*Int J Adv Life Sci Res. Volume 4(1) 01- 06*
https://doi.org/10.31632/ijalsr.20.v04i01.001

**International Journal of Advancement in Life Sciences Research**

Online ISSN: 2581-4877

journal homepage http://ijalsr.org

Review Article

# Autism Spectrum Disorder and Gut Microbiome: A brief review

**Aindrila Banerjee[1], Santi Ranjan Dey[2,], Indrani Basu[3] and Mitu De[4]***

[1]*Majdia Rail Bazar High School (H.S.) Majdia, Nadia, West Bengal. 741507, India.*
[2]*Department of Zoology, Rammohan College, Kolkata 700009, India.*
[3]*Autism Society West Bengal, Kolkata 700032, India.*
[4]*Department of Botany, Gurudas College, Kolkata 700054, India.*

**Correspondence E-mail :* mitude@rediffmail.com

**Abstract**

The human microbiota consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut. The association of the gut microbiota with human health and disease has been widely studied. A number of human disorders and diseases have been directly and indirectly associated with the microbiome. Children with Autism Spectrum Disorder (ASD) have distinctive gut microbiota compared to neurotypical children. Autism spectrum disorder (ASD) is associated with several oropharyngeal abnormalities, including dysbiosis in the oral microbiota. As there is a correlation between abnormal microbiota and development of autism like behaviour, so, modifying the gut microbiome by probiotics, prebiotics, antibiotics and fecal microbiota transplant (FMT) could be a potential route to improve GI and behavioural symptoms in children with ASD.

***Keywords:*** *Microbiome; Autism Spectrum Disorder (ASD); gut microbiota.*

## Introduction

The intimate association between man and microbe over the course of a lifetime has profound implications on human health, including metabolism, immunity and the gut-brain axis. The human microbiota consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut. Oral microbiome, by definition, is the collective genomes of microorganisms that reside in the oral cavity (Kolenbrander *et al,* 2002; Turnbaugh *et al,* 2007). The human microbiome, or community of microbes and collection of genomes found in and on the human body, is now the subject of renewed, intense study (Relman, 2012).

### *Oral microbiome and developmental disorders*

Many researchers believe that the characterisation of oral microbiome is an essential step in understanding oral health and systemic diseases (Dewhirst *et al.,* 2010, De *et al*, 2018). A number of human disorders and diseases have been directly and indirectly associated with the microbiome. The association of the gut microbiota with human health and disease has been widely discussed (Walsh *et al,* 2014, De *et al,* 2019). Current evidences support that alterations in composition and/or metabolic activity of gut microbiota play pivotal role in the pathogenesis of obesity and related disorders (Musso *et al.*, 2010).

### *Autism spectrum disorder (ASD)*

Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication and behavioral challenges. The Diagnostic and

Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) adopted the term Autism Spectrum Disorder (ASD) with a dyadic definition of core symptoms: early-onset of difficulties in social interaction and communication, and repetitive, restricted behaviors, interests, or activities (APA, 2013). ASD is a dynamic disorder with complex changes over time from childhood into adulthood (Lange *et.al*., 2015), and developmental perspective may contribute to interpret some contradictory findings in ASD studies (Uddin *et.al*. , 2013).

***Prevalence of ASD***

The Centers for Disease Control and prevention (CDC), 2018, mentioned that the vulnerability to autism had gone up to 1 in 59 – twice as great as the 2004 rate of 1 in 125. According to 2018 report of the National Autism Spectrum Disorder Surveillance System, 1 in 66 has been diagnosed with ASD in Canada. In Korea, the pervasiveness of ASD amounts to 2.64% in school-age children (Kim *et.al*., 2011). It is found that ASD occurs in males four times more than females (Fombonne, 2005). 1 in 42 males is found to be affected by ASD. 1 in 165 females is diagnosed with ASD. 1% of the world population has ASD (approximately).

***Etiology of ASD***

An inter-play between genetic and environmental factors, as well as both systemic inflammation and inflammation of the central nervous system is said to have an effect on the etiology of ASD (Karimi *et al,* 2017, Wu *et al*, 2017, Siniscalco *et al*, 2018). Twin studies support genetic and environmental contributions to ASD pathogenesis. It has been observed that about 10%-20% individuals with ASD have gene defects and chromosomal anomalies (Herman *et.al*., 2007; Miles 2011). Siblings of individuals with ASD have a 50 times greater risk of ASD compared to neurotypically healthy individuals having a recurrence rate of 5%-8% (Szatmari *et al,* 1998). In identical twins, this concordance rate reaches up to 82%-92% compared with 1%-10% in fraternal twins. Point mutations can change developmental pathways of neurones involved in synaptogenesis and axon motility in the uterus (Chang *et.al*., 2015; Geschwind 2011; Voineagu *et.al*.,2011). Autism spectrum disorder (ASD) is associated with several oropharyngeal abnormalities, including dysbiosis in the oral microbiota (Olsen and Hicks, 2019).

