Title

Autism and Our Intestinal Microbiota

Journal

Microbial Physiology, 25(1)

ISSN

2673-1665

Authors

Reddy, Bhaskara Lakshmi

Saier, Milton H

Publication Date

2015

DOI

10.1159/000375303

Peer reviewed

Review

Journal of Molecular Microbiology and Biotechnology

J Mol Microbiol Biotechnol 2015;25:51–55
DOI: 10.1159/000375303

Published online: March 3, 2015

Autism and Our Intestinal Microbiota

Bhaskara Lakshmi Reddy[a, b] Milton H. Saier[a]

[a]Department of Molecular Biology, Division of Biological Sciences, University of California at San Diego, La Jolla, Calif., and [b]Department of Mathematics and Natural Sciences, College of Letters and Sciences, National University, Ontario, Calif., USA

Key Words
Autism · Microbiota · Gastrointestinal disorders

Abstract
Microbial products, released into the bloodstreams of mammals including humans, cross the blood-brain barrier and influence neurodevelopment. They can either promote or alleviate neurological disorders including autism spectrum disorders (ASD). This editorial describes how our microbiota influence our feelings, attitudes and mental states with particular reference to ASD.

Introduction

The mammalian microbiota is now known to be essential for the maintenance of good health [Ettinger et al., 2014; Schippa and Conte, 2014]. Recently, evidence has been presented suggesting that symbiotic prokaryotes influence brain function and that a balanced microbiota can promote mental health while combating major psychological and physiological disorders [Fond et al., 2014; Tang et al., 2014]. This evidence has led to the use of novel terms such as 'psychobiotics' and 'psychomicrobiotics' to emphasize the possibility that 'bad' intestinal bacteria may negatively influence mental processes [Selhub et al., 2014]. In fact, it has been suggested that microbial imbalance, often referred to as dysbiosis or dysbacteriosis, can give rise to major psychiatric disorders [Dash et al., 2015]. The hope is that probiotics, prebiotics and proper nutrition can help alleviate the symptoms of common neurological disorders. A door to the novel discipline of 'nutritional psychology' is opening. In this short review, we focus on one increasingly prevalent disorder, autism, citing evidence that this condition is responsive to the composition of our microbiota.

Autism has been reported to be associated with multiple phenotypic disorders including impairment of verbal and written communication skills, social isolation and repetitive behaviors [Whitehouse and Stanley, 2013]. It is a neurodevelopmental disorder with high variability in its clinical manifestations. Autism spectrum disorders (ASDs) have been reported to be associated with: (1) genetic mutations giving rise to polymorphisms in specific genes [Dachtler et al., 2014; Hevner, 2015]; (2) epigenetic changes in gene expression [Balan et al., 2014]; (3) environmental pollutants [Volk et al., 2014]; (4) maternal infection with pathogenic agents during pregnancy [Zerbo et al., 2013]; (5) sleeping problems [Kotagal and Broomall, 2012]; (6) gastrointestinal metabolic disorders [Kotagal

1464–1801/15/0251–0051$39.50/0

E-Mail karger@karger.com
www.karger.com/mmb

Milton H. Saier
Department of Molecular Biology, Division of Biological Sciences, Ontario Campus
University of California at San Diego
La Jolla, CA 92093-0116 (USA)
E-Mail msaier@ucsd.edu

and Broomall, 2012]; (7) immune dysregulation [Onore et al., 2012]; (8) homeostatic imbalance in gut-to-brain connections [Kotagal and Broomall, 2012]; (9) oxidative stress; (10) mitochondrial dysfunction, and (11) neuroinflammation during development [Zhang et al., 2015]. However, which of these conditions, if any, are causally related to autism remains an open question.

