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Autism genes and the leukocyte transcriptome in autistic toddlers relate to pathogen interactomes, infection and the immune system. A role for excess neurotrophic sAPPα and reduced antimicrobial Aβ

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ABSTRACT

Prenatal and early childhood infections have been implicated in autism. Many autism susceptibility genes (206 Autworks genes) are localised in the immune system and are related to immune/infection pathways. They are enriched in the host/pathogen interactomes of 18 separate microbes (bacteria/viruses and fungi) and to the genes regulated by bacterial toxins, mycotoxins and Toll-like receptor ligands. This enrichment was also observed for misregulated genes from a microarray study of leukocytes from autistic toddlers. The upregulated genes from this leukocyte study also matched the expression profiles in response to numerous infectious agents from the Broad Institute molecular signatures database. They also matched genes related to sudden infant death syndrome and autism comorbid conditions (autoimmune disease, systemic lupus erythematosus, diabetes, epilepsy and cardiomyopathy) as well as to estrogen and thyrotropin responses and to those upregulated by different types of stressors including oxidative stress, hypoxia, endoplasmic reticulum stress, ultraviolet radiation or 2,4-dinitrofluorobenzene, a hapten used to develop allergic skin reactions in animal models. The oxidative/integrated stress response is also upregulated in the autism brain and may contribute to myelination problems. There was also a marked similarity between the expression signatures of autism and Alzheimer's disease, and 44 shared autism/Alzheimer's disease genes are almost exclusively expressed in the blood-brain barrier. However, in contrast to Alzheimer's disease, levels of the antimicrobial peptide beta-amyloid are decreased and the levels of the neurotrophic/myelinotrophic soluble APP alpha are increased in autism, together with an increased activity of α-secretase. sAPPα induces an increase in glutamatergic and a decrease in GABA-ergic synapses creating and excitatory/inhibitory imbalance that has also been observed in autism. A literature survey showed that multiple autism genes converge on APP processing and that many are able to increase sAPPalpha at the expense of beta-amyloid production. A genetically programmed tilt of this axis towards an overproduction of neurotrophic/gliotrophic sAPPalpha and underproduction of antimicrobial beta-amyloid may explain the brain overgrowth and myelination dysfunction, as well as the involvement of pathogens in autism.

1. Introduction

Many of the genes associated with autism are localised in barrier systems and are enriched in blood/brain, intestinal, skin and placental barrier proteomic datasets. In addition, several are localised to the respiratory cilia that sweep noxious particles from the airways. (Carter, 2016). This barrier function is relevant to the passage of the many environmental pollutants and drugs that have been implicated in autism in epidemiological studies. These include tetrachlorodibenzo-p-dioxin. Pesticides and heavy metals, bisphenol A and phthalates, flame retardants, solvents and air pollutants (Grandjean and Landrigan, 2014; Rossignol et al., 2014), many of which are endocrine disruptors capable of modifying foetal and childhood neurodevelopmental pathways (de Cock et al. 2012, 2014; Gore et al., 2014; Kajta and Wojtowicz, 2010; Kalkbrenner et al., 2014). Autism genes are also selectively targeted by this same group of chemicals and by related pesticides and endocrine disruptors or by endogenous hormones and neurotransmitters relevant to autism (Carter and Blizard, 2016).

In evolutionary terms, barrier function is perhaps more relevant to the passage of pathogens. Barriers form a seal against invading pathogens and such interfaces are also endowed with immunological defence mechanisms designed to inactivate those that breach this seal. In the host/pathogen evolutionary battle, several pathogens have learnt to circumvent barrier systems or the associated immune defence (Doran et al., 2013b; Steukers et al., 2012; Metz-Boutigue et al., 2010). Respiratory cilia also play an important role in clearing mucus-entrapped

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Table 1
Prenatal and postnatal infections associated with the development of autism: The effects of infection in animal models are also shown.

Prenatal infection in mothers associated with autism in offspring	Postnatal infections associated with autism in children	Animal experiments
Congenital rubella (Trottier et al., 1999; Chess et al., 1978)	Influenza infection at the end of the first year of life or at the end of the follow-up period (age 16) (Abdallah et al., 2012)	Neonatal Borna virus infection in rats induces pathological and behavioural changes relevant to autism and schizophrenia (Hornig et al. 2001a, 2001b; Lancaster et al., 2007; Pletnikov et al. 1999, 2003)
Maternal bacterial infections requiring hospitalisation or multiple infections during pregnancy (Zerbo et al., 2015)	High levels of measles antibody in autistic children (Singh and Jensen, 2003)	Prenatal infection with the influenza virus H1N1 strain on embryonic day 16 induces cerebellar changes in fragile X mental retardation protein, glutamate and REELIN signaling in the mouse offspring, as observed in autism and schizophrenia (Fatemi et al., 2016)
Viral infection necessitating maternal hospitalisation in the first trimester or maternal bacterial infection in the second trimester (Atladottir et al., 2010)	Increased HERV-H and HERV-W retrovirus-positive peripheral blood mononuclear cells in autistic patients (Balestrieri et al., 2012)	Prenatal group B streptococcus (GBS) infection in rats leads to reduced thickness of periventricular white matter in the male offspring, which also show autistic-like behaviours (abnormal social interaction and communication, impaired processing of sensory information and hyperactivity). Inactivated GBS also leads to placental damage (Allard et al., 2016; Bergeron et al., 2013).
Maternal genital infections or bacterial infections in the third trimester (Fang et al., 2015)	Mycoplasma species, Chlamydia pneunomiae, and human herpes virus-6 coinfections have been reported at higher frequencies in the blood of autistic patients (Nicolson et al., 2007)	Prenatal lipopolysaccharide administration (gestational day 9.5) in rats produces reduced cerebral dopaminergic activity and autistic relevant social deficits in male pups (Kirsten et al., 2012) and in male mice offspring which also show increases in the number of dendritic spines in the granule cells of the dentate gyrus (Fernandez et al., 2016)
Maternal reports of presumed cervical-vaginal infection during pregnancy (yeast, bacterial or viral (Joseph et al., 2017)	Association with a high titre of Varicella zoster (chicken pox) antibodies (Gentile et al., 2014)	Prenatal administration of the viral mimic polyinosinic:polycytidylic acid (Poly IC) produces autistm relevant behaviour in the male mouse offspring (Xuan and Hampson, 2014).
Relationships with influenza infection possibly related to maternal fever rather than the infectious agent (Atladottir et al., 2012)	Higher levels of HSV-2 herpes virus IgM antibodies (indicative of acute infection) in a sample (N = 40) of autistic children (Mora et al., 2009)	Lipopolysaccharide administration at postnatal day 3 activates microglia and increases cell proliferation in the subventricular zone and the dentate gyrus of the hippocampus, together with an increase in the oligodendrocyte population, without hypermyelination. LPS-exposed rats showed impairments in communicative and cognitive functions (Pang et al., 2016).
General infection during pregnancy not linked to any specific trimester (Lee et al., 2015)	Auditory disorders and infection have a high prevalence in a subgroup of autistic children followed from 0 to 15 years of age (Doshi-Velez et al., 2014)	
Urinary infection during pregnancy (Wilkerson et al., 2002)	Association with a higher prior frequency of the bacterial skin infection impetigo (caused by Staphylococcus aureus, and less frequently by Streptococcus pyogenes), has been reported along with infantile feeding problems (vomiting, reflux, colic and failure to feed) (Whiteley, 2004)	
A synergistic gene/environment interaction between autism-related copy number variations and maternal infection associated with autism in the offspring (Mazina et al., 2015)	High levels of antibodies to Candida albicans reported in autistic children (Hughes and Ashwood, 2018)	
Maternal report of cervical-vaginal infection during pregnancy is associated with increased risk of autism spectrum disorder with intellectual disability, (Joseph et al., 2017)	**Post-mortem studies** Relatively higher levels of polyoma viruses in the temporal cortex post-mortem (BK virus, JC virus, and simian virus 40). Polyviral infections were also more frequent in the autistic group (Lintas et al., 2010).	
High maternal T. gondii IgM antibody levels associated with a *decreased risk* of childhood autism, while low maternal T. gondii IgG antibody was associated with increased risk. The authors suggested that lowered IgG levels might relate to sub-optimal maternal immune function (Spann et al., 2017; Grether et al., 2016)		

pathogens and pollutants (Stannard and O'Callaghan, 2006).

Maternal infection or immune activation during pregnancy have been associated with autism in children and animal studies have shown that prenatal infection has relevant effects on neurodevelopmental pathways (Boksa, 2010; Brown, 2012; Cordeiro et al., 2015; Fatemi et al. 2005, 2008; Harvey and Boksa, 2012; Cordeiro et al. 2015, 2015; Labouesse et al., 2015; Patterson, 2011). In the human dorsolateral prefrontal cortex, autism genes are relatively selectively expressed in the prenatal period (Birnbaum et al., 2014), a factor that is relevant to prenatal infection or exposure to pollution. Some of the pathogens implicated in autism are detailed in Table 1, which also includes details of prenatal infection studies in animal models. Recently it has also been shown that fungal mycotoxins are elevated in the body fluids of autistic children (deoxynivalenol and de-epoxydeoxynivalenol in urine; and aflatoxin M1, ochratoxin A and fumonisin B1 in serum and Ochratoxin A in urine and serum (De Santis et al., 2017b; De Santis et al., 2017a)). It has also been reported that the levels of D-arabinitol, a marker of candidiasis fungal infection, are elevated in the urine of autistic children (Kaluzna-Czaplinska and Blaszczyk, 2012). Higher levels of antibodies to Candida albicans have also been reported in autistic children (Hughes and Ashwood, 2018). The levels of a phenylalanine metabolite of Clostridia species, 3-(3-hydroxyphenyl)-3-hydroxypropionic acid, are

also elevated in the urine of autistic children (Shaw, 2010).

Recent studies from the Danish register have also shown a link between postnatal infections and autism and many other psychiatric disorders (Kohler-Forsberg et al., 2018). It has also been reported that neonatal and postnatal infections are more common in autism patients, particularly in the first 28 days of life and up to the age of three (Sabourin et al., 2018). These data suggest an enhanced vulnerability to infections in early childhood.

Previous studies have noted significant overlaps between disease susceptibility genes and host/pathogen interactomes, where pathogen involvement is suspected. For example, the Epstein-Barr virus causes B cell lymphoma, and has been implicated in multiple sclerosis, and its host interactome overlaps with susceptibility genes for both these diseases (Gulbahce et al., 2012). The interactomes of oncogenic viruses also relate to cancer genes (Rozenblatt-Rosen et al., 2012) suggesting important gene/environment interactions that may condition disease susceptibility. In relation to autism, the host arms of the herpes simplex (HSV-1) or Toxoplasma Gondii interactomes are enriched in autism susceptibility genes, as well as in those for many other psychiatric or neurological disorders (Carter 2013a, 2013b; Ngo et al., 2017). Pathogens have also been implicated in Alzheimer's disease and Alzheimer's disease susceptibility genes also overlap with the interactomes of numerous bacterial, fungal viral and protozoan pathogens. The upregulated genes of the Alzheimer's disease hippocampal transcriptome also match those upregulated by multiple and diverse pathogens (Carter, 2017).

In this study, the host pathogen interactomes of 18 fungal, bacterial, viral and parasite pathogens were analysed in relation to 206 autism susceptibility genes derived from the Autworks/genotator analysis (Nelson et al., 2012). This set of genes is the same as those shown to relate to barrier and ciliary function and to environmental chemicals implicated in autism (Carter, 2016; Carter and Blizard, 2016) and are derived from the initial Autworks study (Nelson et al., 2012). Certain pathogens also possess or secrete toxins, for example bacterial lipopolysaccharide or fungal mycotoxins, whose effects on genes are catalogued at the Comparative Toxicogenomics database (Davis et al., 2015). These chemical/gene interactomes were also compared with the 206 autism genes.

A recent microarray study of leukocytes in autistic male toddlers (aged 1–4 years) revealed an expression signature enriched in translation and immune/inflammation functions (Pramparo et al., 2015). Postmortem studies of cortical tissue in older autistic subjects have also been reported, and these too are enriched in immune response genes (Gupta et al., 2014; Ellis et al., 2016). The leukocyte microarray dataset was compared with numerous immune and other microarray datasets housed at the Molecular signatures database (MSigDB) which contains several thousand microarray gene sets related to immune, infection and other functions (Liberzon et al., 2015b).

The infection data in autism suggest a vulnerability to both prenatal and early childhood infections. Recent studies have shown an imbalance of amyloid precursor protein processing in autism blood and brain leading to the increased production of secreted soluble APP alpha (sAPPα) and reduced production of beta-amyloid (Aβ). Alpha-secretase activity (producing sAPPα) is also increased in the autistic brain. It has been suggested that the neurotrophic effects of sAPPα may contribute to brain overgrowth in autism (Ray et al., 2011) as well as in fragile X syndrome (Ray et al., 2016; Sokol et al., 2006a; Westmark et al., 2016; Bailey et al. 2008, 2013) and that dampening sAPPα production with metabotropic glutamate receptor agonists may be effective in these conditions (Sokol et al., 2011). It has also been shown that acamprosate, a mixed NMDA receptor antagonist and positive allosteric GABA receptor modulator reduced plasma sAPPα levels in autistic youths (Erickson et al., 2014). The gene for fragile X syndrome, fragile X mental retardation 1 (**FMR1**), is within the Autworks autism gene set.

APP processing involves the activity of a number of proteases which are able to generate the antimicrobial peptide Aβ (via beta and gamma secretase) or a secreted soluble fragment, secreted app alpha (sAPPα) which has neuroprotective and neurotrophic properties (Selkoe and Hardy, 2016) (Turner et al., 2003). sAPPα has also been shown to protect myelinated axons from demyelination and to promote remyelination and an increase in the number of mature oligodendrocytes (Llufriu-Daben et al., 2018). Abnormal myelination in the autistic brain has been reported in several brain scan studies (Deoni et al., 2015; Gozzi et al., 2012; Radua et al., 2011; Carmody and Lewis, 2010). sAPPα is produced by alpha secretases (ADAM10, ADAM9, ADAM17 (Allinson et al., 2003)). The formation of sAPPα inhibits the production of Aβ (Peron et al., 2018).

Aβ is antimicrobial peptide with broad-spectrum activity against a number of bacteria, fungi and viruses, including Herpes simplex (HSV-1) and influenza A. (Kumar et al., 2016; Soscia et al., 2010; White et al., 2014) (Bourgade et al., 2016). Given the numerous infections associated with autism, either prenatally or in early childhood it is possible that the diminished production of Aβ could contribute to a generalised diminished ability to combat multiple pathogens.

This sAPPα/Aβ imbalance could well explain several features of autism including problems in brain overgrowth and myelination as well as susceptibility to infection. A literature survey was therefore undertaken to investigate the relationships between the autism susceptibility genes and the various aspects of APP processing.

2. Methods

The original 206 Autworks genes (Nelson et al., 2012) are listed in Supplementary Table 1. Pathway analysis of these autism susceptibility genes (ASGs) was performed using the consensus path database (CDPD) (Kamburov et al., 2011) http://cpdb.molgen.mpg.de/. For the purposes of this review, this analysis was restricted to immune and infection related pathways and to other comorbid medical conditions of interest or to pathways related to autism epidemiology (for example, endocrine disruption). The distribution of the autism genes in immune organs and cell types was analysed using Funrich which accesses genomic and proteomic expression data from > 1.5 million annotations (Pathan et al., 2015) (http://www.funrich.org/).

The host/pathogen interactomes of two fungal species (*Candida albicans, Cryptococcus Neoformans*), 7 viral species (Borna virus, human cytomegalovirus, Dengue virus Ebola virus, Herpes simplex (HSV-1), human endogenous retroviruses HERV-W and HIV-1, Epstein-Barr, hepatitis C and influenza A viruses, 3 bacterial species (*Chlamydia Pneumoniae, Porphyromonas Gingivalis, Helicobacter Pylori)* and 2 protozoans *(Toxoplasma Gondii* and *Trypanosoma Cruzi)* were obtained by literature survey and from extant databases. These referenced interactomes can be accessed at http://www.polygenicpathways.co.uk/HPI.htm. The Dengue virus interactome (DenHunt) is from a recent publication (Karyala et al., 2016) and is posted at http://proline.biochem.iisc.ernet.in/DenHunt/. The HIV-1 interactome is from the HIV-1, human interaction database (Fu et al., 2009).http://www.ncbi.nlm.nih.gov/genome/viruses/retroviruses/hiv-1/interactions.

The mycotoxin and bacterial toxin interactomes are from the Comparative toxicogenomics database http://ctdbase.org/(Davis et al., 2015).

The up regulated (N = 1448) genes from the autism toddler leukocyte study (all significant genes) were compared with MSigDb gene expression datasets (MSigDB) http://software.broadinstitute.org/gsea/msigdb/index.jsp. This database contains several thousand microarray expression datasets, related to diverse stimuli including infections (Liberzon et al., 2015a). These included Hallmark gene sets representing well-defined biological states processes, chemical and genetic perturbations (CGP), canonical pathways (CP) and immunological signatures (C7). For the searched gene sets, most of the data outputs were restricted at source (by MSigDb) to the top regulated genes (usually ~ 200–300).

2.1. Statistics

The statistics from the Consensus path (CDPD) or Molecular signatures database (MSigDb) or from Funrich in relation to the various gene inputs (206 autism susceptibility genes or N genes from the autism toddler microarray study) are generated online by CPDB or MSigDb. The significance of enrichment is based on the hypergeometric test, with the significance p value corrected for false discovery (q value) (Benjamini and Hochberg, 1995).

For the interactome data, assuming a human genome of 26846 genes and 206 autism genes, one would expect 206/26846 autism genes to be found in any comparator set (0.77%). For example the Influenza virus interactome contains 2665 host genes, of which one might expect 2655*(206/26846) to be autism genes, providing an expected value of 23.7. The observed value is 51, (observed/expected = 2.6). The significance of enrichment was calculated using the hypergeometric test, again corrected for false discovery, as for the CPDB and MSigDb data.

3. Results

3.1. Host/pathogen interactome overlaps with autism susceptibility genes

The ASGs were significantly enriched in all of the 18 pathogen interactomes, most significantly so for C. Neoformans, the Borna virus and the human cytomegalovirus. The pathogen profile was distinct when comparing the significance levels between a similar study in Alzheimer's disease (78 genes from genome-wide association studies; GWAS), where the highest ranked pathogens were C. albicans, the Epstein-Barr virus and the oral pathogen P. gingivalis. In addition, the Borna virus, HERV-W and Ebola virus interactomes were not significantly enriched in Alzheimer's disease GWAS genes (Fig 1).

3.2. Bacterial and fungal toxins and toll-like receptor ligands target autism susceptibility genes

Autism genes were significantly enriched as the targets of a number of bacterial toxins including pertussis, shiga, cholera and E. coli endotoxin toxins as well as bacterial cell wall components (Lipopolysaccharides (Toll-like receptor TLR4 ligand), lipoteichoic acid (TLR2 ligand), Peptidoglycan (TLR2 ligand) or compounds released from bacteria (N-Formylmethionine-leucyl-phenylalanine (binding to formyl peptide receptors), and the proteasome inhibitor lactacystin). These compounds also included phycocyanin, derived from cyanobacteria/blue-green algae. The most significant effect was for pertussis toxin (p = 2.94E-15) which has been used as a vaccine adjuvant (Burnette, 1997).

A number of mycotoxins also targeted the autism genes, including three whose levels are elevated in the serum or urine of autistic patients (deoxynivalenol, otrachotoxin A and fumonisin B1) (see introduction).

The autism genes were also targeted by 3 Toll-like receptor ligands, Pam3CSK4 (TLR2 ligand), the viral mimic Polyinosinic: polycytidylic acid (TLR3 ligand) and CPG-oligonucleotide (TLR9 ligand) (Fig 2).

3.3. Immune locations of the autism genes

While many of these genes, particularly those involve in neurotransmission, evidently play an important role in brain function, they are also localised in barrier and ciliary locations (see introduction), and as shown in Table 2, in many immune locations, as well as in the brain. Those genes include those whose function is more classically associated with neurotransmission include acetylcholine (acetylcholinesterase **ACHE**) dopamine receptors (**DRD1**, **DRD4**, catechol-O-methyl transferase (**COMT**), dopamine beta hydroxylase and monoamine oxidase (**DBH**, **MAOA**), dopamine transporter **SLC6A3**), beta2 adrenoceptor (**ADRB2**), serotonin receptors (**HTR1B**, **HTR2A**, **HTR2C**, **HTR3C**), transporter (**SLC6A4**) and tryptophan hydroxylase (**TPH1**, **TPH2**), gamma-aminobutyric acid (GABA) receptors (**ABAT**, **GABBR1**, **GABBR2**, **GABRA1**, **GABRA5**, **GABRB3**,**GABRG2**,**GABRG3**), GABA transaminase and glutamate decarboxylase (**ABAT**, **GAD1**) and glutamatereceptors (**GRIA2**, **GRIK2**, **GRIN2A**) and transporters (**SLC1A1 SLC25A12**) receptors as well as calcium (**CACNA1C**, **CACNA1G**, **CACNA1H**) or sodium (**SCN2A**, **SCN3A**) channels. These are highlighted in bold in Table 2. Overall, many of the ASG's are expressed in plasma and in immunocompetent organs (spleen, bone marrow, tonsils appendix and lymph nodes), in plasma and serum as well as in Leukocytes, neutrophils, dendritic cells, monocytes and macrophages, platelets, diverse T cell subtypes and in B cells.

3.4. Pathway analysis of the 206 autism susceptibility genes

The results of this analysis are shown in Table 3, with references to the relationships of the pathways to autism. This analysis was restricted

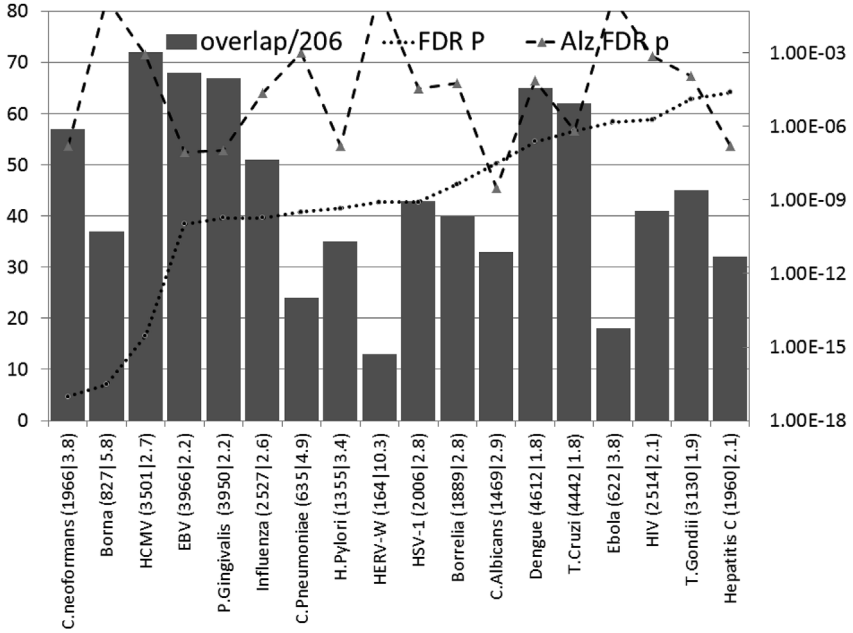

Fig. 1. The number of ASG's (of 206) (left axis) overlapping with diverse host/pathogen interactomes. The identities on the X-axis (e.g. *Borna* (827|5.8) show the pathogen name, appended with the total number of genes in each interactome (827 in this case) followed by the enrichment ratio (5.8 fold). The FDR-corrected p value for enrichment is shown on the right hand axis which is set to a maximum of 0.05. Invisible points are above this value. P values from a recent study of 78 Alzheimer's disease GWAS genes (Alz FDR p) (Carter 2017) are also shown for comparison of the profile (The relative p values (autism versus Alzheimer's) should not be compared as the two gene inputs (78 Alzheimer's disease and 206 autism genes) were different.

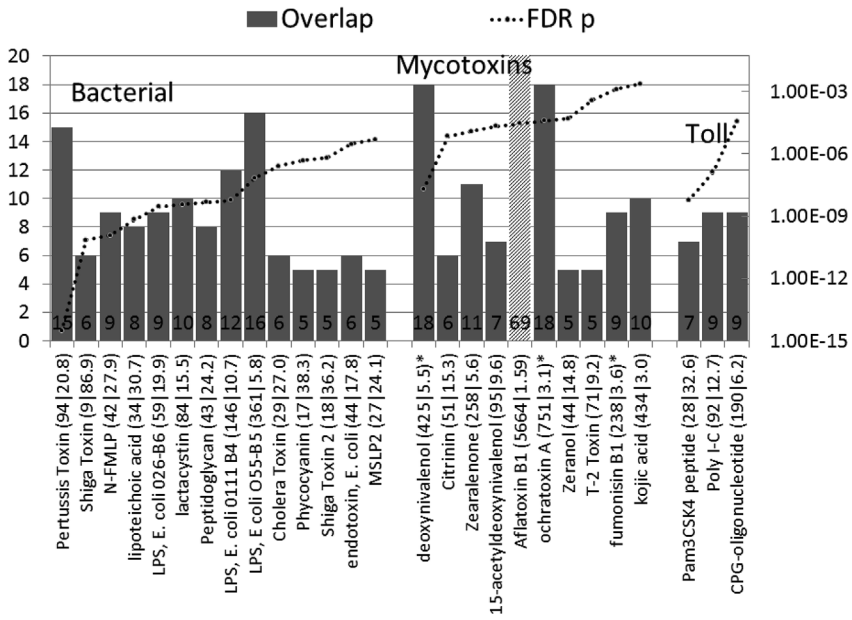

Fig. 2. The number of ASG's (of 206) (left axis) overlapping with genes targeted by bacterial or fungal toxins (mycotoxins) or by Toll-like receptor ligands. The identities on the X-axis (e.g. Pertussis toxin (94: 20.8) show the compound, appended with the total number of genes in each interactome (98 in this case) followed by the enrichment ratio (20.8 fold). The FDR-corrected p value for enrichment is shown on the right hand axis which is set to a maximum of 0.05. The left hand Y axis is set to a maximum of 20 for clarity (Aflatoxin B1 is shaded and affects 69 ASG's). MSLP2 = macrophage stimulatory lipopeptide 2, from mycoplasma bacteria; Pam (3) CSK(4) = a synthetic triacylated lipopeptide that mimics the acylated amino terminus of bacterial lipopolysaccharide, stimulating TLR1/TLR2 dimers:. Poly I-C = Polyinosinic:polycytidylic acid, a viral double stranded RNA mimic activating TLR3. CPG oligonucleotide (a ligand for TLR9 which binds bacterial and viral DNA).

to diverse medical conditions and to pathogen and immune/inflammation related pathways, as well as to endocrine and pollution related pathways.