***Human microbiome and Bio-markers of ASD***

Biomarkers will not replace clinical assessments, which characterize the extent of specific deficits, but could potentially change intervention/treatment goals and methods (Walsh *et al,* 2009). The human microbiome, consisting of the total microbial complement associated with human hosts, is an important emerging area for metagenomic biomarker discovery (Hamady *et al,* 2007). It has been noticed in less than 5% cases that people with certain errors in metabolic pathways, such as, phenylketonuria, creatine deficiency syndromes, adenylosuccinate lyase deficiency, and metabolic purine disorders may develop autistic symptoms (Clifford *et.al*.,2007)

People having certain genetic conditions, such as, Down Syndrome, Fragile X Syndrome, and Rett Syndrome are more susceptible than others to be affected by ASD. Recent studies suggest that in 40% of ASD cases, there is a positive correlation between mutation in cerebellar developmental patterning gene ENGRAILED 2 and autism (Manzi *et.al*.,2008). Other suspected genes responsible for ASD are UBE3A locus, GABA system genes, and serotonin transporter genes (Gharani *et.al*.,2004).

Different pre-natal, peri-natal, and post-natal factors also contribute to ASD (London *et.al*., 2000). Some of the pre-natal factors were viz exposure to teratogens such as thalidomide, intrauterine stress; maternal anticonvulsants such as valproic acid (Kern *et.al.,* 2006; Kolevzon *et.al*., 2007). Some peri-natal factors are Low birth weight, abnormally short gestation length, perinatal depression and birth asphyxia (Kolevzon *et.al*., 2007). Post natal factors include autoimmune disease, viral infection, hypoxia, mercury toxicity, and others (Kern *et.al*., 2006; Ashwood *et.al*., 2004; Courchesne *et.al*.,2011).

***Gut Microbiota & ASD***

The Brain-Gut-Microbiome axis is a concept that refers to the complex interactions between the central nervous system, GI system and the microorganisms of the GI tract. All the microbes in the intestine are called gut microbiota. Collective genomes of gut microbes are called gut microbiome. Gut microbiota, consisted of trillions of microorganisms and modulated mainly by diet (Scott *et al.*, 2012), has recently been recognized as a primary mediator for human health (Cani & Delzenne, 2009; Everard & Cani, 2013). The gut microbiome, which may contain > 100 times the number of genes in our genome, endows us with functional features that we have not had to evolve ourselves (Bäckhed *et al,* 2005).

Based on variation in 16S rRNA genes, it is assumed that the healthy adult gut microbiota comprises four major phyla that in all can correspond to more than 90% of the total bacterial population: Bacteroidetes (gram-negative -- *Bacteroidetes*, *Prevotella*), Firmicutes (gram-positive--*Lactobacillus*, *Clostridium* and *Ruminococcus*), Proteobacteria (*Enterobacter*), Actinobacteria (gram-positive--*Bifidobacterium*) followed by the minor phyla Fusobacteria and Verrucomicrobia. Intestinal dysbiosis, an imbalance in the beneficial organisms in the gastrointestinal tract and/or an overgrowth of pathogenic organisms, can be seen in many individuals with autism.

The Bacteroidetes phylum chiefly generates acetate and propionate, whereas the Firmicutes phylum has butyrate as its primary metabolic end product. Most bacterial activity takes place in the proximal colon where substrate availability is maximum. Toward the distal colon, the availability of substrate falls and the extraction of free water decreases diffusion of substrates and microbial products. This forms the proximal part of the colon, the key site of fermentation. Typically, non-digestible carbohydrates are fermented in the proximal colon by saccharolytic bacteria. Recent studies demonstrate that the intestinal flora of individuals with autism differs from that of individuals without autism (Finegold *et al.,* 2002, 2010, 2011; Kang *et al.*, 2013). Gut microbiome of children with ASD contains abundance of Faecalibacterium, Bacteroides , Suterella, *Clostridium, Lactobacillus, Proteobacterium, Desulfovibrio* and scarcity of *Bifidobacterium, Veillonella*, *Streptococcus, Prevotella, Actinobacteria.* The fecal matter of children with ASD contains increased amount of acetic acid, propionic acid, lactic acid butyric acid and valeric acid producers.