There is increasing evidence that excessive proinflammatory proteins such as interleukin-6 (IL-6), ρ-kinases (ρ-associated, coiled-coil-containing protein kinase 1) and NADPH oxidases (KNOX-2) significantly contribute to neurite outgrowth and retardation. They may contribute to ASDs, Alzheimer's disease and other neurodegenerative diseases [Hernandes et al., 2014; Sorce and Krause, 2009]. NADPH oxidases produce free radicals during the reduction of molecular oxygen and elicit oxidative stress. They are linked to neuroinflammatory diseases and brain injury [El-Ansary and Al-Ayadhi, 2012; Gonzalez et al., 2014; Gotz and Ittner, 2008]. In fact, a correlation between the levels of reactive oxygen species and neurodegenerative diseases has been noted [Ramalingam and Kim, 2012; Tapryal et al., 2009]. Several studies have identified IL-6 as a key cytokine responsible for these abnormalities, possibly because of the altered expression of genes responsible for immunological and neurological development [Meyer and Feldon, 2009; Meyer et al., 2008; Ramalingam and Kim, 2012]. Though several cytokines are released, IL-6 seems to be key, and the inhibition of IL-6 has reversed behavioral abnormalities observed in offspring prenatally exposed to maternal immune activation (MIA) [Smith et al., 2007]. A number of intestinal microbes are known to maintain the integrity of the intestinal barrier and epithelial tight junctions by secreting molecules that inhibit cytokines including IL-6 [Turner, 2009].

Autoantibodies against specific central nervous system proteins and against brain regions such as the cerebellum, thalamus and hypothalamus are known to be present in individuals with autism [Wills et al., 2009]. An altered blood-brain barrier, due to neurological inflammation and increased inflammatory cytokines in the brain, has been reported in ASD children [Noriega and Savelkoul, 2014], along with altered immune properties and cytokine imbalance [Gesundheit et al., 2013; Goines and Ashwood, 2013; Sweeten et al., 2003]. The intestinal mucosa is constantly challenged with antigens from food, microbes, chemicals and allergens. A functional gut mucosa prevents inflammatory diseases while maintaining immune function, mucous production and normal levels of membrane permeability [Pastorelli et al., 2013].

Many children with autism also suffer from gastrointestinal disorders such as diarrhea, vomiting, abdominal pain, chronic constipation and gastroesophageal reflux [Buie et al., 2010]. Abnormalities such as altered gastrointestinal motility and increased intestinal permeability have also been reported in autistic children [D'Eufemia et al., 1996]. A large sample study involving 15,000 individuals also revealed a greater prevalence of inflammatory bowel disease and other gastrointestinal disorders in ASD patients compared to controls [D'Eufemia et al., 1996; Kohane et al., 2012]. Altered gastrointestinal microbial populations were considered to be responsible for the pathogenesis of several of these disorders, including inflammatory bowel disease, obesity and cardiovascular diseases [Casanova et al., 2011; Williams and Gray, 2013]. In fact, disruption of the mucosal microbiota has been extensively reported in ASD children [Finegold et al., 2010, 2012; Kang et al., 2013; Parracho et al., 2005; Williams et al., 2011, 2012]. A reduction in the diversity of microbes in the gastrointestinal tract has been observed in Crohn's disease, a chronic inflammatory disease of the gastrointestinal tract, along with a difference in the composition of fecal bacteria in patients with inflammatory bowel disease compared to healthy controls [Manichanh et al., 2006].

Some studies have suggested a significant risk of autism in children born to mothers with severe infections during pregnancy [Smith et al., 2007]. Moreover, when pregnant female monkeys were exposed to antibodies produced as a result of immune-mediated disorders, the offspring developed pathologies of the central nervous system and exhibited behavioral changes similar to those characteristic of autism [Libbey and Fujinami, 2010]. These were the first studies to report alterations in the intestinal microbiome in offspring born to infected mothers, providing a potential explanation for the gastrointestinal problems suffered by children with autism. Moreover, studies using animal models have suggested that MIA can, in response to pathogens and exposure of the fetus to maternal cytokines, result in neurological, immunological and behavioral abnormalities in the offspring [Smith et al., 2007]. An increased risk of autism in offspring born to pregnant female monkeys infected with pathogens has recently been confirmed [Bauman et al., 2014].

