Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 208-215 | ISSN:2251-6727

Unlocking the Role of Gut Microbe Symbiosis, Leads SCFAS and Epigenetic Modifications in Autism Behavioural Development Among Young Children in Cuddalore District

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(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS

Gastrointestinal,

Autism Spectrum disorder,

Dysbiosis and Epigenetics

ABSTRACT:

Introduction: The significant increase in gastrointestinal (GI) problems observed in individuals with autism spectrum disorder (ASD) has spurred research into the gut microbiota as a potential contributor to the etiology of ASD. Gut microbial dysbiosis, a prevalent condition in individuals with autism, has been linked to alterations in cognitive abilities and behavioural patterns. This study focuses on elucidating the impact of gut microbial dysbiosis on gut permeability, which may contribute to the development of autism disorder, with a particular emphasis on the role of autoimmune triggering bacteria's, autism associated bacteria's leads to short chain fatty acids (SCFAs) changes and causes epigenetics alterations in young children.

Objectives: To Collect the faecal samples from Sri Rishabh Jain Special Intellectual School,To analysis the associated autoimmune disease bacteria by metagenomics studies.

Methods: Faecal samples were collected from a cohort of 25 participants enrolled at Sri Rishabh Jain Special Intellectual School, aged between 3 and 20 years, who met specific criteria for disabilities and behavioural issues. Stool specimens were obtained from 30 of the 25 children diagnosed with neurodevelopmental disorders and autism spectrum disorder (ASD), as well as from all control subjects during their comprehensive physical and psychological assessments. The extraction of fecal microbial DNA was carried out following the manufacturer's recommendations, utilizing the QIAamp Fast DNA Stool Mini kit (Qiagen, Hilden, Germany). The analysis of bacteria associated with autoimmune diseases and involved autism associated bacteria taxa and the analysis of bacteria responsible to produce short-chain fatty acids (SCFAs) involved a multi-faceted approach.

Results: We recruited 25 subjects with neurodevelopmental disorders and five controls without any neurodevelopmental issues. The neuro and behavioural paediatrician diagnosed the children and confirmed the autism spectrum disorder (ASD) by the criteria of the Autism Rating Scale (CARS). We conducted an examination of microbial markers associated with ASD by assessing differential abundance among 607 species, 297 genera, 38 orders, and 15 phyla. Our analysis included autoimmune-triggering bacteria such as *Citrobacter Sp, Fusobacterium Sp, Klebsiella Sp*

Conclusions: We conducted an investigation into the abundance of microbes that produce short-chain fatty acids (SCFAs), which include acetate, lactate, propionate, and butyrate.

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1. Introduction

Autism spectrum disorders (ASD) are increasingly recognized as complex conditions involving multiple genes and environmental stressors that impact neurodevelopment and brain function [1]. The human gut microbiota consists of a diverse and extensive array of bacteria, and the connection between human disorders and gut microbiota has garnered significant attention in recent years. Imbalances in the microbial environment within the gastrointestinal (GI) system, including issues with gut epithelial permeability, intestinal absorption, GI mobility, and visceral sensitivity, are known to influence both brain function and the development of disorders, including ASD [2], [3] This bidirectional influence between the GI system and the brain is crucial for maintaining homeostasis, and it relies on the presence of symbiotic gut microbes [4]. These microbes, in turn, have a profound impact on central and peripheral brain processes, neurodevelopment, and behaviour.

Commensal microbiota plays a well-understood role in generating metabolites that modulate immune responses, support mucosal barrier function, regulate pathogen expansion, contribute to vitamin and energy production, and fulfil other functions [5]. Dysbiosis of the microbiome could initiate a cascading series of events, such as metabolic processing disruption, epigenetic alterations, increased oxidative stress, inflammation, and the development and progression of significant mental disorders like schizophrenia, autism spectrum disorder (ASD), bipolar disorder, and major depressive disorder (MDD) [6], [7].

