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LONGITUDINAL MICROBIOME ANALYSIS REVEALS EARLY *BACTEROIDES* PREDOMINANCE AS A POTENTIAL BIOMARKER FOR AUTISM SPECTRUM DISORDER: A PEDIATRIC CASE STUDY WITH COBALAMIN METABOLIC IMPLICATIONS

The intricate relationship between gut microbiota and neurodevelopmental disorders has emerged as a critical area of research, particularly in autism spectrum disorder (ASD). This case study presents groundbreaking longitudinal evidence of gut microbiota alterations preceding ASD diagnosis in a two-year-old female infant. The research aimed to characterize early-life microbiome dynamics and their potential connection to subsequent ASD development, contributing to our understanding of the gut-brain axis in neurodevelopmental disorders. Using shotgun metagenomic sequencing, we tracked the infant's microbiome composition from birth through 18 months of life, comparing it with 215 control samples. Our methodology incorporated comprehensive bioinformatic analysis using the bioBakery suite, including MetaPhlAn 4 for taxonomic profiling and HUMAnN 3 for functional profiling. The study revealed a persistent and significant elevation in *Bacteroides* abundance, particularly *B. fragilis*, from the first month of life, preceding clinical ASD manifestation. Notably, functional analysis demonstrated an increased presence of cobalamin biosynthesis genes associated primarily with *Bacteroides*, suggesting potential interference with vitamin B12 metabolism. These alterations persisted despite probiotic intervention, indicating a robust dysbiotic state. This research provides valuable insights into early microbiome changes that may serve as potential biomarkers for ASD risk.

Keywords: Autism Spectrum Disorder; *Bacteroides fragilis*; cobalamin; gut metagenome.

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Микробиомның бойлық талдауы аутизм спектрінің бұзылысының әлеуетті биомаркері ретінде *Bacteroides* бактериясының ерте басымдылығын анықтайды: кобаламин метаболизміне әсер ететін педиатриялық клиникалық жағдай

Ішек микробиотасы мен нейродамудың бұзылыстары арасындағы күрделі байланыс зерттеудің маңызды саласына айналды, әсіресе аутизм спектрінің бұзылысында (АСБ). Бұл клиникалық зерттеу екі жасар қыз баланың АСБ диагнозына дейінгі ішек микробиотасының өзгерістері туралы бұрын-соңды болмаған бойлық дәлелдемелерді ұсынады. Зерттеудің мақсаты ерте жастағы микробиомның динамикасын және оның кейінгі АСБ дамуымен ықтимал байланысын сипаттау болды, бұл нейродамудың бұзылыстарындағы ішек-ми осінің түсінігін кеңейтуге үлес қосты. Біз шотган метагеномдық секвенирлеуді қолдана отырып, нәрестенің туғаннан бастап 18 айға дейінгі микробиом құрамын бақылап, оны 215 бақылау үлгісімен салыстырдық. Біздің әдіснамамыз BioBakery жиынтығын қолданып жан-жақты биоинформатикалық талдауды қамтыды, оның ішінде MetaPhlAn 4 таксономиялық профильдеу және HUMAnN 3 функционалдық профильдеу бар. Зерттеу өмірдің бірінші айынан бастап, АСБ-ның клиникалық көрінісіне дейін *Bacteroides*, әсіресе *B. fragilis* мөлшерінің тұрақты және айтарлықтай жоғарылағанын анықтады.

функционалдық талдау негізінен *Bacteroides*-пен байланысты кобаламин биосинтезі гендерінің жоғарылауын көрсетті, бұл B12 дәруменінің метаболизміне ықтимал әсерін көрсетеді. Бұл өзгерістер пробиотикалық араласуға қарамастан сақталды, бұл тұрақты дисбиотикалық жағдайды көрсетеді. Бұл зерттеу АСБ қаупінің ықтимал биомаркерлері ретінде қызмет ете алатын ерте микробиомдық өзгерістер туралы құнды түсінік береді.