***The Gut- Brain Connection in individuals with ASD***

The gut microbiota prove to be an important environmental factor that may exert an influence on symptoms of ASD, and children with ASD have distinctive gut microbiota compared to neurotypical children (De Vadder *et al*, 2012).There is a very close connection between the gut and the brain and for this very connection the gut is often referred to as second brain. Bacteria in the gut effect the central nervous system, that lets for constant communication between the gut and the brain (via this gut-brain axis). After extensive research the gut-brain axis theory, is now well-established and accepted. Studies from several groups now states that the gut and the brain communicate and influence each other (Bienenstock *et al.,* 2015; Mayer *et al*., 2015; Cryan *et al.,* 2019).

The healthy G.I tract imbibes only the small molecules of completely broken down food particles originating from fully digested food. Ideally the intestinal wall should be able to prevent large and undesirable molecules. Children with autism often suffer from a range of GI symptoms, including diarrhoea, abdominal pain, constipation and gastroesophageal reflux. Estimates of the prevalence of such symptoms vary from 9 to 91% across studies (Buie *et al,* 2010). Intestinal dysbiosis, an imbalance in the beneficial organisms in the gastrointestinal tract and/or an overgrowth of pathogenic organisms, can be seen in many individuals with autism. When insufficient beneficial bacteria are present, pathogenic flora can overgrow. These pathogenic organism may then secrete toxic metabolites that have several negative consequences. These toxins may contribute to the development of altered intestinal permeability and may then enter the

circulation and subsequently have secondary effects on brain functioning.

***Intervention for ASD***

Most experts agree that the intervention for ASD should be individualized. Various educational and behavioral treatments have been the mainstay of the management of ASD. If disruptive behaviours such as aggression, agitation, hyperactivity, inattention, irritability, repetitive and self-injurious behaviour are addressed properly it may allow educational and behavioral interventions to proceed more effectively. Two kinds of interventions have been used for individuals with ASD; focused intervention practices and comprehensive approach. The focused intervention practices include prompting, reinforcement, discrete trial teaching, social stories, or peer mediated interventions. These are designed to produce specific behavioral or developmental outcomes for individual children with ASD, and used for a limited time period with the intent of demonstrating a change in the targeted behaviors. The comprehensive treatment models are a set of practices performed over an extended period of time and are intense in their application, and usually have multiple components (Richards *et al.,* 2012). Children with autism showed a significant increase in the *Firmicutes* to *Bacteroidetes* ratio and elevation of the amount of *Lactobacillus* spp (Tomova *et al*, 2015).

Children with ASD with more severe symptoms have been shown to have higher levels of *Desulfovibrio* and *Clostridia* than children with milder symptoms. The level of *Clostridium* abundance has been correlated with the disease severity of ASD, as measured using the Childhood Autism Rating score (Iovene *et al,* 2017). Considering the link between the gut and brain, modulating the gut microbiome by antibiotics, probiotics, prebiotics, and/or fecal microbiota transplant (FMT) could be a viable therapeutic option. Probiotics are helpful live bacteria, such as *Lactobacillus, Bifidobacteria*, and *Saccharomycetes* that provide support to health and body function. It has been proved that these beneficial bacteria prevent and mitigate many issues, including depression, anxiety, obesity, bowel disorders, and autoimmune issues. Prebiotics are food components that let the growth of beneficial bacteria in the gut. Non-digestible oligosaccharides dietary fibers consist major group of prebiotics. In FMT, a large diversity and number of commensal microbes from a healthy donor are used to transform a dysbiotic gut microbiome into a healthy microbiome.

Probiotics and prebiotics can raise the levels of health-supportive bacteria in the gut acting in close connection and it has been shown that they together ameliorate leaky gut, neurotransmitter production, and other brain function. The most promising treatment for neurobehavioural symptoms and bowel dysfunction is the application of probiotics mostly a mixture of *Bifidobacteria, Streptococci* and *Lactobacilli.*

**Conclusion**

The microbiome has emerged as a potential therapeutic target in disorders as diverse as IBS, Parkinson's disease, ASD and depression (Felice *et al,* 2016; Yarandi *et al*, 2016). Many other neuropsychiatric disorders including Alzheimer's disease, amyotrophic lateral sclerosis, autism, stroke and drug addiction have been linked, in one way or another, to the microbiome (Quigley, 2017). More studies need to be conducted to confirm the effectiveness of the therapeutic tools using microbiota for Autism Spectrum Disorder.