3.4.1. Comorbid disease pathways

In relation to other diseases, the autism genes were most highly enriched in the sudden infant death syndrome (SIDS) pathway.

The next highest ranked overlap related to spinal cord injury pathways. A relationship with autism is not immediately apparent although such injuries result in marked immune and inflammatory activation (Anwar et al., 2016; Russo et al., 2016) that could be regarded as similar to the reaction to infection.

The autism genes also overlapped with the Amyotrophic lateral sclerosis (ALS) KEGG pathway. The relationship with autism unclear, although rates of ALS and bleeding disorders shown to be increased among relatives of schizophrenic and autistic probands, compared to relatives of normal probands in Ashkenazi Jews (Goodman, 1994).

The autism genes were also enriched in pathways related to the Antiarrhythmic Pathway and cardiomyocyte hypertrophy/Hypertrophic cardiomyopathy and to inflammatory bowel disease. Comorbidity with autism has been observed for asthma, inflammatory bowel disease, infections, cerebral palsy, dilated cardiomyopathy, muscular dystrophy, and schizophrenia, and shared innate immunity pathways have already been noted between autism and these conditions (Nazeen et al., 2016; Doshi-Velez et al., 2015).

Other significantly enriched pathways included alcoholism and type 2 diabetes/Insulin receptor signaling cascade (Table 2). Autism has been associated with a family history of alcohol use disorders (Sundquist et al., 2014) and adolescents and young adults with autism are more likely to develop type II diabetes (Chen et al., 2016).

The autism genes were also slightly enriched in the Alzheimer's disease pathway. Numerous pathogens have been implicated in Alzheimer's disease (Itzhaki et al., 2016) and Aβ is a broad-spectrum antibacterial/antifungal peptide (Kumar et al., 2016; Soscia et al., 2010) with antiviral activity against the influenza and herpes simplex viruses (White et al., 2014; Bourgade et al. 2015, 2016). Serum Aβ levels are decreased in patients with severe autism, while the levels of a secreted neurotrophic alpha-secretase APP degradation product sAPPα are increased (Ray et al. 2011; Sokol et al., 2006b; Westmark et al., 2016; Ray et al., 2016). A decreased production of antimicrobial Aβ hints at a reduced ability of pathogen destruction, a theme that is developed in a later section.

3.4.2. Epilepsy and autism

Epilepsy and autism are also comorbid conditions which may pivot around an excitatory/inhibitory balance (Bozzi et al., 2018). There is no specific “epilepsy pathway” in any of these pathway analysers. However, a number of autism genes relate to calcium or sodium channels (**CACNA1C, CACNA1G, CACNA1H**, **SCN2A, SCN3A**) or to glutamate ionotropic (**GRIA2, GRIK2, GRIN2A**) and metabotropic (**GRM8**) or GABA ionotropic (**GABRA1, GABRA5, GABRB3, GABRG2, GABRG3**) and metabotropic (**GABBR1,GABBR2**) receptors. The GABA synthetic enzyme glutamate decarboxylase (**GAD1**) and GABA transaminase (**ABAT**), the high affinity glutamate transporter (**SLC1A1**) the mitochondrial glutamate/aspartate carrier (**SLC25A12**) are also ASG's. Several presynaptic proteins (glutamate receptor interacting protein 1 (**GRIP1)** synaptosome associated protein 25 (**SNAP25)**), syntaxin 1A (**STX1A**) and synapsin1 (**SYN1**) or postsynaptic proteins including Neuropilin (NRP) and tolloid (TLL)-like 1 (**NETO1)** which regulates NMDA receptors (Refseq gene definition), **SHANK2** and **SHANK3** (from a family of synaptic proteins that may function as molecular scaffolds in the postsynaptic density of excitatory synapses (Refseq gene definition) are also autism susceptibility genes. Neurexins (**NRXN1, NRXN2**) and neuroligins (**NLGN1, NLGN3, NLGN4X, NLGN4Y**) are involved in the formation of both glutamatergic and GABAergicsynapses (Craig and Kang, 2007). These 33/206 ASG's are relevant to the excitation/inhibition imbalance in epilepsy. Several pathways relevant to epilepsy and autism including neurexins and neuroligins, GABAergic and glutamatergic synapses, calcium signaling and long-term potentiation are enriched in autism genes (Table 3).

3.4.3. Macrocephaly and autism

Autism has been associated with macrocephaly and brain overgrowth (Sacco et al., 2015). Several growth factors including brain derived neurotrophic factor, **BDNF**, Epidermal growth factor (**EGF**), hepatocyte growth factor (**HGF**) and neurotrophin 3 (**NTF3**) as well as the neurotrophic receptor kinase **NTRK2** are within the Autworks genes set and a number of growth related pathways are significantly over-represented in the autism gene set (Table 3). A recent genetics study has also highlighted the presence of brain growth related genes within autism gene sets (Li et al., 2017). Genes common to brain growth and autism reported in this paper also include several within the Autworks gene set (**CDH8; HEPACAM; MAOA; MCPH1; MECP2; NIPBL; NLGN1; NRXN1; NSD1; PAX6; PTEN;RAB39B; RELN; UBE3A**).

Prenatal infection or inflammation can produce macrocephaly in

Table 2
Sites of expression of the autism susceptibility genes according to functional enrichment data (Funrich). Those more typically associated with neurotransmitter function (e.g. monoamines, acetylcholine, serotonin, GABA, glutamate and ion channels) are highlighted in bold.

Site of expression	No. of genes/ 206	Gene symbols
Plasma	161	ABAT; ADA; ADRB2; ADSL; AGAP1; AHI1; ANKRD11; APBA2; APC; AR; ARVCF; ARX; ATP10A; ATP1A1; AUTS2; AVPR1A; BCL2; BDNF; C4B; CACNA1C; CACNA1G; CACNA1H; CADPS2; CALB1; CD38; CDH10; CDH8; CDH9; CDKL5; CEP41; CFTR; CNTN4; CNTNAP2; COL11A1; COMT; CREBBP; CRH; CSMD3; CTSD; DBH; DDX53; DISC1; DLGAP2; DLX2; DMPK; DOCK4; DRD1; EGF; EGR2; EIF4E; EN2; FMR1; FOXP1; FOXP2; GABBR1; GABBR2; GABRA1; GABRB3; GABRG3; GAD1; GAP43; GFAP; GJA1; GPR50; GPX1; GRIN2A; GRIP1; GRM8; GSTM1; HGF; HIRA; HLA-DRB1; HTR2C; HTR3C; IL1RAP; IL1RAPL1; IL6; ITGA4; ITGB3; JMJD1C; KIF17; KLF16; LEP; MAG; MAOA; MAPK1; MAPK3; MARK1; MCPH1; MECP2; MET; MIF; MTNR1A; NETO1; NF1; NFKB1; NIPBL; NLGN1; NOS1; NOS2; NPAS2; NRCAM; NRP2; NRXN1; NRXN2; NSD1; NTRK2; NUB1; OXTR; PARK2; PAX6; PCDH10; PCDH11Y; PCDH19; PECAM1; PER1; PON1; PRKCB; PTCHD1; PTEN; PTGS2; PTK2; PXN; RAB11FIP5; RAPGEF4; RBFOX1; REEP3; RELN; RFC1; RFX4; RNF212; RORA; RP1L1; RPL10; RPP25; SCN2A; SCN3A; SEMA5A; SEZ6L2; SHANK2; SHANK3; SLC19A1; SLC1A1; SLC25A12; SLC6A4; SLC6A8; SNAP25; SRC; SSTR5; STS; STX1A; SYN1; SYNGAP1; TAC1; TNF; TPH1; TPH2; TUBA1B; TXNRD2; UBE3A; UPF3B;
Brain	133	ABAT; ACHE; ADA; ADORA2A; ADSL; AGAP1; ANKRD11; APBA2; APC; AQP4; ARVCF; ARX; ASMT; ATP10A; ATP1A1; AUTS2; AVP; AVPR1A; C4B; CACNA1G; CACNA1H; CADPS2; CALB1; CD38; CDH9; CDKL5; CNTN4; CNTNAP2; COMT; CSMD3; CTSD; DISC1; DLGAP2; DMPK; DOCK4; DRD1; DRD4; DYX1C1; EGR2; EIF4E; FOXP1; FOXP2; GABBR1; GABBR2; GABRA1; GABRA5; GABRB3; GABRG2; GAD1; GAP43; GFAP; GJA1; GPX1; GRIA2; GRIN2A; GRM8; GSTM1; HEPACAM; HTR1B; HTR2C; IL1RAPL1; IL6; KIF17; KLF16; MAG; MAOA; MAPK1; MAPK3; MAPK8IP2; MARK1; MCPH1; MECP2; MIF; MOG; MTHFR; MTNR1A; MTNR1B; NCS1; NETO1; NF1; NIPBL; NLGN1; NLGN3; NLGN4X; NLGN4Y; NOS1; NOS2; NRCAM; NRP2; NRXN1; NRXN2; NTF3; NTRK2; PARK2; PAX6; PCDH10; PCDH11Y; PCDH19; PER1; PRKCB; PTEN; PTK2; PXN; RAB11FIP5; RAB39B; RAPGEF4; RBFOX1; RELN; RFC1; RIMS3; RORA; RPL10; SCAMP5; SCN2A; SCN3A; SCT; SHANK2; SHANK3; SLC19A1; SLC25A12; SLC6A3; SLC6A4; SLC6A8; SNAP25; SRC; STX1A; SYN1; SYNGAP1; TPH2; TUBA1B; TXNRD2; UBE3A; UPF3B;
Spleen	109	ABAT; ACHE; ADA; ADORA2A; ADRB2; ADSL; AGAP1; ANKRD11; APC; AQP4; ARVCF; AUTS2; BCL2; BDNF; CACNA1G; CADPS2; CD38; CDKL5; CNTN4; COMT; CREBBP; CSMD3; CTSD; CXorf36; DDX53; DISC1; DRD1; DYX1C1; EGF; EIF4E; EN2; FOXP1; FOXP2; GABBR2; GABRA1; GJA1; GPX1; GRIA2; GRIK2; HEPACAM; HGF; HLA-DRB1; HTR2A; HTR2C; IL10; IL1RAP; IL1RAPL1; ITGB3; JMJD1C; KIF17; LEP; MAG; MAOA; MAPK1; MAPK3; MAPK8IP2; MARK1; MCPH1; MECP2; MET; MIF; MTHFR; NCS1; NF1; NFKB1; NIPBL; NPAS2; NRCAM; NRXN2; NSD1; NTF3; NTRK2; NUB1; OXTR; PCDH10; PCDH19; PECAM1; PON1; PRKCB; PTEN; PTK2; PXN; RAB11FIP5; RAB39B; RAPGEF4; RELN; RFC1; RIMS3; RORA; RPL10; SCT; SEMA5A; SHANK2; SHANK3; SLC19A1; SLC1A1; SLC25A12; SLC6A3; SLC6A8; SRC; SSTR5; STS; SYN1; TAC1; TPH1; TUBA1B; TXNRD2; UBE3A; UPF3B;
Bone marrow	99	ABAT; ACHE; ADA; ADRB2; ADSL; ANKRD11; APC; AQP4; ARVCF; ATP1A1; BCL2; BDNF; CACNA1G; CD38; CDH9; CDKL5; CFTR; CNTNAP2; COMT; CREBBP; CSMD3; CTSD; CXorf36; DDX53; DISC1; DLGAP2; DRD1; EGF; EIF4E; EN2; FMR1; FOXP1; FOXP2; GABBR2; GAD1; GJA1; GPX1; GRIA2; GRIK2; HGF; HLA-DRB1; HTR2A; HTR2C; IL10; IL1RAP; IL1RAPL1; IL6; ITGB3; MAPK1; MAPK3; MAPK8IP2; MARK1; MCPH1; MECP2; MET; MIF; NCS1; NF1; NFKB1; NLGN1; NPAS2; NRCAM; NRP2; NSD1; NTF3; NTRK2; OXTR; PARK2; PCDH10; PCDH11Y; PECAM1; PON1; PRKCB; PTEN; PTGS2; PTK2; PXN; RAB39B; RAPGEF4; REEP3; RFC1; RIMS3; RORA; RPL10; SHANK2; SLC19A1; SLC1A1; SLC25A12; SLC6A8; SNAP25; SRC; SSTR5; STS; TAC1; TPH1; TUBA1B; TXNRD2; UBE3A; UPF3B;
Tonsils	98	ACHE; ADA; ADSL; ANKRD11; APC; AQP4; ARVCF; ATP1A1; AUTS2; BCL2; BDNF; C4B; CACNA1G; CD38; CDH9; CDKL5; CFTR; CNTN4; COMT; CREBBP; CSMD3; CTSD; CXorf36; DDX53; DISC1; DLGAP2; DRD1; EGF; EIF4E; EN2; FMR1; FOXP1; FOXP2; GABBR2; GABRA1; GJA1; GPX1; GRIA2; GRIK2; HGF; HLA-DRB1; HOXA1; HTR2A; HTR2C; IL10; IL1RAPL1; IL6; MAG; MAOA; MAPK1; MAPK3; MARK1; MCPH1; MECP2; MET; MIF; NCS1; NF1; NFKB1; NLGN1; NLGN3; NOS2; NPAS2; NRCAM; NTF3; NTRK2; OXTR; PARK2; PCDH10; PCDH19; PECAM1; PON1; PRKCB; PTEN; PTGS2; PTK2; PXN; RAB39B; RAPGEF4; RFC1; RIMS3; RORA; RPL10; SEMA5A; SHANK2; SLC1A1; SLC25A12; SLC6A3; SLC6A8; SRC; SSTR5; STS; SYN1; TAC1; TPH1; TUBA1B; TXNRD2; UPF3B;
Appendix	96	ACHE; ADA; ADSL; ANKRD11; APC; AQP4; ATP1A1; AUTS2; BDNF; C4B; CACNA1G; CALB1; CD38; CDH8; CDH9; CDKL5; CFTR; CNTNAP2; COMT; CSMD3; CTSD; CXorf36; DDX53; DISC1; DLGAP2; DMPK; DRD1; EGF; EIF4E; FMR1; FOXP1; FOXP2; GABBR2; GABRA1; GRIA2; GRIK2; GSTM1; HEPACAM; HGF; HLA-DRB1; HOXA1; HTR2A; HTR2C; IL10; IL1RAPL1; IL6; MAG; MAOA; MAPK1; MAPK3; MARK1; MCPH1; MECP2; MET; MIF; NF1; NFKB1; NOS2; NPAS2; NRCAM; NTF3; NTRK2; OXTR; PARK2; PAX6; PCDH11Y; PECAM1; PON1; PTEN; PTGS2; PTK2; PXN; RAB39B; RAPGEF4; RFC1; RIMS3; RORA; RPL10; SCN2A; SEMA5A; SHANK2; SHANK3; SLC1A1; SLC25A12; SLC6A3; SLC6A4; SLC6A8; SRC; SSTR5; STS; SYN1; TAC1; TPH1; TUBA1B; TXNRD2; UPF3B;
Lymph nodes	95	ABAT; ACHE; ADA; ADSL; ANKRD11; APC; AQP4; AR; ARVCF; BCL2; BDNF; CACNA1G; CALB1; CD38; CDH10; CDH9; CDKL5; CFTR; COMT; CREBBP; CSMD3; CTSD; CXorf36; DDX53; DISC1; DLGAP2; EGF; EIF4E; EN2; FMR1; FOXP1; FOXP2; GABBR2; GJA1; GPX1; GRIA2; GRIK2; GSTM1; HGF; HLA-DRB1; HOXA1; HTR2A; HTR2C; IL10; IL1RAPL1; IL6; MAG; MAPK1; MAPK3; MAPK8IP2; MARK1; MCPH1; MECP2; MET; MIF; NCS1; NF1; NFKB1; NLGN1; NOS2; NPAS2; NRCAM; NTF3; NTRK2; NUB1; OXTR; PCDH10; PCDH19; PECAM1; PON1; PRKCB; PTEN; PTK2; PXN; RAB39B; RAPGEF4; RFC1; RIMS3; RORA; RPL10; SEMA5A; SHANK2; SLC19A1; SLC1A1; SLC25A12; SLC6A3; SLC6A8; SRC; SSTR5; SYN1; TAC1; TPH1; TUBA1B; TXNRD2; UPF3B;

(*continued on next page*)

Table 2 (*continued*)

Site of expression	No. of genes/ 206	Gene symbols
Serum	89	ADRB2; ADSL; ANKRD11; APBA2; APC; AR; ATP1A1; AUTS2; BCL2; BDNF; C4B; CACNA1G; CACNA1H; CADPS2; CALB1; CDKL4; CDKL5; CNTN4; CNTNAP2; COL11A1; COMT; CREBBP; CSMD3; CTSD; DBH; DDX53; DISC1; DLX2; EIF4E; FMR1; FOXP1; GABBR1; GABBR2; GAD1; GAP43; GFAP; GRIK2; GRIN2A; GRPR; HIRA; IL1RAP; ITGA4; ITGB3; MAG; MAPK8IP2; MARK1; MECP2; MET; MIF; MTHFR; NF1; NFKB1; NIPBL; NLGN1; NOS1; NOS2; NPAS2; NRCAM; NSD1; NUB1; PCDH10; PCDH11Y; PON1; PRKCB; PTGS2; PTK2; PXN; RAB11FIP5; RAPGEF4; RBFOX1; REEP3; RELN; RFC1; RORA; RP1L1; SCN2A; SCN3A; SEZ6L2; SLC19A1; SLC25A12; SNAP25; SRC; STS; STX1A; TNF; TPH1; TUBA1B; UBE3A; UPF3B;
Jurkat A3 T Cells	38	ABAT; ADA; ADSL; ARVCF; BCL2; CADPS2; CD38; CFTR; COMT; CREBBP; CTSD; DHFR; DLX2; EIF4E; FMR1; GAD1; GFAP; GPX1; HIRA; ITGA4; ITGB3; JMJD1C; MAPK1; MAPK3; MIF; NF1; NSD1; OXTR; PRKCB; PTK2; RELN; RFC1; RPL10; SEZ6L2; SLC25A12; SRC; TUBA1B; UPF3B;
CD8 T cells	32	ABAT; ADSL; ATP1A1; BCL2; C4B; CALB1; COMT; CTSD; DHFR; EIF4E; FOXP1; GFAP; GPX1; GSTM1; HLA-DRB1; ITGA4; ITGB3; KLF16; MAPK1; MAPK3; MECP2; MIF; NFKB1; NUB1; PON1; PRKCB; PXN; RFC1; SLC25A12; SRC; UBE3A; UPF3B;
Leukocytes	31	ABAT; ADORA2A; AUTS2; CACNA1G; CD38; CNTN4; CTSD; DYX1C1; FOXP1; GABBR2; GPX1; IL1RAP; ITGB3; JMJD1C; MAPK1; MAPK8IP2; MIF; NIPBL; NOS2; NSD1; NUB1; PRKCB; PXN; RAB39B; RIMS3; RORA; SLC19A1; SRC; TNF; TUBA1B; TXNRD2;
Platelets	30	ADORA2A; ADSL; ANKRD11; APC; ATP1A1; BDNF; CACNA1G; COL11A1; COMT; EIF4E; GFAP; GPX1; GSTM1; HTR2A; ITGB3; MAPK1; MIF; NRCAM; PECAM1; PON1; PRKCB; PTEN; PTGS2; PTK2; SLC25A12; SLC6A4; SRC; TAC1; TUBA1B; TXNRD2;
Monocyte	29	ADSL; AR; ARVCF; ATP1A1; BCL2; C4B; COMT; CTSD; DBH; EIF4E; GFAP; GPX1; GSTM1; HLA-DRB1; ITGB3; MAOA; MAPK1; MARK1; MECP2; MIF; NETO1; NF1; NFKB1; PON1; PRKCB; PXN; SEZ6L2; SLC25A12; SRC;
B Cell	23	ACHE; ADORA2A; ADSL; ATP1A1; BCL2; COMT; CTSD; GFAP; GPX1; HLA-DRB1; IL6; ITGB3; MAPK1; MAPK3; MECP2; MIF; NFKB1; NOS2; PTK2; RAB39B; RPL10; SLC25A12; TUBA1B;
Neutrophil	22	ADSL; ANKRD11; APC; ATP1A1; C4B; COMT; CTSD; DBH; EIF4E; GFAP; GPX1; HLA-DRB1; ITGB3; MAPK1; MIF; NFKB1; PON1; RAB11FIP5; RELN; RFC1; RPP25; TXNRD2;
T cells	20	ADORA2A; ATP1A1; CD38; CREBBP; EGR2; EIF4E; FMR1; FOXP1; GPX1; IL10; KLF16; MAPK1; MECP2; MIF; NFKB1; NIPBL; PTK2; RFC1; RPL10; TUBA1B;
CD4 (found on T helper cells, monocytes, macrophages, and dendritic cells)	20	ADSL; ATP1A1; BCL2; C4B; COMT; CTSD; DBH; EIF4E; GFAP; GPX1; HLA-DRB1; ITGB3; MAPK1; MAPK3; MECP2; MIF; NFKB1; PON1; PXN; SLC25A12;
Dendritic cells	19	ADORA2A; ADSL; ATP1A1; COMT; CTSD; EIF4E; GPX1; HLA-DRB1; IL6; MAOA; MAPK1; MAPK3; MIF; MTHFR; PECAM1; RPL10; SLC25A12; TNF; TUBA1B;
Monocytes	18	ADORA2A; ATP1A1; CD38; COMT; FOXP1; GPX1; IL10; IL6; ITGB3; MIF; NOS2; PECAM1; PER1; PRKCB; PTGS2; PXN; TAC1; TUBA1B;
Lymphocytes	9	ADRB2; FOXP1; GJA1; SCN2A; SLC25A12; SLC6A3; STX1A; SYN1; TAC1;
Neutrophils	7	ADORA2A; GPX1; HGF; MIF; NOS2; PRKCB; STX1A;
Macrophages	7	ADORA2A; CD38; CRH; IL10; PTK2; TAC1; TNF;

animal models. For example, influenza infection in mice on day 9 of pregnancy increased pyramidal cell density in the offspring at birth and increases in both pyramidal and non-pyramidal cell density 14 weeks after birth as well as brain enlagement in the adult progeny (Fatemi et al., 2002). Similarly, bacterial lipopolysaccharide administration at day 9 of pregnancy produced brain overgrowth in the offspring. This effect was enhanced in **PTEN** heterozygotes and was related to increased NADPH oxidase-phosphoinositide-3-kinase pathway signaling and hyperproliferation of neural stem and progenitor cells and increased forebrain microglia (Le Belle et al., 2014). Prenatal lipopolysaccharide administration in monkeys also produces brain enlargement in the offspring characterised by increased gray and white matter growth (Willette et al., 2011) These studies show that infection or inflammation *per se* can induce brain overgrowth and that these effects can be gene-regulated. However, it should be noted that viruses, notably the Zika virus but also the cytomegalovirus and rubella and rarely herpes simplex can also induce microcephaly (Devakumar et al., 2018), factors that may depend upon the timing of infection and on the particularities of the host/pathogen interactions.

3.4.4. Pathogen-related pathways

In relation to pathogens, The ASG's were significantly enriched in pathways related to Leishmaniasis, hepatitis B, tuberculosis, pertussis (whooping cough), malaria, amoebiasis, toxoplasmosis, Chagas disease, influenza and salmonella infection, as well as in the NOD-like receptor pathway which is involved in viral detection and activation of antiviral and immune responses (Coutermarsh-Ott et al., 2016). The Toll-like receptor signaling pathway is also involved in the recognition of diverse pathogens (Akira and Takeda, 2004) and was also enriched in ASG's, Of the pathogens, relationships with autism were only found for influenza infection, malaria and toxoplasmosis. Influenza infection at the end of the first year of life or at the end of the follow-up period (age 16) have been associated with autism (Abdallah et al., 2012). Two studies did not find associations between prenatal influenza infection and autism. It has also been proposed that any such risk may be due to activation of the maternal immune system following infection rather than to direct foetal infection (Zerbo et al., 2017; Mahic et al., 2017). An onset of autism following recovery from severe malaria has been reported in some cases from Tanzania (Mankoski et al., 2006). In relation to prenatal toxoplasmosis infection, two recent studies have reported that high maternal T. gondii IgM antibody levels associated with a decreased risk of childhood autism, while low maternal T. gondii IgG antibody was associated with increased risk. The authors suggested that lowered IgG levels might relate to sub-optimal maternal immune function (Spann et al., 2017; Grether et al., 2016).

Leishmaniasis, caused by trypanosome parasites has not been linked to autism. The parasites are absolutely dependent on host-derived purines for survival (Boitz et al., 2013) and two ASG's (adenylosuccinate lyase (**ADSL**) and dihydrofolate reductase (**DHFR**)) are involve in purine synthesis (see Supplementary Table 1). ADSL deficiency can cause severe psychomotor retardation, microcephaly, seizures, and autistic features (Jurecka et al., 2015).

3.4.5. Immune-related pathways

The ASG's were significantly enriched in many immune-related pathways including interleukin pathways (**IL6**, IL3, IL2, 3, 4, 5 and 9),

Table 3
Pathway enrichment analysis of the 206 ASG's using the Consensus path database (CPDB). The first column denotes the pathway and its source (e.g. KEGG or reactome; PID = Pathway interaction database) and the number of ASG's relative to the total number of genes in the pathway (e.g. 23/159 for the SIDS pathway). The significance of enrichment (q value) calculated by CPDB is based on the hypergeometric test. The autism genes involved are shown in the final column. The genes in bold represent a signaling module common to many of these pathways (**MAPK1: MAPK3: NFKB1: SRC: TNF: PTK2: IL6: PRKCB)**.