Phyla such as Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria are among those involved in these processes.[8]. Healthy colonization with commensal microbes typically begins shortly after birth and continues throughout life due to ongoing interactions. However, dysbiosis, characterized by an imbalance in the microbiome within this microbial ecosystem, can predispose individuals to various conditions, including ASD. Multiple studies have identified alterations in gut microbial ecology in ASD patients when compared to neurotypically developing children.[9]

2. Objectives

The current study emphasizes the dysbiosis of gut microbiota and the role of short-chain fatty acids (SCFAs) metabolites leading to epigenetic changes that cause autistic behaviours in the children of Cuddalore district.

3. Methods

3.1. Study Design

Fecal samples were collected from a cohort of 25 participants enrolled at Sri Rishab Jain Special Intellectual School, aged between 3 and 20 years, who met specific criteria for disabilities and behavioural issues. Exclusion criteria included a lack of prior gastrointestinal disease and no antibiotic usage within the preceding 3 months. The children were diagnosed with neurodevelopmental disorders and autism spectrum disorder (ASD) in accordance with the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) by the American Psychiatric Association (2013). Diagnostic confirmation was conducted by experienced neuro and behavioural paediatricians employing the Childhood Autism Rating Scale (CARS).

A control group comprising typically developing 5 children of similar age was also included in this study. Ethical approval for this research was granted by the Institutional Review Board of Annamalai University and the University Ethics Committee. All experiments and procedures adhered strictly to the guidelines and regulations stipulated in the Institutional Review Board (IRB) protocol. Additionally, informed consent was obtained from all participating donors.

3.2. ETHICAL APPROVAL

The institutional Human Ethics Committee, Rajah Muthiah Medical College and Hospital approved the research work. The ethical registration number of IEC is EC/NEW/INST/2020/1249.

3.3. SAMPLE COLLECTION AND DNA EXTRACTION

Stool specimens were obtained from 30 of the 25 children diagnosed with neurodevelopmental disorders and autism spectrum disorder (ASD), as well as from all control subjects during their comprehensive physical and

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psychological assessments. The parental involvement was solicited for the collection of stool samples at home, wherein they were placed into sterile plastic containers. Subsequently, these home-collected samples were refrigerated and then transported to the research facility within 12 hours, employing a cooler with ice packs for preservation. These specimens were expeditiously frozen at -80°C and remained in cold storage until the DNA extraction process.

The extraction of fecal microbial DNA was carried out following the manufacturer's recommendations, utilizing the QIAamp Fast DNA Stool Mini kit (Qiagen, Hilden, Germany), starting with 250 mg of fecal material. The concentration and purity of the extracted DNA were meticulously assessed using 1% agarose gels. Following this assessment, the DNA was securely stored at -20°C in preparation for subsequent analysis.

3.4. FECAL MICROBIOTA SEQUENCING AND ANALYSIS

To amplify the bacterial 16S rRNA genes from each DNA sample, a primer set specific for the V3-V4 hypervariable regions, along with a unique barcode for multiplexing, was employed. All polymerase chain reaction (PCR) reactions were conducted utilizing Phusion® High-Fidelity PCR Master Mix sourced from New England Biolabs, facilitating metagenome sequencing. Subsequently, for the analysis of microbial diversity, the QIIME software (Version 1.7.0), as developed by Caporaso was utilized. This software enabled the calculation of both alpha and beta diversity estimates.[10]

3.5. SCFA PRODUCING TAXA ANALYSIS

The analysis of bacteria responsible to produce short-chain fatty acids (SCFAs) involved a multi-faceted approach. First, metagenomic sequencing was employed to both identify and quantify bacterial species contributing to SCFA production within the gut. Subsequently, bioinformatics tools were applied to analyze the sequencing data, with a specific focus on discerning the genes and pathways associated with the synthesis of SCFAs, including acetic acid, lactic acid, propionic acid, and butyric acid.

