genetic mechanisms of transmission in ASD. Molecular psychiatry, 18(2), 137.

Cope, E. C., Britone, B. A., Brockett, A. T., Martinez, S., Vigneron, P.-A., Opendik, M., . . . Gould, E. (2016). Immature Neurons and Radial Glia, But Not Astrocytes or Microglia, Are Altered in Adult Cntnap2 and Shank3 Mice, Models of Autism. eNeuro, 3(5), ENEURO.0196-0116.2016. doi:10.1523/ENEURO.0196-16.2016

Corthals, K., Henkamp, A. S., Kossen, R., Großhennig, I., Hahn, N., Gras, H., . . . Geurten, B. R. H. (2017). neurelins nlg2 and nlg4 affect social behavior in Drosophila melanogaster. Frontiers in psychiatry, 8, 113.

Coughesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of Brain Overgrowth in the First Year of Life in Autism. JAMA, 290(3), 337-344. doi:10.1001/jama.290.3.3337

Coughesne, E., Mouton, P. R., Calhoun, M. E.,Semendeferi, K., Ahrens-Barbeau, C., Hallet, M. J., . . . Pierce, K. (2011). Neuron Number and Size in Prefrontal Cortex of Children With Autism. JAMA, 306(18), 2001-2010. doi:10.1001/jama.2011.1638

Craig, A. M., & Kang, Y. (2007). Neurexin–neuroligin signaling in synapse development. Current opinion in neurobiology, 17(1), 43-52.

Crepel, A., Steyaert, J., Durand, C. M., Betancur, C., Bochsers, T. M., Bockmann, J., Chaste, P., Fauchereau, F., . . . Bourgeron, T. (2007). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nature genetics, 39(1), 25-27. doi:10.1038/ng1933

Edmonson, C., Ziats, M. N., & Rennert, O. M. (2014). Altered glial marker expression in autistic post-mortem prefrontal cortex and cerebellum. Molecular autism, 5(1), 3-3. doi:10.1186/2040-2392-5-3

Eroglu, C., & Barres, B. A. (2010). Regulation of synaptic connectivity by glia. Nature, 468(7321), 223.

Escarilla, C. O., Filonova, I., Walker, A. K., Xuan, Z. X., Holehonnur, R., Espinosa, F., . . . Mendloza, D. B. (2017). Kctd13 deletion reduces synaptic transmission via increased RhoA. Nature, 551(7679), 227.

Eva, R., Koseki, H., Kanamarlapudi, V., & Fawcett, J. W. (2017). EFA6 regulates selective polarised transport and axon regeneration from the axon initial segment. J Cell Sci, 130(21), 3663-3675.

Fan, R., He, H., Yao, W., Zhu, Y., Zhou, X., Gu, M., . . . Fan, M. (2018). SOX7 suppresses Wnt signaling by disrupting β-Catenin/BCL9 interaction. DNA and cell biology, 37(2), 126-132.

Fang, W.-Q., Chen, W.-W., Jiang, L., Liu, K., Yung, W.-H., Fu, Amy K. Y., & Ip, Nancy Y. (2014).
Overproduction of Upper-Layer Neurons in the Neocortex Leads to Autism-like Features in Mice. Cell Reports, 9(5), 1635-1643. doi:https://doi.org/10.1016/j.celrep.2014.11.003

Fassio, A., Patry, L., Congiu, S., Onofri, F., Piton, A., Gauthier, J., ... Fadda, M. (2011). SYN1 loss-of-function mutations in autism and partial epilepsy cause impaired synaptic function. Human molecular genetics, 20(12), 2297-2307.

Faterni, S. H., Folsom, T. D., Reutiman, T. J., & Lee, S. (2008). Expression of astrocytic markers aquaporin 4 and connexin 43 is altered in brains of subjects with autism. Synapse (New York, N.Y.), 62(7), 501-507. doi:10.1002/syn.20519

Filice, F., Vöckel, K. J., Sungur, A. Ö., Wörh, M., & Schwaller, B. (2016). Reduction in parvalbumin expression not loss of the parvalbumin-expressing GABA interneuron subpopulation in genetic parvalbumin and shank mouse models of autism. Molecular brain, 9, 10-10. doi:10.1186/s13041-016-0192-8

Finogold, S. M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M.-L., Bolte, E., ... Kaul, A. (2002). Gastrointestinal Microflora Studies in Late-Onset Autism. Clinical Infectious Diseases, 35(Supplement_1), S6-S16. doi:10.1086/341914

Finlay, J. M., Dunham, G. A., Isherwood, A. M., Newton, C. J., Nguyen, T. V., Reppar, P. C., ... Greene, R. W. (2015). Effects of prefrontal cortex and hippocampal NMDA NR1-subunit deletion on complex cognitive and social behaviors. Brain research, 1600, 70-83. doi:10.1016/j.brainsci.2014.10.037

Flores-Pajot, M.-C., Offner, M., Do, M. T., Lavigne, E., & Villeneuve, P. J. (2016). Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis. Environmental Research, 151, 763-776. doi:https://doi.org/10.1016/j.envres.2016.07.030

Fombonne, E., Rogé, B., Claverie, J., Courty, S., & Krack, J. (1999). Microcephaly and Macrocephaly in Autism. Journal of Autism and Developmental Disorders, 29, 113-119. doi:10.1023/A:1023036509476

Fonnum, F. (1984). Glutamate: A Neurotransmitter in Mammalian Brain. Journal of Neurochemistry, 42(1), 1-11. doi:10.1111/j.1471-4159.1984.tb09689.x

Fornasiero, E. F., Raimondi, A., Guarnieri, F. C., Orlando, M., Fesse, R., Benfenati, F., & Vallorti, F. (2012). Synapsins contribute to the dynamic spatial organization of synaptic vesicles in an activity-dependent manner. Journal of Neuroscience, 32(35), 12214-12227.