Pathway	q-value	Autism Genes involved
Medical conditions		
Sudden infant death Susceptibility (SIDS) Pathways (23/159) Wikipathways	8.94E-14	SLC6A4; RORA; BDNF; GABRA1; TAC1; NTRK2; HTR2A; C4B; **NFKB1**; DLX2; AQP4; GJA1; MECP2; TPH1; TPH2; AR; SNAP25; IL10; AVP; **IL6**; MAOA; **TNF**; CREBBP
Spinal Cord Injury (15/116)Wikipathways	2.03E-08	PTGS2; AQP4; GAP43; GJA1; NOS2; MIF; **IL6**; **MAPK3**; NOS1; **TNF**; MAG; LEP; **MAPK1**; BDNF; GFAP
Amyotrophic lateral sclerosis (ALS) (6/51)KEGG	0.0008	NOS1; GRIA2; GPX1; **TNF**; BCL2; GRIN2A
Antiarrhythmic Pathway, Pharmacodynamics (6/55) PharmGKB	0.001	CACNA1H; GJA1; CACNA1C; CACNA1G; ADRB2; ATP1A1
MicroRNAs in cardiomyocyte hypertrophy (6/102)Wikipathways	0.01	**PRKCB**; **MAPK3**; **TNF**; **NFKB1**; **MAPK1**; EGF
Hypertrophic cardiomyopathy (HCM) (5/83) KEGG	0.02	**IL6**; ITGB3; CACNA1C; ITGA4; **TNF**
Alcoholism (10/180)KEGG	0.002	SLC6A3; ADORA2A; NTRK2**; DRD1**; **MAPK3**; MAOA; GRIN2A; **MAPK1**; BDNF; CRH
Inflammatory bowel disease (IBD) (6/65)KEGG	0.002	IL10; HLA-DRB1; RORA; **IL6**; **TNF**; **NFKB1**
Type II diabetes mellitus (5/48)KEGG	0.003	**MAPK1**; CACNA1C; **MAPK3**; **TNF**; CACNA1G
Insulin receptor signaling cascade (10/238)Reactome	0.009	**SRC**; ITGB3; **PTK2**; SYNGAP1; **MAPK3**; **MAPK1**; NF1; EIF4E; EGF; GRIN2A
Alzheimers Disease (6/144)Wikipathways	0.04	NOS1; CACNA1C; **MAPK3**; **TNF**; **MAPK1**; GRIN2A
Epilepsy related pathways		
Neurexins and neuroligins (12/57) (Reactome)	1.89E-09	STX1A; APBA2; NLGN3; NLGN1; NLGN4Y; NLGN4X; NRXN2; NRXN1; DLGAP2; GRIN2A; SHANK3; SHANK2
GABAergic synapse (12/88) KEGG	1.88E-07	**SRC**; **PRKCB**; GABRG3; GABRG2; CACNA1C; ABAT; GABRA5; GABBR1; GABBR2; GABRB3; GABRA1; GAD1
Calcium signaling pathway (16/186) KEGG	3.0E-07	CACNA1H; ADORA2A; NOS2; AVPR1A; CD38; NOS1; CACNA1C; **PRKCB**; CACNA1G; ADRB2; GRIN2A; HTR2A; HTR2C; OXTR; GRPR; DRD1
Glutamatergic synapse (11/114) KEGG	1.54E-05	**PRKCB**; GRIA2; GRIK2; CACNA1C; SHANK2; MAPK3; GRIN2A; GRM8; MAPK1; SHANK3; SLC1A1
Long-term potentiation (7/67) (KEGG)	0.0003	CACNA1C; GRIA2; **PRKCB; MAPK3**; GRIN2A; **MAPK1**; CREBBP
Growth related		
Brain-Derived Neurotrophic Factor (BDNF) signaling pathway (15/144) Wikipathways	9.54E-08	**SRC;** NTF3; **MAPK3;** EGR2; GRIP1; NTRK2; GRIA2; CDKL5; **MAPK1**; **NFKB1**; EIF4E; APC; BDNF; GABRB3; SYN1
Signaling of Hepatocyte Growth Factor Receptor (8/34) Wikipathways	7.91E-07	**SRC**; **PTK2**; MAPK3; PTEN; **MAPK1**; PXN; HGF; MET
Activated NTRK2 signals through FYN (3/4) (Reactome)	0.00015	**SRC**; BDNF; NTRK2
NCAM signaling for neurite out-growth (7/59) Reactome	0.0002	CACNA1H; **SRC; PTK2**; CACNA1C; CACNA1G; MAPK3; MAPK1
VEGFA-VEGFR2 Signaling Pathway (13/236) Wikipathways	0.0003	PTGS2; ITGB3; **PTK2; SRC; PRKCB; MAPK3; MAPK1**; PXN; EIF4E; **NFKB1**; GJA1; NRP2; BCL2
Neurotrophin signaling pathway (7/119) KEGG	0.004	NTF3; NTRK2; **MAPK3; MAPK1**; **NFKB1**; BDNF; BCL2
Infectious agents and pattern recognition		
Leishmaniasis (10/72)KEGG	5.13E-06	PTGS2; NOS2; **PRKCB**; **MAPK3**; IL10; HLA-DRB1; ITGA4; **MAPK1**; **TNF**; **NFKB1**
Hepatitis B (11/146)KEGG	0.0002	**SRC**; **MAPK1**; EGR2; **PRKCB**; **IL6**; PTEN; **TNF**; **NFKB1**; **MAPK3**; CREBBP; BCL2
Tuberculosis (12/177)KEGG	0.0002	**SRC**; NOS2; **MAPK3**; IL10; HLA-DRB1; CTSD; **IL6**; **MAPK1**; **TNF**; **NFKB1**; CREBBP; BCL2
Pertussis (8/75)KEGG	0.0002	NOS2; IL10; **IL6**; **MAPK3**; **TNF**; C4B; **NFKB1**; **MAPK1**
Malaria (6/49)KEGG	0.0007	PECAM1; IL10; **IL6**; MET; **TNF**; HGF
Amoebiasis (8/109)KEGG	0.001	NOS2; **PTK2**; COL11A1; IL10; **PRKCB**; **IL6**; **TNF**; **NFKB1**
Toxoplasmosis (8/118)KEGG	0.002	NOS2; **MAPK3**; IL10; HLA-DRB1; **MAPK1**; **TNF**; **NFKB1**; BCL2
Chagas disease (American trypanosomiasis) (7/104)KEGG	0.004	NOS2; **MAPK3**; IL10; **IL6**; **MAPK1**; **TNF**; **NFKB1**
Influenza A (8/175) KEGG	0.01	**PRKCB**; **MAPK3**; HLA-DRB1; **IL6**; **MAPK1**; **TNF**; **NFKB1**; CREBBP
Salmonella infection (5/86)KEGG	0.02	**IL6**; **NFKB1**; NOS2; **MAPK1**; **MAPK3**
Viral carcinogenesis (8/206)KEGG	0.03	**SRC**; EGR2; UBE3A; **MAPK3**; **MAPK1**; PXN; **NFKB1**; CREBBP
NOD-like receptor signaling pathway (5/57)	0.006	**IL6**; **NFKB1**; **TNF**; **MAPK1**; **MAPK3**
Toll-like receptor signaling pathway (5/102)Wikipathways	0.03	**IL6**; **MAPK3**; **TNF**; **MAPK1**; **NFKB1**
General immune and inflammation related		
Interleukin 6 pathway (7/74)NetPath	0.0008	**MAPK3**; **IL6**; **MAPK1**; AR; EIF4E; **NFKB1**; CREBBP
Signaling by Interleukins (13/270)Reactome	0.001	**SRC**; ITGB3; **PTK2**; **MAPK3**; SYNGAP1; **IL6**; **MAPK1**; NF1; IL1RAP; HGF; **NFKB1**; EGF; GRIN2A
Fc-epsilon receptor I signaling in mast cells (6/62)PID	0.002	**PTK2**; **PRKCB**; **MAPK3**; **MAPK1**; PXN; **NFKB1**
TWEAK (TNFSF12 tumor necrosis factor superfamily member 12) Signaling Pathway (5/42)Wikipathways	0.002	**IL6**; **NFKB1**; **TNF**; **MAPK1**; **MAPK3**
AGE-RAGE pathway (6/66)Wikipathways (	0.002	**SRC**; NOS2; **PRKCB**; **MAPK3**; **MAPK1**; **NFKB1**
Cytokine Signaling in Immune system (15/376)Reactome	0.002	SYNGAP1; ITGB3; **PTK2**; **SRC**; EIF4E; **IL6**; **MAPK3**; GRIN2A; NF1; IL1RAP; HGF; **NFKB1**; EGF; **TNF**; **MAPK1**
Thymic stromal lymphopoietin (TSLP)Signaling Pathway (5/47) Wikipathways	0.003	**IL6**; **SRC**; **MAPK1**; **MAPK3**; **NFKB1**
IL3 (5/51)NetPath:	0.004	**NFKB1**; **MAPK1**; **MAPK3**; **PRKCB**; BCL2
TGF Beta Signaling Pathway (5/55)	0.006	**NFKB1**; **TNF**; EGF; CREBBP; **MAPK3**
Kit receptor signaling pathway (5/59)Wikipathways	0.007	**SRC**; **MAPK1**; **MAPK3**; **PRKCB**; BCL2
Hematopoietic cell lineage (6/87)KEGG	0.007	CD38; ITGB3; HLA-DRB1; ITGA4; **IL6**; **TNF**
Platelet activation, signaling and aggregation (10/229)Reactome	0.007	PECAM1; ITGB3; **PTK2**; **SRC**; **PRKCB**; RAPGEF4; **MAPK3**; **MAPK1**; HGF; EGF
IL4 (5/63)NetPath	0.008	**MAPK1**; **NFKB1**; **PTK2**; CREBBP; **MAPK3**
Hemostasis (16/493)Reactome	0.008	PECAM1; NOS2; **PTK2**; **SRC**; **PRKCB**; ITGA4; ITGB3; DOCK4; RAPGEF4; **MAPK3**; NOS1; **MAPK1**; MAG; JMJD1C; HGF; EGF
TNF alpha Signaling Pathway (6/93)Wikipathways	0.008	**IL6**; **MAPK3**; **TNF**; **NFKB1**; **MAPK1**; CREBBP
Interleukin-2 signaling (9/202)Reactome	0.009	**SRC**; ITGB3; **PTK2**; SYNGAP1; **MAPK3**; **MAPK1**; NF1; EGF; GRIN2A

(*continued on next page*)

Table 3 (*continued*)

Pathway	q-value	Autism Genes involved
T cell receptor (10/244)NetPath	0.01	PECAM1; **PTK2**; **SRC**; **MAPK3**; **MAPK1**; PXN; ATP1A1; ADA; **NFKB1**; CREBBP
Interleukin-3, 5 and GM-CSF signaling (9/211) Reactome	0.01	**SRC**; ITGB3; **PTK2**; SYNGAP1; **MAPK3**; **MAPK1**; NF1; EGF; GRIN2A
IL2 (5/76)NetPath	0.015	EIF4E; **NFKB1**; **MAPK1**; BCL2; **MAPK3**
Leukocyte transendothelial migration (6/118)KEGG	0.02	PECAM1; **PTK2**; **PRKCB**; ITGA4; RAPGEF4; PXN
DAP12 signaling (10/282)Reactome:	0.02	**SRC**; ITGB3; **PTK2**; **MAPK3**; SYNGAP1; PTEN; **MAPK1**; NF1; EGF; GRIN2A .
Response to elevated platelet cytosolic Ca2+ (5/87)Reactome	0.02	HGF; PECAM1; ITGB3; **PRKCB**; EGF
CXCR4-mediated signaling events (5/88)PID	0.02	**SRC**; HLA-DRB1; **PTK2**; PXN; PTEN
IL9 (2/12)NetPath	0.03	**MAPK3**; **MAPK1**
Inflammatory mediator regulation of TRP channels (5/99)KEGG	0.03	**SRC**; **PRKCB**; **HTR2A**; **HTR2C**; IL1RAP
B cell receptor signaling (5/102)INOH	0.03	**NFKB1**; **MAPK1**; **MAPK3**; **PRKCB**; **SRC**
Immune System (26/1174)Reactome	0.04	**PTK2**; ITGA4; RAPGEF4; EIF4E; EGF; UBE3A; PARK2; **MAPK3**; **MAPK1**; NF1; **NFKB1**; **SRC**; ITGB3; **PRKCB**; C4B; HLA-DRB1; CTSD; SYNGAP1; **TNF**; IL1RAP; HGF; **IL6**; PTEN; GRIN2A; CREBBP; BCL2
Endocrine pathways		
Ghrelin (7/39)NetPath	5.23E-05	**SRC**; **PRKCB**; DRD1; **MAPK3**; **MAPK1**; SSTR5; HTR2C
Corticotropin-releasing hormone (9/92)Wikipathways	0.0002	CACNA1H; GJA1; **PTK2**; **PRKCB**; **MAPK3**; **MAPK1**; **NFKB1**; CRH; BCL2
Prolactin (8/70)NetPath	0.0002	**SRC**; **PTK2**; CTSD; **MAPK3**; **MAPK1**; PXN; **NFKB1**; CREBBP
Leptin signaling pathway (8/76)Wikipathways	0.0003	**SRC**; **PTK2**; **MAPK3**; LEP; PTEN; **MAPK1**; EIF4E; **NFKB1**
Prolactin Signaling Pathway (8/76)Wikipathways	0.0003	**SRC**; NOS2; **PTK2**; CTSD; **MAPK3**; **MAPK1**; PXN; **NFKB1**
Nongenotropic Androgen signaling (5/31)PID	0.0007	**SRC**; AR; **PTK2**; **MAPK1**; **MAPK3**
Gastrin-CREB signaling pathway via PKC and MAPK (16/382)Reactome	0.001	**SRC**; ITGB3; AVPR1A; NF1; TAC1; GRPR; AVP; SYNGAP1; **MAPK3**; GRIN2A; HTR2A; HTR2C; OXTR; **MAPK1**; **PTK2**; EGF
Gastrin (5/41)NetPath	0.002	**NFKB1**; **PTK2**; PXN; **MAPK1**; **MAPK3**
Signaling by Leptin (10/193)Reactome	0.003	SYNGAP1; ITGB3; **PTK2**; **SRC**; LEP; **MAPK3**; **MAPK1**; NF1; EGF; GRIN2A
Insulin secretion (6/86)KEGG	0.006	STX1A; SNAP25; **PRKCB**; CACNA1C; RAPGEF4; ATP1A1
Thyroid hormone signaling pathway (7/119)KEGG	0.007	**SRC**; ITGB3; **PRKCB**; **MAPK3**; **MAPK1**; ATP1A1; CREBBP
Androgen receptor signaling pathway (6/89)Wikipathways	0.007	**SRC**; **PTK2**; UBE3A; PTEN; AR; CREBBP
Oxytocin signaling pathway (8/159)KEGG	0.008	CD38; PTGS2; **PRKCB**; **SRC**; CACNA1C; **MAPK3**; **MAPK1**; OXTR
Glucocorticoid receptor regulatory network (5/80)PID	0.017	**IL6**; **NFKB1**; **MAPK1**; CREBBP; **MAPK3**
GnRH signaling pathway (5/92)KEGG	0.025	**SRC**; CACNA1C; **MAPK3**; **PRKCB**; **MAPK1**
Estrogen signaling pathway (5/100)KEGG	0.03	GABBR1; **SRC**; GABBR2; **MAPK1**; **MAPK3**
AndrogenReceptor (6/143)NetPath	0.03	**SRC**; **PTK2**; PTEN; AR; PXN; NSD1
Insulin Signaling (6/160)Wikipathways	0.05	SNAP25; **MAPK3**; **PRKCB**; PTEN; **MAPK1**; EIF4E
Pollution		
Overview of nanoparticle effects (5/15)Wikipathways	5.71E-05	**IL6**; PTGS2; **PTK2**; **TNF**; **BCL2**
Aryl Hydrocarbon Receptor (6/46)Wikipathways	0.0005	PTGS2; **SRC**; **MAPK1**; NF1; **NFKB1**; **TNF**
Number of pathways, (in brackets) affected by each of these genes		
MAPK1/MAPK3 (55): NFKB1 (37): SRC (35): PRKCB (31); TNF (30): PTK2 (26): IL6 (25): CREBBP/GRIN2A (16) ITGB3 (15); EGF (14); NOS2 (12); BCL2/CACNA1C/NF1 (10); IL10/PXN/SYNGAP1 (9); HLA-DRB1/PTEN (8); EIF4E/HGF (7); ITGA4/PECAM1 (6); AR//NOS1 PTGS2/RAPGEF4 (5); ATP1A1/CTSD/GJA1/HTR2A/IL1RAP (4); BDNF/C4B/CACNA1G/CACNA1H/CD38/CRHLEP/SNAP25/UBE3A (3); ADRB2/AQP4/AVP/EGR2/GABBR1/GABBR2/GABRA1/MAG/MAOA/NTRK2/RORA/STX1A/TAC1 (2); ABAT/ADORA2A/APBA2/AVPR1A/COL11A1/DLX2/DOCK4/DRD1/GABRA5/GAD1/GAP43/GFAP/GPX1/GRIK2/JMJD1C/MECP2/MET/MIF/NLGN1/NLGN3/NLGN4X/NLGNY/NSD1/OXTR/SHANK2/SHANK3/SLC6A3/SLC6A4/TPH1/TPH2 (1)		

Tumor necrosis factor (**TNF**) related and cytokine pathways and T- and B-cell pathways. A limited number of ASG's were also enriched in Pattern recognition receptor pathways (nucleotide-binding oligomerization domain-like receptors (NOD) and Toll-like receptors (TLR). Immune activation is covered in the discussion. Allergy related pathways (Fc-epsilon receptor I signaling in mast cells and thymic stromal lymphopoietin (TSLP) Signaling Pathway) were also enriched in ASG's. Maternal or infantile atopic diseases (asthma, eczema, food allergies and food intolerance) all involve activation of mast cells. These are located around blood vessels in all tissues, including the brain and mast cell derived inflammatory and vasoactive mediators increase blood-brain barrier permeability (Theoharides et al., 2016b). TSLP is involved in allergic diseases including asthma, food allergies and inflammatory bowel disease (Wang, 2016; Park et al., 2016; Tan et al., 2016), which in turn are also associated with autism (Theoharides et al., 2016b).

3.4.6. Endocrine related pathways

Several hormonal pathways, including androgen, estrogen, and thyroid hormone, gonadotrophin releasing hormone, prolactin and oxytocin signaling were enriched in ASG's. There are evidently relevant to the implication of endocrine disruption in neurodevelopmental disorders (Colborn, 2004). Ghrelin and leptin pathways were also enriched in ASG's. Blood ghrelin levels are decreased in autistic boys while leptin levels are increased. Ghrelin plays an important role in apoptosis and inflammation in addition to its effects on satiety (Al Zaid et al., 2014). Leptin also plays a role in neurodevelopment and increased circulating leptin is often found in childhood neurodevelopmental disorders including autism and Rhett disorder (Valleau and Sullivan, 2014).

3.4.7. Pollution-related pathways

The ASGs were also enriched in pathways related to the effects of nanoparticles (found for example in vehicle emissions), and in the aryl hydrocarbon receptor pathway. The links between infection and pollution in relation to the aryl hydrocarbon receptor are covered in the discussion.

In general and for most types of pathways, it should be noted that the overlap between the ASG's involved many common genes related to inflammatory cytokine (Interleukin 6 and tumor necrosis factor: **IL6, TNF**) intracellular signaling modules. For example ASG's common to many pathways included (N pathways in brackets) MAP kinases **MAPK1/MAPK3 (55):** Nuclear factor NF-kappa-B **NFKB1 (37):** proto-oncogene, non-receptor tyrosine kinase **(SRC) (35**): protein kinase c beta **(PRKCB) (31): TNF (30):** protein tyrosine kinase 2 (**PTK2) (26): IL6 (25):** (Table 2).

Interestingly, the top 10 ASG's affected by the most exogenous chemicals from the comparative toxicogenomics database were (N chemicals in brackets) **TNF** (1652), map kinases **MAPK1** (1179), **MAPK3** (1154), **IL6** (1082), apoptosis regulator **BCL2** (997), cyclooxygenase **PTGS2** (977), nitric oxide synthase **NOS2** (862), androgen receptor **AR** (584), nuclear factor kappa B subunit 1 **NFKB1** (469), **IL10**

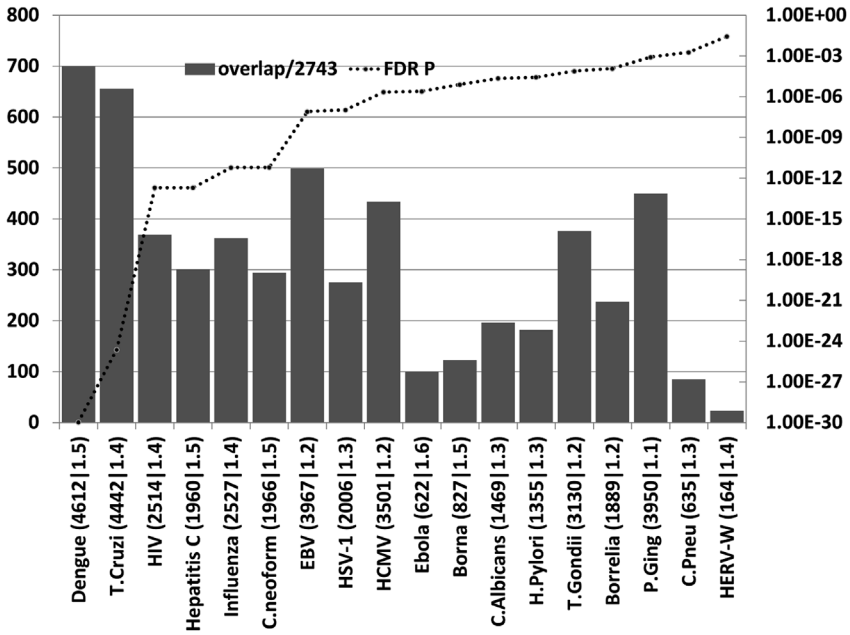

Fig. 3. The overlap between the host genes affected by diverse pathogens and those misregulated in the leukocytes of autistic toddlers (2743 combined up and downregulated genes). The overlap is shown on the left Y axis and the q value for enrichment on the right Y axis. The identities on the X-axis (e.g. Dengue (4612: 1.5) show the pathogen, appended with the total number of genes in each interactome (4612 in this case) followed by the enrichment ratio (observed/expected = 1.5).

(443) (unpublished data from (Carter and Blizard, 2016)), highlighting a similar cytokine signaling module within foreign chemical and immune/infection pathways.

3.5. Host/pathogen interactome overlaps with misregulated genes in leukocytes from autistic children

The combined up and down regulated genes from the autism toddlers leukocyte microarray were all enriched in all interactomes from viral, bacterial, fungal and protozoan datasets (Fig 3).

3.5.1. Analysis of the leukocyte disrupted genes in autistic toddlers

The differentially expressed genes in this study have already been shown to be enriched in immune/inflammation function and in protein translation (Pramparo et al., 2015). The upregulated genes in this autism leukocyte study were reanalysed using MSigDb which uses canonical pathways from multiple sources (KEGG, Biocarta, Reactome, pathway interaction database, signaling gateway). As this review is primarily concerned with pathogens and the immune system, the subsequent analysis and figures are primarily restricted to this aspect, although certain other features germane to autism are also reported.

MSigDb microarrays (upregulated genes) that significantly overlapped with the upregulated genes from the autism toddlers leukocyte study included those related to influenza, respiratory syncytial virus, lymphocytic choriomeningitis virus or Leishmania major infection, as well as those related to the toll-like receptor (TLR4) ligand, lipopolysaccharide, or to the yellow fever YF17D vaccine (one based on a live, attenuated viral strain) (Table 4).

The most significant infection/immune pathways influenced by the upregulated genes in the autism toddler leukocytes related to influenza infection, and specifically those involved in influenza viral RNA Transcription and Replication. With regard to the enrichment in protein translation pathways already reported in this study (Pramparo et al., 2015), one might also consider that these host processes are usurped by many viruses to synthesise their own proteins (Flint et al., 2008). Numerous immune signaling networks were also represented. These included T cell receptor signaling, Genes involved in MHC class II antigen presentation, Fc-epsilon receptor I signaling in mast cells, Fc epsilon RI signaling and Fc gamma R-mediated phagocytosis, as well as several cytokine and chemokine pathways. Haemostasis and platelet activation pathways were also significantly enriched. Platelets, although primarily concerned with haemostasis/blood clotting, also play an important role in the innate immune system, possessing a variety of receptors, including adhesion and junction molecules, Toll-like and chemokine receptors as well as cytokines, chemokines and antimicrobial peptides (Iannacone, 2016) (Table 4).

3.5.2. Other microarray datasets

The up-regulated genes in the autism toddlers leukocyte study were also enriched in genes upregulated in the Alzheimer's disease (AD) hippocampus post-mortem, both in early (incipient) and late stages of the disease. These upregulated AD genes are also enriched in MsigDB upregulated gene datasets from multiple pathogen microarrays (viral, fungal, bacterial and protozoan) as well as in genes upregulated by Toll-like receptor ligands (Carter, 2017). This concords with the diverse viral, fungal and bacterial pathogens that have been associated with AD or detected in the AD brain (Itzhaki et al., 2016).

The upregulated genes in the autism toddler's leukocyte study were also enriched in upregulated gene sets related to the autoimmune disease, systemic lupus erythematosus (SLE) and to both type 2 and type 1 diabetes. Several studies have noted that autism is more frequent in children born from mothers with systemic lupus erythematosus and other autoimmune diseases including Type 1 diabetes, adult rheumatoid arthritis or hypothyroidism (Vinet et al., 2015; Brimberg et al., 2013; Libbey and Fujinami, 2010; Comi et al., 1999). There are also many reports of autoimmunity in autism patients (Gottfried et al., 2015; Gesundheit et al., 2013; Becker, 2012; Brown and Mehl-Madrona, 2011). Type 2 diabetes mellitus and related risk factors (obesity and dyslipidaemia) have also been associated with autism (Chen et al., 2016).

The upregulated autism genes also concurred with those related to estrogen and thyrotropin responses and to those upregulated by different types of stressors including oxidative stress (hydrogen peroxide), hypoxia and endoplasmic reticulum stress, ultraviolet rediation or 2,4-dinitrofluorobenzene, a hapten used to develop allergic skin reactions in animal models (Eisen et al., 1952). Food and skin allergies such as atopic dermatitis are common in autism patients (Billeci et al., 2015; Theoharides et al., 2016a).

Lymphocyte mitochondria from autistic children (aged 2–5 years) have lower pyruvate dehydrogenase activity and generate more hydrogen peroxide than controls (2-fold increase) (Giulivi et al., 2010). Increased mitochondrial DNA damage related to oxidative stress has

Table 4
A comparison of the upregulated genes in the leukocytes of autistic toddler with those upregulated in infection/immune datasets from MSigDB.