Offspring of MIA mice with behavioral abnormalities exhibit altered gut bacteria and gastrointestinal abnormalities, and similar defects in intestinal integrity have also been reported in human cases of ASD [Hsiao et al., 2013]. Thus, children with ASD have an increased perme-

ability of the gastrointestinal tract, called 'leaky gut', causing microbial products to escape into the bloodstream and possibly reach the brain [de Magistris et al., 2010]. These products alter the immune system, resulting in a progression of the disease [Turner, 2009]. Increased gastrointestinal permeability has even been suggested to be a cause of inflammatory bowel disease, Crohn's disease and autism [Liu et al., 2005]. Differences in the gut microbiota between MIA offspring and controls were observed due primarily to changes in the diversity of Clostridia and Bacteroidia [Hsiao et al., 2013]. The intestines of some ASD patients with intestinal abnormalities are known to bear *Sutterella* and *Clostridium bolteae* [Parracho et al., 2005], organisms lacking in control populations with similar gastrointestinal problems.

The microbiota normally inhabiting the human gut are dominated by 4 major phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria [Qin et al., 2010]. Children with autism proved to have lower levels of the *Bifidobacterium* species and higher levels of the *Lactobacillus* species, along with other differences in the members of the actinobacterial and proteobacterial phyla [Finegold et al., 2010]. In one study, dietary supplementation with prebiotics significantly increased the populations of *Bifidobacterium breve, B. longum* and *Bacteroides distasonis*, while decreasing the populations of *Escherichia coli* and *Clostridium perfringens* [Martin et al., 2008].

Bacteroides fragilis, a common probiotic bacterium, but also an opportunistic pathogen, is part of the normal microbial ecosystem [Cao et al., 2014]. *B. fragilis* treatment has been shown to alleviate symptoms of experimental colitis [Round and Mazmanian, 2010]. It can also decrease inflammation caused by *Helicobacter hepaticus*, another commensal organism in the gastrointestinal tract with a potential for pathogenicity [Mazmanian et al., 2008]. Abnormalities in gastrointestinal tract permeability have been ameliorated by the introduction of *B. fragilis* into the gastrointestinal tracts of 8-week-old offspring of MIA mice [Hsiao et al., 2013]. MIA-induced serum metabolite levels were also corrected by *B. fragilis* treatment, in part by reducing levels of 4-ethylphenylsulfate, a metabolite known to induce behavioral abnormalities in naïve mice [Hsiao et al., 2013]. A depletion of microbes, including *B. fragilis,* was also reported in ASD children with gastrointestinal problems [Kang et al., 2013].

There is a growing interest in fecal microbiota transplantation to treat many diseases caused by an imbalance of gut microbiota [Petrof and Khoruts, 2014]. The first fecal transplantions were performed in 1958 at the University of Colorado Medical School in Denver, and since then, there have been more than 500 published cases [Yong, 2013]. Borody's clinic has now performed over 1,500 fecal transplantations with promising results in patients with inflammatory bowel disease, irritable bowel disease and chronic constipation [Borody et al., 2004]. In spite of these successes, many in the scientific community are unconvinced; we are still trying to overcome the 'yuck factor' and our loathing for human waste. Considering the difficulties of physicians to obtain licenses to perform such transplantations, it is not surprising that many patients are opting to do their own transplantations at home, with an enema kit and stools from a healthy relative [Swaminath, 2014].

Through millions of years of evolution, we have acquired a delicate balance of normally beneficial bacteria in our gastrointestinal tracts and elsewhere throughout our bodies. These bacteria coevolved with us and forged essential symbiotic relationships with us, influencing our physiologies and behaviors, especially through the gut-brain axis [Peeters, 2015]. Even the pathogenic bacterium *H. pylori*, which causes gastric ulcer, is known to be useful to us by preventing esophageal cancer through the beneficial effects of the inflammation it causes [Blaster, 2014]. Re-establishing this delicate balance and maintaining the useful gut bacteria are crucial to our health and feeling of well-being.