Franklin, T. B., Silva, B. A., Perova, Z., Marrone, L., Masferrer, M. E., Zhan, Y., ... Gross, C. T. (2017). Prefrontal cortical control of a brainstem social behavior circuit. Nature neuroscience, 20(2), 260-270. doi:10.1038/nn.4470

Froehlich-Santino, W., Londondo Tobon, A., Cleveland, S., Torres, A., Phillips, J., Cohen, B., ... Hallmayer, J. (2014). Prenatal and perinatal risk factors in a twin study of autism spectrum disorders. Journal of psychiatric research, 54, 100-108. doi:10.1016/j.jpsychires.2014.03.019

Gauthier, J., Spiegelman, D., Piton, A., Lafrenière, R. G., Laurent, S., St-Onge, J., ... Rouleau, G. A. (2009). Novel de novo SHANK3 mutation in autistic patients. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150B(3), 421-424. doi:10.1002/ajmg.b.30822

Geetha, B., Sukumar, C., Dhivyadeepa, E., Reddy, J. K., & Balachandar, V. (2019). Autism in India: a case-control study to understand the association between socio-economic and environmental risk factors. Acta Neurologica Belgica, 119(3), 393-401. doi:10.1007/s13760-018-01057-4

Gidaya, N. B., Lee, B. K., Burstyn, I., Yudell, M., Mortensen, E. L., & Newshaffer, C. J. (2014). In Utero Exposure to Selective Serotonin Reuptake Inhibitors and Risk for Autism Spectrum Disorder. Journal of Autism and Developmental Disorders, 44(10), 2558-2567. doi:10.1007/s10803-014-2128-4

Gizzi, J., Urbanski, M. J., Prestori, F., Bandyopadhyay, B., Yan, A., Friedrich, V., ... Goldfarb, M. (2010). Behavioral and cerebellar transmission deficits in mice lacking the autism-linked gene islet brain-2. The Journal of Neuroscience : the official journal of the Society for Neuroscience, 30(44), 14805-14816. doi:10.1523/JNEUROSCI.1161-10.2010

Gladwyn-Ng, L., Huang, L., Ngo, L., Li, S. S., Qu, Z., Vanyai, H. K., ... Heng, J. I. T. (2016). Bacard1/Kctd13 and Bacard2/Tnfaip1 are interacting partners to Rnd proteins which influence the long-term positioning and dendritic maturation of cerebral cortical neurons. Neural development, 11(1), 7.

Glynn, L. M., Howland, M. A., Sandman, C. A., Davis, E. P., Phelan, M., Baram, T. Z., & Stern, H. S. (2018). Prenatal maternal mood patterns predict...
child temperament and adolescent mental health. *Journal of Affective Disorders*, 228, 83-90. doi:10.1016/j.jad.2017.11.065

Goffin, A., Hoefslott, L. H., Bosgoed, E., Swillen, A., & Fryns, J. P. (2001). PTEN mutation in a family with Cowden syndrome and autism. *American journal of medical genetics, 105*(6), 521-524.

Goodbourn, P. T., Bosten, J. M., Bargary, G., Hogg, R. E., Lawrance-Owen, A. J., & Mollon, J. D. (2014). Variants in the 1q21 risk region are associated with a visual endophenotype of autism and schizophrenia. *Genes, Brain and Behavior, 13*(2), 144-151.

Graciarena, M., Seiffge, A., Naït-Oumesmar, B., & Depino, A. M. (2019). Hypomyelination and Oligodendroglial Alterations in a Mouse Model of Autism Spectrum Disorder. *Frontiers in cellular neuroscience, 12*, 517-517. doi:10.3389/fncel.2018.00157

Greco, B., Manago, F., Tucci, V., Kao, H.-T., Valtorta, F., & Benfenati, F. (2013). Autism-related behavioral abnormalities in synapsin knockout mice. *Behavioural brain research, 251*, 65-74.

Grelotti, D. J., Gauthier, I., & Schultz, R. T. (2002). Social interest and the development of cortical face specialization: What autism teaches us about face processing. *Developmental Psychobiology, 40*(3), 213-225. doi:10.1002/dev.10028

Griesi-Oliveira, K., Acab, A., Gupta, A. R., Sunaga, D. Y., Chialiangkum, T., Nicol, X., . . . Muotri, A. R. (2015). Modeling non-syndromic autism and the impact of TRPC6 disruption in human neurons. *Molecular Psychiatry, 20*(11), 1350-1365. doi:10.1038/mp.2014.141

Grove, J., Ripke, S., Als, T. D., Mattheisen, M., Walters, R. K., Won, H., . . . andMe Research, T. (2019). Identification of common genetic risk variants for autism spectrum disorder. *Nature Genetics*, 51(3), 431-444. doi:10.1038/s41588-019-0344-8

Gunnersen, J. M., Kim, M. H., Fuller, S. J., De Silva, M., Britto, J. M., Hammond, V. E., . . . Sah, P. (2007). Sez6 proteins affect dendritic arborization patterns and excitability of cortical pyramidal neurons. *Neuron, 56*(4), 621-639.

Gutiérrez, R. C., Hung, J., Zhang, Y., Kertesz, A. C., Espina, F. J., & Colicos, M. A. (2009). Altered synchrony and connectivity in neuronal networks expressing an autism-related mutation of neurexin 3. *Neuroscience, 162*(1), 208-221.

Ha, S., Lee, D., Cho, Y. S., Chung, C., Yoo, Y.-E., Kim, J., . . . Ba, Y. C. (2016). Cerebellar Shank2 regulates excitatory synapse density, motor coordination, and specific repetitive and anxiety-like behaviors. *Journal of Neuroscience, 36*(48), 12129-12143.

Hagberg, K. W., Robijn, A. L., & Jick, S. (2018). Maternal depression and antidepressant use during pregnancy and the risk of autism spectrum disorder in offspring. *Clinical epidemiology, 10*, 1599-1612. doi:10.2147/CLEP.S180618

Hanisch, U. K. (2002). Microgliosis as a source and target of cytokines. *Glia, 40*(2), 140-155.

Harrington, A. J., Raisi, A., Rajkovich, K., Berto, S., Kumar, J., Molinaro, G., . . . Cowan, C. W. (2016). MEF2C regulates cortical inhibitory and excitatory synapses and behaviors relevant to neurodevelopmental disorders. *eLife, 5*, e20059. doi:10.7554/eLife.20059

Hattori, T., Kaji, M., Ishii, H., Jurepont, R., Takarada-Iemata, M., Minh Ta, H., . . . Hori, O. (2017). CD38 positively regulates postnatal development of astrocytes cell-autonomously and oligodendrocytes non-cell-autonomously. *Glia, 65*(6), 974-989. doi:10.1002/glia.23139

Heron, J., O’Connor, T. G., Evans, J., Goldberg, J., & Glover, V. (2004). The course of anxiety and depression through pregnancy and the postpartum in a community sample. *Journal of Affective Disorders, 80*(1), 65-73. doi:https://doi.org/10.1016/j.jad.2003.08.004

Higashimori, H., Schin, C. S., Chiang, M. S. R., Morel, L., Shoneye, T. A., Nelson, D. L., & Yang, Y. (2016). Selective Deletion of Astroglial FMRP Dysregulates Glutamate Transporter GLT1 and Contributes to Fragile X Syndrome Phenotypes In Vivo. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 36*(27), 7079-7094. doi:10.1523/JNEUROSCI.1069-16.2016

Huang, G., Chen, S., Chen, X., Zheng, J., Xu, Z., Doostparast Torshizi, A., . . . Shi, L. (2019). Uncovering the Functional Link Between SHANK3 Deletions and Deficiency in Neurodevelopment Using iPSC-Derived Human Neurons. *Frontiers in neuroanatomy, 13*, 23-23. doi:10.3389/fnana.2019.00023