To further our investigation, we utilized the QIIME 2 platform for the assessment of SCFA-producing bacteria diversity. This assessment centered on the taxonomic composition of the gut microbiota, allowing us to gauge the relative abundance of these specific bacteria and thereby ascertain their prevalence within the intricate gut ecosystem. Additionally, we delved into the functional potential of these SCFA-producing bacteria by examining the presence and expression of genes associated with SCFA synthesis pathways, encompassing those governing acetate, lactate, propionate, and butyrate production

4. Results

4.1. CHARACTERISTICS OF STUDY PARTICIPANTS

We recruited 25 subjects with neurodevelopmental disorders and five controls without any neurodevelopmental issues. The neuro and behavioural paediatrician diagnosed the children and confirmed the autism spectrum disorder (ASD) by the criteria of the Autism Rating Scale (CARS).

4.2. GUT MICROBIAL DIVERSITY

The analysis of gut microbial diversity composition between children with ASD and healthy children, at the phylum level, included Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. We found no significant difference in the microbial composition at the phylum level between the two groups. However, the Firmicutes/Bacteroidetes ratio showed a significant distinction between children with ASD and their healthy counterparts. Notably, Bacteroides was the most abundant genus in children with ASD compared to the healthy control groups. Furthermore, the analysis of beta diversity unveiled distinct microbiota profiles between the two groups, suggesting an altered microbial community structure in the ASD group.

4.3. AUTOIMMUNE AND AUTISM ASSOCIATE ABUNDANT TAXA

We conducted an examination of microbial markers associated with ASD by assessing differential abundance among 607 species, 297 genera, 38 orders, and 15 phyla. Our analysis included autoimmune-triggering bacteria such as *Citrobacter Spp*, *Fusobacterium Spp, Klebsiella Spp, Prevotella S*, and *Proteus Spp* The results of our analysis revealed an overabundance of *Prevotella Spp* as the most prevalent in patients with ASD, as shown in Fig

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JCHR (2024) 14(2), 208-215 | ISSN:2251-6727

1. *Prevotella copri*, previously described as a pathogenic factor in rheumatoid arthritis, was notably present.[11], [12],[13],[14] and [15].

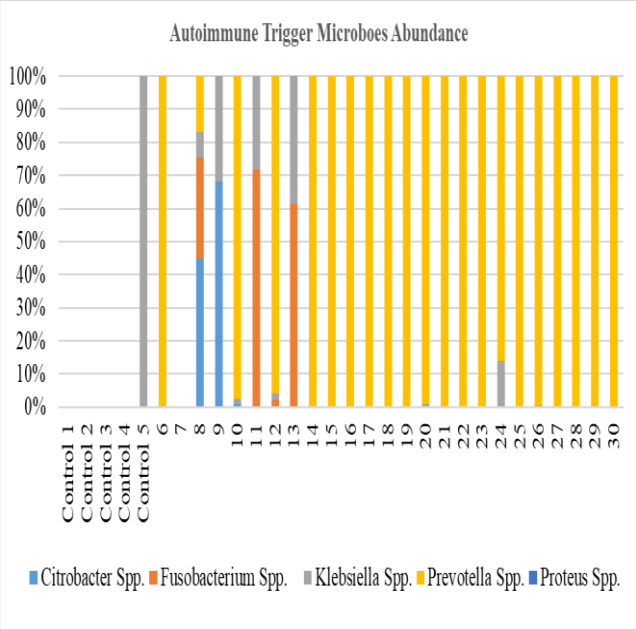

Figure 1: Autoimmune Trigger microbes abundance level.

Bar plot showing autoimmune trigger microbes at the genus level in the stool microbiomes of autism spectrum disorder (ASD) patients and control groups.