Түйін сөздер: Аутизм спектрінің бұзылысы; *Bacteroides fragilis*; кобаламин; ішек метагеномы.

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Продольное исследование микробиома обнаруживает раннее преобладание *Bacteroides* в качестве потенциального биомаркера аутизма: клинический случай у ребенка с последствиями для метаболизма витамина B12

Сложная связь между микробиотой кишечника и нарушениями нейроразвития стала важнейшей областью исследований, особенно при расстройствах аутистического спектра (РАС). В этом исследовании представлены новаторские продольные доказательства изменений микробиоты кишечника, предшествующих диагностике РАС у двухлетней девочки. Целью исследования было охарактеризовать динамику микробиома в раннем возрасте и ее потенциальную связь с последующим развитием РАС, что способствовало нашему пониманию оси кишечник-мозг при нарушениях нейроразвития. Используя дробное метагеномное секвенирование, мы отслеживали состав микробиома младенца с рождения до 18 месяцев жизни, сравнивая его с 215 контрольными образцами. Наша методология включала комплексный биоинформационный анализ с использованием пакета bioBakery, включая MetaPhlAn 4 для таксономического профилирования и HUMAnN 3 для функционального профилирования. Исследование выявило постоянное и значительное повышение численности *Bacteroides*, в частности *B. fragilis*, с первого месяца жизни, предшествующего клиническому проявлению РАС. В частности, функциональный анализ продемонстрировал повышенное присутствие генов биосинтеза кобаламина, связанных в первую очередь с *Bacteroides*, что указывает на потенциальное вмешательство в метаболизм витамина B12. Эти изменения сохранялись, несмотря на пробиотическое вмешательство, что указывает на сильное дисбиотическое состояние. Это исследование дает ценную информацию о ранних изменениях микробиома, которые могут служить потенциальными биомаркерами риска РАС.

Ключевые слова: Расстройство аутистического спектра; *Bacteroides fragilis*; кобаламин; метагеном кишечника.

1. Introduction

Recent studies highlight the complex nature of autism spectrum disorder (ASD), a neurodevelopmental condition characterized by difficulties in social communication and stereotypical behavior. The prevalence of ASD has increased significantly, with current estimates at approximately 2.8% [1]. Statistical data from Kazakhstan also indicate a rise in ASD cases over the past decade [2].

Recent research has identified a substantial impact of gut microbiota on neurotransmitters such as glutamate and GABA, and a significant association with mental disorders such as depression, schizophrenia, and ASD [3,4]. Studies from different national cohorts demonstrated significantly altered microbiota composition features in ASD patients, and in many cases, an increase in the short-chain fatty acid (SCFA) producer *Bacteroides* [5-8]. Consistent with this, some studies have reported elevated levels of propionic acid (PPA) in ASD patients [9,10]. PPA, can cross the blood-brain barrier and may lead to neuroinflammation, increased oxidative stress, glutathione depletion, altered phospholipid/acylcarnitine profiles, effects on mitochondrial function, and altered gene expression. Noteworthy *Bacteroides* is known to be able to interfere with vitamin B utilization. It has been shown that the human gut bacterium *Bacteroides* can not only bind to vitamin B12 with high affinity, but also remove it from human intrinsic factor, a B12 transport protein in humans [11]. Vitamin B12 is essential for optimal brain development, neural myelination, and cognitive function. Significantly low or high levels of B12 during pregnancy have been associated with an increased risk of offspring with ASD [12].

2. Materials and methods

Recruiting

We recruited healthy newborns immediately after birth from the maternity ward of the Perinatal Center in Astana. After providing all necessary information, parents (mothers) signed an informed consent document, officially confirming their agreement for their child's participation in the study. Collection of infant fecal samples was conducted immediately after birth (first-pass meconium) and at dynamic observation points at 1, 3, 6, 12, and 18 months of life. Maternal fecal samples were collected one month postpartum. The study protocol was approved by the ethics committee of the National Laboratory Astana, Nazarbayev University (protocol #05-2022). The studies were conducted in accordance with the World Medical Association Declaration of Helsinki.