Hutsler, J. J., & Zhang, H. (2010). Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Research, 1309*, 83-94. doi:https://doi.org/10.1016/j.brainres.2009.09.120

Hvid, A., Melbye, M., & Pasternak, B. (2013). Use of Selective Serotonin Reuptake Inhibitors during Pregnancy and Risk of Autism. *New England Journal of Medicine, 369*(25), 2406-2415. doi:10.1056/NEJMoa1301449

Idring, S., Lundberg, M., Sturm, H., Dalmann, C., Gumpert, C., Rai, D., . . . Magnusson, C. (2015). Changes in Prevalence of Autism Spectrum Disorder.
Disorders in 2001–2011: Findings from the Stockholm Youth Cohort. Journal of Autism and Developmental Disorders, 45(6), 1766-1773. doi:10.1007/s10803-014-2336-y

Idring, S., Magnusson, C., Lundberg, M., Ek, M., Rai, D., Svensson, A. C., . . . Lee, B. K. (2014). Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort. International Journal of Epidemiology, 43(1), 107-115. doi:10.1093/ije/dys262

Iossifov, I., O’Roak, B. J., Sanders, S. J., Ronemus, M., Krumm, N., Levy, D., . . . Patterson, K. E. (2014). The contribution of de novo coding mutations to autism spectrum disorder. Nature, 515(7526), 216.

Ito, H., Morishita, R., Mizuno, M., Kawamura, N., Tabuta, H., & Nagata, K.-i. (2018). Biochemical and Morphological Characterization of a Neurodevelopmental Disorder-Related Mono-ADP-Ribosylhydrolase, MACRO Domain Containing 2. Developmental neuroscience, 40(3), 278-287.

Jacot-Descombes, S., Uppul, N., Wicinski, B., Santos, M., Schmeidler, J., Giannakopoulos, P., . . . Hof, P. R. (2012). Decreased pyramidal neuron size in Brodmann areas 44 and 45 in patients with autism. Acta Neuropathologica, 124(1), 67-79. doi:10.1007/s00401-012-0976-6

Jain, S., Quach, H., Betancur, C., Rastam, M., Colineux, C., Gillberg, I. C., . . . Gillberg, C. (2003). Mutations of the X-linked genes encoding neurexins NLGN3 and NLGN4 are associated with autism. Nature genetics, 34(1), 27.

Jang, S.-W., Liu, X., Fu, H., Rees, H., Yepes, M., Levey, A., & Ye, K. (2009). Interaction of Akt-phosphorylated SRPK2 with 14-3-3 mediates cell cycle and cell death in neurons. Journal of Biological Chemistry, 284(36), 24512-24525.

Janssen, A. B., Savory, K. A., Garay, S. M., Sumption, L., Watkins, W., Garcia-Martin, L., . . . John, R. M. (2018). Persistence of anxiety symptoms after elective caesarean delivery. BJPsych Open, 4(5), 354-360. doi:DOI: 10.1192/bjo.2018.48

Jarrar, W., Dias, J. M., Ericson, J., Arnold, H.-H., & Holz, A. (2015). Nkx2. 2 and Nkx2. 9 are the key regulators to determine cell fate of branchial and visceral motor neurons in caudal hindbrain. PLoS one, 10(4), e0124408.

Jarrar, W., Vauti, F., Arnold, H.-H., & Holz, A. (2015). Generation of a Nkx2. 2Cre knock-in mouse line: Analysis of cell lineages in the central nervous system. Differentiation, 89(3-4), 70-76.

Jiang, Y.-h., Yue, R. K. C., Jin, X., Wang, M., Chen, N., Wu, X., . . . Scherer, S. W. (2013). Detection of clinically relevant genetic variants in autism spectrum disorder by whole-genome sequencing. American journal of human genetics, 93(2), 249-263. doi:10.1016/j.ajhg.2013.06.012

Joseph, R. M., & Taniaka, J. (2003). Holistic and part-based face recognition in children with autism. Journal of Child Psychology and Psychiatry, 44(4), 529-542. doi:10.1111/1469-7610.00142

Kalkbrenner, A. E., Schmidt, R. J., & Penlesky, A. C. (2014). Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Current problems in pediatric and adolescent health care, 44(10), 277-318. doi:10.1016/j.pcp.2014.06.001

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The Fusiform Face Area: A Module in Human Extrastriate Cortex Specialized for Face Perception. The Journal of Neuroscience, 17(11), 4302. doi:10.1523/JNEUROSCI.17-11-04302.1997

Kataja, E. L., Karlsson, L., Parsons, C. E., Pelto, J., Pesonen, H., Hiiiko, T., . . . Karlsson, H. (2019). Maternal pre- and postnatal anxiety symptoms and infant attention disengagement from emotional faces. J Affect Disord, 243, 280-289. doi:10.1016/j.jad.2018.09.064

Ketzel, M., & Gitler, D. (2012). Epileptic synapsin triple knockout mice exhibit progressive long-term aberrant plasticity in the entorhinal cortex. Cerebral Cortex, 22(4), 996-1008.

Kim, H.-G., Kishikawa, S., Higgins, A. W., Seong, I.-S., Donovon, D. J., Shen, Y., . . . Kutsche, K. (2008). Disruption of neurexin 1 associated with autism spectrum disorder. The American Journal of Human Genetics, 82(1), 199-207.

Kim, H. J., Cho, M. H., Shim, W. H., Kim, J. K., Jeon, E. Y., Kim, D. H., & Yoon, S. Y. (2017). Deficient autophagy in microglia impairs synaptic pruning and causes social behavioral defects. Molecular psychiatry, 22(11), 1576-1584. doi:10.1038/mp.2016.103

Kim, S., Kim, H., Yim, Y. S., Ha, S., Atarashi, K., Tan, T. G., . . . Huh, J. R. (2017). Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. Nature, 549, 528.

Kouwenhoven, W. M., van Oertelh, L., & Smidt, M. P. (2017). Pitx3 and En1 determine the size and molecular programming of the dopaminergic neuronal pool. PloS one, 12(8), e0182421.

Laurence, J. A., & Paterni, S. H. (2005). Glial fibillary acidic protein is elevated in superior frontal, parietal and cerebellar cortices of autistic subjects. The Cerebellum, 4(3), 206-210. doi:10.1080/14734220500208846
Lauritsen, M. B., Astup, A., Pedersen, C. B., Obel, C., Schendel, D. E., Schieve, L., . . . Pamer, E. T. (2014). Urbanicity and autism spectrum disorders. *Journal of autism and developmental disorders*, 44(2), 394-404. doi:10.1007/s10803-013-1875-y

Le, W., Zhang, L., Xie, W., Li, S., & Dani, J. A. (2015). Pitx3 deficiency produces decreased dopamine signaling and induces motor deficits in Pitx3 (−/−) mice. *Neurobiology of aging*, 36(12), 3314-3320.