**Acknowledgments:**

The author are thankful to Autism Society, West Bengal, India.

**Conflicts of Interest:**
The authors declare no conflict of interest.

**References**

American Psychiatric Publishing (2013). Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. American Psychiatric Publishing, Arlington, VA.

Ashwood P, Van de Water J (2004). Is autism an autoimmune disease? *Autoimmun Rev* 3:557-562.

Bäckhed F, *et al. (*2005). Host-Bacterial Mutualism in the Human Intestine. *Science,* 307 (5717): 1915-1920.

Bienenstock, J., Kunze, W., and Forsythe, P. (2015). Microbiota and the gut–brain axis. *Nutr. Rev.* 73, 28–31.

Buie T, Campbell DB, Fuchs GJ 3rd, Furuta GT, Levy J, Vandewater J, et al. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics*. Jan;125(Suppl 1):S1–18.

Cani PD. Delzenne NM. (2009). Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. *Curr. Opin Pharmacol*.;9:737–743.

Chang J, Gilman SR, Chiang AH, Sanders SJ, Vitkup D (2015). Genotype to phenotype relationships in autism spectrum disorders. *Nat Neurosci* 18:191-198.

Clifford S, Dissanayake C, Bui QM, Huggins R, Taylor AK, Loesch DZ (2007). Autism spectrum phenotype in malesand females with fragile X full mutation and premutation. *J Autism Dev Disord* 37:738-747.

Courchesne E, Campbell K, Solso S. (2011). Brain growth across the life span in autism: age-specific changes in anatomical pathology. *Brain Res.* ;1380:138–145.

Cryan, J. F., O'riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., et al. (2019). The microbiota-gut-brain axis. *Physiol. Rev.* 99, 1877–2013.

De, Mitu, Bhattacharya, Manisha, Saha, Animita C., Basu, Indrani, Ganguli, Sayak and Dey, Santi Ranjan. (2019). Influence of Oral Microbiome on Human Health: an Overview. International Journal of Advancement in Life Sciences Research. Online (ISSN: 2581-4877) Volume 2(1): 16-21 pp.

De, Mitu, Ganguli, Sayak and Dey, Santi Ranjan. (2018). Microbiome, Human Health and Biomarkers: A brief review. Harvest- Online Journal (ISSN 2456-6551) Vol 3 (2), pp. 37-48.

De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Backhed F, Mithieux G. (2014). Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell. ;* 156(1-2):84–96.

Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, Lakshmanan A, Wade WG. (2010). The human oral microbiome. *J Bacteriol*192 (19): 5002–5017.

Everard A. Cani PD. (2013). Diabetes, obesity and gut microbiota. *Best Pract Res Clin Gastroenterol*.; 27:73–83.

Felice, V.D.; Quigley, E.M.; Sullivan, A.M.; O'Keeffe, G.W.; O'Mahony, S.M. 2016. Microbiota-Gut-Brain signalling in Parkinson's disease: Implications for Non-Motor Symptoms. *Parkinsonism Relat. Disord.* 27, 1–8.

Finegold SM, Molitoris D, Song Y, *et al.* 2002.Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. September1; 35(Suppl 1):S6–16.

Finegold SM, Dowd SE, Gontcharova V, *et al.* (2010) Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe.* 16(4):444–53

Finegold SM. (2011) State of the art; microbiology in health and disease. Intestinal bacterial flora in autism. *Anaerobe.* 17(6):367–8

Fombonne E. (2005) Epidemiology of autistic disorder and other pervasive developmental disorders. *J Clin Psychiatry.* 66 (suppl 10):3–8.

Gharani N, Benayed R, Mancuso V, Brzustowicz LM, Millonig JH (2004) Association of the homeobox transcription factor, ENGRAILED 2, 3, with autism spectrum disorder. *Mol Psychiatry* 9:474-484.

Geschwind DH (2011) Genetics of autism spectrum disorders. *Trends Cogn Sci* 15:409-416.

Hamady M, Fraser-Liggett CM, Turnbaugh PJ, Ley RE, Knight R, Gordon JI. (2007). The Human Microbiome Project. Nature., 449: 804-810.

Herman GE, Henninger N, Ratliff-Schaub K, Pastore M, Fitzgerald S, McBride KL (2007). Genetic testing in autism: how much is enough? Genet Med 9:268-274.

Iovene MR, Bombace F, Maresca R, Sapone A, Iardino P, Picardi A, et al. (2017). Intestinal dysbiosis and yeast isolation in stool of subjects with autism spectrum disorders. *Mycopathologia*.; 182:349–363.