This study included one child diagnosed with ASD and 215 samples basic group. ASD diagnosis was made by pediatric psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM, 5th Ed. 2013) at the age of 2 years. Exclusion criteria for neurotypical children included a positive family history of ASD. Exclusion criteria for both groups were neurological disorders, intellectual disability, depressive disorders, and other gastrointestinal tract-related diseases. All recruits included in this report had not taken antibiotics in the three months preceding sample collection.

DNA Extraction from Fecal Samples and Sequencing

Fecal samples were collected using DNA/RNA Shield Fecal Collection Tubes (Cat. # R1101, ZymoResearch). The samples were transported to the laboratory within 24 hours and stored at +4°C until DNA extraction. Bacterial genomic DNA was isolated from the fecal samples using the ZymoBIOMICS DNA Miniprep Kit (Zymo Research, D4300), with sterile μQ water as a negative extraction control. Quality control of DNA isolation was performed using OD260/280 Nanodrop and 1% agarose gel electrophoresis. The concentration and purity of each DNA sample were determined using an Invitrogen Qubit 3.0 fluorometer (Invitrogen, Carlsbad, CA, USA). Sterile μQ water served as a negative control. Following standard Illumina protocols, sequencing was conducted on the Illumina NovaSeq 6000 platform at Novogene Laboratory (Beijing, China).

Data Processing and Statistical Analysis

Our research took a comprehensive approach to the analysis of raw sequencing data. We employed the bioBakery suite, which integrates a range of methods for taxonomic and phylogenetic profiling of metagenomes. MetaPhlAn 4 was used for taxonomic profiling, and HUMAnN 3 for functional profiling. We applied the recommended parameters provided by the developers to all tools used in the analysis, ensuring a thorough and rigorous approach.

To identify taxonomic and functional markers across time points and at individual time points, the DESeq2 algorithm from the PyDESeq2 0.4.9 library was implemented. Markers were considered significant at $p \leq 0.05$ after correction for multiple comparisons (BH FDR). The relative abundance of bacterial genes was analysed based on the results of HUMAnN 3 profiling. Annotation of HUMAnN 3 profiling results at the gene level was performed based on UniProt annotations, considering only current entries.

3. Results and discussion

We present a case of a female newborn subsequently diagnosed with early childhood autism. The child was born from the seventh pregnancy, complicated by gestational hypertension and chronic pyelonephritis. Spontaneous vaginal delivery occurred at 265 days of gestation. The newborn was in good condition (Apgar score 8/9), requiring no resuscitation, with a birth weight of 4,630 grams and a length of 56 cm. The infant was discharged after 72 hours with moderate risk of perinatal central nervous system involvement.

Follow-up examinations revealed persistent intestinal dysbiosis from 6 months of age (continuing through 36 months), positive IgG antibodies to cytomegalovirus, and mild anaemia. At 21 months of age, the child experienced initial absence seizures, which progressed to clonic-tonic seizures by 22 months, occurring twice daily with a duration of 1-20 minutes. Magnetic resonance imaging revealed the right frontal lobe pachygyria and focal brain matter changes. Treatment included magnesium sulfate for 3 days and carbamazepine 75 mg twice daily (15 mg/kg) for one month, followed by oxcarbazepine 1.5 mL in the morning and 2.0 mL in the evening. At 24 months, autism spectrum disorder was diagnosed. The child had been receiving bifidobacteria-containing probiotics since 3 months of age.

To comprehensively understand the microbiome characteristics prior to ASD manifestation, we me-

ticulously conducted a comparative analysis of fecal samples from the child and mother against a control group (total 215 samples: 41 mothers and their children Female/Male: T2 – 37 children (19/18), T3 – 30 children (15/15), T6 – 33 children (15/18), T12 – 26 children (13/13), T18 – 22 children (11/11)). The average sequencing depth was 7.0 Gigabases per metagenome. All samples underwent a standardized processing protocol to minimize technical variability.