Lee, H., Thacker, S., Sam, N., Dutta, R., & Eng, C. (2019). Constitutional mislocalization of Pen drives precocious maturation in oligodendrocytes and aberrant myelination in model of autism spectrum disorder. *Translational psychiatry*, 9(1), 13-13. doi:10.1038/s41398-018-0364-7

Lee, T. T., Skaffidas, E., Dottori, M., Zantorno, D., Pantelis, C., Everall, I., & Chana, G. (2017). No preliminary evidence of differences in astrocyte density within the white matter of the dorsolateral prefrontal cortex in autism. *Molecular autism*, 8, 64-64. doi:10.1186/s13229-017-0181-5

Li, J., Zhao, L., You, Y., Lu, T., Jia, M., Yu, H., . . . Lu, L. (2015). Schizophrenia related variants in CACNA1C also confer risk of autism. *PloS one*, 10(7), e0133247.

Li, Q., Zheng, S., Han, A., Lin, C.-H., Stoilov, P., Fu, X.-D., & Black, D. L. (2014). The splicing regulator PTBP2 controls a program of embryonic splicing required for neuronal maturation. *Elife*, 3, e01201.

Li, Y., Muffat, J., Omer, A., Bosch, I., Lancaster, M. A., Sur, M., . . . Jaenisch, R. (2017). Induction of expansion and folding in human cerebral organoids. *Cell stem cell*, 20(3), 385-396.

Li, Y.-M., Ou, J.-J., Liu, L., Zhang, D., Zhao, J.-P., & Tang, S.-Y. (2016). Association between maternal obesity and autism spectrum disorder in offspring: a meta-analysis. *Journal of autism and developmental disorders*, 46(1), 95-102.

Liu, F., Li, J., Wu, F., Zheng, H., Peng, Q., & Zhou, H. (2019). Altered composition and function of intestinal microbiota in autism spectrum disorders: a systematic review. *Translational psychiatry*, 9(1), 43-43. doi:10.1038/s41398-019-0389-6

Liu, Y., Murphy, S. K., Murtha, A. P., Fuemmeler, B. F., Schilkraut, J., Huang, Z., . . . Hoyo, C. (2012). Depression in pregnancy, infant birth weight and DNA methylation of imprint regulatory elements. *Epigenetics*, 7(7), 735-746. doi:10.4161/epi.20734

Loane, D. J., Stoica, B. A., Pajoohesh-Ganji, A., Byrnes, K. R., & Faden, A. I. (2009). Activation of metabotropic glutamate receptor 5 modulates microglial reactivity and neurotoxicity by inhibiting NADPH oxidase. *The Journal of biological chemistry*, 284(23), 15629-15639. doi:10.1074/jbc.M806139200

Lockwood Estrin, G., Ryan, E. G., Trevillion, K., Demilew, J., Bick, D., Pickles, A., & Howard, L. M. (2019). Young pregnant women and risk for mental disorders: findings from an early pregnancy cohort. *BJPsych Open*, 5(2), e21. doi:10.1192/bjo.2019.6

Luo, T., Liu, P., Wang, X.-Y., Li, L.-Z., Zhao, L.-P., Huang, J., . . . Peng, X.-Q. (2019). Effect of the autism-associated lncRNA Shank2-AS on architecture and growth of neurons. *Journal of Cellular Biochemistry*, 120(2), 1754-1762. doi:10.1002/jcb.27471

Ma, D., Salyakina, D., Jaworski, J. M., Konidari, I., Whitehead, P. L., Andelsen, A. N., . . . Cukier, H. N. (2009). A genome-wide association study of autism reveals a common novel risk locus at 5p14. 1. *Annals of human genetics*, 73(3), 263-273.

Man, J., & Zhang, X. (2011). CUEDC2: an emerging key player in inflammation and tumorigenesis. *Protein & cell*, 2(9), 699-703.

Manoli, M., & Driever, W. (2014). nklc2.1 and nklc2.4 genes function partially redundant during development of the zebrafish hypothalamus, preoptic region, and pallidum. *Frontiers in neuroanatomy*, 8, 145.

Maramara, L. A., He, W., & Ming, X. (2014). Pre- and Perinatal Risk Factors for Autism Spectrum Disorder in a New Jersey Cohort. *Journal of Child Neurology*, 29(12), 1645-1651. doi:10.1177/0883073813512899

Marchetto, M. C., Belinson, H., Tian, Y., Freitas, B. C., Fu, C., Vadodaria, K., . . . Muotri, A. R. (2017). Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. *Molecular psychiatry*, 22(6), 820-835. doi:10.1038/mp.2016.95

Mariani, J., Coppola, G., Zhang, P., Abyzov, A., Provini, L., Tomasini, L., . . . Vaccarino, F. M. (2015). FOXC1-Dependent Dysregulation of GABA/Glutamate Neuron Differentiation in Autism Spectrum Disorders. *Cell*, 162(2), 375-390. doi:10.1016/j.cell.2015.06.034

Marie, C., Clavairoly, A., Fröhlich, M., Hmaidan, H., Yan, J., Zhao, C., . . . Parras, C. (2018). Oligodendrocyte precursor survival and differentiation requires chromatin remodelling by Chd7 and Chd8. *Proceedings of the National Academy of Sciences of the United States of America*, 115(35), E8246-E8255. doi:10.1073/pnas.1802620115

McBride, K. L., Varga, E. A., Pastore, M. T., Prior, T. W., Manickam, K., Atkin, J. F., & Herman, G. E. (2010). Confirmation study of PTEN mutations
among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Research, 3*(3), 137-141. doi:10.1002/aur.132

Meyer, G., Varoqueaux, F., Neeb, A., Oschlies, M., & Brose, N. (2004). The complexity of PDZ domain-mediated interactions at glutamatergic synapses: a case study on neurexin. *Neuropharmacology, 47*(5), 724-733.