Description	N Genes in MsigDB set	Autism Overlap	FDR q-value	Reference
Genes up-regulated in peripheral blood mononuclear cells (PBMC) from infant with acute influenza infection.	200	54	3.00E-33	C7|(Ioannidis et al., 2012)
Genes up-regulated in PBMC from infant with acute respiratory syncytial virus infection.	200	48	4.15E-27	C7|(Ioannidis et al., 2012)
Genes up-regulated in PBMC from patients with acute influenza infection.	172	41	5.30E-23	C7|(Ramilo et al., 2007)
Genes up-regulated in Ly6c/CXCR5 expressing CD4 T cells during acute infection of lymphocytic choriomeningitis virus	200	43	2.76E-22	C7|(Hale et al., 2013)
Genes up-regulated in T reg cells (2h): medium versus **TNF** [GeneID = 7124].	200	43	2.76E-22	C7|(Nagar et al., 2010)
Genes up-regulated in PBMC 7 days after stimulation with yellow fever YF17D vaccine.	200	39	9.25E-19	C7|(Querec et al., 2009)
Genes up-regulated in CD8 T cells at the peak expansion phase (day8 after lymphocytic choriomeningitis virus -Armstrong infection).	200	39	9.25E-19	C7|(Kaech et al., 2002)
Genes up-regulated in comparison of unstimulated dendritic cells (DC) at 0 h versus DCs stimulated with lipopolysaccharide (TLR4 agonist) for 8 h.	200	36	2.50E-16	C7|(Napolitani et al., 2005)
Genes up-regulated in dendritic cells infected by Leishmania major: 2h versus 24h.	200	36	2.50E-16	C7|(Favila et al., 2014)
Genes up-regulated in comparison of unstimulated dendritic cells (DC) versus 1 day DC stimulated with LPS (TLR4 agonist).	200	35	1.55E-15	C7|(Abbas et al., 2005)
Genes up-regulated in bone marrow-derived macrophages with **IL6** [GeneID = 3569] knockout and 45 min of stimulation by: LPS versus IL10 [GeneID = 3586] and LPS.	200	35	1.55E-15	C7|(El Kasmi et al., 2006)
Genes up-regulated by STAT5 in response to IL2 stimulation.	200	23	4.72E-07	Hallmark
Pathway analysis (canonical pathways from MSigDb)				
Genes involved in Influenza Viral RNA Transcription and Replication	169	33	2.69E-15	Reactome
Genes involved in Influenza Life Cycle	203	34	5.83E-14	Reactome
Genes involved in Immune System	933	78	6.46E-14	Reactome
Genes involved in Adaptive Immune System	539	56	1.03E-13	Reactome
Genes involved in Hemostasis	466	47	4.24E-11	Reactome
TCR signaling in naive $CD4^+$ T cells	66	17	5.41E-10	PID
TCR signaling in naive $CD8^+$ T cells	53	15	1.89E-09	PID
T Cell Receptor Signaling Pathway	49	13	7.31E-08	Biocarta
T cell receptor signaling pathway	108	18	1.71E-07	KEGG
Genes involved in Costimulation by the CD28 family (CD28 is essential for T-cell proliferation and survival, cytokine production, and T-helper type-2 development. [provided by RefSeq, Jul 2011])	63	14	1.89E-07	Reactome
IL-7 Signal Transduction	17	8	4.96E-07	Biocarta
IL8- and CXCR2-mediated signaling events	34	10	1.37E-06	PID
Genes involved in TCR signaling	54	12	1.66E-06	Reactome
CXCR4-mediated signaling events CXCR4 is a CXC chemokine receptor specific for stromal cell-derived factor-1 (Refseq).	102	16	1.93E-06	PID
Genes involved in The role of Nef in HIV-1 replication and disease pathogenesis	28	9	2.34E-06	Reactome
Genes involved in Platelet activation, signaling and aggregation	208	23	2.42E-06	Reactome
Genes involved in cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibitory signaling CTLA4 transmits an inhibitory signal to T cells (Refseq)	21	8	2.63E-06	Reactome
Fc-epsilon receptor I signaling in mast cells	62	12	6.84E-06	PID
Genes related to chemotaxis	45	10	1.55E-05	SIG
Lck and Fyn tyrosine kinases in initiation of TCR Activation	13	6	2.19E-05	Biocarta
Genes involved in MHC class II antigen presentation	91	13	6.29E-05	Reactome
Fc epsilon RI signaling pathway	79	12	7.40E-05	KEGG
Genes involved in HIV Infection	207	20	8.44E-05	Reactome
Fc gamma R-mediated phagocytosis	97	13	1.15E-04	KEGG
Genes related to IL4 rceptor signaling in B lymphocytes	27	7	1.83E-04	SIG
Genes involved in MAP kinase activation in TLR cascade	50	9	2.36E-04	Reactome
TNFR1 Signaling Pathway	29	7	2.65E-04	Biocarta
Genes involved in Antigen Activates B Cell Receptor Leading to Generation of Second Messengers	29	7	2.65E-04	Reactome
Fc Epsilon Receptor I Signaling in Mast Cells	41	8	3.37E-04	Biocarta
Role of Tob in T-cell activation	21	6	3.45E-04	Biocarta
Genes involved in Nef-mediates down modulation of cell surface receptors by recruiting them to clathrin adapters	21	6	3.45E-04	Reactome

also been observed in peripheral blood monocytic cells from autistic children (Napoli et al., 2013). Lower mitochondrial oxidative phosphorylation has been reported in granulocytes from autistic children. accompanied by increased free radical production (Napoli et al., 2014).

Endoplasmic reticulum stress is caused by a number of mutated proteins related to autism (cell adhesion molecule 1 (CADM1), G protein-coupled receptor 37 (GPR37), neuroligin 3(NLGN3) (Fujita et al., 2010; Fujita-Jimbo et al., 2012; Ulbrich et al., 2016). ER stress can also be induced by viruses (Frabutt and Zheng, 2016), pollutants including pesticides (Mostafalou and Abdollahi, 2013) and heavy metals (Thevenod and Lee, 2013; Shinkai and Kaji, 2012) or bisphenol A or phthalates (Asahi et al., 2010; Peropadre et al., 2015).

4. APP processing and autism genes

A literature survey showed that many of the 206 autism susceptibility genes (in **bold** in the subsequent section) target APP expression, transport or processing, with several exerting effects that increase sAPPα production and/or decrease Aβ production (see Fig. 3). These effects are illustrated in Fig. 4. Other ASG's are involved in the signaling networks downstream of sAPPα activation. For example **MAPK1**, **MAPK3** and **NFKB1** mediate the neurotrophic and neuroprotective actions of sAPPα (Cheng et al., 2002) while **NFKB1** prevents apoptosis induced by Aβ(Guo et al., 1998). The kinase **SRC** binds to ADAM10 (Ebsen et al., 2014) and is involved in the 5HT4 serotonin receptor-mediated activation of alpha-secretase (Pimenova et al., 2014). sAPPα also partially exerts its neuroprotective effects via signaling though

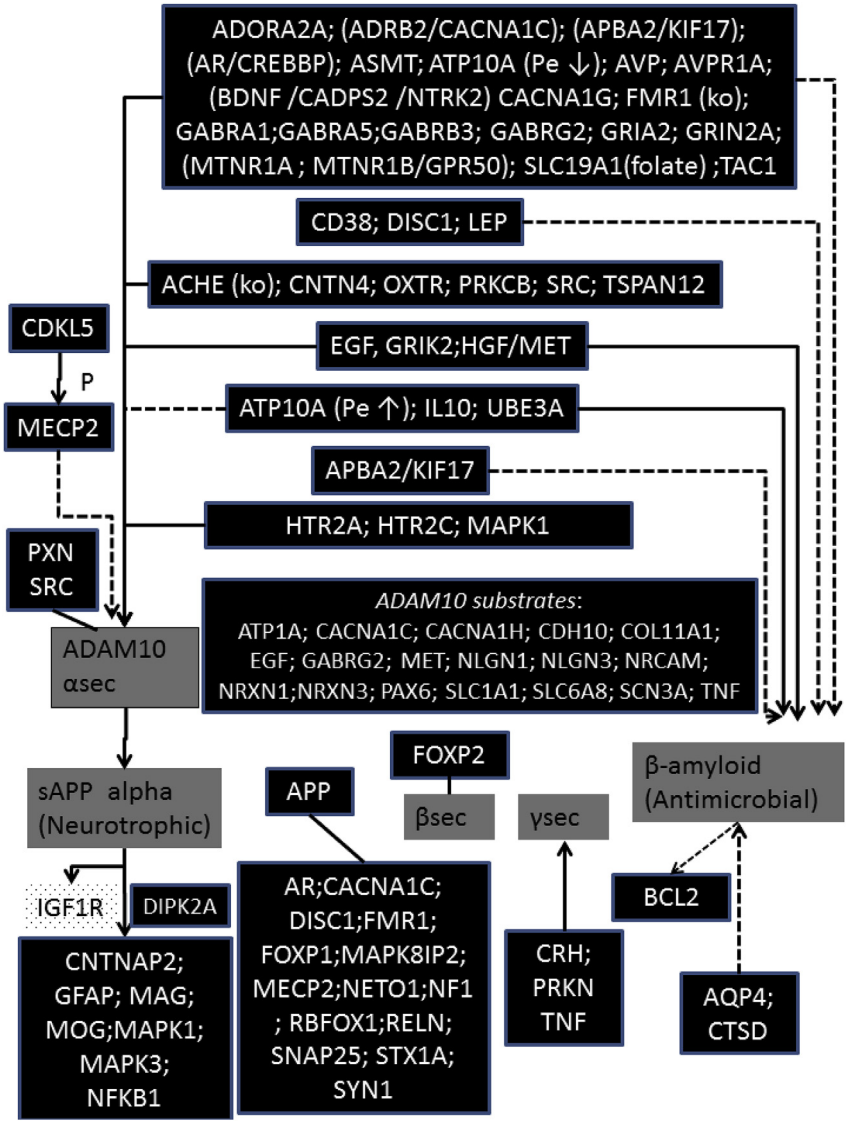

Fig. 4. A resume of the effects of autism susceptibility genes on APP processing in relation to alpha (ADAM10) beta and gamma secretases. = Stimulation; = inhibition; = binding to gene, RNA or protein. Pe ↓ = phosphatidylethanolamine reduction; Pe ↑ = phosphatidylethanolamine increase; KO = gene knockout; P = phosphorylation; Genes in brackets or/represent binding partners.

insulin and the insulin like growth factor (IGF1R) receptors (Jimenez et al., 2011). **C3orf58** (now named divergent protein kinase domain 2A; **DIPK2A**) is a ligand for the insulin like growth factor receptor (Bareja et al., 2017). IGF1 is known to increase the ADAM10-mediated shedding of sAPPα (Jacobsen et al., 2010).

Protein kinase C beta (**PRKCB**) activation also correlates with increased alpha-secretase processing of APP in the guinea pig neocortex (Rossner et al., 2001). sAPPα induces gliogenesis and upregulates glial fibrillary acidic protein (**GFAP**) levels (Kwak et al. 2010, 2014; Bailey et al., 2013; Baratchi et al., 2012).

A number of neurotransmitter receptors modulate APP processing to favour sAPPα production For example glutamatergic AMPA receptor stimulation (**GRIA2**) increases non-amyloidogenic α-secretase-mediated APP processing and inhibits Aβ production in cultured mouse cortical neurones (Hoey et al., 2013). Synaptic activation facilitates non-amyloidogenic APP processing and cell survival, primarily through synaptic NMDA receptors and specifically those containing **GRIN2A** –subunits (Rush and Buisson, 2014). NMDA receptor activation also upregulates ADAM10 and β-catenin proteins in mouse cortical neurones (Wan et al., 2012). Neuropilin tolloid-like 1 (**NETO1**) is a component of the NMDA receptor complex associating with **GRIN2A** and GRIN2B and also regulates the transport of an NMDA receptor/APP complex (Cousins et al., 2013).

Kainic acid can enhance amyloidogenic processing of APP via its receptor (**GRIK1**) leading to increased production/secretion of Aβ-related peptides from activated astrocytes (Ourdev et al., 2018). Kainate also increases ADAM10 activity in B cells and in the hippocampus (Sturgill et al., 2011; Ortiz et al., 2005). The high affinity glutamate transporter (**SLC1A1**) is relevant to these effects.

Etazolate, a selective GABA(A) receptor modulator, stimulates sAPPα production in rat cortical neurons and in guinea pig brains via alpha-secretase (Marcade et al., 2008). In cell cultures, baicalein, a GABAA receptor modulator reduces the production of Aβ by increasing sAPPα processing (Zhang et al., 2013). Gamma-amino butyric acid GABAA receptors associated with autism include **GABRA1, GABRA5, GABRB3, GABRG2, GABRG3** while the GABA synthesis enzyme glutamate decarboxylase (**GAD1**) and GABA transaminase (**ABAT**) are also relevant to GABA transmission. sAPPα secretion is also increased by serotonin receptor **HTR2A** and **HTR2C** activation (Nitsch et al., 1996). The serotonin transporter (**SLC6A4**) is relevant to these effects, as are two tryptophan hydroxylases involved in serotonin synthesis (**TPH1, TPH2**) and tryptophan 2,3-dioxygenase (**TDO2**). Adenosine receptor

(**ADORA2A)** inhibition, favours the non-amyloidogenic pathway, counteracting Aβ production, formation (Cellai et al., 2018). Adenosine is metabolised to inosine by adenosine deaminase (**ADA**). Activation of the beta-2 adrenoceptor (**ADRB2**) decreases cerebral amyloid plaques through the up-regulation of α-secretase activity and by decreasing the phosphorylation of APP in APP/PS1 mice. This receptor also activates ADAM10 in B cells.(Chai et al., 2017; Padro et al., 2013). **ADRB2** is directly coupled to a calcium channel subunit **CACNA1C** (Patriarchi et al., 2016). APP also binds to this particular calcium channel subunit (Yang et al., 2009). Downregulation or pharmacological inhibition of a further calcium channel subunit (**CACNA1G**) increases Aβ production via reductions in non-amyloidogenic processing, accompanied by a decrease in the levels of mature ADAM10 (Rice et al., 2014). The neuropeptide, substance P (**TAC1**) reduces Aβ production in favour of sAPPα via alpha-secretase stimulation (Marolda et al., 2012). Inhibition of acetylcholinesterase (**ACHE**) in human neuroblastoma cells (SH-SY5Y) increases ADAM10 levels in membrane compartments and the secretion of sAPPα (Zimmermann et al., 2004). The tetraspanin (**TSPAN12**) promotes ADAM10 maturation and enhances the alpha-secretase metabolism of APP resulting in sAPPα production (Xu et al., 2009). Amyloid plaque formation is reduced in ubiquitin protein ligase **(UBE3A)** deficient mice possibly via increased activity of ADAM10 (Singh et al., 2017). Angelman syndrome is a neurodevelopmental disorder associated with the loss of maternal expression of **UBE3A**. Total APP, sAPPα and Aβ levels are elevated in the plasma of patients with Angelman Syndrome and the increases in APP and, sAPPα levels were positively correlated with **BDNF** levels (Erickson et al., 2016). Presynaptic proteins co-assembling with APP in transport vesicles include **SNAP25** and synapsin 1 (**SYN1**) (Brunholz et al., 2012). APP also associates with syntaxin 1-containing microdomains (**STX1A**) an effect that inhibits the APP-BACE1 interaction and beta cleavage of APP (Sakurai et al., 2008).

Melatonin, synthesised by acetylserotonin O-methyltransferase (**ASMT**) stimulates non-amyloidogenic processing and inhibits the amyloidogenic processing of APP by stimulating α -secretases and down regulating both β- and γ-secretases (Shukla et al., 2017). This effect is mediated by melatonin receptors (**MTNR1A, MTNR1B**) in human neuronal SH-SY5Y cells (Panmanee et al., 2015). A related G-protein coupled receptor (**GPR50**) with homology to melatonin receptors does not itself bind melatonin, but inhibits **MTNR1A** and **MTNR1B** by heterodimerisation (Levoye et al., 2006). Bradykinin and vasopressin (**AVP**) can increase alpha-secretase processing of APP in PC-12 or NRK-49F cells accompanied by a decrease in Aβ, an effect mediated by vasopressin g-protein-coupled receptors (**AVPR1A**) (Nitsch et al., 1998). Leptin (**LEP**) reduces BACE1 expression and Aβ production in cultured human neuroblastoma SH-SY5Y cells. It also reduces gamma-secretase expression in mouse brains (Marwarha et al., 2014; Niedowicz et al., 2013). Folic acid (transported by **SLC19A1**) decreases Aβ deposition in APP/PS1 transgenic mice brain and increases the expression of the alpha-secretases ADAM9 and ADAM10 (Tian et al., 2016). Receptor for Advanced Glycation End products (RAGE) shedding is also mediated by ADAM10 which is stimulated by pituitary adenylate cyclase-activating polypeptide and by oxytocin via G-protein coupled receptors including the oxytocin receptor (**OXTR**) (Metz et al., 2012).

Brain-derived neurotrophic factor (**BDNF**) reduces Aβ production via increased alpha-secretase and reduced BACE1 activity (Nigam et al., 2017; MacPherson, 2017). **BDNF** signals via the growth factor receptor **NTRK2** which is a gamma-secretase substrate (Tejeda et al., 2016). Depletion of the ankyrin repeat domain protein (**ANKRD11**) in cortical neurones decreases both **BDNF** and **NTRK2** levels (Ka and Kim, 2018) Ca++-dependent secretion activator 2 (**CADPS2)** is associated with secretory vesicles containing **BDNF** and neurotrophin-3 (**NTF3**). It enhances **BDNF** and **NTF3** release in the cerebellum (Sadakata and Furuichi, 2009). **EGF** also stimulates alpha-secretase activity (Slack et al., 1997) but can also stimulate APP proteolysis via gamma secretase (Amigoni et al., 2011). APP level, sAPPα secretion, and Aβ production in HEK293 cells transfected with either wild-type APP(751) or APP (751) carrying the Swedish mutation are all elevated by hepatocyte growth factor (**HGF**).(Liu et al., 2003). Reelin (**RELN**) is an APP ligand and increases sAPPα levels in COS7 cells overexpressing APP (Rice et al., 2013). **CD38** synthesizes and hydrolyzes cyclic adenosine 5′-diphosphate-ribose, an intracellular calcium ion mobilizing messenger that regulates inflammatory processes. **CD38** knockout in APPswePS1ΔE9 (APP.PS) mice decreases beta and gamma secretase activity and Aβ deposition (Blacher et al., 2015). Contactin 4 (**CNTN4**) functions as an adhesion molecule playing a role in axon development. APP binds to **CNTN4** and **CNTN4** increases sAPPα levels (Rice et al., 2013). **ATP10A** is an aminophospholipid translocase which transports phosphatidylserine and phosphatidylethanolamine from one side of a bilayer to another. Phosphatidylserine inhibits gamma-secretase activity (Holmes et al., 2012) but is without effect on ADAM10 (Grimm et al., 2013). Knockout of phosphatidylethanolamine synthesis increases α-secretase cleavage and decreased γ-secretase processing of APP (Nesic et al., 2012)

Disrupted in schizophrenia (**DISC1**) binds to and regulates the traffic of APP and **DISC1** knockdown in mature primary cortical neurons increases sAPPα and decreases Aβ production (Shahani et al., 2015).

Certain autism genes increase Aβ rather than sAPPα levels. For example cathepsin D (**CTSD**) possesses beta-secretase activity (Chevallier et al., 1997) and is involved in the amyloidogenic processing of APP (Chevallier et al., 1997; Sadik et al., 1999). However **CTSD** can also degrade Aβ (McDermott and Gibson, 1996). Corticotropin releasing hormone (**CRH**) increases Aβ levels via an increased activity of gamma-secretase (Futch et al., 2017). The cytokine interleukin 10 (**IL10**) increases Aβ levels in APP transgenic mice and impairsglial Aβ phagocytosis (Chakrabarty et al., 2015). **IL10** also reduces ADAM10 expression in mast cells (Faber et al., 2014) while **TNF** stimulates gamma-secretase activity (Kuo et al., 2008). Cyclooxygenase 2 (**PTGS2**) also promotes Aβ generation via mechanisms that involve Prostaglandin-E2-mediated potentiation of gamma-secretase activity (Qin et al., 2003).

APP-binding protein (**APBA2**), an adaptor protein regulating APP transport and processing, suppresses the amyloidogenic but not amyloidolytic processing of APP, inhibiting Aβ production (Sano et al., 2006; Miller et al., 2006). sAPPα levels in the cortex and hippocampus are decreased in **APBA2** deficient mice (Saito et al., 2008). Kinesin 17 (**KIF17**) is potentially involved in APP transport via its binding to **APBA2** (Muresan and Ladescu, 2015). Mitogen-activated protein kinase 8 interacting protein 2 (**MAPK8IP2**) is also involved in APP transport and bridges APP to a form of the motor protein kinesin (Matsuda et al., 2003). It also binds to the cytoplasmic AICD region of APP (Scheinfeld et al., 2002). methyl CpG binding protein 2 (Rett syndrome) (**MECP2**) is also involved in **BDNF** and APP axonal transport which are impaired in **MECP2** deficient mice (Roux et al., 2012). **MECP2** also inhibits ADAM10 in neural progenitor cells via microRNA mir-197 (Wang et al., 2018). **MECP2** is phosphorylated by the kinase **CDKL5** (Mari et al., 2005). Neurofibromin 1 (**NF1**) Binds to APP in melanosomes and this interaction may play a role in melanosome transport (De Schepper et al., 2006).

APP transcription is also controlled by certain autism genes. For example fragile X mental retardation 1 (**FMR1**) binds to the coding region of APP mRNA (Westmark and Malter, 2007). Brain sAPPα levels are also increased and Aβ levels decreased in **FMR1** knockout mice, together with increased surface expression of ADAM10 (Pasciuto et al., 2015).

The RNA binding protein (**RBFOX1**) regulates APP splicing, inducing exon7 skipping (Alam et al., 2014). A beta secretase, BACE2. is a target of the forkhead transcription factor **FOXP2** (Oswald et al., 2017). APP is also a transcriptional target of the androgen receptor (**AR**) (Takayama et al., 2009). Forkhead box P1 (**FOXP1**) is recruited to **AR** binding sites, including those on the APP gene (Takayama et al., 2014).

AR also increases the transcription and activity of the Aβ degrading enzyme neprilysin and decreases beta amyloid levels (Yao et al., 2008). The **AR** ligand testosterone has also been shown to increase the secretion of sAPPα (Goodenough et al., 2000). CREB binding protein (**CREBBP**) is a coactivator for the androgen receptor (Fronsdal et al., 1998). The androgen receptor (**AR**) also co-precipitates with ADAM10 in the nucleus of human androgen-dependent PC cells (Arima et al., 2007). Parkin (**PARK2)** increases presenilin-1-associated gamma-secretase activity and reduces presenilin-2-linked caspase-3 activation via direct effects on the presenilin promoters (Duplan et al., 2013).

A number of autism genes (proteins) are also substrates for the alpha-secretase ADAM10. These include the ATPase (**ATP1A**), the calcium channel subunits **CACNA1C** and **CACNA1H**, sodium channel subunit **SCN3A**, cadherin **(CDH10),** collagen **(COL11A1),** the GABA receptor subunit **(GABRG2)** and the glutamate **(SLC1A1)** and creatine **(SLC6A8)** transporters (Kuhn et al., 2016), neuroligins (**NLGL1, NLGL3)** (Suzuki et al., 2012; Saftig and Lichtenthaler, 2015), neurexins (**NRXN1** and **NRXN3**) (Tong et al., 2017; Borcel et al., 2016), the adhesion molecule **NRCAM** (Kuhn et al., 2016) and the growth factor **EGF** (Sahin et al., 2004). The **HGF** tyrosine kinase receptor (**MET**) is also processed by ADAM10 and ADAM17 (Chalupsky et al., 2013). ADAM10 also acts as a **TNF** sheddase (Mezyk-Kopec et al., 2009). Paxillin (**PXN**) affects ADAM10 by regulating the shuttling of ADAM10 into vesicles in melanoma cells (Lee et al., 2013).

Aquaporin (**AQP4**) plays a role in the clearance of Aβ in brain via lymphatic clearance, transcytotic delivery, and glial degradation (Yang et al., 2016). Aβ is able to promote apoptosis in human neuroblastoma cells, an effect related to decreased expression of the anti-apoptotic gene, **BCL2** (Clementi et al., 2006).

sAPPα has been shown to promote remyelination following CNS demyelination in mice (see above). It also promoted the reappearance of **CNTNAP2** (contactin associated protein 2) adjacent to the nodes of Ranvier (Llufriu-Daben et al., 2018) sAPPα -induced remyelination was associated with the reappearance of the myelin basic protein (MBP). It is also likely to have affected the myelin associated oligodendrocyte proteins (**MAG** and **MOG**).

Finally, in primary hippocampal neurones, sAPPα increases the number of glutamatergic synapses, as well as the layer thickness of postsynaptic densities while decreasing GABAergic synapses (Hesse et al., 2018). This might be expected to affect a number of synaptic scaffold proteins (**GRIP1, SHANK2, SHANK3,SNAP25, STX1A, SYN1, SYNGAP1**) as well as glutamatergic (**GRIA2, GRIK2, GRIN2A, GRM8**) and GABAergic (**GABBR1, GABBR2, GABRA1, GABRA5 GABRB3, GABRG2, GABRG3**) receptors and associated transporter (**SLC1A1**) or related synthesis (**GAD1**) and degradative (**ABAT**) enzymes.

This excitatory/inhibitory imbalance has also been observed in autism and might also explain the increased propensity for epileptic conditions in autism patients (Uzunova et al., 2016), although these are as likely to be related to the numerous calcium and sodium channels and ionotropic glutamate and GABA receptors within the autism gene set. Neuronal APP levels are markedly increased in the temporal lobe in patients with intractable epilepsy with no evidence of beta-amyloid deposition (Sheng et al., 1994). However, CSF levels of Aβ or sAPPα were unaltered in patients with seizures (Shahim et al., 2014). Post-mortem studies in a small study autistic patients (idiopathic or 5q11.2-q13 duplication), some with epilepsy recorded as the cause of death, have also shown intraneuronal deposits of Aβ17–40/42, a form generated by alpha and gamma secretase, rather than the toxic form af Aβ produced by beta and gamma secretase, suggesting an increase in alpha secretase processing. sAPPα levels were not measured (Wegiel et al., 2012). Thus far, the role of sAPPalpha in autism-related epilepsy is unclear and further research is needed.

Alzheimer's disease and autism.

Given the opposing effects of the two diseases on APP processing, one might expect an inverse relationship between the incidence of the two conditions. However, as noted above, there have been no studies relating autism to Alzheimer's disease risk and the early mortality in autism might preclude the later development of Alzheimer's disease.

A microarray study of the cerebellar transcriptome in autistic patients has also shown an abundance of misregulated transcripts related to Alzheimer's disease pathways. Expression of the NMDA receptor subunit, GRIN1 and map kinase **MAP3K1** was elevated while the expression of the gamma-secretase subunit presenilin 2 was reduced. The authors proposed a model of NMDA glutamate receptor-mediated ERK kinase activation of α-secretase activity that could result in the increased formation of sAPPα (Zeidan-Chulia et al., 2014). There is also genetic evidence for a relationship between autism and Alzheimer's disease.