Our longitudinal analysis of taxonomic diversity showed no significant increase in alpha diversity (Observed index, p=0.28; Shannon index, p=0.19) in the ASD child's samples from birth to 18 months. This finding contrasts with some recent reports suggesting increased alpha diversity in ASD cohorts [6], which traditionally challenges prevailing notions as decreased alpha diversity has been associated with compromised health in various conditions. The maintained alpha diversity in our case may reflect the early intervention with probiotics, though it did not prevent the underlying dysbiotic changes. However, our comparison of relative microbial abundance (Fig. 1A) revealed significant differences between the control and ASD groups at all analyzed points, which aroused our interest. Longitudinal monitoring of the *Bacteroides* genus (Fig. 1B) demonstrated its significant predominance in the microbial structure from the first to sixth month of life (p=0.037) in the child with ASD, peaking at approximately 55.0% in the first month (T2).

Recent experimental evidence demonstrates that *B. fragilis*-treated male mice display social behavior dysfunction, increased repetitive behaviors, and gene expression dysregulation in the prefrontal cortex, while female mice do not display behavioral deficits [6]. While our case involves a female infant, the early and persistent *Bacteroides* elevation suggests that the timing of exposure may be more critical than sex-specific susceptibility during early neurodevelopmental windows. The *Collinsella* genus also showed consistent elevation in the ASD group (p=0.007), particularly notable until 3 months of age (T3), maintaining elevated levels at T12 and T18 time points. Additionally, non-significant decreases in *Escherichia coli* (p=0.24) and *Bifidobacterium* (p=0.37) were observed from the early months of life.

Notably, administering bifidobacteria-containing probiotics at 3 months did not increase the relative abundance of the *Bifidobacterium* genus. Conversely, by 6 months, an increase in *Bacteroides* was observed, predominantly due to *B. fragilis*. This resistance to probiotic intervention aligns with emerging evidence that different microbial interventions may have varying effectiveness in ASD, with some studies exploring more comprehensive approaches such as microbiota transfer therapy [13]. By 12 months of age, the fecal microbiome was dominated by *Bacteroides* and *Faecalibacterium prausnitzii* (Fig.1 A). Notably, the *Bifidobacterium* level in the mother of the child with future ASD status was below the group average (0.6% vs 7% in controls). This observation is consistent with emerging research on the maternal exposome and autism risk [14], suggesting that maternal microbiome composition may influence offspring neurodevelopmental trajectories.

Functional gene profiling based on the UniProt database revealed a significantly increased presence of cobalamin biosynthesis genes (KW0169), primarily associated with *Bacteroides* and, to a lesser extent, with *Collinsella* and *Blautia*, as illustrated in the taxonomic distribution diagram of cobalamin biosynthesis genes (Fig. 1C). The discovered association between microbial composition and metabolic disturbances is of utmost importance. The increased potential ability of *Bacteroides* for B12 synthesis (Fig. 1C) and utilization [11] may indicate possible cobalamin sequestration by the microbiota. Recent systematic reviews have identified 17 studies examining B12 as a treatment in ASD, with most studies using oral or injected methylcobalamin, demonstrating potential therapeutic benefits [15]. Vitamin B12 is critical in myelin synthesis, DNA methylation, and nervous system development, potentially significantly affecting cognitive functions and neurodevelopment [16]. The early-life elevation of *Bacteroides* in our case study suggests that microbial sequestration of cobalamin may occur during critical neurodevelopmental windows, potentially contributing to the pathophysiology of ASD.

Interestingly, recent studies have shown that *Bacteroides*-dominant gut microbiomes in late infancy are associated with enhanced neurodevelopment, with different species of *Bacteroides* including *B. fragilis* and *B. uniformis* positively associated with increased cognitive development [17]. This apparent contradiction with our findings highlights the importance of timing, dose-response relationships, and individual susceptibility factors in microbiome-neurodevelopment interactions. The persistence of *Bacteroides* elevation from the first month of life in our case suggests that early, excessive colonization may disrupt normal neurodevelopmental processes, whereas moderate levels at later time points may be beneficial.