Morgan, J. T., Burger, N., Amaral, D. G., & Schumann, C. M. (2014). Stereological study of amygdala populations in adolescents and adults with autism spectrum disorder. *PloS one, 9*(10), e10356-e10356. doi:10.1371/journal.pone.010356

Morgan, J. T., Chuna, G., Abramson, I., Semendeferi, K., Courchesne, E., & Everall, I. P. (2012). Abnormal microglial-neuronal spatial organization in the dorsolateral prefrontal cortex in autism. *Brain Research, 1456*, 72-81. doi:https://doi.org/10.1016/j.brainres.2012.03.036

Morgan, J. T., Chuna, G., Pardo, C. A., Achim, C., Semendeferi, K., Buckwalter, J., . . . Everall, I. P. (2010). Microglial Activation and Increased Microglial Density Observed in the Dorsolateral Prefrontal Cortex in Autism. *Biological Psychiatry, 68*(4), 368-376. doi:10.1016/j.biopsych.2010.05.024

Munesue, T., Yokoyama, S., Nakamura, K., Anitha, A., Yamada, K., Hayashi, K., . . . Higashida, H. (2010). Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. *Neuroscience Research, 67*(2), 181-191. doi:https://doi.org/10.1016/j.neures.2010.03.004

Nutall, J. R. (2017). The plausibility of maternal toxicant exposure and nutritional status as contributing factors to the risk of autism spectrum disorders. *Nutritional Neuroscience, 20*(4), 209-218. doi:10.1080/1028415X.2015.1103437

O’Connor, T. G., Heron, J., Goldberg, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children’s behavioural/emotional problems at 4 years: Report from the Avon Longitudinal Study of Parents and Children. *British Journal of Psychiatry, 180*(6), 502-508. doi:10.1192/bjp.180.6.502

O’Roak, B. J., Deriżotis, P., Lee, C., Vives, L., Schwartz, J. J., Girirajan, S., . . . Baker, C. (2011). Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nature genetics, 43*(6), 585.

Oikonomakis, V., Kosma, K., Mitrikas, A., Sofocleous, C., Pervanidou, P., Symou, A., . . . Kanavakis, E. (2016). Recurrent copy number variations as risk factors for autism spectrum disorders: analysis of the clinical implications. *Clinical genetics, 89*(6), 708-718.

Ooga, M., Funaya, S., Hashioka, Y., Fujii, W., Naito, K., Suzuki, M. G., & Aoki, F. (2018). Chd9 mediates highly loosened chromatin structure in growing mouse oocytes. *Biochemical and biophysical research communications, 500*(3), 583-588.

Orosco, L. A., Ross, A. P., Cates, S. L., Scott, S. E., Wu, D., Sohn, J., . . . Zarbalis, K. S. (2014). Loss of Wdfy3 in mice alters cerebral cortical neurogenesis reflecting aspects of the autism pathology. *Nature communications, 5*, 4692-4692. doi:10.1038/ncomms5692

Ozonoff, S., Young, G. S., Carter, A., Messinger, D., Yimiyi, N., Zwaigenbaum, L., . . . Dobkins, K. (2011). Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics, 128*(3), e488-e495.

Paolicelli, R. C., Bolosco, G., Pagani, F., Maggi, L., Sciammi, N., Panzanelli, P., . . . Gross, C. T. (2011). Symaptic Pruning by Microglia Is Necessary for Normal Brain Development. *Science, 333*(6048), 1456. doi:10.1126/science.1202529

Patel, A. B., Tsilioni, I., Leeman, S. E., & Theoharis, T. C. (2016). Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism. *Proceedings of the National Academy of Sciences of the United States of America, 113*(45), E7049-E7058. doi:10.1073/pnas.1604992113

Peng, N., Liu, S., Xia, Z., Ren, S., Feng, J., Jing, M., . . . Zhu, Y. (2016). Inducible major vault protein plays a pivotal role in double-stranded RNA–or virus-induced proinflammatory response. *The Journal of Immunology, 196*(6), 2753-2766.

Peça, J., Feliciano, C., Ting, J. T., Wang, W., Wells, M. F., Venkatraman, T. N., . . . Feng, G. (2011). Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. *Nature, 472*(7344), 437-442. doi:10.1038/nature09965

Phelan, K., & McDermid, H. E. (2012). The 22q13.3 Deletion Syndrome (Phelan-McDermid Syndrome). *Molecular syndromology, 2*(3-5), 186-201. doi:10.1159/000334260

Pinborough-Zimmerman, J., Bildner, D., Bakian, A., Satterfield, R., Carbone, P. S., Nangle, B. E., . . . McMahon, W. M. (2011). Sociodemographic risk factors associated with autism spectrum disorders and intellectual disability. *Autism Research, 4*(6), 438-448. doi:10.1002/aur.224

Pinto, D., Pagnamenta, A. T., Klei, L., Anney, R., Marzo, D., Regan, R., . . . Abrahams, B. S. (2010).
Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*, 466(7304), 368.

Pirone, A., Alexander, J. M., Koenig, J. B., Cook-Snyder, D. R., Palmati, M., Wickham, R. J., . . . Jacob, M. H. (2018). Social Stimulus Causes Aberrant Activation of the Medial Prefrontal Cortex in a Mouse Model With Autism-Like Behaviors. *Frontiers in synaptic neuroscience*, 10, 35-35. doi:10.3389/fnsyn.2018.00035

Polo-Kantola, P., Lampi, K. M., Hinikka-Yli-Salminiä, S., Gissler, M., Brown, A. S., & Sourander, A. (2014). Obstetric Risk Factors and Autism Spectrum Disorders in Finland. *The Journal of Pediatrics*, 164(2), 358-365. doi:10.1016/j.jpeds.2013.09.044

Prakash, N., Brodski, C., Naserke, T., Puelles, E., Gogoi, R., Hall, A., . . . Weisenhorn, D. M. V. (2006). A Wnt1-regulated genetic network controls the identity and fate of midbrain-dopaminergic progenitors in vivo. *Development*, 133(1), 89-98.

Puclowska, J., Vijayamahal, J., Tavares, E. J., Kelly, C., Karlo, J. C., & Landreth, G. E. (2015). The 16p11.2 deletion mouse model of autism exhibits altered cortical progenitor proliferation and brain cytoarchitecture linked to the ERK MAPK pathway. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 35(7), 3190-3200. doi:10.1523/JNEUROSCI.4864-13.2015

Ranga, A., Gjorevski, N., & Lutolf, M. P. (2014). Drug discovery through stem cell-based organoid models. *Advanced drug delivery reviews*, 69, 19-28.

Roboon, J., Hattori, T., Ishii, H., Takarada-Iemata, M., Le, T. M., Shinashiy, Y., . . . Hori, O. (2019). Deletion of CD38 Suppresses Glial Activation and Neuroinflammation in a Mouse Model of Demyelination. *Frontiers in Cellular Neuroscience*, 13, 258.

Rosenberg, R. E., Law, J. K., Yenokyan, G., McGready, J., Kaufmann, W. E., & Law, P. A. (2009). Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Archives of pediatrics & adolescent medicine*, 163(10), 907-914.

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, 2(5), 255-267. doi:10.1034/j.1601-183X.2003.00037.x

Russo, F. B., Freitas, B. C., Pignatari, G. C., Fernandes, I. R., Sebat, J., Muoti, A. R., & Beltrão-Braga, P. C. B. (2018). Modeling the Interplay Between Neurons and Astrocytes in Autism Using Human Induced Pluripotent Stem Cells. *Biological Psychiatry*, 83(7), 569-578. doi:https://doi.org/10.1016/j.biopsych.2017.09.021

Sakagami, H., Horuma, T., Sukegawa, J., Owada, Y., Yanagisawa, T., & Kondo, H. (2007). Somatodendritic localization of EFA6A, a guanine nucleotide exchange factor for ADP-ribosylation factor 6, and its possible interaction with α-actinin in dendritic spines. *European Journal of Neuroscience*, 25(3), 618-628.