GWASdb is a database curating genome-wide association studies where p values are < 1X10-3 (Li et al., 2012). GWASdb contains 1591 Alzheimer's disease genes, 44 of which are within this Autworks gene set. KEGG pathway enrichment analysis was not considered viable for so few genes but, based on KEGG pathway genes, many are involved in adhesion/integrin/semaphorin related properties (**CDH8; CDH9; CNTN4; CNTNAP2; CNTNAP5; EGF; ITGA4;NRCAM; NRP2; NRXN1; PTK2; RELN; SEMA5A)** Gaba (**GABBR2; GABRB3; GABRG3;)** or glutamate synapses **(GRIK2; GRIN2A; GRIP1; GRM8; NETO1)** cytokine-related (**IL1RAP; IL1RAPL1;)** calcium and sodium channels or sensors and ion pumps **(ATP10A; CACNA1G; CADPS2; NCS1; SCN2A; SCN3A),** growth related **(EGF; NTRK2)** adrenaline receptor and tachykinins **(ADRB2, TAC1)** and diverse others (**AGAP1; AUTS2; CSMD3; DISC1; DLGAP2; MCPH1; MECP2; NIPBL; NOS2; PARK2; RAPGEF4; RBFOX1; RORA**). The autism genes are thus highly enriched in Alzheimer's disease genes which represent 44/206 (21.4%) of the total ASG's.

Previous work has shown that the autism genes are highly enriched in genes related to barrier function (Carter, 2016).104/206 (50.4%) of the ASG's are expressed in blood brain barrier proteomics datasets from mouse cerebral arteries (Badhwar et al., 2014), and 75/206 (36.4%) from mouse brain microvessels and basal lamina (Chun et al., 2011). 34/44 of the overlapping autism/Alzheimer's genes (77.3%) are common to the combined artery and microvessel datasets. The blood-brain barrier is compromised in Alzheimer's disease (Carter, 2017) and in psychiatric disorders including autism (Kealy et al., 2018) where the expression of barrier-forming tight junction components is decreased, and that of pore-forming claudins is increased in the cortex and cerebellum (Fiorentino et al., 2016).

The genes common to both Alzheimer ‘s disease and autism are thus almost exclusively concerned with the blood brain barrier function which is designed to limit the entry of both pathogens and pollutants.

5. Myelination and the integrated stress response in the autism brain

In the original toddlers leukocyte study, the authors noted that several modules concerned with protein synthesis, translation initiation, elongation and termination were misregulated. The genes upregulated in the autistic toddlers leukocyte study also included genes related to oxidative stress, hypoxia and endoplasmic reticulum stress (Pramparo et al., 2015) (See above and Table 5).

This is related to the integrated stress response that shuts down protein synthesis in response to diverse stressors. This is achieved by the activation of any of four tranlation initiation factor EIF2α kinases by heat (fever) or oxidative stress (EIF2AK1 or Hri), double stranded viral RNA, bacterial toxins, inflammatory cytokines or growth factor deprivation (EIF2AK2 or pkr) endoplasmic reticulum stress (EIF2AK3 or perk), and amino acid or glucose deprivation and viral infection (EIF2AK4 or Gcn2). These kinases phosphorylate EIF2α leading to inhibition of the translation initiation factor EIF2B and the arrest of protein synthesis. Mutations in EIF2B cause vanishing white matter disease and it would seem that this pathway is thus essential for oligodendrocytes and myelination. Growth factors and the plastic

Table 5
A comparison of the upregulated genes in the leukocytes of autistic toddler with those upregulated in disease and exogenous stimuli datasets from MSigDB.

Description, database and reference	N Genes in MSigDB Dataset	Autism Overlap	FDR q-value
Genes up-regulated in brain from patients with Alzheimer's disease. CGP (Blalock et al., 2004)	1691	194	1.32E-56
Genes up-regulated in patients at the incipient stage of Alzheimer's disease. CGP (Blalock et al., 2004)	390	54	5.07E-19
Genes up-regulated in comparison of systemic lupus erythematosus CD4 T cells versus systemic lupus erythematosus B cells. C7| (Hutcheson et al., 2008)	200	66	3.11E-46
Genes up-regulated in comparison of systemic lupus erythematosus CD4 [GeneID = 920] T cells versus systemic lupus erythematosus myeloid cells. C7| (Hutcheson et al., 2008)	200	56	2.24E-35
Genes up-regulated in dendritic cells: hydrogen peroxide versus diphenyleneiodonium (NADPH oxidase inhibitor :inhibits free radical production). C7| (Miyazawa and Takashima, 2012)	200	40	1.27E-19
Genes up-regulated in comparison of peripheral blood mononuclear cells (PBMC) from healthy donors versus PBMCs from patients with type 2 diabetes at the time of diagnosis. C7|(Kaizer et al., 2007)	200	38	5.86E-18
Genes up-regulated in normal epidermal keratinocyte cells after ultra-violet B irradiation. CGP (Enk et al., 2006)	530	59	2.38E-16
Genes up-regulated in response to ultraviolet (UV) radiation.hallmark	158	12	5.69E-03
Genes up-regulated in dendritic cells: control versus 2,4-dinitrofluorobenzene (DNFB) and diphenyleneiodonium (NADPH oxidase inhibitor). C7| (Miyazawa and Takashima, 2012)	199	36	2.50E-16
Genes up-regulated in bone marrow-derived mast cells treated with IL3 [GeneID = 3562]: control versus IL33 [GeneID = 90865]. C7|(Jung et al., 2013)	200	36	2.50E-16
Genes up-regulated in CD8 T cells 3 days after immunization: control versus IL2 [GeneID = 3558] treatment. C7|(Castro et al., 2012)	200	35	1.55E-15
Genes up-regulated in comparison of peripheral blood mononuclear cells (PBMC) from healthy donors versus PBMCs from patients with type 1 diabetes at the time of diagnosis. C7|(Kaizer et al., 2007)	200	35	1.55E-15
Genes defining early response to estrogen. hallmark	200	22	9.07E-07
Genes defining late response to estrogen. hallmark	200	18	1.00E-04
Genes up-regulated in primary thyrocyte cultures in response to cAMP signaling pathway activation by thyrotropin (TSH). c6onco (van Staveren et al., 2006)	200	23	1.43E-06
Genes up-regulated in response to low oxygen levels (hypoxia).hallmark	200	20	1.01E-05
Genes up-regulated during unfolded protein response, a cellular stress response related to the endoplasmic reticulum. hallmark	113	12	3.99E-04
Genes up-regulated in CEM-C1 cells (T-CLL) by rapamycin (sirolimus) [PubChem = 6610346], an mTOR pathway inhibitor. c6 oncology (Wei et al., 2006)	196	16	1.44E-03
Genes up-regulated in response to TGFB1 hallmark	54	7	2.50E-03

postsynaptic growth induced by NMDA receptor activation (long-term potentiation) activate protein synthesis via EIF2α activation, while metabotropic glutamate receptors repress protein synthesis via EIF2α inhibition (long-term depression). This pathway and its downstream outputs are related to susceptibility genes for bipolar disorder and schizophrenia, which are also related to demyelination (Carter, 2007)). Viruses and bacterial toxins or the inflammation they produce can directly activate EIF2AK2/pkr but may also cause amino acid deprivation related to the synthesis of viral proteins (EIF2AK4/Gcn2) while bacteria may also activate EIF2AK4/Gcn2 via amino acid and glucose scavenging. Fever (heat) related to infection is also relevant to EIF2AK1/hri. Many autism genes (**in bold**) are also relevant to this pathway including those related to oxidative stress (glutathione transferase **GSTM1)**, nitric oxide synthases (**NOS1; NOS2**) inflammatory cytokines (**IL1RAP; IL1RAPL1; IL6; TNF**), growth factors (**BDNF, EGF, NTF3, HGF; NTRK2**), and the **BDNF** signaling pathway (**APC; BDNF; CDKL5; EGR2;; EIF4E; GABRB3; GRIA2; GRIP1; MAPK1; MAPK3; NFKB1; NTF3; NTRK2; SRC; SYN1**), the hepatocyte growth factor pathway (**HGF; MAPK1; MAPK3; MET; PTK2; PTEN; PXN; SRC**); neurotrophin signaling (**BCL2; BDNF, MAPK1; MAPK3; NTF3; NTRK2; NFKB1**); NMDA (**GRIN2A**) and metabotropic glutamate receptors (**GRM8**) and the long-term potentation signaling pathway (**CACNA1C; CREBBP; GRIA2; GRIN2A; MAPK1; MAPK3; PRKCB CREBBP**) (see Table 3 for these and related pathways).

Endoplasmic reticulum stress genes, including EIF2AK3/perk and downstream effectors are upregulated in the middle frontal gyrus of autism subjects (Crider et al., 2017). Endoplasmic stress genes were also upregulated in the prefrontal cortex, hippocampus, cerebellum in another study, although perk levels were unchanged. However a downstream target, activating transcription factor 6 (ATF6) was activated in the hippocampus and a further downstream target inositol-requiring enzyme 1 alpha (ERN1) activated in the frontal cortex and cerebellum. The expression of the ER stress marker C/EBP-homologous protein (CHOP/DDIT3) and other endoplasmic reticulum chaperones was elevated in all regions. Apoptosis was also detected and the activation of this stress pathway was related to oxidative stress (Dong et al., 2018).

It would thus appear this pathways is relevant to the myelination problems in autism and other psychiatric conditions.

6. Discussion

Prenatal and childhood infections or immune activation have been implicated in autism. This study has shown that subsets of 206 genes implicated in autism are also used or influenced by many pathogens, or by pathogen-related toxins, including mycotoxins that have been associated with autism. They also related to the genes regulated by Toll-like pathogen receptor ligands. Pathway analysis also showed that these genes also play a role in the immune pathways designed to defend against pathogens. Many of these genes, including those more commonly associated with neurotransmission are localised in immune organs or in immunocompetent blood cells. The autism genes are also enriched in those misregulated in leukocytes of autistic toddlers. The upregulated leukocyte genes in the autistic toddler study also overlap with other infection or immune related microarray datasets. The pathways etched out by the autism genes, and/or the genes upregulated in the autistic toddlers study also relate to infection but also to endocrine pathways and to certain of the comorbid conditions associated with autism, including diabetes, cardiomyopathy, epilepsy and brain growth, lupus and inflammatory bowel disease.

To date, this same set of 206 autism genes has been shown to play an important role in barrier function and in the control of respiratory cilia that sweep noxious particles and pathogens from the respiratory tract (Carter, 2016). They are also targeted by many of the environmental pollutants and drugs implicated in autism, and by multiple endocrine disruptors (Carter and Blizard, 2016). They are also focussed on the immune system, which plays an important role at barrier interfaces

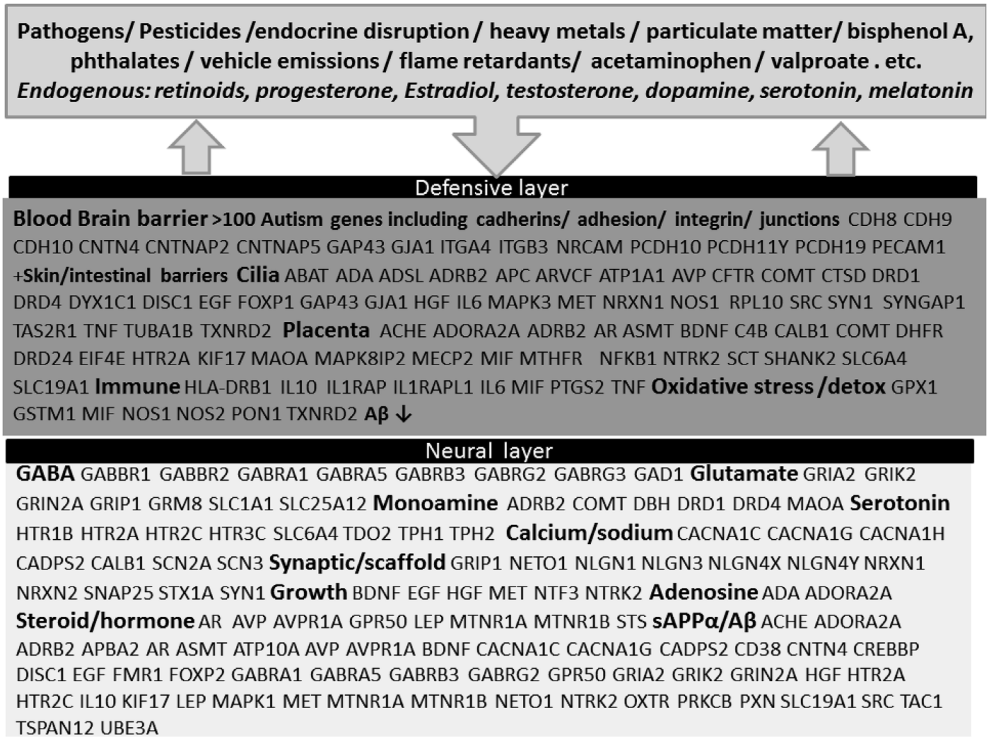

Fig. 5. A summary of the environmental risk factors that target the 206 autism genes (top layer). The general functions and locations of the autism genes are shown in the defensive (barriers, cilia, placenta, immune, oxidative stress, detoxification and decreased Aβ levels (Aβ↓) and neural layers (adenosine,GABA, glutamate, monoamine, serotonin, synaptic, channels) including steroid and hormone related genes as well as those involved in the regulation of sAPPα and Aβ. See supplementary table for gene symbol definitions.

(Doran et al., 2013a; Veiga-Fernandes and Mucida, 2016).

A summary of the autism genes involved in these effects (from Carter, 2016; Carter and Blizard, 2016) and this paper is shown in Fig. 5. The autism genes are selectively targeted by a variety of infectious agents, pesticides, pollutants, endocrine disruptors and drugs implicated in autism. The endogenous compounds related to the autism genes primarily include sex steroids (related to endocrine disruption) as well as melatonin, dopamine and serotonin which all play a role in autism.

A large block of autism genes are dedicated to prevent the passage of these pathogens or pollutants and are localised in the blood-brain and other barriers (skin and intestinal) and in cilia that also play a role in sweeping pathogens and pollutants from the airways. Many are localised in the placenta and several are immune related or play a role in detoxification.

Beneath this defensive layer lie diverse autism genes related to neurotransmission including adenosine, GABA, Glutamate, dopamine adrenaline and serotonin, and synaptic and channel genes. Others relate to growth factors, the androgen receptor (AR), and steroid sulfatase (STS), vasopressin (AVP, AVPR1A), leptin (LEP), melatonin receptors (MTNR1A, MTNR1B, GPR50) and tachykinins (TAC1; coding for substance P, neurokinin A, and neuropeptides K and gamma). These are also targeted by pathogens and pollutants. They play a clear role in brain and behaviour and might be regarded as effector genes in this respect. Many are involved in regulating the sAPPα/Aβ balance, which will also have an effect on antimicrobial defense in the upper defensive layer of genes.

While many of these neurotransmitter, channel and synaptic autism genes evidently play a role in brain function they are also localised in immune-related organs and blood cells (see Table 2), placing many in the upper defensive layer of autism genes.

This summary highlights multiple gene/environment interactions which together dictate the eventual outcome of environmental influencers. These relationships are reciprocal, i.e. the risk factors target the autism genes, and the polymorphic genes, as well as influencing human physiology are likely to influence the effects of the pathogens and pollutants with which they interact. This places the autism genes at the interface between cause and effect, suggesting that measures to reduce pollutants and the use of endocrine disruptors as well as to tackle infection might help reduce the incidence of autism.

There are certain similarities between the effects of pollution and infection. Pesticides, airborne pollutants, particulate matter, bisphenol A, phthalates and flame retardants, endocrine disruption as well as heavy metals, *inter alia* have all been implicated as autism risk factors (Carter and Blizard, 2016; Kalkbrenner et al., 2014). Toll-like receptors are pattern recognition receptors that primarily recognise viral, bacterial and fungal ligands and their activation mounts the appropriate inflammatory, immune and defence pathways in response to diverse infections (Takeda and Akira, 2005). There appears to be significant cross-talk between infection and pollutant pathways. A number of endocrine disruptors (Alachlor, atrazine, benomyl, bisphenol A, carbaryl, diethyl phthalate, dipropyl phthalate, kelthane, kepone, malathion, methoxychlor, octachlorostyrene, pentachlorophenol, nonyl phenol, p-octylphenol, simazine and ziram) inhibit the activation of the interferon-beta promotor by bacterial lipolysaccharide via toll-like receptor TLR4. Particulate matter/air pollution are also able to activate TLR2, TLR4 and TLR5 (Becker et al., 2005) (Woodward et al., 2017; Ryu et al., 2018; Yokota et al., 2007). TLR4 has also been implicated in the effects of the pesticides diazinon (Win-Shwe et al., 2012) and chlorpyrifos (Tian et al., 2015).

Many pollutants, including tetrachlorodibenzo-p-dioxin and benzo [a]pyrene also activate the xenobiotic-sensing aryl hydrocarbon receptor (AHR) and this also modulates the effects of Toll-like receptor ligands (Kado et al., 2016). AHR also regulates the transcription of the amyloid precursor protein (APP) (Sartor et al., 2009).

This suggests that such compounds, many of which have been implicated in autism (Kajta and Wojtowicz, 2010; Kajta and Wojtowicz, 2013; Kalkbrenner et al., 2014), could deleteriously affect pathways relevant to infection (Yokota et al., 2007).

The autism genes or leukocyte transcriptome also appear to be involved in two unexpected diseases, sudden infant death syndrome (SIDS) and Alzheimer's disease, both of which have been associated with infection. SIDS has been associated with pathogens, particularly respiratory infections (Moscovis et al., 2015). It has also been noted

that diphtheria-tetanus-pertussis vaccination has reduced the incidence of SIDS in the USA (Muller-Nordhorn et al., 2015). Other vaccinations also reduce the risk of SIDS (meta-analysis) (Vennemann et al., 2007). Many studies have linked Alzheimer's disease to infection (Carter, 2017; Itzhaki et al., 2016). As yet, there appear to be no studies linking autism to the prevalence of Alzheimer's disease in later life. However, the relatively high premature mortality of autism patients (Bilder et al., 2013) (Hirvikoski et al., 2016) might preclude the relatively later development of Alzheimer's disease.

Neonatal disorders including diarrhoea, pneumonia, and malaria (many caused by infection), as well as being underweight (malnutrition/starvation), account for most of the child deaths worldwide, but not in developed countries, where childhood mortality has markedly decreased (Pallapies, 2006).

According to Centers for disease control and prevention (CDC) figures (https://www.cdc.gov/reproductivehealth/maternalinfanthealth/infantmortality.htm the 5 leading causes of infant deaths in the USA (2015) included birth defects, preterm birth and low birthweight, SIDS, maternal pregnancy complications and injuries (e.g. suffocation).

Several of these, including birth defects (Schendel et al., 2009) preterm birth and low birthweight (Joseph et al., 2017; Wang et al., 2017), foetal hypoxia (Burstyn et al., 2011), maternal pregnancy complications including diabetes, obesity, caesarean section (Modabbernia et al., 2017), or a necessity to delay or induce labour (Polo-Kantola et al., 2014) are also associated with autism. A reduction in the incidence of SIDS subsequent to advice to sleep babies on the back has been noted to correlate with a rise in the incidence of autism (Bergman, 2016).

Reproductive fitness is low in autism and other psychiatric disorders (Power et al., 2013; Mullins et al., 2017) and a large Swedish register study has shown that premature mortality is higher than normal in autism. The higher mortality included diverse causes of death (including neoplasms, endocrine, neurological (epilepsy), respiratory, cardiovascular and gastrointestinal) but not specifically infection (Hirvikoski et al., 2016). Other studies have also noted an increased mortality in autism due to diverse causes (Schendel et al., 2016; Bilder et al., 2013). Autism patients also show an increased incidence of multiple health conditions including cardiovascular disease, motor problems, ear problems, urinary problems, digestive problems, side effects from long-term medication use, and nonspecific lab tests and encounters (Bishop-Fitzpatrick et al., 2018).

There thus exists a link between the factors responsible for infant and premature mortality and autism. Prenatal and early infantile infections are also strongly implicated in autism (see introduction). The autistic children have however survived these risks, suggesting either that the autistic infants or their mothers are more resistant to these mortality factors or that medical advances particularly around the perinatal period have favoured the survival of children who prior to the advent of antibiotics, vaccines and better care during pregnancy and birth, might otherwise have succumbed. In other words a reduction in natural selection pressure, due to medical advances and increased survival rates in infancy could in part explain the increased incidence of autism.

Finally, many of the autism related genes converge on the pathway regulating APP processing. High levels of sAPPα and lower levels of Aβ have been observed in autistic patients, and it has been suggested that the neurotrophic effects of sAPPα may contribute to the brain overgrowth in autism (Ray et al. 2011a, 2016; Westmark et al., 2016). Aβ is a potent antimicrobial agent and this imbalance in APP processing in autism, leading to lower Aβ production could well explain the high prevalence of prenatal and infantile infection in relation to autism. sAPPα also promotes an excitatory/inhibitory imbalance that has also been observed in autism. Problems in myelination can also be related to infection via the integrated stress response pathway.

Although aberrant APP processing has been observed in autistic patients there appear to have been no studies related to the specific effects of any autism genetic variants on APP processing and further work in this area is warranted.

Nevertheless, the convergence of so many genes on APP processing suggests that the increases in neurotrophic/myelinotrophic sAPPα and the reduction in antimicrobial Aβ production in autism could be genetically predetermined. In particular, the reductions in antimicrobial Aβ levels would tend to favour the persistence of pathogens following infection and could partially explain the prenatal involvement of pathogens in autism and the association with infections that continues into childhood. This pivot could provide a coherent explanation for the brain overgrowth/myelination problems, the excitatory/inhibitory imbalance and the relationship of infections to the pathogenesis of autism.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.03.007.

References

Abbas, A.R., Baldwin, D., Ma, Y., Ouyang, W., Gurney, A., Martin, F., Fong, S., van Lookeren, C.M., Godowski, P., Williams, P.M., Chan, A.C., Clark, H.F., 2005. Immune response in silico (IRIS): immune-specific genes identified from a compendium of microarray expression data. Genes Immun. 6, 319–331.

Abdallah, M.W., Hougaard, D.M., Norgaard-Pedersen, B., Grove, J., Bonefeld-Jorgensen, E.C., Mortensen, E.L., 2012. Infections during pregnancy and after birth, and the risk of autism spectrum disorders: a register-based study utilizing a Danish historic birth cohort. Türk Psikiyatri Derg. 23, 229–235.

Akira, S., Takeda, K., 2004. Toll-like receptor signalling. Nat. Rev. Immunol. 4, 499–511.

Al Zaid, F.S., Alhader, A.A., Al Ayadhi, L.Y., 2014. Altered ghrelin levels in boys with autism: a novel finding associated with hormonal dysregulation. Sci. Rep. 4, 6478.

Alam, S., Suzuki, H., Tsukahara, T., 2014. Alternative splicing regulation of APP exon 7 by RBFox proteins. Neurochem. Int. 78, 7–17.

Allard, M.J., Bergeron, J.D., Baharnoori, M., Srivastava, L.K., Fortier, L.C., Poyart, C., Sebire, G., 2016. A sexually dichotomous, autistic-like phenotype is induced by Group B Streptococcus maternofetal immune activation. Autism Res.

Allinson, T.M., Parkin, E.T., Turner, A.J., Hooper, N.M., 2003. ADAMs family members as amyloid precursor protein alpha-secretases. J. Neurosci. Res. 74, 342–352.

Amigoni, L., Ceriani, M., Belotti, F., Minopoli, G., Martegani, E., 2011. Activation of amyloid precursor protein processing by growth factors is dependent on Ras GTPase activity. Neurochem. Res. 36, 392–398.

Anwar, M.A., Al Shehabi, T.S., Eid, A.H., 2016. Inflammogenesis of secondary spinal cord injury. Front. Cell. Neurosci. 10, 98.

Arima, T., Enokida, H., Kubo, H., Kagara, I., Matsuda, R., Toki, K., Nishimura, H., Chiyomaru, T., Tatarano, S., Idesako, T., Nishiyama, K., Nakagawa, M., 2007. Nuclear translocation of ADAM-10 contributes to the pathogenesis and progression of human prostate cancer. Cancer Sci. 98, 1720–1726.

Asahi, J., Kamo, H., Baba, R., Doi, Y., Yamashita, A., Murakami, D., Hanada, A., Hirano, T., 2010. Bisphenol A induces endoplasmic reticulum stress-associated apoptosis in mouse non-parenchymal hepatocytes. Life Sci. 87, 431–438.

Atladottir, H.O., Henriksen, T.B., Schendel, D.E., Parner, E.T., 2012. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. Pediatrics 130, e1447–e1454.

Atladottir, H.O., Thorsen, P., Ostergaard, L., Schendel, D.E., Lemcke, S., Abdallah, M., Parner, E.T., 2010. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J. Autism Dev. Disord. 40, 1423–1430.

Badhwar, A., Stanimirovic, D.B., Hamel, E., Haqqani, A.S., 2014. The proteome of mouse cerebral arteries. J. Cereb. Blood Flow Metab. 34, 1033–1046.

Bailey, A.R., Giunta, B.N., Obregon, D., Nikolic, W.V., Tian, J., Sanberg, C.D., Sutton, D.T., Tan, J., 2008. Peripheral biomarkers in Autism: secreted amyloid precursor protein-alpha as a probable key player in early diagnosis. Int. J. Clin. Exp. Med. 1, 338–344.

Bailey, A.R., Hou, H., Song, M., Obregon, D.F., Portis, S., Barger, S., Shytle, D., Stock, S., Mori, T., Sanberg, P.G., Murphy, T., Tan, J., 2013. GFAP expression and social deficits in transgenic mice overexpressing human sAPPalpha. Glia 61, 1556–1569.

Balestrieri, E., Arpino, C., Matteucci, C., Sorrentino, R., Pica, F., Alessandrelli, R., Coniglio, A., Curatolo, P., Rezza, G., Macciardi, F., Garaci, E., Gaudi, S., Sinibaldi-Vallebona, P., 2012. HERVs expression in autism spectrum disorders. PLoS One 7, e48831.

Baratchi, S., Evans, J., Tate, W.P., Abraham, W.C., Connor, B., 2012. Secreted amyloid precursor proteins promote proliferation and glial differentiation of adult hippocampal neural progenitor cells. Hippocampus 22, 1517–1527.