Furthermore, we identified high-abundance bacteria associated with autism, including *Alistipes putredinis*, *Bacteroides coprocola*, *Bacteroides stercoris*, *Bacteroides hetaiotaomicron*, *Desulfovibro desulfuricans*, *Eggerthella lenta*, *Enterococcus faecium*, *Sutterella Spp* ,*Turicibacter sanguinis Terrisporobacter glycolicus*, and *Romboutsia timonensis*.[16].[17],[18] and [19]. Notably, our Principal Coordinates Analysis (PCoA) conducted on the Bray-Curtis dissimilarity and unweighted UniFrac distances demonstrated that the gut microbiota of autoimmune and autism-associated taxa clustered separately from other taxa. *Romboutsia timonensis* and *Sutterella Spp*. were found to be most abundant in children with ASD, while *Turicibacter sanguinis* and *Bacteroides spp*. exhibited significantly higher abundance in 70% of children with ASD. Additionally, we observed an increased presence of sulfate-reducing bacteria (SRB) from the *Desulfovibrio* genus in children with ASD compared to healthy children (fig 2).

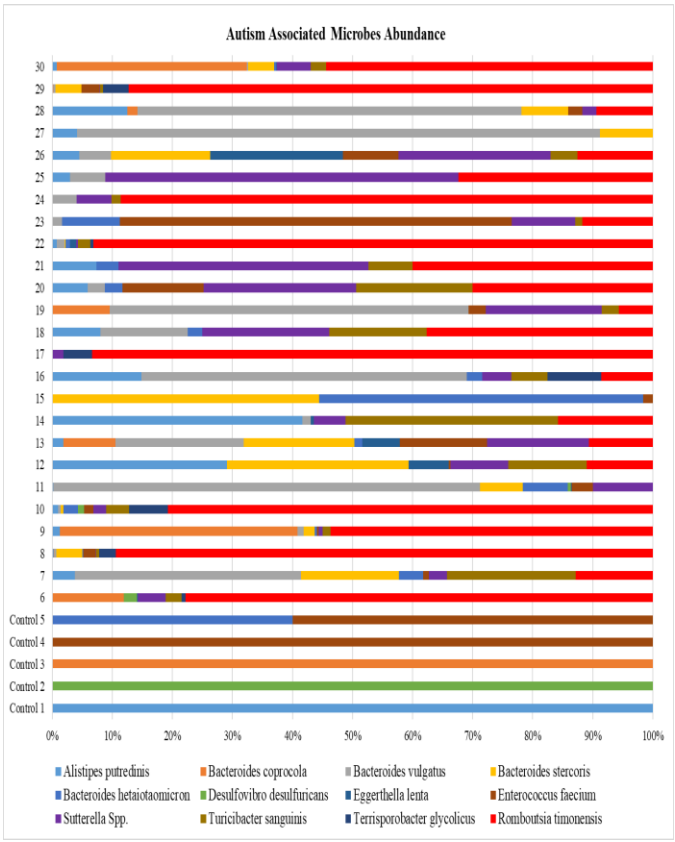

Figure 2: Autism Associate microbes abundance level.

Bar chart of the bacteria represented by 16S rRNA sequences recovered from stool sample.

The abundance levels are calculated based on counts represented in metagenomic sequencing.

4.4. SCFA PRODUCING TAXA ANALYSIS

We conducted an investigation into the abundance of microbes that produce short-chain fatty acids (SCFAs), which include acetate, lactate, propionate, and butyrate (as illustrated in Figure 3). These SCFAs play a pivotal role in promoting gut health by exerting various local effects, such as maintaining intestinal barrier integrity, stimulating mucus production, and offering protection against inflammation. In the control group, SCFAs were present at their expected levels without the presence of any elements. However, in children with ASD, we observed higher levels of propionate and the presence of elements including Lead (Pb), Arsenic (As), Copper

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(Cu), Zinc (Zn), Magnesium (Mg), and Mercury (Hg) compared to the control group.