Sakagami, H., Matsuya, S., Nishimura, H., Suzuki, R., & Kondo, H. (2004). Somatodendritic localization of the mRNA for EFA6A, a guanine nucleotide exchange protein for ARF6, in rat hippocampus and its involvement in dendritic formation. *European Journal of Neuroscience*, 19(4), 863-870.

Sanagi, T., Sasaki, T., Nakagaki, K., Minamimoto, T., Kohsaka, S., & Ichinohe, N. (2019). Segmented Ibb1-Positive Processes of Microglia in Autism Model Marmosets. *Frontiers in cellular neuroscience*, 13, 344-344. doi:10.3389/fncel.2019.00344

Santos, A. R., Kanellopoulos, A. K., & Bagni, C. (2014). Learning and behavioral deficits associated with the absence of the fragile X mental retardation protein: what a fly and mouse model can teach us. *Learning & memory*, 21(10), 543-555.

Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M., De Ruibeis, S., An, J.-Y., . . . Klei, L. (2018). Novel genes for autism implicate both excitatory and inhibitory cell lineages in risk. *bioRxiv*, 484113.

Scott, F. J., Baron-Cohen, S., Bolton, P., & Brayne, C. (2002). Brief Report Prevalence of Autism Spectrum Conditions in Children Aged 5-11 Years in Cambridgeshire, UK. *Autism*, 6(3), 231-237. doi:10.1177/136236130200600002.

Shen, T., Ji, F., Wang, Y., Lei, X., Zhang, D., & Jiao, J. (2017). Brain-specific deletion of histone variant H2A.Z results in cortical neurogenesis defects and neurodevelopmental disorder. *Nucleic acids research*, 46(5), 2290-2307.

Shigemori, T., Sakai, A., Takumi, T., Itoh, Y., & Suzuki, H. (2015). Altered Microglia in the Amygdala Are Involved in Anxiety-Related Behaviours of a Copy Number Variation Mouse Model of Autism. *Journal of Nippon Medical School*, 82(2), 92-99. doi:10.1272/jnms.82.92

Shin Yim, Y., Park, A., Berrios, J., Lafourcade, M., Pascual, L. M., Soares, N., . . . Choi, G. B. (2017). Reversing behavioural abnormalities in mice exposed to maternal inflammation. *Nature*, 549(7673), 482-487. doi:10.1038/nature23909

https://jfrtdd.com
Silva, A. I., Haddon, J. E., Syed, Y. A., Trent, S., Lin, T.-C. E., Patel, Y., . . . Humby, T. (2019). Cytop1 haploinsufficient rats show white matter changes, myelin thinning, abnormal oligodendrocytes and behavioural inflexibility. *Nature communications*, 10(1), 3455.

Sironi, C., Teesalu, T., Muggia, A., Fontana, G., Marino, F., Savarese, S., & Talanico, D. (2009). EFA6A encodes two isoforms with distinct biological activities in neuronal cells. *J Cell Sci*, 122(12), 2108-2118.

Smith, K. R., Jones, K. A., Kopeikina, K. J., Burette, A. C., Copits, B. A., Yoon, S., . . . Weinberg, R. J. (2017). Cadherin-10 maintains excitatory/inhibitory ratio through interactions with synaptic proteins. *Journal of Neuroscience*, 37(46), 11127-11139.

Soda, T., Mapelli, L., Locatelli, F., Botta, L., Goldfarb, M., Prestori, F., & Angelo, E. (2019). Hyperexcitability and Hyperplasticity Disrupt Cerebellar Signal Transfer in the Iβ2 KO Mouse Model of Autism. *The Journal of Neuroscience*, 39(13), 2383. doi:10.1523/JNEUROSCI.1895-18.2019

Sujara, A. C., Rickert, M. E., Öberg, A. S., Quinín, P. D., Hernández-Díaz, S., Almqvist, C., . . . D’Onofrio, B. M. (2017). Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. *JAMA*, 317(15), 1553-1562. doi:10.1001/jama.2017.3413

Suzuki, K., Sugihara, G., Ouchi, Y., Nakamura, K., Futatsubashi, M., Takebayashi, K., . . . Mori, N. (2013). Microglial Activation in Young Adults With Autism Spectrum Disorder. *JAMA Psychiatry*, 70(1), 49-58. doi:10.1001/jamapsychiatry.2013.2722

Südhof, T. C. (2008). Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*, 455(7215), 903.

Talbott, E. O., Marshall, L. P., Rager, J. R., Arena, V. C., Sharma, R. K., & Stacy, S. L. (2015). Air toxics and the risk of autism spectrum disorder: the results of a population based case-control study in southwestern Pennsylvania. *Environmental health: a global access science source*, 14, 80-80. doi:10.1186/s12940-015-0064-1

Tang, G., Gudsnuk, K., Kuo, S.-H., Cotrina, Marisa L., Rosklijja, G., Sosunov, A., . . . Sulzer, D. (2014). Loss of mTOR-Dependent Macrophagy Causes Autistic-like Synaptic Pruning Deficits. *Neuron*, 83(5), 1131-1143.

doi:https://doi.org/10.1016/j.neuron.2014.07.040

Tetreault, N. A., Hakeem, A. Y., Jiang, S., Williams, B. A., Allman, E., Wold, B. J., & Allman, J. M. (2012). Microgliosis in the Cerebral Cortex in Autism. *Journal of Autism and Developmental Disorders*, 42(12), 2569-2584. doi:10.1007/s10803-012-1513-0

Tewari, S. G., & Parpura, V. (2016). Astrocytes modulate local field potential rhythm. *Frontiers in integrative neuroscience*, 9, 69.

Thakur, P. C., Stuckenholz, C., Rivera, M. R., Davison, J. M., Yao, J. K., Amstel, A., . . . Bahary, N. (2011). Lack of de novo phosphatidylinositol synthesis leads to endoplasmic reticulum stress and hepatic steatosis in edipt-deficient zebrafish. *Hepatology*, 54(2), 452-462.