Bareja, A., Hodgkinson, C.P., Payne, A.J., Pratt, R.E., Dzau, V.J., 2017. HASF (C3orf58) is a novel ligand of the insulin-like growth factor 1 receptor. Biochem. J. 474, 771–780.

Becker, K.G., 2012. Male gender bias in autism and pediatric autoimmunity. Autism Res. 5, 77–83.

Becker, S., Dailey, L., Soukup, J.M., Silbajoris, R., Devlin, R.B., 2005. TLR-2 is involved in

airway epithelial cell response to air pollution particles. Toxicol. Appl. Pharmacol. 203, 45–52.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B 57, 289–300.
Bergeron, J.D., Deslauriers, J., Grignon, S., Fortier, L.C., Lepage, M., Stroh, T., Poyart, C., Sebire, G., 2013. White matter injury and autistic-like behavior predominantly affecting male rat offspring exposed to group B streptococcal maternal inflammation. Dev. Neurosci. 35, 504–515.
Bergman, N.J., 2016. Hypothesis on supine sleep, sudden infant death syndrome reduction and association with increasing autism incidence. World J. Clin. Pediatr. 5, 330–342.
Bilder, D., Botts, E.L., Smith, K.R., Pimentel, R., Farley, M., Viskochil, J., McMahon, W.M., Block, H., Ritvo, E., Ritvo, R.A., Coon, H., 2013. Excess mortality and causes of death in autism spectrum disorders: a follow up of the 1980s Utah/UCLA autism epidemiologic study. J. Autism Dev. Disord. 43, 1196–1204.
Billeci, L., Tonacci, A., Tartarisco, G., Ruta, L., Pioggia, G., Gangemi, S., 2015. Association between atopic dermatitis and autism spectrum disorders: a systematic review. Am. J. Clin. Dermatol. 16, 371–388.
Birnbaum, R., Jaffe, A.E., Hyde, T.M., Kleinman, J.E., Weinberger, D.R., 2014. Prenatal expression patterns of genes associated with neuropsychiatric disorders. Am. J. Psychiatry.
Bishop-Fitzpatrick, L., Movaghar, A., Greenberg, J.S., Page, D., DaWalt, L.S., Brilliant, M.H., Mailick, M.R., 2018. Using machine learning to identify patterns of lifetime health problems in decedents with autism spectrum disorder. Autism Res.
Blacher, E., Dadali, T., Bespalko, A., Haupenthal, V.J., Grimm, M.O., Hartmann, T., Lund, F.E., Stein, R., Levy, A., 2015. Alzheimer's disease pathology is attenuated in a CD38-deficient mouse model. Ann. Neurol. 78, 88–103.
Blalock, E.M., Geddes, J.W., Chen, K.C., Porter, N.M., Markesbery, W.R., Landfield, P.W., 2004. Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses. Proc. Natl. Acad. Sci. U. S. A. 101, 2173–2178.
Boitz, J.M., Strasser, R., Yates, P.A., Jardim, A., Ullman, B., 2013. Adenylosuccinate synthetase and adenylosuccinate lyase deficiencies trigger growth and infectivity deficits in Leishmania donovani. J. Biol. Chem. 288, 8977–8990.
Boksa, P., 2010. Effects of prenatal infection on brain development and behavior: a review of findings from animal models. Brain Behav. Immun. 24, 881–897.
Borcel, E., Palczynska, M., Krzisch, M., Dimitrov, M., Ulrich, G., Toni, N., Fraering, P.C., 2016. Shedding of neurexin 3beta ectodomain by ADAM10 releases a soluble fragment that affects the development of newborn neurons. Sci. Rep. 6, 39310.
Bourgade, K., Garneau, H., Giroux, G., Le Page, A.Y., Bocti, C., Dupuis, G., Frost, E.H., Fulop Jr., T., 2015. beta-Amyloid peptides display protective activity against the human Alzheimer's disease-associated herpes simplex virus-1. Biogerontology 16, 85–98.
Bourgade, K., Le Page, A., Bocti, C., Witkowski, J.M., Dupuis, G., Frost, E.H., Fulop, T., 2016. Protective effect of amyloid-beta peptides against herpes simplex virus-1 infection in a neuronal cell culture model. J. Alzheimer's Dis. 50, 1227–1241.
Bozzi, Y., Provenzano, G., Casarosa, S., 2018. Neurobiological bases of autism-epilepsy comorbidity: a focus on excitation/inhibition imbalance. Eur. J. Neurosci. 47, 534–548.
Brimberg, L., Sadiq, A., Gregersen, P.K., Diamond, B., 2013. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. Mol. Psychiatr. 18, 1171–1177.
Brown, A.C., Mehl-Madrona, L., 2011. Autoimmune and gastrointestinal dysfunctions: does a subset of children with autism reveal a broader connection? Expert Rev. Gastroenterol. Hepatol. 5, 465–477.
Brown, A.S., 2012. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev. Neurobiol. 72, 1272–1276.
Brunholz, S., Sisodia, S., Lorenzo, A., Deyts, C., Kins, S., Morfini, G., 2012. Axonal transport of APP and the spatial regulation of APP cleavage and function in neuronal cells. Exp. Brain Res. 217, 353–364.
Burnette, W.N., 1997. Bacterial ADP-ribosylating toxins: form, function, and recombinant vaccine development. Behring Inst. Mitt. 434–441.
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 Med. Res. Methodol. 11, 2.
Carmody, D.P., Lewis, M., 2010. Regional white matter development in children with autism spectrum disorders. Dev. Psychobiol. 52, 755–763.
Carter, C.J., 2007. eIF2B and oligodendrocyte survival: where nature and nurture meet in bipolar disorder and schizophrenia? Schizophr. Bull. 33, 1343–1353.
Carter, C.J., 2013a. Susceptibility genes are enriched in those of the HSV-1/host interactome in psychiatric and neurological disorders. Pathog. Dis.
Carter, C.J., 2013b. Toxoplasmosis and polygenic disease susceptibility genes: extensive Toxoplasma gondii host/pathogen interactome enrichment in nine psychiatric or neurological disorders. J. Pathog. 2013, 1–29.
Carter, C.J., 2016. The barrier, airway particle clearance, placental and detoxification functions of autism susceptibility genes. Neurochem. Int. 99, 42–51.
Carter, C.J., 2017. Genetic, transcriptome, proteomic, and epidemiological evidence for blood-brain barrier disruption and polymicrobial brain invasion as determinant factors in alzheimer's disease. J. Alzheimers Dis. Rep. 1, 125–157.
Carter, C.J., Blizard, R.A., 2016. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. Neurochem. Int. https://doi.org/10.1016/j.neuint.2016.10.011.
Castro, I., Dee, M.J., Malek, T.R., 2012. Transient enhanced IL-2R signaling early during priming rapidly amplifies development of functional CD8+ T effector-memory cells. J. Immunol. 189, 4321–4330.
Cellai, L., Carvalho, K., Faivre, E., Deleau, A., Vieau, D., Buee, L., Blum, D., Meriaux, C., Gomez-Murcia, V., 2018. The adenosinergic signaling: a complex but promising therapeutic target for alzheimer's disease. Front. Neurosci. 12, 520.
Chai, G.S., Wang, Y.Y., Zhu, D., Yasheng, A., Zhao, P., 2017. Activation of beta2-adrenergic receptor promotes dendrite ramification and spine generation in APP/PS1 mice. Neurosci. Lett. 636, 158–164.
Chakrabarty, P., Li, A., Ceballos-Diaz, C., Eddy, J.A., Funk, C.C., Moore, B., DiNunno, N., Rosario, A.M., Cruz, P.E., Verbeeck, C., Sacino, A., Nix, S., Janus, C., Price, N.D., Das, P., Golde, T.E., 2015. IL-10 alters immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. Neuron 85, 519–533.
Chalupsky, K., Kanchev, I., Zbodakova, O., Buryova, H., Jirouskova, M., Korinek, V., Gregor, M., Sedlacek, R., 2013. ADAM10/17-dependent release of soluble c-Met correlates with hepatocellular damage. Folia Biol. (Praha) 59, 76–86.
Chen, M.H., Lan, W.H., Hsu, J.W., Huang, K.L., Su, T.P., Li, C.T., Lin, W.C., Tsai, C.F., Tsai, S.J., Lee, Y.C., Chen, Y.S., Pan, T.L., Chang, W.H., Chen, T.J., Bai, Y.M., 2016. Risk of developing type 2 diabetes in adolescents and young adults with autism spectrum disorder: a nationwide longitudinal study. Diabetes Care 39, 788–793.
Cheng, G., Yu, Z., Zhou, D., Mattson, M.P., 2002. Phosphatidylinositol-3-kinase-Akt kinase and p42/p44 mitogen-activated protein kinases mediate neurotrophic and excitoprotective actions of a secreted form of amyloid precursor protein. Exp. Neurol. 175, 407–414.
Chess, S., Fernandez, P., Korn, S., 1978. Behavioral consequences of congenital rubella. J. Pediatr. 93, 699–703.
Chevallier, N., Vizzavona, J., Marambaud, P., Baur, C.P., Spillantini, M., Fulcrand, P., Martinez, J., Goedert, M., Vincent, J.P., Checler, F., 1997. Cathepsin D displays in vitro beta-secretase-like specificity. Brain Res. 750, 11–19.
Chun, H.B., Scott, M., Niessen, S., Hoover, H., Baird, A., Yates III, J., Torbett, B.E., Eliceiri, B.P., 2011. The proteome of mouse brain microvessel membranes and basal lamina. J. Cereb. Blood Flow Metab. 31, 2267–2281.
Clementi, M.E., Pezzotti, M., Orsini, F., Sampaolese, B., Mezzogori, D., Grassi, C., Giardina, B., Misiti, F., 2006. Alzheimer's amyloid beta-peptide (1-42) induces cell death in human neuroblastoma via bax/bcl-2 ratio increase: an intriguing role for methionine 35. Biochem. Biophys. Res. Commun. 342, 206–213.
Colborn, T., 2004. Neurodevelopment and endocrine disruption. Environ. Health Perspect. 112, 944–949.
Comi, A.M., Zimmerman, A.W., Frye, V.H., Law, P.A., Peeden, J.N., 1999. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J. Child Neurol. 14, 388–394.
Cordeiro, C.N., Tsimis, M., Burd, I., 2015. Infections and brain development. Obstet. Gynecol. Surv. 70, 644–655.
Cousins, S.L., Innocent, N., Stephenson, F.A., 2013. Neto1 associates with the NMDA receptor/amyloid precursor protein complex. J. Neurochem. 126, 554–564.
Coutermarsh-Ott, S., Eden, K., Allen, I.C., 2016. Beyond the inflammasome: regulatory NOD-like receptor modulation of the host immune response following virus exposure. J. Gen. Virol. 97, 825–838.
Craig, A.M., Kang, Y., 2007. Neurexin-neuroligin signaling in synapse development. Curr. Opin. Neurobiol. 17, 43–52.
Crider, A., Ahmed, A.O., Pillai, A., 2017. Altered expression of endoplasmic reticulum stress-related genes in the middle frontal cortex of subjects with autism spectrum disorder. Mol. Neuropsychiatr. 3, 85–91.
Davis, A.P., Grondin, C.J., Lennon-Hopkins, K., Saraceni-Richards, C., Sciaky, D., King, B.L., Wiegers, T.C., Mattingly, C.J., 2015. The Comparative Toxicogenomics Database's 10th year anniversary: update 2015. Nucleic Acids Res. 43, D914–D920.
de Cock, M., de Boer, M.R., Lamoree, M., Legler, J., van de, B.M., 2014. First year growth in relation to prenatal exposure to endocrine disruptors - a Dutch prospective cohort study. Int. J. Environ. Res. Public Health 11, 7001–7021.
de Cock, M., Maas, Y.G., van de, B.M., 2012. Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. Acta Paediatr. 101, 811–818.
De Santis, B., Brera, C., Mezzelani, A., Soricelli, S., Ciceri, F., Moretti, G., Debegnach, F., Bonaglia, M.C., Villa, L., Molteni, M., Raggi, M.E., 2017a. Role of mycotoxins in the pathobiology of autism: a first evidence. Nutr. Neurosci. 1–13.
De Santis, B., Raggi, M.E., Moretti, G., Facchiano, F., Mezzelani, A., Villa, L., Bonfanti, A., Campioni, A., Rossi, S., Camposeo, S., Soricelli, S., Moracci, G., Debegnach, F., Gregori, E., Ciceri, F., Milanesi, L., Marabotti, A., Brera, C., 2017b. Study on the association among mycotoxins and other variables in children with autism. Toxins 9.
De Schepper, S., Boucneau, J.M., Westbroek, W., Mommaas, M., Onderwater, J., Messiaen, L., Naeyaert, J.M., Lambert, J.L., 2006. Neurofibromatosis type 1 protein and amyloid precursor protein interact in normal human melanocytes and colocalize with melanosomes. J. Investig. Dermatol. 126, 653–659.
Deoni, S.C., Zinkstok, J.R., Daly, E., Ecker, C., Williams, S.C., Murphy, D.G., 2015. White-matter relaxation time and myelin water fraction differences in young adults with autism. Psychol. Med. 45, 795–805.
Devakumar, D., Bamford, A., Ferreira, M.U., Broad, J., Rosch, R.E., Groce, N., Breuer, J., Cardoso, M.A., Copp, A.J., Alexandre, P., Rodrigues, L.C., Abubakar, I., 2018. Infectious causes of microcephaly: epidemiology, pathogenesis, diagnosis, and management. Lancet Infect. Dis. 18, e1–e13.
Dong, D., Zielke, H.R., Yeh, D., Yang, P., 2018. Cellular stress and apoptosis contribute to the pathogenesis of autism spectrum disorder. Autism Res. 11, 1076–1090.
Doran, K.S., Banerjee, A., Disson, O., Lecuit, M., 2013a. Concepts and mechanisms: crossing host barriers. Cold Spring Harb. Perspect. Med. 3.
Doran, K.S., Banerjee, A., Disson, O., Lecuit, M., 2013b. Concepts and mechanisms: crossing host barriers. Cold Spring Harb. Perspect. Med. 3.
Doshi-Velez, F., Avillach, P., Palmer, N., Bousvaros, A., Ge, Y., Fox, K., Steinberg, G., Spettell, C., Juster, I., Kohane, I., 2015. Prevalence of inflammatory bowel disease among patients with autism spectrum disorders. Inflamm. Bowel Dis. 21, 2281–2288.

Doshi-Velez, F., Ge, Y., Kohane, I., 2014. Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis. Pediatrics 133, e54–e63.
Duplan, E., Sevalle, J., Viotti, J., Goiran, T., Bauer, C., Renbaum, P., Levy-Lahad, E., Gautier, C.A., Corti, O., Leroudier, N., Checler, F., da Costa, C.A., 2013. Parkin differently regulates presenilin-1 and presenilin-2 functions by direct control of their promoter transcription. J. Mol. Cell Biol. 5, 132–142.
Ebsen, H., Lettau, M., Kabelitz, D., Janssen, O., 2014. Identification of SH3 domain proteins interacting with the cytoplasmic tail of the a disintegrin and metalloprotease 10 (ADAM10). PLoS One 9, e102899.
Eisen, H.N., Orris, L., Belman, S., 1952. Elicitation of delayed allergic skin reactions with haptens; the dependence of elicitation on hapten combination with protein. J. Exp. Med. 95, 473–487.
El Kasmi, K.C., Holst, J., Coffre, M., Mielke, L., de Pauw, A., Lhocine, N., Smith, A.M., Rutschman, R., Kaushal, D., Shen, Y., Suda, T., Donnelly, R.P., Myers Jr., M.G., Alexander, W., Vignali, D.A., Watowich, S.S., Ernst, M., Hilton, D.J., Murray, P.J., 2006. General nature of the STAT3-activated anti-inflammatory response. J. Immunol. 177, 7880–7888.
Ellis, S.E., Panitch, R., West, A.B., Arking, D.E., 2016. Transcriptome analysis of cortical tissue reveals shared sets of downregulated genes in autism and schizophrenia. Transl. Psychiatry 6, e817.
Enk, C.D., Jacob-Hirsch, J., Gal, H., Verbovetski, I., Amariglio, N., Mevorach, D., Ingber, A., Givol, D., Rechavi, G., Hochberg, M., 2006. The UVB-induced gene expression profile of human epidermis in vivo is different from that of cultured keratinocytes. Oncogene 25, 2601–2614.
Erickson, C.A., Ray, B., Maloney, B., Wink, L.K., Bowers, K., Schaefer, T.L., McDougle, C.J., Sokol, D.K., Lahiri, D.K., 2014. Impact of acamprosate on plasma amyloid-beta precursor protein in youth: a pilot analysis in fragile X syndrome-associated and idiopathic autism spectrum disorder suggests a pharmacodynamic protein marker. J. Psychiatr. Res. 59, 220–228.
Erickson, C.A., Wink, L.K., Baindu, B., Ray, B., Schaefer, T.L., Pedapati, E.V., Lahiri, D.K., 2016. Analysis of peripheral amyloid precursor protein in Angelman Syndrome. Am. J. Med. Genet. 170, 2334–2337.
Faber, T.W., Pullen, N.A., Fernando, J.F., Kolawole, E.M., McLeod, J.J., Taruselli, M., Williams, K.L., Rivera, K.O., Barnstein, B.O., Conrad, D.H., Ryan, J.J., 2014. ADAM10 is required for SCF-induced mast cell migration. Cell. Immunol. 290, 80–88.
Fang, S.Y., Wang, S., Huang, N., Yeh, H.H., Chen, C.Y., 2015. Prenatal infection and autism spectrum disorders in childhood: a population-based case-control study in taiwan. Paediatr. Perinat. Epidemiol. 29, 307–316.
Fatemi, S.H., Earle, J., Kanodia, R., Kist, D., Emamian, E.S., Patterson, P.H., Shi, L., Sidwell, R., 2002. Prenatal viral infection leads to pyramidal cell atrophy and macrocephaly in adulthood: implications for genesis of autism and schizophrenia. Cell. Mol. Neurobiol. 22, 25–33.
Fatemi, S.H., Folsom, T.D., Liesch, S.B., Kneeland, R.E., Karkhane, Y.M., Thuras, P.D., 2016. The effects of prenatal H1N1 infection at E16 on FMRP, glutamate, GABA, and reelin signaling systems in developing murine cerebellum. J. Neurosci. Res.
Fatemi, S.H., Pearce, D.A., Brooks, A.I., Sidwell, R.W., 2005. Prenatal viral infection in mouse causes differential expression of genes in brains of mouse progeny: a potential animal model for schizophrenia and autism. Synapse 57, 91–99.
Fatemi, S.H., Reutiman, T.J., Folsom, T.D., Huang, H., Oishi, K., Mori, S., Smee, D.F., Pearce, D.A., Winter, C., Sohr, R., Juckel, G., 2008. Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: implications for genesis of neurodevelopmental disorders. Schizophr. Res. 99, 56–70.
Favila, M.A., Geraci, N.S., Zeng, E., Harker, B., Condon, D., Cotton, R.N., Jayakumar, A., Tripathi, V., McDowell, M.A., 2014. Human dendritic cells exhibit a pronounced type I IFN signature following Leishmania major infection that is required for IL-12 induction. J. Immunol. 192, 5863–5872.
Fernandez, d. C., Guzman, A., van, d., V., Luheshi, G.N., 2016. Prenatal infection leads to ASD-like behavior and altered synaptic pruning in the mouse offspring. Brain Behav. Immun.
Fiorentino, M., Sapone, A., Senger, S., Camhi, S.S., Kadzielski, S.M., Buie, T.M., Kelly, D.L., Cascella, N., Fasano, A., 2016. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. Mol. Autism. 7, 49.
Flint, S.J., Enquist, L.W., Racaniello, V.R., Skalka, A.M., 2008. Principles of Virology. ASM Press, Herndon. VA.
Frabutt, D.A., Zheng, Y.H., 2016. Arms race between enveloped viruses and the host ERAD machinery. Viruses 8.
Fronsdal, K., Engedal, N., Slagsvold, T., Saatcioglu, F., 1998. CREB binding protein is a coactivator for the androgen receptor and mediates cross-talk with AP-1. J. Biol. Chem. 273, 31853–31859.
Fu, W., Sanders-Beer, B.E., Katz, K.S., Maglott, D.R., Pruitt, K.D., Ptak, R.G., 2009. Human immunodeficiency virus type 1, human protein interaction database at NCBI. Nucleic Acids Res. 37, D417–D422.
Fujita-Jimbo, E., Yu, Z.L., Li, H., Yamagata, T., Mori, M., Momoi, T., Momoi, M.Y., 2012. Mutation in Parkinson disease-associated, G-protein-coupled receptor 37 (GPR37/PaelR) is related to autism spectrum disorder. PLoS One 7, e51155.
Fujita, E., Dai, H., Tanabe, Y., Zhiling, Y., Yamagata, T., Miyakawa, T., Tanokura, M., Momoi, M.Y., Momoi, T., 2010. Autism spectrum disorder is related to endoplasmic reticulum stress induced by mutations in the synaptic cell adhesion molecule, CADM1. Cell Death Dis. 1, e47.
Futch, H.S., Croft, C.L., Truong, V.Q., Krause, E.G., Golde, T.E., 2017. Targeting psychologic stress signaling pathways in Alzheimer's disease. Mol. Neurodegener. 12, 49.
Gentile, I., Zappulo, E., Bonavolta, R., Maresca, R., Riccio, M.P., Buonomo, A.R., Portella, G., Settimi, A., Pascotto, A., Borgia, G., Bravaccio, C., 2014. Exposure to Varicella Zoster Virus is higher in children with autism spectrum disorder than in healthy controls. Results from a case-control study. In Vivo 28, 627–631.
Gesundheit, B., Rosenzweig, J.P., Naor, D., Lerer, B., Zachor, D.A., Prochazka, V., Melamed, M., Kristt, D.A., Steinberg, A., Shulman, C., Hwang, P., Koren, G., Walfisch, A., Passweg, J.R., Snowden, J.A., Tamouza, R., Leboyer, M., Farge-Bancel, D., Ashwood, P., 2013. Immunological and autoimmune considerations of autism spectrum disorders. J. Autoimmun. 44, 1–7.
Giulivi, C., Zhang, Y.F., Omanska-Klusek, A., Ross-Inta, C., Wong, S., Hertz-Picciotto, I., Tassone, F., Pessah, I.N., 2010. Mitochondrial dysfunction in autism. J. Am. Med. Assoc. 304, 2389–2396.
Goodenough, S., Engert, S., Behl, C., 2000. Testosterone stimulates rapid secretory amyloid precursor protein release from rat hypothalamic cells via the activation of the mitogen-activated protein kinase pathway. Neurosci. Lett. 296, 49–52.
Goodman, A.B., 1994. A family history study of schizophrenia spectrum disorders suggests new candidate genes in schizophrenia and autism. Psychiatr. Q. 65, 287–297.
Gore, A.C., Martien, K.M., Gagnidze, K., Pfaff, D., 2014. Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. Endocr. Rev. 35, 961–991.
Gottfried, C., Bambini-Junior, V., Francis, F., Riesgo, R., Savino, W., 2015. The impact of neuroimmune alterations in autism spectrum disorder. Front. Psychiatry 6, 121.
Gozzi, M., Nielson, D.M., Lenroot, R.K., Ostuni, J.L., Luckenbaugh, D.A., Thurm, A.E., Giedd, J.N., Swedo, S.E., 2012. A magnetization transfer imaging study of corpus callosum myelination in young children with autism. Biol. Psychiatry 72, 215–220.
Grimm, M.O., Haupenthal, V.J., Rothhaar, T.L., Zimmer, V.C., Grosgen, S., Hundsdorfer, B., Lehmann, J., Grimm, H.S., Hartmann, T., 2013. Effect of Different Phospholipids on alpha-Secretase Activity in the Non-Amyloidogenic Pathway of Alzheimer's Disease. Int. J. Mol. Sci. 14, 5879–5898.
Grandjean, P., Landrigan, P.J., 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 13, 330–338.
Grether, J.K., Ashwood, P., Van de, W.J., Yolken, R.H., Anderson, M.C., Torres, A.R., Westover, J.B., Sweeten, T., Hansen, R.L., Kharrazi, M., Croen, L.A., 2016. Prenatal and newborn immunoglobulin levels from mother-child pairs and risk of autism spectrum disorders. Front. Neurosci. 10, 218.
Gulbahce, N., Yan, H., Dricot, A., Padi, M., Byrdsong, D., Franchi, R., Lee, D.S., Rozenblatt-Rosen, O., Mar, J.C., Calderwood, M.A., Baldwin, A., Zhao, B., Santhanam, B., Braun, P., Simonis, N., Huh, K.W., Hellner, K., Grace, M., Chen, A., Rubio, R., Marto, J.A., Christakis, N.A., Kieff, E., Roth, F.P., Roecklein-Canfield, J., Decaprio, J.A., Cusick, M.E., Quackenbush, J., Hill, D.E., Munger, K., Vidal, M., Barabasi, A.L., 2012. Viral perturbations of host networks reflect disease etiology. PLoS Comput. Biol., e1002531. https://doi.org/10.1371/journal.pcbi.1002531. Epub 2012 Jun 28.
Guo, Q., Robinson, N., Mattson, M.P., 1998. Secreted beta-amyloid precursor protein counteracts the proapoptotic action of mutant presenilin-1 by activation of NF-kappaB and stabilization of calcium homeostasis. J. Biol. Chem. 273, 12341–12351.
Gupta, S., Ellis, S.E., Ashar, F.N., Moes, A., Bader, J.S., Zhan, J., West, A.B., Arking, D.E., 2014. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nat. Commun. 5, 5748.
Hale, J.S., Youngblood, B., Latner, D.R., Mohammed, A.U., Ye, L., Akondy, R.S., Wu, T., Iyer, S.S., Ahmed, R., 2013. Distinct memory CD4+ T cells with commitment to T follicular helper- and T helper 1-cell lineages are generated after acute viral infection. Immunity 38, 805–817.
Harvey, L., Boksa, P., 2012. Prenatal and postnatal animal models of immune activation: relevance to a range of neurodevelopmental disorders. Dev Neurobiol 72, 1335–1348.
Hesse, R., von Einem, B., Wagner, F., Bott, P., Schwanzar, D., Jackson, R.J., Fohr, K.J., Lausser, L., Kroker, K.S., Proepper, C., Walther, P., Kestler, H.A., Spires-Jones, T.L., Boeckers, T., Rosenbrock, H., von Arnim, C.A.F., 2018. sAPPbeta and sAPPalpha increase structural complexity and E/I input ratio in primary hippocampal neurons and alter Ca(2+) homeostasis and CREB1-signaling. Exp. Neurol. 304, 1–13.
Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., Bolte, S., 2016. Premature mortality in autism spectrum disorder. Br. J. Psychiatr. 208, 232–238.
Hoey, S.E., Buonocore, F., Cox, C.J., Hammond, V.J., Perkinton, M.S., Williams, R.J., 2013. AMPA receptor activation promotes non-amyloidogenic amyloid precursor protein processing and suppresses neuronal amyloid-beta production. PLoS One 8, e78155.
Holmes, O., Paturi, S., Ye, W., Wolfe, M.S., Selkoe, D.J., 2012. Effects of membrane lipids on the activity and processivity of purified gamma-secretase. Biochemistry 51, 3565–3575.
Hornig, M., Briese, T., Lipkin, W.I., 2001a. Bornavirus tropism and targeted pathogenesis: virus-host interactions in a neurodevelopmental model. Adv. Virus Res. 56, 557–582.
Hornig, M., Solbrig, M., Horscroft, N., Weissenbock, H., Lipkin, W.I., 2001b. Borna disease virus infection of adult and neonatal rats: models for neuropsychiatric disease. Curr. Top. Microbiol. Immunol. 253, 157–177.
Hughes, H.K., Ashwood, P., 2018. Anti-Candida albicans IgG antibodies in children with autism spectrum disorders. Front. Psychiatry 9, 627.
Hutcheson, J., Scatizzi, J.C., Siddiqui, A.M., Haines, G.K., Wu III, T., Li, Q.Z., Davis, L.S., Mohan, C., Perlman, H., 2008. Combined deficiency of proapoptotic regulators Bim and Fas results in the early onset of systemic autoimmunity. Immunity 28, 206–217.
Iannacone, M., 2016. Platelet-mediated modulation of adaptive immunity. Semin. Immunol.
Ioannidis, I., McNally, B., Willette, M., Peeples, M.E., Chaussabel, D., Durbin, J.E., Ramilo, O., Mejias, A., Flano, E., 2012. Plasticity and virus specificity of the airway epithelial cell immune response during respiratory virus infection. J. Virol. 86, 5422–5436.
Itzhaki, R.F., Lathe, R., Balin, B.J., Ball, M.J., Bearer, E.L., Braak, H., Bullido, M.J., Carter, C., Clerici, M., Cosby, S.L., Del Tredici, K., Field, H., Fulop, T., Grassi, C., Griffin, W.S., Haas, J., Hudson, A.P., Kamer, A.R., Kell, D.B., Licastro, F., Letenneur, L., Lovheim, H., Mancuso, R., Miklossy, J., Otth, C., Palamara, A.T., Perry, G., Preston,