Kang DW, Park JG, Ilhan ZE, et al. (2013). Reduced incidence of *Prevotella* and other fermenters in intestinal microflora of autistic children. *PLoS One*.; 8(7):e68322.

Karimi P., Kamali E., Mousavi S., Karahmadi M. (2017) Environmental factors influencing the risk of autism. J. Res. Med. Sci; 22: 27.

Kern JK, Jones AM (2006). Evidence of toxicity, oxidative stress, and neuronal insult in autism. *J Toxicol Environ Health B Crit Rev* 9: 485-499.

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

Kolenbrander PE, Andersen RN, Blehert DS. et al. (2002). Communication among Oral Bacteria*. Microbiol Mol Biol Rev*. 66: 486–505.

Kolevzon A, Gross R, Reichenberg A (2007). Prenatal and perinatal risk factors for autism: a review and integration of findings. *Arch Pediatr Adolesc Med* 161:326-333.

Quigley, E.M.M. (2017). Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. *Curr. Neurol. Neurosci. Rep.* 17, 94.

Lange N, Travers BG, Bigler ED, Prigge MB, Froehlich AL, Nielsen JA, Cariello AN, Zielinski BA, Anderson JS, Fletcher PT, Alexander AA, Lainhart JE. 2015. Longitudinal volumetric brain changes in autism spectrum disorder ages 6-35 years. *Autism Res.* ;8: 82–93.

London EA, Etzel RA (2000) The environment as an etiologic factor in autism: a new direction for research. *Environ Health Perspect* 108 Suppl 3:401-404.

Manzi B, Loizzo AL, Giana G, Curatolo P (2008). Autism and metabolic diseases. *J Child Neurol* 23:307-314.

Mayer, E. A., Tillisch, K., and Gupta, A. (2015). Gut/brain axis and the microbiota. *J. Clin. Invest.* 125, 926–938.

Miles JH (2011). Autism spectrum disorders--a genetics review. *Genet Med* 13:278-294.

Musso G, Gambino R. Cassader M. (2010). Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care*.; 33: 2277–2284.

Olsen I, Hicks SD. Oral microbiota and autism spectrum disorder (ASD). J Oral Microbiol. 2019 12;12(1):1702806. doi: 10.1080/20002297.2019.1702806. PMID: 31893019; PMCID: PMC6913665.

Relman, David A. (2012).The human microbiome: ecosystem resilience and health. *Nutr Rev*. 70 (Suppl 1): S2–S9.

Richards C, Oliver C, Nelson L, Moss J (2012). Self-injurious behaviour in individuals with autism spectrum disorder and intellectual disability. *J Intellect Disabil Res* 56:476-489.

Scott KP, Gratz SW, Sheridan PO, Flint HJ. Duncan SH. (2012). The influence of diet on the gut microbiota. *Pharmacol Res.* 69:52–60.

Siniscalco D., Schultz S., Brigida A., Antonucci N. (2018). Inflammation and Neuro-Immune Dysregulations in Autism Spectrum Disorders. *Pharmaceuticals*;11:56.

Szatmari P, Jones MB, Zwaigenbaum L, MacLean JE (1998). Genetics of autism: overview and new directions. *J Autism Dev Disord* 28:351-368.

Tomova A, Husarova V, Lakatosova S, Bakos J, Vlkova B, Babinska K, et al. (2015). Gastrointestinal microbiota in children with autism in Slovakia. *Physiol Behav.* 138: 179–187.

Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. (2007). The human microbiome project. *Nature*. 449: 804–810.

Uddin LQ, Supekar K, Menon V. (2013). Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Front Hum Neurosci*.;7:458.

Walsh, C. J., Guinane, C. M., O'Toole, P. W. & Cotter, P. D. (2014). Beneficial modulation of the gut microbiota. FEBS Letters 588, 4120-4130,

Walsh P, Elsabbagh M, Bolton P, Singh I. (2011) In search of biomarkers for autism: scientific, social and ethical challenges*. Nat Rev Neurosci*; 12: 603–612.

Wu M., Wu Y., Yu L., Liu J., Zhang M., Kong X., Wu B. (2017) A Survey of Epidemiological Studies and Risk Factors of ASD, with a Focus on China. *N. Am. J. Med. Sci*. 10:1–9

Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH (2011) Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 474:380-384.

Yarandi, S. S., Peterson, D. A., Treisman, G. J., Moran, T. H., & Pasricha, P. J. (2016). Modulatory effects of gut microbiota on the central nervous system: how gut could play a role in neuropsychiatric health and diseases. Journal of Neurogastroenterology and motility, *22*(2), 201-212.