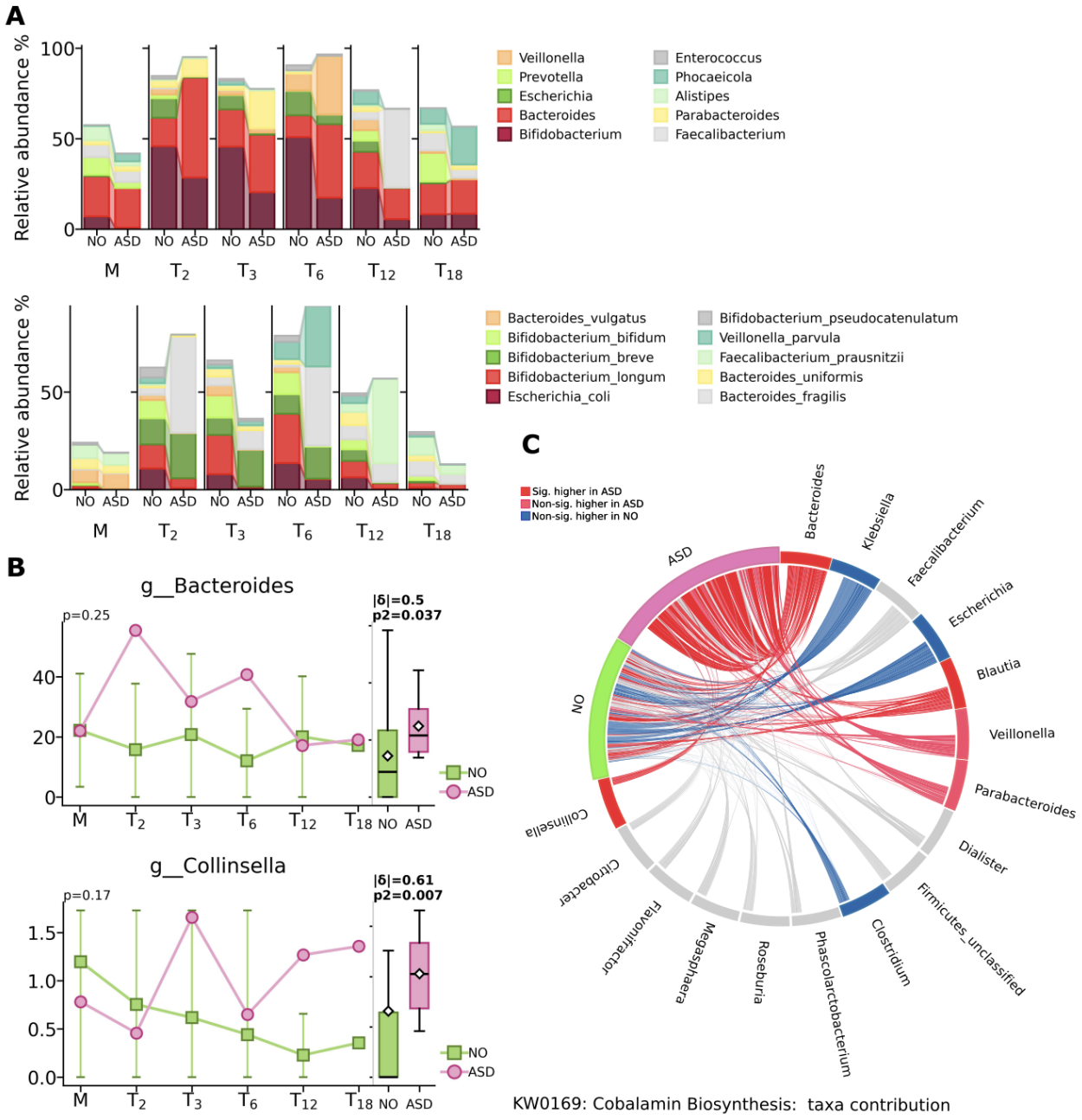

Figure 1 – Relative abundance of microbial taxa in fecal samples from control group children (NO) and child with autism spectrum disorder (ASD) during the first 18 months of life, as well as their mothers. A) Mean relative abundance of taxa at taxonomic levels: genus and species levels. B) Relative abundance of *Bacteroides* in *Collinsella* genera in NO and ASD. Data are presented for six time points: mother microbiome (M), at 1 month (T2), 3 months (T3), 6 months (T6), 12 months (T12), and 18 months (T18). C) Chord diagram of the taxonomic distribution of cobalamin biosynthesis genes (KW0169) at genera level

Our study highlights the critical importance of developing an altered microbial structure in a child who subsequently develops ASD. From the first month of early life, we detected significant dysbiotic changes in the feces of the child with future ASD status, characterized by the predominance of *Bacteroides* (31.0% vs 18.5% in controls on average), mainly due to *B. fragilis* (19.1% vs 3.8% in controls), which chronologically preceded clinical disease manifestation. Recent research suggests that interventions targeting the gut microbiota through various approaches, including fecal microbiota

transplantation, may be promising for treating gastrointestinal disorders and behavioral traits associated with ASD [13]. Our findings support the potential for early microbiome screening as a risk assessment tool, potentially enabling interventions before clinical symptoms manifest.

The gut-brain axis and its complex bidirectional communication system between the central nervous system and the enteric nervous system have revealed the central role of the gut microbiome in regulating neuroimmune networks, modifying neural networks, and communicating directly with the brain [4]. Our case study contributes to this understanding by providing longitudinal evidence of microbiome alterations preceding clinical diagnosis. Recent randomized clinical trials have demonstrated that specific *Bacteroides* strains, such as *B. fragilis* BF839, can significantly improve abnormal behavior and gastrointestinal symptoms in children with ASD [18]. However, our findings suggest that the therapeutic window and strain-specific effects require careful consideration, as early-life overgrowth of certain *Bacteroides* species may be detrimental.