In summary, numerous studies indicate that gastrointestinal alterations of the microbial ecosystem promote gut permeability, causing the leaky gut syndrome. This condition results in an escape of microbial products and cytokines into the bloodstream, causing neurodevelopmental disorders. Autism is just one of the disorders that may result in part from this condition. The extent to which and mechanisms by which our microbiota influence our feelings, attitudes and mental states represent rich fields for investigation for young microbiologists.

References

- Balan S, Iwayama Y, Maekawa M, Toyota T, Ohnishi T, Toyoshima M, Shimamoto C, Esaki K, Yamada K, Iwata Y, Suzuki K, Ide M, Ota M, Fukuchi S, Tsujii M, Mori N, Shinkai Y, Yoshikawa T: Exon resequencing of H3K9 methyltransferase complex genes, EHMT1, EHMT2 and WIZ, in Japanese autism subjects. Mol Autism 2014;5:49.
- Bauman MD, Iosif AM, Smith SE, Bregere C, Amaral DG, Patterson PH: Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. Biol Psychiatry 2014;75:332–341.

Blaster MJ: Missing Microbes: How the Overuse of Antibiotics Is Fueling Our Modern Plagues. New York, Holt & Company, 2014, pp 222–223.

Borody TJ, Warren EF, Leis SM, Surace R, Ashman O, Siarakas S: Bacteriotherapy using fecal flora: toying with human motions. J Clin Gastroenterol 2004;38:475–483.

Buie T, Fuchs GJ 3rd, Furuta GT, Kooros K, Levy J, Lewis JD, Wershil BK, Winter H: Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics 2010;125(suppl 1):S19–S29.

Cao Y, Rocha ER, Smith CJ: Efficient utilization of complex N-linked glycans is a selective advantage for *Bacterioides fagilis* in extraintestinal infections. Proc Natl Acad Sci USA 2014; 35:12901–12906.

Casanova MF, El-Baz A, Elnakib A, Switala AE, Williams EL, Williams DL, Minshew NJ, Conturo TE: Quantitative analysis of the shape of the corpus callosum in patients with autism and comparison individuals. Autism 2011;15:223–238.

D'Eufemia P, Celli M, Finocchiaro R, Pacifico L, Viozzi L, Zaccagnini M, Cardi E, Giardini O: Abnormal intestinal permeability in children with autism. Acta Paediatr 1996;85:1076–1079.

Dachtler J, Glasper J, Cohen RN, Ivorra JL, Swiffen DJ, Jackson AJ, Harte MK, Rodgers RJ, Clapcote SJ: Deletion of α-neurexin II results in autism-related behaviors in mice. Transl Psychiatry 2014;4:e484.

Dash S, Clarke G, Berk M, Jacka FN: The gut microbiome and diet in psychiatry: focus on depression. Curr Opin Psychiatry 2015;28:1–6.

De Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, Carteni M, De Rosa M, Francavilla R, Riegler G, Militerni R, Bravaccio C: Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. J Pediatr Gastroenterol Nutr 2010;51:418–424.

El-Ansary A, Al-Ayadhi L: Neuroinflammation in autism spectrum disorders. J Neuroinflammation 2012;9:265.

Ettinger R, MacDonald K, Reid G, Burton JP: The influence of the human microbiome and probiotics on cardiovascular health. Gut Microbes 2014;5:719–728.

Finegold SM, Dowd SE, Gontcharova V, Liu C, Henley KE, Wolcott RD, Youn E, Summanen PH, Granpeesheh D, Dixon D, Liu M, Molitoris DR, Green JA 3rd: Pyrosequencing study of fecal microflora of autistic and control children. Anaerobe 2010;16:444–453.