C., Pretorius, E., Strandberg, T., Tabet, N., Taylor-Robinson, S.D., Whittum-Hudson, J.A., 2016. Microbes and alzheimer's disease. J. Alzheimer's Dis. 51, 979–984.
Jacobsen, K.T., Adlerz, L., Multhaup, G., Iverfeldt, K., 2010. Insulin-like growth factor-1 (IGF-1)-induced processing of amyloid-beta precursor protein (APP) and APP-like protein 2 is mediated by different metalloproteinases. J. Biol. Chem. 285, 10223–10231.
Jimenez, S., Torres, M., Vizuete, M., Sanchez-Varo, R., Sanchez-Mejias, E., Trujillo-Estrada, L., Carmona-Cuenca, I., Caballero, C., Ruano, D., Gutierrez, A., Vitorica, J., 2011. Age-dependent accumulation of soluble amyloid beta (Abeta) oligomers reverses the neuroprotective effect of soluble amyloid precursor protein-alpha (sAPP (alpha)) by modulating phosphatidylinositol 3-kinase (PI3K)/Akt-GSK-3beta pathway in Alzheimer mouse model. J. Biol. Chem. 286, 18414–18425.
Joseph, R.M., Korzeniewski, S.J., Allred, E.N., O'Shea, T.M., Heeren, T., Frazier, J.A., Ware, J., Hirtz, D., Leviton, A., Kuban, K., 2017. Extremely low gestational age and very low birthweight for gestational age are risk factors for autism spectrum disorder in a large cohort study of 10-year-old children born at 23-27 weeks' gestation. Am. J. Obstet. Gynecol. 216, 304.
Jung, M.Y., Smrz, D., Desai, A., Bandara, G., Ito, T., Iwaki, S., Kang, J.H., Andrade, M.V., Hilderbrand, S.C., Brown, J.M., Beaven, M.A., Metcalfe, D.D., Gilfillan, A.M., 2013. IL-33 induces a hyporesponsive phenotype in human and mouse mast cells. J. Immunol. 190, 531–538.
Jurecka, A., Zikanova, M., Kmoch, S., Tylki-Szymanska, A., 2015. Adenylosuccinate lyase deficiency. J. Inherit. Metab. Dis. 38, 231–242.
Ka, M., Kim, W.Y., 2018. ANKRD11 associated with intellectual disability and autism regulates dendrite differentiation via the BDNF/TrkB signaling pathway. Neurobiol. Dis. 111, 138–152.
Kado, S., Chang, W.L., Chi, A.N., Wolny, M., Shepherd, D.M., Vogel, C.F., 2016. Aryl hydrocarbon receptor signaling modifies Toll-like receptor-regulated responses in human dendritic cells. Arch. Toxicol.
Kaech, S.M., Hemby, S., Kersh, E., Ahmed, R., 2002. Molecular and functional profiling of memory CD8 T cell differentiation. Cell 111, 837–851.
Kaizer, E.C., Glaser, C.L., Chaussabel, D., Banchereau, J., Pascual, V., White, P.C., 2007. Gene expression in peripheral blood mononuclear cells from children with diabetes. J. Clin. Endocrinol. Metab. 92, 3705–3711.
Kajta, M., Wojtowicz, A., 2010. Neurodevelopmental disorders in response to hormonally active environmental pollutants. Przegl. Lek. 67, 1194–1199.
Kajta, M., Wojtowicz, A.K., 2013. Impact of endocrine-disrupting chemicals on neural development and the onset of neurological disorders. Pharmacol. Rep. 65, 1632–1639.
Kalkbrenner, A.E., Schmidt, R.J., Penlesky, A.C., 2014. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Curr. Probl. Pediatr. Adolesc. Health Care.
Kaluzna-Czaplinska, J., Blaszczyk, S., 2012. The level of arabinitol in autistic children after probiotic therapy. Nutrition 28, 124–126.
Kamburov, A., Pentchev, K., Galicka, H., Wierling, C., Lehrach, H., Herwig, R., 2011. ConsensusPathDB: toward a more complete picture of cell biology. Nucleic Acids Res. 39, D712–D717.
Karyala, P., Metri, R., Bathula, C., Yelamanchi, S.K., Sahoo, L., Arjunan, S., Sastri, N.P., Chandra, N., 2016. DenHunt - a comprehensive database of the intricate network of dengue-human interactions. PLoS Neglected Trop. Dis. 10, e0004965.
Kealy, J., Greene, C., Campbell, M., 2018. Blood-brain barrier regulation in psychiatric disorders. Neurosci. Lett.
Kirsten, T.B., Chaves-Kirsten, G.P., Chaible, L.M., Silva, A.C., Martins, D.O., Britto, L.R., Dagli, M.L., Torrao, A.S., Palermo-Neto, J., Bernardi, M.M., 2012. Hypoactivity of the central dopaminergic system and autistic-like behavior induced by a single early prenatal exposure to lipopolysaccharide. J. Neurosci. Res. 90, 1903–1912.
Kohler-Forsberg, O., Petersen, L., Gasse, C., Mortensen, P.B., Dalsgaard, S., Yolken, R.H., Mors, O., Benros, M.E., 2018. A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. JAMA Psychiatr.
Kuhn, P.H., Colombo, A.V., Schusser, B., Dreymueller, D., Wetzel, S., Schepers, U., Herber, J., Ludwig, A., Kremmer, E., Montag, D., Muller, U., Schweizer, M., Saftig, P., Brase, S., Lichtenthaler, S.F., 2016. Systematic substrate identification indicates a central role for the metalloprotease ADAM10 in axon targeting and synapse function. Elife 5.
Kumar, D.K., Choi, S.H., Washicosky, K.J., Eimer, W.A., Tucker, S., Ghofrani, J., Lefkowitz, A., McColl, G., Goldstein, L.E., Tanzi, R.E., Moir, R.D., 2016. Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci. Transl. Med. 8 340ra72.
Kuo, L.H., Hu, M.K., Hsu, W.M., Tung, Y.T., Wang, B.J., Tsai, W.W., Yen, C.T., Liao, Y.F., 2008. Tumor necrosis factor-alpha-elicited stimulation of gamma-secretase is mediated by c-Jun N-terminal kinase-dependent phosphorylation of presenilin and nicastrin. Mol. Biol. Cell 19, 4201–4212.
Kwak, Y.D., Dantuma, E., Merchant, S., Bushnev, S., Sugaya, K., 2010. Amyloid-beta precursor protein induces glial differentiation of neural progenitor cells by activation of the IL-6/gp130 signaling pathway. Neurotox. Res. 18, 328–338.
Kwak, Y.D., Hendrix, B.J., Sugaya, K., 2014. Secreted type of amyloid precursor protein induces glial differentiation by stimulating the BMP/Smad signaling pathway. Biochem. Biophys. Res. Commun. 447, 394–399.
Labouesse, M.A., Langhans, W., Meyer, U., 2015. Long-term pathological consequences of prenatal infection: beyond brain disorders. Am. J. Physiol. Regul. Integr. Comp. Physiol. 309, R1–R12.
Lancaster, K., Dietz, D.M., Moran, T.H., Pletnikov, M.V., 2007. Abnormal social behaviors in young and adult rats neonatally infected with Borna disease virus. Behav. Brain Res. 176, 141–148.
Le Belle, J.E., Sperry, J., Ngo, A., Ghochani, Y., Laks, D.R., Lopez-Aranda, M., Silva, A.J., Kornblum, H.I., 2014. Maternal inflammation contributes to brain overgrowth and autism-associated behaviors through altered redox signaling in stem and progenitor cells. Stem Cell Rep. 3, 725–734.
Lee, B.K., Magnusson, C., Gardner, R.M., Blomstrom, A., Newschaffer, C.J., Burstyn, I., Karlsson, H., Dalman, C., 2015. Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav. Immun. 44, 100–105.
Lee, J.H., Wittki, S., Brau, T., Dreyer, F.S., Kratzel, K., Dindorf, J., Johnston, I.C., Gross, S., Kremmer, E., Zeidler, R., Schlotzer-Schrehardt, U., Lichtenheld, M., Saksela, K., Harrer, T., Schuler, G., Federico, M., Baur, A.S., 2013. HIV Nef, paxillin, and Pak1/2 regulate activation and secretion of TACE/ADAM10 proteases. Mol. Cell 49, 668–679.
Levoye, A., Dam, J., Ayoub, M.A., Guillaume, J.L., Couturier, C., Delagrange, P., Jockers, R., 2006. The orphan GPR50 receptor specifically inhibits MT1 melatonin receptor function through heterodimerization. EMBO J. 25, 3012–3023.
Li, J., Wang, L., Guo, H., Shi, L., Zhang, K., Tang, M., Hu, S., Dong, S., Liu, Y., Wang, T., Yu, P., He, X., Hu, Z., Zhao, J., Liu, C., Sun, Z.S., Xia, K., 2017. Targeted sequencing and functional analysis reveal brain-size-related genes and their networks in autism spectrum disorders. Mol. Psychiatr. 22, 1282–1290.
Li, M.J., Wang, P., Liu, X., Lim, E.L., Wang, Z., Yeager, M., Wong, M.P., Sham, P.C., Chanock, S.J., Wang, J., 2012. GWASdb: a database for human genetic variants identified by genome-wide association studies. Nucleic Acids Res. 40, D1047–D1054.
Libbey, J.E., Fujinami, R.S., 2010. Role for antibodies in altering behavior and movement. Autism Res. 3, 147–152.
Liberzon, A., Birger, C., Thorvaldsdottir, H., Ghandi, M., Mesirov, J.P., Tamayo, P., 2015a. The Molecular Signatures Database (MSigDB) hallmark gene set collection. Cell Syst 1, 417–425.
Liberzon, A., Birger, C., Thorvaldsdottir, H., Ghandi, M., Mesirov, J.P., Tamayo, P., 2015b. The Molecular Signatures Database (MSigDB) hallmark gene set collection. Cell Syst 1, 417–425.
Lintas, C., Altieri, L., Lombardi, F., Sacco, R., Persico, A.M., 2010. Association of autism with polyomavirus infection in postmortem brains. J. Neurovirol. 16, 141–149.
Liu, F., Su, Y., Li, B., Ni, B., 2003. Regulation of amyloid precursor protein expression and secretion via activation of ERK1/2 by hepatocyte growth factor in HEK293 cells transfected with APP751. Exp. Cell Res. 287, 387–396.
Llufriu-Daben, G., Carrete, A., Chierto, E., Mailleux, J., Camand, E., Simon, A., Vanmierlo, T., Rose, C., Allinquant, B., Hendriks, J.J.A., Massaad, C., Meffre, D., Jafarian-Tehrani, M., 2018. Targeting demyelination via alpha-secretases promoting sAPPalpha release to enhance remyelination in central nervous system. Neurobiol. Dis. 109, 11–24.
MacPherson, R.E.K., 2017. Filling the void: a role for exercise-induced BDNF and brain amyloid precursor protein processing. Am. J. Physiol. Regul. Integr. Comp. Physiol. 313, R585–R593.
Mahic, M., Che, X., Susser, E., Levin, B., Reichborn-Kjennerud, T., Magnus, P., Stoltenberg, C., Chauhan, L., Briese, T., Bresnahan, M., Suren, P., Hornig, M., Mjaaland, S., Lipkin, W.I., 2017. Epidemiological and serological investigation into the role of gestational maternal influenza virus infection and autism spectrum disorders. mSphere 2.
Mankoski, R.E., Collins, M., Ndosi, N.K., Mgalla, E.H., Sarwatt, V.V., Folstein, S.E., 2006. Etiologies of autism in a case-series from Tanzania. J. Autism Dev. Disord. 36, 1039–1051.
Marcade, M., Bourdin, J., Loiseau, N., Peillon, H., Rayer, A., Drouin, D., Schweighoffer, F., Desire, L., 2008. Etazolate, a neuroprotective drug linking GABA(A) receptor pharmacology to amyloid precursor protein processing. J. Neurochem. 106, 392–404.
Mari, F., Azimonti, S., Bertani, I., Bolognese, F., Colombo, E., Caselli, R., Scala, E., Longo, I., Grosso, S., Pescucci, C., Ariani, F., Hayek, G., Balestri, P., Bergo, A., Badaracco, G., Zappella, M., Broccoli, V., Renieri, A., Kilstrup-Nielsen, C., Landsberger, N., 2005. CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome. Hum. Mol. Genet. 14, 1935–1946.
Marolda, R., Ciotti, M.T., Matrone, C., Possenti, R., Calissano, P., Cavallaro, S., Severini, C., 2012. Substance P activates ADAM9 mRNA expression and induces alpha-secretase-mediated amyloid precursor protein cleavage. Neuropharmacology 62, 1954–1963.
Marwarha, G., Raza, S., Meiers, C., Ghribi, O., 2014. Leptin attenuates BACE1 expression and amyloid-beta genesis via the activation of SIRT1 signaling pathway. Biochim. Biophys. Acta 1842, 1587–1595.
Matsuda, S., Matsuda, Y., D'Adamio, L., 2003. Amyloid beta protein precursor (AbetaPP), but not AbetaPP-like protein 2, is bridged to the kinesin light chain by the scaffold protein JNK-interacting protein 1. J. Biol. Chem. 278, 38601–38606.
Mazina, V., Gerdts, J., Trinh, S., Ankenman, K., Ward, T., Dennis, M.Y., Girirajan, S., Eichler, E.E., Bernier, R., 2015. Epigenetics of autism-related impairment: copy number variation and maternal infection. J. Dev. Behav. Pediatr. 36, 61–67.
McDermott, J.R., Gibson, A.M., 1996. Degradation of Alzheimer's beta-amyloid protein by human cathepsin D. Neuroreport 7, 2163–2166.
Metz-Boutigue, M.H., Shooshtarizadeh, P., Prevost, G., Haikel, Y., Chich, J.F., 2010. Antimicrobial peptides present in mammalian skin and gut are multifunctional defence molecules. Curr. Pharmaceut. Des. 16, 1024–1039.
Metz, V.V., Kojro, E., Rat, D., Postina, R., 2012. Induction of RAGE shedding by activation of G protein-coupled receptors. PLoS One 7, e41823.
Mezyk-Kopec, R., Bzowska, M., Stalinska, K., Chelmicki, T., Podkalicki, M., Jucha, J., Kowalczyk, K., Mak, P., Bereta, J., 2009. Identification of ADAM10 as a major TNF sheddase in ADAM17-deficient fibroblasts. Cytokine 46, 309–315.
Miller, C.C., McLoughlin, D.M., Lau, K.F., Tennant, M.E., Rogelj, B., 2006. The X11 proteins, Abeta production and Alzheimer's disease. Trends Neurosci. 29, 280–285.
Miyazawa, M., Takashima, A., 2012. Development and validation of a new in vitro assay designed to measure contact allergen-triggered oxidative stress in dendritic cells. J. Dermatol. Sci. 68, 73–81.

Modabbernia, A., Velthorst, E., Reichenberg, A., 2017. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol. Autism. 8, 13.
Mora, M., Quintero, L., Cardenas, R., Suarez-Roca, H., Zavala, M., Montiel, N., 2009. Association between HSV-2 infection and serum anti-rat brain antibodies in patients with autism. Investig. Clin. 50, 315–326.
Moscovis, S.M., Gordon, A.E., Al Madani, O.M., Gleeson, M., Scott, R.J., Hall, S.T., Burns, C., Blackwell, C., 2015. Virus infections and sudden death in infancy: the role of interferon-gamma. Front. Immunol. 6, 107.
Mostafalou, S., Abdollahi, M., 2013. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicol. Appl. Pharmacol. 268, 157–177.
Muller-Nordhorn, J., Hettler-Chen, C.M., Keil, T., Muckelbauer, R., 2015. Association between sudden infant death syndrome and diphtheria-tetanus-pertussis immunisation: an ecological study. BMC Pediatr. 15, 1.
Mullins, N., Ingason, A., Porter, H., Euesden, J., Gillett, A., Olafsson, S., Gudbjartsson, D.F., Lewis, C.M., Sigurdsson, E., Saemundsen, E., Gudmundsson, O.O., Frigge, M.L., Kong, A., Helgason, A., Walters, G.B., Gustafsson, O., Stefansson, H., Stefansson, K., 2017. Reproductive fitness and genetic risk of psychiatric disorders in the general population. Nat. Commun. 8, 15833.
Muresan, V., Ladescu, M.Z., 2015. Amyloid-beta precursor protein: multiple fragments, numerous transport routes and mechanisms. Exp. Cell Res. 334, 45–53.
Nagar, M., Jacob-Hirsch, J., Vernitsky, H., Berkun, Y., Ben Horin, S., Amariglio, N., Bank, I., Kloog, Y., Rechavi, G., Goldstein, I., 2010. TNF activates a NF-kappaB-regulated cellular program in human CD. J. Immunol. 184, 3570–3581.
Napoli, E., Wong, S., Giulivi, C., 2013. Evidence of reactive oxygen species-mediated damage to mitochondrial DNA in children with typical autism. Mol. Autism. 4, 2.
Napoli, E., Wong, S., Hertz-Picciotto, I., Giulivi, C., 2014. Deficits in bioenergetics and impaired immune response in granulocytes from children with autism. Pediatrics.
Napolitani, G., Rinaldi, A., Bertoni, F., Sallusto, F., Lanzavecchia, A., 2005. Selected Toll-like receptor agonist combinations synergistically trigger a T helper type 1-polarizing program in dendritic cells. Nat. Immunol. 6, 769–776.
Nazeen, S., Palmer, N.P., Berger, B., Kohane, I.S., 2016. Integrative analysis of genetic data sets reveals a shared innate immune component in autism spectrum disorder and its co-morbidities. Genome Biol. 17, 228.
Nelson, T.H., Jung, J.Y., Deluca, T.F., Hinebaugh, B.K., St Gabriel, K.C., Wall, D.P., 2012. Autworks: a cross-disease network biology application for Autism and related disorders. BMC Med. Genomics 5, 56.
Nesic, I., Guix, F.X., Vennekens, K., Michaki, V., Van Veldhoven, P.P., Feiguin, F., De Strooper, B., Dotti, C.G., Wahle, T., 2012. Alterations in phosphatidylethanolamine levels affect the generation of Abeta. Aging Cell 11, 63–72.
Ngo, H.M., Zhou, Y., Lorenzi, H., Wang, K., Kim, T.K., Zhou, Y., Bissati, K.E., Mui, E., Fraczek, L., Rajagopala, S.V., Roberts, C.W., Henriquez, F.L., Montpetit, A., Blackwell, J.M., Jamieson, S.E., Wheeler, K., Begeman, I.J., Naranjo-Galvis, C., Alliey-Rodriguez, N., Davis, R.G., Soroceanu, L., Cobbs, C., Steindler, D.A., Boyer, K., Noble, A.G., Swisher, C.N., Heydemann, P.T., Rabiah, P., Withers, S., Soteropoulos, P., Hood, L., McLeod, R., 2017. Toxoplasma modulates signature pathways of human epilepsy, neurodegeneration & cancer. Sci. Rep. 7, 11496.
Nicolson, G.L., Gan, R., Nicolson, N.L., Haier, J., 2007. Evidence for Mycoplasma ssp., Chlamydia pneunomiae, and human herpes virus-6 coinfections in the blood of patients with autistic spectrum disorders. J. Neurosci. Res. 85, 1143–1148.
Niedowicz, D.M., Studzinski, C.M., Weidner, A.M., Platt, T.L., Kingry, K.N., Beckett, T.L., Bruce-Keller, A.J., Keller, J.N., Murphy, M.P., 2013. Leptin regulates amyloid beta production via the gamma-secretase complex. Biochim. Biophys. Acta 1832, 439–444.
Nigam, S.M., Xu, S., Kritikou, J.S., Marosi, K., Brodin, L., Mattson, M.P., 2017. Exercise and BDNF reduce Abeta production by enhancing alpha-secretase processing of APP. J. Neurochem. 142, 286–296.
Nitsch, R.M., Deng, M., Growdon, J.H., Wurtman, R.J., 1996. Serotonin 5-HT2a and 5-HT2c receptors stimulate amyloid precursor protein ectodomain secretion. J. Biol. Chem. 271, 4188–4194.
Nitsch, R.M., Kim, C., Growdon, J.H., 1998. Vasopressin and bradykinin regulate secretory processing of the amyloid protein precursor of Alzheimer's disease. Neurochem. Res. 23, 807–814.
Ortiz, R.M., Karkkainen, I., Huovila, A.P., Honkaniemi, J., 2005. ADAM9, ADAM10, and ADAM15 mRNA levels in the rat brain after kainic acid-induced status epilepticus. Brain Res. Mol. Brain Res. 137, 272–275.
Oswald, F., Kloble, P., Ruland, A., Rosenkranz, D., Hinz, B., Butter, F., Ramljak, S., Zechner, U., Herlyn, H., 2017. The FOXP2-driven network in developmental disorders and neurodegeneration. Front. Cell. Neurosci. 11, 212.
Ourdev, D., Schmaus, A., Kar, S., 2018. Kainate receptor activation enhances amyloidogenic processing of APP in astrocytes. Mol. Neurobiol.
Padro, C.J., Shawler, T.M., Gormley, M.G., Sanders, V.M., 2013. Adrenergic regulation of IgE involves modulation of CD23 and ADAM10 expression on exosomes. J. Immunol. 191, 5383–5397.
Pallapies, D., 2006. Trends in childhood disease. Mutat. Res. 608, 100–111.
Pang, Y., Dai, X., Roller, A., Carter, K., Paul, I., Bhatt, A.J., Lin, R.C., Fan, L.W., 2016. Early postnatal lipopolysaccharide exposure leads to enhanced neurogenesis and impaired communicative functions in rats. PLoS One 11, e0164403.
Panmanee, J., Nopparat, C., Chavanich, N., Shukla, M., Mukda, S., Song, W., Vincent, B., Govitrapong, P., 2015. Melatonin regulates the transcription of betaAPP-cleaving secretases mediated through melatonin receptors in human neuroblastoma SH-SY5Y cells. J. Pineal Res. 59, 308–320.
Park, J.H., Jeong, D.Y., Peyrin-Biroulet, L., Eisenhut, M., Shin, J.I., 2016. Insight into the role of TSLP in inflammatory bowel diseases. Autoimmun. Rev.
Pasciuto, E., Ahmed, T., Wahle, T., Gardoni, F., D'Andrea, L., Pacini, L., Jacquemont, S., Tassone, F., Balschun, D., Dotti, C.G., Callaerts-Vegh, Z., D'Hooge, R., Muller, U.C., Di Luca, M., De Strooper, B., Bagni, C., 2015. Dysregulated ADAM10-mediated processing of APP during a critical time window leads to synaptic deficits in fragile X syndrome. Neuron 87, 382–398.
Pathan, M., Keerthikumar, S., Ang, C.S., Gangoda, L., Quek, C.Y., Williamson, N.A., Mouradov, D., Sieber, O.M., Simpson, R.J., Salim, A., Bacic, A., Hill, A.F., Stroud, D.A., Ryan, M.T., Agbinya, J.I., Mariadason, J.M., Burgess, A.W., Mathivanan, S., 2015. FunRich: an open access standalone functional enrichment and interaction network analysis tool. Proteomics 15, 2597–2601.
Patriarchi, T., Qian, H., Di, B.,V., Malik, Z.A., Chowdhury, D., Price, J.L., Hammes, E.A., Buonarati, O.R., Westenbroek, R.E., Catterall, W.A., Hofmann, F., Xiang, Y.K., Murphy, G.G., Chen, C.Y., Navedo, M.F., Hell, J.W., 2016. Phosphorylation of Cav1.2 on S1928 uncouples the L-type Ca2+ channel from the beta2 adrenergic receptor. EMBO J. 35, 1330–1345.
Patterson, P.H., 2011. Maternal infection and immune involvement in autism. Trends Mol. Med. 17, 389–394.
Peron, R., Vatanabe, I.P., Manzine, P.R., Camins, A., Cominetti, M.R., 2018. Alpha-secretase ADAM10 regulation: insights into alzheimer's disease treatment. Pharmaceuticals 11.
Peropadre, A., Fernandez, F.P., Perez Martin, J.M., Herrero, O., Hazen, M.J., 2015. Endoplasmic reticulum stress as a novel cellular response to di (2-ethylhexyl) phthalate exposure. Toxicol. Vitro 30, 281–287.
Pimenova, A.A., Thathiah, A., De Strooper, B., Tesseur, I., 2014. Regulation of amyloid precursor protein processing by serotonin signaling. PLoS One 9, e87014.
Pletnikov, M.V., Rubin, S.A., Moran, T.H., Carbone, K.M., 2003. Exploring the cerebellum with a new tool: neonatal Borna disease virus (BDV) infection of the rat's brain. Cerebellum 2, 62–70.
Pletnikov, M.V., Rubin, S.A., Vasudevan, K., Moran, T.H., Carbone, K.M., 1999. Developmental brain injury associated with abnormal play behavior in neonatally Borna disease virus-infected Lewis rats: a model of autism. Behav. Brain Res. 100, 43–50.
Polo-Kantola, P., Lampi, K.M., Hinkka-Yli-Salomaki, S., Gissler, M., Brown, A.S., Sourander, A., 2014. Obstetric risk factors and autism spectrum disorders in Finland. J. Pediatr. 164, 358–365.
Power, R.A., Kyaga, S., Uher, R., MacCabe, J.H., Langstrom, N., Landen, M., McGuffin, P., Lewis, C.M., Lichtenstein, P., Svensson, A.C., 2013. Fecundity of patients with schizophrenia, autism, bipolar disorder, depression, anorexia nervosa, or substance abuse vs their unaffected siblings. JAMA Psychiatr. 70, 22–30.
Pramparo, T., Pierce, K., Lombardo, M.V., Carter, B.C., Marinero, S., Ahrens-Barbeau, C., Murray, S.S., Lopez, L., Xu, R., Courchesne, E., 2015. Prediction of autism by translation and immune/inflammation coexpressed genes in toddlers from pediatric community practices. JAMA Psychiatr. 72, 386–394.
Qin, W., Ho, L., Pompl, P.N., Peng, Y., Zhao, Z., Xiang, Z., Robakis, N.K., Shioi, J., Suh, J., Pasinetti, G.M., 2003. Cyclooxygenase (COX)-2 and COX-1 potentiate beta-amyloid peptide generation through mechanisms that involve gamma-secretase activity. J. Biol. Chem. 278, 50970–50977.
Querec, T.D., Akondy, R.S., Lee, E.K., Cao, W., Nakaya, H.I., Teuwen, D., Pirani, A., Gernert, K., Deng, J., Marzolf, B., Kennedy, K., Wu, H., Bennouna, S., Oluoch, H., Miller, J., Vencio, R.Z., Mulligan, M., Aderem, A., Ahmed, R., Pulendran, B., 2009. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. Nat. Immunol. 10, 116–125.
Radua, J., Via, E., Catani, M., Mataix-Cols, D., 2011. Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls. Psychol. Med. 41, 1539–1550.
Ramilo, O., Allman, W., Chung, W., Mejias, A., Ardura, M., Glaser, C., Wittkowski, K.M., Piqueras, B., Banchereau, J., Palucka, A.K., Chaussabel, D., 2007. Gene expression patterns in blood leukocytes discriminate patients with acute infections. Blood 109, 2066–2077.
Ray, B., Long, J.M., Sokol, D.K., Lahiri, D.K., 2011. Increased secreted amyloid precursor protein-alpha (sAPPalpha) in severe autism: proposal of a specific, anabolic pathway and putative biomarker. PLoS One 6, e20405.
Ray, B., Sokol, D.K., Maloney, B., Lahiri, D.K., 2016. Finding novel distinctions between the sAPPalpha-mediated anabolic biochemical pathways in Autism Spectrum Disorder and Fragile X Syndrome plasma and brain tissue. Sci. Rep. 6, 26052.
Rice, H.C., Young-Pearse, T.L., Selkoe, D.J., 2013. Systematic evaluation of candidate ligands regulating ectodomain shedding of amyloid precursor protein. Biochemistry 52, 3264–3277.
Rice, R.A., Berchtold, N.C., Cotman, C.W., Green, K.N., 2014. Age-related downregulation of the CaV3.1 T-type calcium channel as a mediator of amyloid beta production. Neurobiol. Aging 35, 1002–1011.
Rossignol, D.A., Genuis, S.J., Frye, R.E., 2014. Environmental toxicants and autism spectrum disorders: a systematic review. Transl. Psychiatr. 4, e360.
Rossner, S., Mendla, K., Schliebs, R., Bigl, V., 2001. Protein kinase Calpha and beta1 isoforms are regulators of alpha-secretory proteolytic processing of amyloid precursor protein in vivo. Eur. J. Neurosci. 13, 1644–1648.
Roux, J.C., Zala, D., Panayotis, N., Borges-Correia, A., Saudou, F., Villard, L., 2012. Modification of Mecp2 dosage alters axonal transport through the Huntingtin/Hap1 pathway. Neurobiol. Dis. 45, 786–795.
Rozenblatt-Rosen, O., Deo, R.C., Padi, M., Adelmant, G., Calderwood, M.A., Rolland, T., Grace, M., Dricot, A., Askenazi, M., Tavares, M., Pevzner, S.J., Abderazzaq, F., Byrdsong, D., Carvunis, A.R., Chen, A.A., Cheng, J., Correll, M., Duarte, M., Fan, C., Feltkamp, M.C., Ficarro, S.B., Franchi, R., Garg, B.K., Gulbahce, N., Hao, T., Holthaus, A.M., James, R., Korkhin, A., Litovchick, L., Mar, J.C., Pak, T.R., Rabello, S., Rubio, R., Shen, Y., Singh, S., Spangle, J.M., Tasan, M., Wanamaker, S., Webber, J.T., Roecklein-Canfield, J., Johannsen, E., Barabasi, A.L., Beroukhim, R., Kieff, E., Cusick, M.E., Hill, D.E., Munger, K., Marto, J.A., Quackenbush, J., Roth, F.P., Decaprio, J.A., Vidal, M., 2012. Interpreting cancer genomes using systematic host network