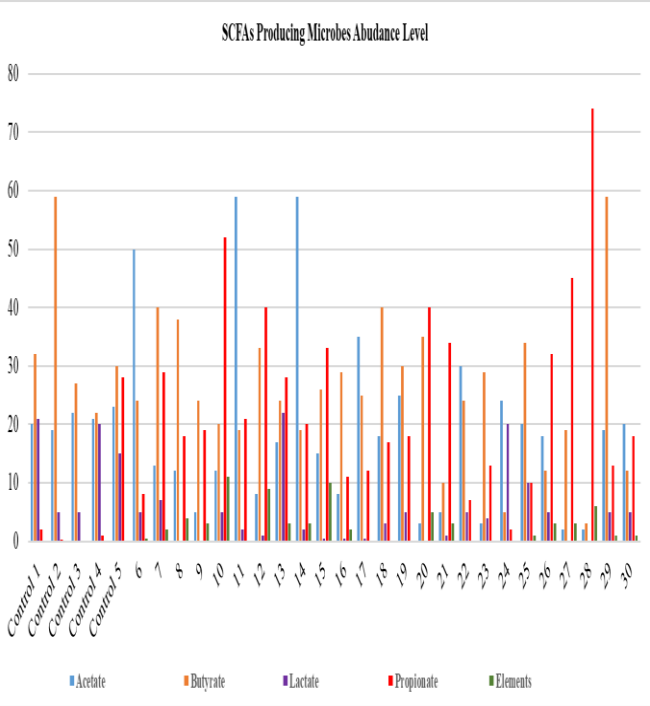

Figure 3: SCFAs producing Microbes abundance level.

(SCFAs) metagenomic sequencing were identify and quantify bacterial species contributing to SCFA production within the gut.

5. Discussion

Lorem ipsum dolor sit amet, consectetur adipiscing elit, The gut microbiome plays a significant role in influencing intestinal permeability and is closely linked to the inflammatory processes involved in the pathophysiology of ASD. The gut microbiota metabolites can alter the brain physiology through neuroendocrine, and neuroimmune pathway.

A study reported a notable increase in the Firmicutes/Bacteroidetes ratio among ASD patients, which was associated with a reduction in Bacteroidetes species. [20]. Accumulating evidence highlights the central significance of gut microbiota and its metabolites, specifically short-chain fatty acids (SCFAs), in gastrointestinal (GI) disorders and the development of autism spectrum disorder (ASD). SCFAs are thought to play a pivotal role in facilitating communication between the microbiota, the gut, and the brain.

In this research, we conducted a comprehensive investigation that encompassed the sequencing of the bacterial 16S rRNA gene, analysis of fecal short-chain fatty acids (SCFAs), assessment of autoimmune-triggering bacteria, autism-associated bacterial abundance, evaluation of GI symptoms, and exploration of the intricate relationship between the gut microbiome and fecal SCFAs in individuals with autism spectrum disorder (ASD) and neurotypical counterparts.

Bacteroides produces short-chain fatty acids and their metabolites, especially propionic acid, which may influence autism behavior through the gut-brain axis. [21]. Clostridia species, more prevalent in individuals with ASD, are implicated in propionate formation. Additionally, we observed increased abundances of Bacteroides, Desulfovibrio, and Clostridium in individuals with ASD, and cognitive abnormalities in ASD patients may be associated with defective propionic acid metabolism, potentially linked to changes in propionate-producing bacteria.[22]. Propionic acid readily crosses the blood-brain barrier, initiating mitochondrial dysfunction through the disruption of the Electron Transport Chain (ETC), resulting in the production of reactive oxygen species (ROS) due to oxidative stress.[23] Propionate, a neurotoxin, hinders the production of Nicotinamide Adenine Dinucleotide (NADH), contributing to nervous system impairment.[24].