Finegold SM, Downes J, Summanen PH: Microbiology of regressive autism. Anaerobe 2012; 18:260–262.

Fond G, Boukouaci W, Chevalier G, Regnault A, Eberl G, Hamdani N, Dickerson F, Macgregor A, Boyer L, Dargel A, Oliveira J, Tamouza R, Leboyer M: The 'psychomicrobiotic': targeting microbiota in major psychiatric disorders: a systematic review. Pathol Biol (Paris) 2015;63:35–42.

Gesundheit B, Rosenzweig JP, Naor D, Lerer B, Zachor DA, Prochazka V, Melamed M, Kristt DA, Steinberg A, Shulman C, Hwang P, Koren G, Walfisch A, Passweg JR, Snowden JA, Tamouza R, Leboyer M, Farge-Bancel D, Ashwood P: Immunological and autoimmune considerations of autism spectrum disorders. J Autoimmun 2013;44:1–7.

Goines PE, Ashwood P: Cytokine dysregulation in autism spectrum disorders (ASD): possible role of the environment. Neurotoxicol Teratol 2013;36:67–81.

Gonzalez H, Elgueta D, Montoya A, Pacheco R: Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases. J Neuroimmunol 2014;274:1–13.

Gotz J, Ittner LM: Animal models of Alzheimer's disease and frontotemporal dementia. Nat Rev Neurosci 2008;9:532–544.

Hernandes MS, D'Avila JC, Trevelin SC, Reis PA, Kinjo ER, Lopes LR, Castro-Faria-Neto HC, Cunha FQ, Britto LR, Bozza FA: The role of Nox2-derived ROS in the development of cognitive impairment after sepsis. J Neuroinflammation 2014;11:36.

Hevner RF: Brain overgrowth in disorders of RTK-PI3K-AKT signaling: a mosaic of malformations. Semin Perinatol 2015;39:36–43.

Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK: Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 2013; 155:1451–1463.

Kang DW, Park JG, Ilhan ZE, Wallstrom G, Labaer J, Adams JB, Krajmalnik-Brown R: Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. PLoS One 2013;8:e68322.

Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, Bickel J, Wattanasin N, Spence S, Murphy S, Churchill S: The comorbidity burden of children and young adults with autism spectrum disorders. PLoS One 2012;7:e33224.

Kotagal S, Broomall E: Sleep in children with autism spectrum disorder. Pediatr Neurol 2012; 47:242–251.

Libbey JE, Fujinami RS: Role for antibodies in altering behavior and movement. Autism Res 2010;3:147–152.

Liu Z, Li N, Neu J: Tight junctions, leaky intestines, and pediatric diseases. Acta Paediatr 2005;94:386–393.

Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, Nalin R, Jarrin C, Chardon P, Marteau P, Roca J, Dore J: Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut 2006;55:205–211.

Martin FP, Wang Y, Sprenger N, Yap IK, Lundstedt T, Lek P, Rezzi S, Ramadan Z, van Bladeren P, Fay LB, Kochhar S, Lindon JC, Holmes E, Nicholson JK: Probiotic modulation of symbiotic gut microbial-host metabolic interactions in a humanized microbiome mouse model. Mol Syst Biol 2008;4:157.

Mazmanian SK, Round JL, Kasper DL: A microbial symbiosis factor prevents intestinal inflammatory disease. Nature 2008;453:620–625.

Meyer U, Feldon J: Prenatal exposure to infection: a primary mechanism for abnormal dopaminergic development in schizophrenia. Psychopharmacology (Berl) 2009;206:587–602.

Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J: Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. Brain Behav Immun 2008;22:469–486.

Noriega DB, Savelkoul HF: Immune dysregulation in autism spectrum disorder. Eur J Pediatr 2014;173:33–43.

Onore C, Van de Water J, Ashwood P: Decreased levels of EGF in plasma of children with autism spectrum disorder. Autism Res Treat 2012;2012:205362.