perturbations by tumour virus proteins. Nature 487, 491–495.
Rush, T., Buisson, A., 2014. Reciprocal disruption of neuronal signaling and Abeta production mediated by extrasynaptic NMDA receptors: a downward spiral. Cell Tissue Res. 356, 279–286.
Russo, M.A., Magrone, T., Jirillo, E., 2016. Role of immune cells in the course of central nervous system injury: modulation with natural products. Curr. Pharmaceut. Des. 22, 701–708.
Ryu, Y.S., Kang, K.A., Piao, M.J., Ahn, M.J., Yi, J.M., Hyun, Y.M., Kim, S.H., Ko, M.K., Park, C.O., Hyun, J.W., 2018. Particulate matter induces inflammatory cytokine production via activation of NFkappaB by TLR5-NOX4-ROS signaling in human skin keratinocyte and mouse skin. Redox Biol. 21, 101080.
Sabourin, K.R., Reynolds, A., Schendel, D., Rosenberg, S., Croen, L.A., Pinto-Martin, J.A., Schieve, L.A., Newschaffer, C., Lee, L.C., DiGuiseppi, C., 2018. Infections in children with autism spectrum disorder: study to explore early development (SEED). Autism Res.
Sacco, R., Gabriele, S., Persico, A.M., 2015. Head circumference and brain size in autism spectrum disorder: a systematic review and meta-analysis. Psychiatr. Res. 234, 239–251.
Sadakata, T., Furuichi, T., 2009. Developmentally regulated Ca2+-dependent activator protein for secretion 2 (CAPS2) is involved in BDNF secretion and is associated with autism susceptibility. Cerebellum 8, 312–322.
Sadik, G., Kaji, H., Takeda, K., Yamagata, F., Kameoka, Y., Hashimoto, K., Miyanaga, K., Shinoda, T., 1999. In vitro processing of amyloid precursor protein by cathepsin D. Int. J. Biochem. Cell Biol. 31, 1327–1337.
Saftig, P., Lichtenthaler, S.F., 2015. The alpha secretase ADAM10: a metalloprotease with multiple functions in the brain. Prog. Neurobiol. 135, 1–20.
Sahin, U., Weskamp, G., Kelly, K., Zhou, H.M., Higashiyama, S., Peschon, J., Hartmann, D., Saftig, P., Blobel, C.P., 2004. Distinct roles for ADAM10 and ADAM17 in ectodomain shedding of six EGFR ligands. J. Cell Biol. 164, 769–779.
Saito, Y., Sano, Y., Vassar, R., Gandy, S., Nakaya, T., Yamamoto, T., Suzuki, T., 2008. X11 proteins regulate the translocation of amyloid beta-protein precursor (APP) into detergent-resistant membrane and suppress the amyloidogenic cleavage of APP by beta-site-cleaving enzyme in brain. J. Biol. Chem. 283, 35763–35771.
Sakurai, T., Kaneko, K., Okuno, M., Wada, K., Kashiyama, T., Shimizu, H., Akagi, T., Hashikawa, T., Nukina, N., 2008. Membrane microdomain switching: a regulatory mechanism of amyloid precursor protein processing. J. Cell Biol. 183, 339–352.
Sano, Y., Syuzo-Takabatake, A., Nakaya, T., Saito, Y., Tomita, S., Itohara, S., Suzuki, T., 2006. Enhanced amyloidogenic metabolism of the amyloid beta-protein precursor in the X11L-deficient mouse brain. J. Biol. Chem. 281, 37853–37860.
Sartor, M.A., Schnekenburger, M., Marlowe, J.L., Reichard, J.F., Wang, Y., Fan, Y., Ma, C., Karyala, S., Halbleib, D., Liu, X., Medvedovic, M., Puga, A., 2009. Genomewide analysis of aryl hydrocarbon receptor binding targets reveals an extensive array of gene clusters that control morphogenetic and developmental programs. Environ. Health Perspect. 117, 1139–1146.
Scheinfeld, M.H., Roncarati, R., Vito, P., Lopez, P.A., Abdallah, M., D'Adamio, L., 2002. Jun NH2-terminal kinase (JNK) interacting protein 1 (JIP1) binds the cytoplasmic domain of the Alzheimer's beta-amyloid precursor protein (APP). J. Biol. Chem. 277, 3767–3775.
Schendel, D.E., Autry, A., Wines, R., Moore, C., 2009. The co-occurrence of autism and birth defects: prevalence and risk in a population-based cohort. Dev. Med. Child Neurol. 51, 779–786.
Schendel, D.E., Overgaard, M., Christensen, J., Hjort, L., Jorgensen, M., Vestergaard, M., Parner, E.T., 2016. Association of psychiatric and neurologic comorbidity with mortality among persons with autism spectrum disorder in a Danish population. JAMA Pediatr. 170, 243–250.
Selkoe, D.J., Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med. 8, 595–608.
Shahani, N., Seshadri, S., Jaaro-Peled, H., Ishizuka, K., Hirota-Tsuyada, Y., Wang, Q., Koga, M., Sedlak, T.W., Korth, C., Brandon, N.J., Kamiya, A., Subramaniam, S., Tomoda, T., Sawa, A., 2015. DISC1 regulates trafficking and processing of APP and Abeta generation. Mol. Psychiatr. 20, 874–879.
Shahim, P., Rejdak, R., Ksiazek, P., Blennow, K., Zetterberg, H., Mattsson, N., Rejdak, K., 2014. Cerebrospinal fluid biomarkers of beta-amyloid metabolism and neuronal damage in epileptic seizures. Eur. J. Neurol. 21, 486–491.
Shaw, W., 2010. Increased urinary excretion of a 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), an abnormal phenylalanine metabolite of Clostridia spp. in the gastrointestinal tract, in urine samples from patients with autism and schizophrenia. Nutr. Neurosci. 13, 135–143.
Sheng, J.G., Boop, F.A., Mrak, R.E., Griffin, W.S., 1994. Increased neuronal beta-amyloid precursor protein expression in human temporal lobe epilepsy: association with interleukin-1 alpha immunoreactivity. J. Neurochem. 63, 1872–1879.
Shinkai, Y., Kaji, T., 2012. Cellular defense mechanisms against lead toxicity in the vascular system. Biol. Pharm. Bull. 35, 1885–1891.
Shukla, M., Govitrapong, P., Boontem, P., Reiter, R.J., Satayavivad, J., 2017. Mechanisms of melatonin in alleviating alzheimer's disease. Curr. Neuropharmacol. 15, 1010–1031.
Singh, B.K., Vatsa, N., Kumar, V., Shekhar, S., Sharma, A., Jana, N.R., 2017. Ube3a deficiency inhibits amyloid plaque formation in APPswe/PS1deltaE9 mouse model of Alzheimer's disease. Hum. Mol. Genet. 26, 4042–4054.
Singh, V.K., Jensen, R.L., 2003. Elevated levels of measles antibodies in children with autism. Pediatr. Neurol. 28, 292–294.
Slack, B.E., Breu, J., Muchnicki, L., Wurtman, R.J., 1997. Rapid stimulation of amyloid precursor protein release by epidermal growth factor: role of protein kinase C. Biochem. J. 327 (Pt 1), 245–249.
Sokol, D.K., Chen, D., Farlow, M.R., Dunn, D.W., Maloney, B., Zimmer, J.A., Lahiri, D.K., 2006a. High levels of Alzheimer beta-amyloid precursor protein (APP) in children with severely autistic behavior and aggression. J. Child Neurol. 21, 444–449.
Sokol, D.K., Chen, D., Farlow, M.R., Dunn, D.W., Maloney, B., Zimmer, J.A., Lahiri, D.K., 2006b. High levels of Alzheimer beta-amyloid precursor protein (APP) in children with severely autistic behavior and aggression. J. Child Neurol. 21, 444–449.
Sokol, D.K., Maloney, B., Long, J.M., Ray, B., Lahiri, D.K., 2011. Autism, Alzheimer disease, and fragile X: APP, FMRP, and mGluR5 are molecular links. Neurology 76, 1344–1352.
Soscia, S.J., Kirby, J.E., Washicosky, K.J., Tucker, S.M., Ingelsson, M., Hyman, B., Burton, M.A., Goldstein, L.E., Duong, S., Tanzi, R.E., Moir, R.D., 2010. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One 5, e9505.
Spann, M.N., Sourander, A., Surcel, H.M., Hinkka-Yli-Salomaki, S., Brown, A.S., 2017. Prenatal toxoplasmosis antibody and childhood autism. Autism Res. 10, 769–777.
Stannard, W., O'Callaghan, C., 2006. Ciliary function and the role of cilia in clearance. J. Aerosol Med. 19, 110–115.
Steukers, L., Glorieux, S., Vandekerckhove, A.P., Favoreel, H.W., Nauwynck, H.J., 2012. Diverse microbial interactions with the basement membrane barrier. Trends Microbiol. 20, 147–155.
Sturgill, J.L., Mathews, J., Scherle, P., Conrad, D.H., 2011. Glutamate signaling through the kainate receptor enhances human immunoglobulin production. J. Neuroimmunol. 233, 80–89.
Sundquist, J., Sundquist, K., Ji, J., 2014. Autism and attention-deficit/hyperactivity disorder among individuals with a family history of alcohol use disorders. Elife 3, e02917.
Suzuki, K., Hayashi, Y., Nakahara, S., Kumazaki, H., Prox, J., Horiuchi, K., Zeng, M., Tanimura, S., Nishiyama, Y., Osawa, S., Sehara-Fujisawa, A., Saftig, P., Yokoshima, S., Fukuyama, T., Matsuki, N., Koyama, R., Tomita, T., Iwatsubo, T., 2012. Activity-dependent proteolytic cleavage of neuroligin-1. Neuron 76, 410–422.
Takayama, K., Suzuki, T., Tsutsumi, S., Fujimura, T., Takahashi, S., Homma, Y., Urano, T., Aburatani, H., Inoue, S., 2014. Integrative analysis of FOXP1 function reveals a tumor-suppressive effect in prostate cancer. Mol. Endocrinol. 28, 2012–2024.
Takayama, K., Tsutsumi, S., Suzuki, T., Horie-Inoue, K., Ikeda, K., Kaneshiro, K., Fujimura, T., Kumagai, J., Urano, T., Sakaki, Y., Shirahige, K., Sasano, H., Takahashi, S., Kitamura, T., Ouchi, Y., Aburatani, H., Inoue, S., 2009. Amyloid precursor protein is a primary androgen target gene that promotes prostate cancer growth. Cancer Res. 69, 137–142.
Takeda, K., Akira, S., 2005. Toll-like receptors in innate immunity. Int. Immunol. 17, 1–14.
Tan, H.T., Sugita, K., Akdis, C.A., 2016. Novel biologicals for the treatment of allergic diseases and asthma. Curr. Allergy Asthma Rep. 16, 70.
Tejeda, G.S., Ayuso-Dolado, S., Arbeteta, R., Esteban-Ortega, G.M., Vidaurre, O.G., Diaz-Guerra, M., 2016. Brain ischaemia induces shedding of a BDNF-scavenger ectodomain from TrkB receptors by excitotoxicity activation of metalloproteinases and gamma-secretases. J. Pathol. 238, 627–640.
Theoharides, T.C., Tsilioni, I., Patel, A.B., Doyle, R., 2016a. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. Transl. Psychiatry 6, e844.
Theoharides, T.C., Tsilioni, I., Patel, A.B., Doyle, R., 2016b. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. Transl. Psychiatry 6, e844.
Thevenod, F., Lee, W.K., 2013. Cadmium and cellular signaling cascades: interactions between cell death and survival pathways. Arch. Toxicol. 87, 1743–1786.
Tian, J., Dai, H., Deng, Y., Zhang, J., Li, Y., Zhou, J., Zhao, M., Zhao, M., Zhang, C., Zhang, Y., Wang, P., Bing, G., Zhao, L., 2015. The effect of HMGB1 on sub-toxic chlorpyrifos exposure-induced neuroinflammation in amygdala of neonatal rats. Toxicology 338, 95–103.
Tian, T., Bai, D., Li, W., Huang, G.W., Liu, H., 2016. Effects of folic acid on secretases involved in abeta deposition in APP/PS1 mice. Nutrients 8.
Tong, X.J., Lopez-Soto, E.J., Li, L., Liu, H., Nedelcu, D., Lipscombe, D., Hu, Z., Kaplan, J.M., 2017. Retrograde synaptic inhibition is mediated by alpha-neurexin binding to the alpha2delta subunits of N-type calcium channels. Neuron 95, 326–340.
Trottier, G., Srivastava, L., Walker, C.D., 1999. Etiology of infantile autism: a review of recent advances in genetic and neurobiological research. J. Psychiatry Neurosci. 24, 103–115.
Turner, P.R., O'Connor, K., Tate, W.P., Abraham, W.C., 2003. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. Prog. Neurobiol. 70, 1–32.
Ulbrich, L., Favaloro, F.L., Trobiani, L., Marchetti, V., Patel, V., Pascucci, T., Comoletti, D., Marciniak, S.J., De Jaco, A., 2016. Autism-associated R451C mutation in neuroligin3 leads to activation of the unfolded protein response in a PC12 Tet-On inducible system. Biochem. J. 473, 423–434.
Uzunova, G., Pallanti, S., Hollander, E., 2016. Excitatory/inhibitory imbalance in autism spectrum disorders: implications for interventions and therapeutics. World J. Biol. Psychiatr. 17, 174–186.
Valleau, J.C., Sullivan, E.L., 2014. The impact of leptin on perinatal development and psychopathology. J. Chem. Neuroanat. 61–62, 221–232.
van Staveren, W.C., Solis, D.W., Delys, L., Venet, D., Cappello, M., Andry, G., Dumont, J.E., Libert, F., Detours, V., Maenhaut, C., 2006. Gene expression in human thyrocytes and autonomous adenomas reveals suppression of negative feedbacks in tumorigenesis. Proc. Natl. Acad. Sci. U. S. A. 103, 413–418.
Veiga-Fernandes, H., Mucida, D., 2016. Neuro-immune interactions at barrier surfaces. Cell 165, 801–811.
Vennemann, M.M., Hoffgen, M., Bajanowski, T., Hense, H.W., Mitchell, E.A., 2007. Do immunisations reduce the risk for SIDS? A meta-analysis. Vaccine 25, 4875–4879.
Vinet, E., Pineau, C.A., Clarke, A.E., Scott, S., Fombonne, E., Joseph, L., Platt, R.W., Bernatsky, 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 Rheum. 67, 3201–3208.
Wan, X.Z., Li, B., Li, Y.C., Yang, X.L., Zhang, W., Zhong, L., Tang, S.J., 2012. Activation of NMDA receptors upregulates a disintegrin and metalloproteinase 10 via a Wnt/MAPK signaling pathway. J. Neurosci. 32, 3910–3916.
Wang, C., Geng, H., Liu, W., Zhang, G., 2017. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. Medicine (Baltim.) 96, e6696.
Wang, Y.H., 2016. Developing food allergy: a potential immunologic pathway linking skin barrier to gut. F1000Res 5.
Wang, Y.M., Zheng, Y.F., Yang, S.Y., Yang, Z.M., Zhang, L.N., He, Y.Q., Gong, X.H., Liu, D., Finnell, R.H., Qiu, Z.L., Du, Y.S., Wang, H.Y., 2018. MicroRNA-197 controls ADAM10 expression to mediate MeCP2's role in the differentiation of neuronal progenitors. Cell Death Differ.
Wegiel, J., Frackowiak, J., Mazur-Kolecka, B., Schanen, N.C., Cook Jr., E.H., Sigman, M., Brown, W.T., Kuchna, I., Wegiel, J., Nowicki, K., Imaki, H., Ma, S.Y., Chauhan, A., Chauhan, V., Miller, D.L., Mehta, P.D., Flory, M., Cohen, I.L., London, E., Reisberg, B., de Leon, M.J., Wisniewski, T., 2012. Abnormal intracellular accumulation and extracellular Abeta deposition in idiopathic and Dup15q11.2-q13 autism spectrum disorders. PLoS One 7, e35414.
Wei, G., Twomey, D., Lamb, J., Schlis, K., Agarwal, J., Stam, R.W., Opferman, J.T., Sallan, S.E., den Boer, M.L., Pieters, R., Golub, T.R., Armstrong, S.A., 2006. Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL1 and glucocorticoid resistance. Cancer Cell 10, 331–342.
Westmark, C.J., Malter, J.S., 2007. FMRP mediates mGluR5-dependent translation of amyloid precursor protein. PLoS Biol. 5, e52.
Westmark, C.J., Sokol, D.K., Maloney, B., Lahiri, D.K., 2016. Novel roles of amyloid-beta precursor protein metabolites in fragile X syndrome and autism. Mol. Psychiatr. 21, 1333–1341.
White, M.R., Kandel, R., Tripathi, S., Condon, D., Qi, L., Taubenberger, J., Hartshorn, K.L., 2014. Alzheimer's associated beta-amyloid protein inhibits influenza a virus and modulates viral interactions with phagocytes. PLoS One 9, e101364.
Whiteley, P., 2004. Developmental, behavioural and somatic factors in pervasive developmental disorders: preliminary analysis. Child Care Health Dev. 30, 5–11.
Wilkerson, D.S., Volpe, A.G., Dean, R.S., Titus, J.B., 2002. Perinatal complications as predictors of infantile autism. Int. J. Neurosci. 112, 1085–1098.
Willette, A.A., Lubach, G.R., Knickmeyer, R.C., Short, S.J., Styner, M., Gilmore, J.H., Coe, C.L., 2011. Brain enlargement and increased behavioral and cytokine reactivity in infant monkeys following acute prenatal endotoxemia. Behav. Brain Res. 219, 108–115.
Win-Shwe, T.T., Nakajima, D., Fujimaki, H., 2012. Involvement of TLR4 in diazinon-induced neurotoxicity in mice. J. UOEH 34, 1–13.
Woodward, N.C., Levine, M.C., Haghani, A., Shirmohammadi, F., Saffari, A., Sioutas, C., Morgan, T.E., Finch, C.E., 2017. Toll-like receptor 4 in glial inflammatory responses to air pollution in vitro and in vivo. J. Neuroinflammation 14, 84.
Xu, D., Sharma, C., Hemler, M.E., 2009. Tetraspanin12 regulates ADAM10-dependent cleavage of amyloid precursor protein. FASEB J. 23, 3674–3681.
Xuan, I.C., Hampson, D.R., 2014. Gender-dependent effects of maternal immune activation on the behavior of mouse offspring. PLoS One 9, e104433.
Yang, C., Huang, X., Huang, X., Mai, H., Li, J., Jiang, T., Wang, X., Lu, T., 2016. Aquaporin-4 and alzheimer's disease. J. Alzheimer's Dis. 52, 391–402.
Yang, L., Wang, Z., Wang, B., Justice, N.J., Zheng, H., 2009. Amyloid precursor protein regulates Cav1.2 L-type calcium channel levels and function to influence GABAergic short-term plasticity. J. Neurosci. 29, 15660–15668.
Yao, M., Nguyen, T.V., Rosario, E.R., Ramsden, M., Pike, C.J., 2008. Androgens regulate neprilysin expression: role in reducing beta-amyloid levels. J. Neurochem. 105, 2477–2488.
Yokota, S., Ohnishi, T., Muroi, M., Tanamoto, K., Fujii, N., Amano, K., 2007. Highly-purified Helicobacter pylori LPS preparations induce weak inflammatory reactions and utilize Toll-like receptor 2 complex but not Toll-like receptor 4 complex. FEMS Immunol. Med. Microbiol. 51, 140–148.
Zeidan-Chulia, F., de Oliveira, B.H., Salmina, A.B., Casanova, M.F., Gelain, D.P., Noda, M., Verkhratsky, A., Moreira, J.C., 2014. Altered expression of Alzheimer's disease-related genes in the cerebellum of autistic patients: a model for disrupted brain connectome and therapy. Cell Death Dis. 5, e1250.
Zerbo, O., Qian, Y., Yoshida, C., Fireman, B.H., Klein, N.P., Croen, L.A., 2017. Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder. JAMA Pediatr. 171, e163609.
Zerbo, O., Qian, Y., Yoshida, C., Grether, J.K., Van de, W.J., Croen, L.A., 2015. Maternal infection during pregnancy and autism spectrum disorders. J. Autism Dev. Disord. 45, 4015–4025.
Zhang, S.Q., Obregon, D., Ehrhart, J., Deng, J., Tian, J., Hou, H., Giunta, B., Sawmiller, D., Tan, J., 2013. Baicalein reduces beta-amyloid and promotes nonamyloidogenic amyloid precursor protein processing in an Alzheimer's disease transgenic mouse model. J. Neurosci. Res. 91, 1239–1246.
Zimmermann, M., Gardoni, F., Marcello, E., Colciaghi, F., Borroni, B., Padovani, A., Cattabeni, F., Di Luca, M., 2004. Acetylcholinesterase inhibitors increase ADAM10 activity by promoting its trafficking in neuroblastoma cell lines. J. Neurochem. 90, 1489–1499.