Toedebusch, C. M., Snyder, J. C., Jones, M. R., Garcia, V. B., Johnson, G. C., Villalón, E. L., . . . Garcia, M. L. (2018). Arginase-1 expressing microglia in close proximity to motor neurons were increased early in disease progression in canine degenerative myelopathy, a model of amyotrophic lateral sclerosis. *Molecular and Cellular Neuroscience*, 88, 148-157. doi:https://doi.org/10.1016/j.mcn.2018.01.009

Trutuz, I. M., García-Cabezas, M. A., & Zikopoulos, B. (2019). Postnatal development and maturation of layer 1 in the lateral prefrontal cortex and its disruption in autism. *Acta neuropathologica communications*, 7(1), 40-40. doi:10.1186/s40478-019-0684-8

Uguz, F., Sahinoguz, M., Sonmez, E. O., Karsidag, C., Yuksel, G., Annagur, B. B., & Annagur, A. (2013). The effects of maternal major depression, generalized anxiety disorder, and panic disorder on birth weight and gestational age: a comparative study. *J Psychosom Res*, 75(1), 87-89. doi:10.1016/j.jpsychores.2013.02.008

Valicenti-McDermott, M., McVicar, K., Rapin, I., Wershil, B. K., Cohen, H., & Shinnar, S. (2006). Frequency of Gastrointestinal Symptoms in Children with Autistic Spectrum Disorders and Association with Family History of Autoimmune Disease. *Journal of Developmental & Behavioral Pediatrics*, 27(2).

Valnegri, P., Huang, J., Yamada, T., Yang, Y., Mejia, L. A., Cho, H. Y., . . . Bonni, A. (2017). RNF8/UBC13 ubiquitin signaling suppresses synapse formation in the mammalian brain. *Nature communications*, 8(1), 1271.

van der Burg, J. W., Sen, S., Chomitz, V. R., Seidell, J. C., Leviton, A., & Dammann, O. (2015). The role of systemic inflammation linking maternal BMI to
neurodevelopment in children. *Pediatric Research*, 79(3).

van Kooten, I. A. J., Palmen, S. J. M. C., van Cappeln, P., Steinbusch, H. W. M., Korr, H., Heinsen, H., . . . Schmitz, C. (2008). Neurons in the fusiform gyrus are fewer and smaller in autism. *Brain*, 131(4), 987-999. doi:10.1093/brain/awn33

van Tilborg, E., Achterberg, E. J. M., van Kammen, C. M., van der Toom, A., Groenendaal, F., Dijkstra, R., M., . . . Nijboer, C. H. A. (2018). Combined fetal inflammation and postnatal hypoxia causes myelin deficits and autism-like behavior in a rat model of diffuse white matter injury. *Glia*, 66(1), 78-93. doi:10.1002/glia.23216

Vargas, D. L., Nascimento, C., Krishnan, C., Zimmerman, A. W., & Pardo, C. A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology*, 57(1), 67-81. doi:10.1002/ana.20315

Vinet, É., Pineau, C. A., Clarke, A. E., Scott, S., Fornbonne, É., Joseph, L., . . . Bermatisky, S. (2015). Increased Risk of Autism Spectrum Disorders in Children Born to Women With Systemic Lupus Erythematosus: Results From a Large Population-Based Cohort. *Arthritis & Rheumatology*, 67(12), 3201-3208. doi:10.1002/art.39320

Vinkhuyzen, A. A. E., Achterberg, E. J. M., van der Toorn, A., Groenendaal, F., Dijkstra, R., M., . . . Nijboer, C. H. A. (2018). Combined fetal inflammation and postnatal hypoxia causes myelin deficits and autism-like behavior in a rat model of diffuse white matter injury. *Glia*, 66(1), 78-93. doi:10.1002/glia.23216

Vink, L. M. E., Kruithof, C. J., Verhulst, F., . . . Oosterling, I. J., van der Gaag, R. J., & Buitelaar, J. K. (2013). Narrowly Versus Broadly Defined Autism Spectrum Disorders: Differences in Pre- and Perinatal Risk Factors. *Journal of Autism and Developmental Disorders*, 43(7), 1505-1516. doi:10.1007/s10803-012-1678-6

Wake, H., Moorhouse, A. J., Jinno, S., Kohsaka, S., & Nabekura, J. (2009). Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *The Journal of Neuroscience: the official journal of the Society for Neuroscience*, 29(13), 3974-3980. doi:10.1523/JNEUROSCI.4363-08.2009

Wang, C., Qin, L., Min, Z., Zhao, Y., Zhu, L., Zhu, J., & Yu, S. (2015). SOX 7 interferes with β-catenin activity to promote neuronal apoptosis. *European Journal of Neuroscience*, 41(11), 1430-1437.

Wang, J., Gong, J., Li, L., Chen, Y., Liu, L., Gu, H., . . . Song, R. (2018). Neurexin gene family variants as risk factors for autism spectrum disorder. *Autism Research*, 11(1), 37-43.

Wang, K., Zhang, H., Ma, D., Bucan, M., Glessner, J. T., Abrahams, B. S., . . . Sleiman, P. M. A. (2009). Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature*, 459(7246), 528.

Wang, P., Lin, M., Pedrosa, E., Hrabovsky, A., Zhang, Z., Guo, W., . . . Zheng, D. (2015). CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in neurodevelopment. *Molecular autism*, 6(1), 55.

Wang, P., Mokhtari, R., Pedrosa, E., Kirschbaum, M., Baynak, C., Zheng, D., & Lachman, H. M. (2017). CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in cerebral organoids derived from iPS cells. *Molecular autism*, 8(1), 11.

Wegener, S., Buschler, A., Stempel, A. V., Kang, S. J., Lim, C.-S., Kaang, B.-K., . . . Schmitz, C. (2018). Defective Synapse Maturation and Enhanced Synaptic Plasticity in Shank2 Δex7/– Mice. *eNeuro*, 5(3).

Wegiel, J., Brown, W. T., La Fuci, G., Adiyev, T., Kascak, R., Kascak, R., . . . Wegiel, J. (2018). The role of reduced expression of fragile X mental retardation protein in neurons and increased expression in astrocytes in idiopathic and syndromic autism (duplications 15q11.2). *Autism Research*, 11(10), 1316-1331. doi:10.1002/aur.2003

Wegiel, J., Flory, M., Kuchna, I., Nowicki, K., Ma, S. Y., Imaki, H., . . . Brown, W. T. (2015). Neuronal nucleus and cytoplasm volume deficit in children with autism and volume increase in adolescents and adults. *Acta Neuropathologica Communications*, 3(1), 2. doi:10.1186/s40478-015-0183-5

Wegiel, J., Kuchna, I., Nowicki, K., Imaki, H., Marchi, E., . . . Wisniewski, T. (2010). The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta neuropathologica*, 119(6), 755-770. doi:10.1007/s00404-010-0655-4

Wei, H., Ma, Y., Liu, J., Ding, C., Hu, F., & Yu, L. (2016). Proteomic analysis of cortical brain tissue from the BTBR mouse model of autism: Evidence for changes in STOP and myelin-related proteins. *Neuroscience*, 312, 26-34. doi:https://doi.org/10.1016/j.neuroscience.2015.1.003

Wei, H., Zou, H., Sheikh, A. M., Malik, M., Dobkin, C., Brown, W. T., & Li, X. (2011). IL-6 is increased in the cerebellum of autistic brain and alters neural growth.
cell adhesion, migration and synaptic formation. *Journal of neuroinflammation, 8*, 52-52. doi:10.1186/s12035-017-0143-3

Wen, Z., Cheng, T.-L., Li, G.-z., Sun, S.-B., Yu, S.-Y., Zhang, Y., . . . Qiu, Z. (2017). Identification of autism-related MECP2 mutations by whole-exome sequencing and functional validation. *Molecular Autism, 8*(1), 43.