While our case study provides valuable longitudinal data, several limitations must be acknowledged. First, this is a single case study, limiting generalizability. Second, the complex interplay between genetic predisposition, environmental factors, and microbiome composition requires larger cohort studies to disentangle. Third, the functional implications of elevated cobalamin biosynthesis genes require direct metabolomic validation. Recent systematic reviews of pediatric and adult studies have highlighted the functional contribution of intestinal microbiomes in various neurodevelopmental disorders [19], emphasizing the need for standardized methodologies and larger sample sizes. Our study contributes to this growing body of evidence while acknowledging the need for replication in larger cohorts.

The relationship between eating issues, microbiome, and gastrointestinal symptoms in autism spectrum disorder has become increasingly recognized, with food selectivity and nutritional deficiencies being closely associated with altered gut microbiota composition [20]. Our case study supports these associations, as the child showed selective eating patterns and required nutritional interventions. The findings of this case report shed light on the formation of an altered gut microbiome prior to ASD, indicating a potential role for the microbiota in the development of the pathological process. The increase in the copy number of vitamin B12 biosynthetic genes, a significant finding in this study, suggests a potential link between gut microbiome and vitamin B12 metabolism in ASD. Given that most existing studies have focused on cross-sectional observation of microbiota after the onset of ASD, there is a significant opportunity for further research in this area.

Conclusion

This case study identified significant changes in the gut microbiota in the first months of early life, characterized by *Bacteroides* dominance and increased cobalamin biosynthesis genes, preceding the onset of ASD. The persistence of these changes despite probiotic therapy, along with a similar maternal microbiota profile, reveals potential microbial markers of ASD risk. These findings highlight the importance of early screening of the microbiota and its metabolic activity. However, they also underscore the urgent need for extensive prospective studies to confirm these associations and advance our understanding of ASD.

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Data Availability Statement

The raw sequence data in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: NCBI BioProject [accession number PRJNA949528].

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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