Our findings revealed significant alterations in the composition of gut microbiota abundance and SCFA levels among individuals with ASD. Specifically, ASD subjects exhibited diminished levels of fecal acetic acid and butyrate, along with an elevated presence of fecal propionic acid. These changes coincided with reduced abundances of key butyrate-producing taxa, such as *Ruminococcacea*e, *Eubacterium*, *Lachnospiraceae*, and *Erysipelotrichacea*e, as well as an increased prevalence of propionic acid-associated bacteria, including Acidobacteria. The Prevotella-dominated microbiota produced 2–3 times more propionate than the Bacteroides-dominated microbiota, indicating distinct carbohydrate fermentation patterns resulting in varying SCFA amounts and ratios.

Furthermore, our analysis identified an enrichment of autoimmune-triggering *Prevotella spp* and heightened levels of bacteria associated with autism

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(*Romboutsia timonensis* and *Sutterella Spp*.) among individuals with ASD and behavioral challenges (as shown in Figure 2). Sutterella is known to regulate mucosal metabolism and the integrity of intestinal epithelial cells, suggesting that alterations in mucus-degrading microbes could potentially affect the integrity of the gut's mucosal barrier.

Exposure to autoimmune-triggering microbes and autism-associated microbes has the potential to produce propionic and induce epigenetic alterations in host cells, leading to modifications in gene expression patterns. These alterations could influence the development of autoimmune diseases by modulating immune responses or increasing susceptibility to autoimmunity.

Romboutsia timonensis was the sole taxa associated with autism diagnosis and exhibited high abundance levels in most ASD children. On the other researcher, suggested that the propionate and butyrate, especially, exert their effects through the inhibition of histone deacetylase activity (HDAC) [25]

Turicibacter expresses the protein CUW_0748, which shares sequence and predicted homology with the mammalian serotonin transporter (SERT). SERT is a membrane transporter responsible for the reuptake and inactivation of serotonin in various organs, including the gut. [26]. The high abundance of Turicibacter in ASD children may lead to serotonin inactivation and could potentially impact social skills and cognitive function, as observed in most ASD children in our study (Figure 2).

The microbiome can induce changes in the host's epigenome through three distinct pathways: (1) alterations in the allocation of chemical donors for DNA or histone modifications, influenced by nutrient intake and metabolic functions governed by the microbiome; (2) DNA modifications driven by pathways resulting from the integration of foreign genetic material into the host genome; and (3) direct interactions with enzymes responsible for host epigenome changes. Bidirectional communication between the microbiota and the epigenome is evident, with the microbiota affecting the epigenome through the metabolites it produces. Microbiome-derived SCFAs also act as histone deacetylase inhibitors and play essential roles in various physiological processes, including promoting T cell differentiation, neurotransmitter production, immune regulation, inhibition of pro-inflammatory macrophage function, regulation of gut and blood-brain barrier (BBB) permeability, and neuroprotection. Propionic acid, in particular, can induce reversible behavioural, neuro-inflammatory, metabolic, and epigenetic changes in ASD children, with high levels of propionate leading to microglia activation, neurotoxic cytokine production, genetic expression alterations, abnormal hippocampal histology, and abnormal neurobehaviors such as repetitive actions and impaired social interaction. These epigenetic changes result in enhanced transcription of inhibitory neurotransmitter pathways in the frontal cortex, primarily through HDAC inhibition. [27]. High abundance levels of autoimmune, autism associated bacteria produce propionic acid induced epigenetic changes and causes the ASD in the Cuddalore district children. [28].

6. Conclusion

Despite the association of gut microbial dysbiosis with ASD etiology, it is currently unlikely that a specific microbe can be identified as a defining characteristic of ASD. This approach will aid researchers in understanding the connections between genes and environmental factors in ASD. It is evident that research in the field of epigenetics holds great potential for individuals with ASD. This potential includes the development of consistently reproducible epigenetic biomarkers for assessing the risk, diagnosis, and prognosis of this disorder. A better understanding of microbiota-related epigenomic processes could contribute to the development of future therapeutic approaches for microbiome disorders like autism.

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