Parracho HM, Bingham MO, Gibson GR, McCartney AL: Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol 2005;54:987–991.

Pastorelli L, De Salvo C, Mercado JR, Vecchi M, Pizarro TT: Central role of the gut epithelial barrier in the pathogenesis of chronic intestinal inflammation: lessons learned from animal models and human genetics. Front Immunol 2013;4:280.

Peeters TL: Gastrointestinal hormones and gut motility. Curr Opin Endocrinol Diabetes Obes 2015;22:9–13.

Petrof EO, Khoruts A: From stool transplants to next-generation microbiota therapeutics. Gastroenterology 2014;146:1573–1582.

Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Jian M, Zhou Y, Li Y, Zhang X, Qin N, Yang H, Wang J, Brunak S, et al: A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59–65.

Ramalingam M, Kim SJ: Reactive oxygen/nitrogen species and their functional correlations in neurodegenerative diseases. J Neural Transm 2012;119:891–910.

Round JL, Mazmanian SK: Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci USA 2010;107:12204–12209.

Schippa S, Conte MP: Dysbiotic events in gut microbiota: impact on human health. Nutrients 2014;6:5786–5805.

Selhub EM, Logan AC, Bested AC: Fermented foods, microbiota, and mental health: ancient practice meets nutritional psychiatry. J Physiol Anthropol 2014;33:2.

Smith SE, Li J, Garbett K, Mirnics K, Patterson PH: Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 2007;27:10695–10702.

Sorce S, Krause KH: Nox enzymes in the central nervous system: from signaling to disease. Antioxid Redox Signal 2009;11:2481–2504.

Swaminath A: The power of poop: patients getting ahead of their doctors using self-administered fecal transplants. Am J Gastroenterol 2014;109:777–778.

Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ: Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. Pediatrics 2003;112:e420.

Tang F, Reddy BL, Saier MH Jr: Psychobiotics and their involvement in mental health. J Mol Microbiol Biotechnol 2014;24:211–214.

Tapryal N, Mukhopadhyay C, Das D, Fox PL, Mukhopadhyay CK: Reactive oxygen species regulate ceruloplasmin by a novel mRNA decay mechanism involving its 3′-untranslated region: implications in neurodegenerative diseases. J Biol Chem 2009;284:1873–1883.

Turner JR: Intestinal mucosal barrier function in health and disease. Nat Rev Immunol 2009;9:799–809.

Volk HE, Kerin T, Lurmann F, Hertz-Picciotto I, McConnell R, Campbell DB: Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Epidemiology 2014;25:44–47.

Whitehouse AJ, Stanley FJ: Is autism one or multiple disorders? Med J Aust 2013;198:302–303.

Williams BL, Hornig M, Buie T, Bauman ML, Cho Paik M, Wick I, Bennett A, Jabado O, Hirschberg DL, Lipkin WI: Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS One 2011;6:e24585.

Williams BL, Hornig M, Parekh T, Lipkin WI: Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of *Sutterella* species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. MBio 2012;3:e00261-11.

Williams BT, Gray KM: The relationship between emotion recognition ability and social skills in young children with autism. Autism 2013;17:762–768.

Wills S, Cabanlit M, Bennett J, Ashwood P, Amaral DG, Van de Water J: Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders. Brain Behav Immun 2009;23:64–74.

Yong E: Faecal transplants succeed in clinical trial. Unorthodox technique is far more effective than antibiotics at treating recurrent gut infections. Nature 2013, DOI: 10.1038/nature.2013.12227.

Zerbo O, Qian Y, Yoshida C, Grether JK, Van de Water J, Croen LA: Maternal infection during pregnancy and autism spectrum disorders. J Autism Dev Disord 2013, Epub ahead of print.

Zhang QB, Gao SJ, Zhao HX: Thioredoxin: a novel, independent diagnosis marker in children with autism. Int J Dev Neurosci 2015;92–96.