Wiggins, L. D., Robins, D. L., Bakeman, R., & Adamson, L. B. (2009). Brief Report: Sensory Abnormalities as Distinguishing Symptoms of Autism Spectrum Disorders in Young Children. *Journal of Autism and Developmental Disorders, 39*(7), 1087-1091. doi:10.1007/s10803-009-0711-x

Williams, B. L., Homig, M., Parekh, T., & Lipkin, W. I. (2012). Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of Sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *mBio, 3*(1), e00261-00211. doi:10.1128/mBio.00261-11

Williams, E. C., Zhong, X., Mohamed, A., Li, R., Liu, Y., Dong, Q., . . . Lu, J. (2014). Mutant astrocytes differentiated from Rett syndrome patient-specific iPSCs have adverse effects on wild-type neurons. *Human molecular genetics, 23*(11), 2968-2980.

Williams, K., Helmer, M., Duncan, G. W., Peat, J. K., & Mellis, C. M. (2008). Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. *Child: Care, Health and Development, 34*(2), 249-256. doi:10.1111/j.1365-2214.2007.00796.x

Williams, M. E., Wilke, S. A., Daggett, A., Davis, E., Otto, S., Ravi, D., . . . Klein, G. (2011). Cadherin-9 regulates synapto-specific differentiation in the developing hippocampus. *Neuron, 71*(4), 640-655.

Windham, G. C., Anderson, M., Lyall, K., Daniels, J. L., Knul, T. V. E., Croen, L. A., . . . Schieve, L. A. (2019). Maternal Pre-pregnancy Body Mass Index and Gestational Weight Gain in Relation to Autism Spectrum Disorder and other Developmental Disorders in Offspring. *Autism Research, 12*(2), 316-327. doi:10.1002/aur.2057

Xia, K., Guo, H., Hu, Z., Xun, G., Zuo, L., Peng, Y., . . . Zhang, F. (2013). Common genetic variants on 1p13.2 associate with risk of autism. *Molecular Psychiatry, 19*, 1212.

Xu, Q., Liu, Y.-Y., Wang, X., Tan, G.-H., Li, H.-P., Hultert, S. W., . . . Jiang, Y.-H. (2018). Autism-associated CHD8 deficiency impairs axon development and migration of cortical neurons. *Molecular autism, 9*, 65-65. doi:10.1186/s13229-018-0244-2

Yaguchi, H., Yabe, I., Takahashi, H., Watanabe, M., Nomura, T., Kano, T., . . . Hatakeyama, S. (2017). Szer62 regulates phosphorylation of ADD and neuregion. *Biochemical and biophysical research communications, 479*(4-1), 234-241.

Yang, X., Sun, R., Ci, L., Wang, N., Yang, S., Shi, J., . . . Fei, J. (2018). Tracing the dynamic expression of the Nfixb2 gene during inflammatory processes by in vivo bioluminescence imaging in transgenic mice. *Biochemical and biophysical research communications, 501*(1), 41-47.

Yao, W., Huang, J., & He, H. (2019). Over-expressed LOC101277196 suppressed oxidative stress levels and neuron cell proliferation in a rat model of autism through disrupting the Wnt signaling pathway by targeting FZD3. *Cellular Signalling, 62*, 109328. doi:10.1016/j.cellsig.2019.05.013

Ylisaukko-oja, T., Rehrström, K., Auranen, M., Vanhala, R., Alen, R., Kempas, E., . . . Ritkonen, R. (2005). Analysis of four neurilogen genes as candidates for autism. *European Journal of Human Genetics, 13*(12), 1285.

Yuen, R. K. C., Metro, D., Cao, H., Pellechga, G., Alipanah, B., Thiruvahindrapuram, B., . . . Zhang, T. (2016). Genome-wide characteristics of de novo mutations in autism. *NPJ genomic medicine, 1*, 16027.

Zeidan-Chulaf, F., de Oliveira, B.-H. N., Casanova, M. F., Casanova, E. L., Noda, M., Salmin, A. B., & Verkhatsky, A. (2016). Up-Regulation of Oligodendrocyte Lineage Markers in the Cerebellum of Autistic Patients: Evidence from Network Analysis of Gene Expression. *Molecular Neurobiology, 53*(6), 4019-4025. doi:10.1007/s12035-015-9351-7

Zerbo, O., Iosif, A.-M., Walker, C., Ozonoff, S., Hansen, R. L., & Hertz-Picciotto, I. (2013). Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) study. *Journal of autism and developmental disorders, 43*(1), 25-33. doi:10.1007/s10803-012-1540-x

Zermack, M. C., Pletnikov, M., Connors, S. L., Vargas, D. L., Seidler, F. J., Zimmerman, A. W., . . . Pardo, C. A. (2007). Neuroinflammation and Behavioral Abnormalities after Neonatal Terbutaline Treatment in Rats: Implications for Autism. *Journal of Pharmacology and Experimental Therapeutics, 322*(1), 16. doi:10.1124/jpet.107.121483
Zhan, Y., Paolicelli, R. C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., . . . Gross, C. T. (2014). Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nature Neuroscience, 17*(3), 400-406. doi:10.1038/nn.3641

Zhang, C., Milunsky, J. M., Newton, S., Ko, J., Zhao, G., Maher, T. A., . . . Boucard, A. A. (2009). A neurelin-4 missense mutation associated with autism impairs neurelin-4 folding and endoplasmic reticulum export. *Journal of Neuroscience, 29*(35), 10843-10854.

Zhang, K., & Sejnowski, T. J. (2000). A universal scaling law between gray matter and white matter of cerebral cortex. *Proceedings of the National Academy of Sciences, 97*(10), 5621-5626.

Zhang, M., Ergin, V., Lin, L., Stork, C., Chen, L., & Zheng, S. (2019). Axonogenesis Is Coordinated by Neuron-Specific Alternative Splicing Programming and Splicing Regulator PTBP2. *Neuron, 101*(4), 690-706.

Zhu, Q., Zhao, X., Zheng, K., Li, H., Huang, H., Zhang, Z., . . . Sussel, L. (2014). Genetic evidence that Ncx2.2 and Pdgfra are major determinants of the timing of oligodendrocyte differentiation in the developing CNS. *Development, 141*(3), 548-555.

Zoghbi, H. Y., & Bear, M. F. (2012). Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. *Cold Spring Harbor perspectives in biology, 4*(3), a009886.