論　文　内　容　要　旨

Altered microbiota composition reflects enhanced communication in 15q11-13 CNV mice

(15q11-13 CNV マウスにおいて腸内細菌叢の変化がコミュニケーションを改善する)

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ABSTRACT

Autism spectrum disorder (ASD) is a complex and heterogeneous neurodevelopmental disorder. In addition to the core symptoms of ASD, many patients with ASD also show comorbid gut dysbiosis, which may lead to various gastrointestinal (GI) problems. Intriguingly, there is evidence that gut microbiota communicate with the central nervous system to modulate behavioral output through the gut-brain axis. Although many studies have reported differences in microbiota between patients with ASD and control subjects, no particular gut bacteria species is currently implicated in ASD. Based on the emerging link between gut microbiota and ASD and the lack of consensus on specific causative gut bacteria, we aimed to investigate the microbiota composition in a mouse model of ASD and to identify the specific microbiota community involved in ASD-related behavioral symptoms. In this study we performed a 16s rRNA gene-based metagenomics analysis in an ASD mouse model. Here, we focused on a model mouse with human 15q11-13 duplication (*15q dup*), the most frequent chromosomal aberration or copy number variation (CNV) found in ASD.

Metagenomic analysis revealed that microbiome species richness was significantly decreased in *15q dup* mice. No differences were found in microbiota relative abundances in phylum and genus level between WT and *15q dup* mice. However, in species level, 13 OTUs were more abundant in WT mice, among which 7 OTUs were not detected in *15q dup* mice. Combination of 4 weeks antibiotics treatment of ampicillin or neomycin followed by behavioral analysis showed that neomycin improved USV call number in *15q dup* mice. However, the antibiotics treatment didn't affect locomotor activity and anxiety-like behavior in any mice. Metagenomic analysis after antibiotics treatment and behavioral test showed an increase in species richness in *15q dup* mice treated with neomycin but not in WT, as shown by OTUs number, Chao1, and ACE index. UniFrac-PCoA also suggested differences in microbiota composition between WT and *15q dup* mice after neomycin treatment. In *15q dup* mice, neomycin increased the relative abundance of *Bacteroides* and *Parabacteroides* and decreased that of *Parasutterella*. But in WT, neomycin increased the relative abundance of *Roseburia* and *Oscillibacter* but decreased that of Lactobacillus. In species level, 6 OTUs which included *Barnesiella viscericola, Clostridium hathewayi, Oscillibacter valericigenes, Prevotella sp. Smarlab 121567, Clostridium clostridioforme, Hydrogenoanaerobacterium saccharovorans,* and *Roseburia inulinivorans* were more abundant in *15q dup* mice treated with neomycin. Moreover, these 6 OTUs are included in the 13 OTUs that were more abundant in WT. These findings suggest that neomycin treatment in *15q dup* mice altered the microbiota composition in favors of the growth of bacteria with beneficial effect on USV

call number.

Most of these candidates of beneficial OTUs belong to Clostridium clusters XIVa and IV. *Clostridium hathewayi*, *Clostridium clostridioforme*, and *Roseburia inulinivorans* belong to Clostridium cluster XIVa, while *Oscillibacter valericigenes* and *Hydrogenoanaerobacterium saccharovorans* belong to Clostridium cluster IV. Clostridium clusters XIVa and IV are known for their anti-inflammatory properties and also abundantly produce short chain fatty acids (SCFAs), including butyrate, propionate, and acetate. SCFAs may regulate brain function through many pathways, including inhibition of histone deacetylase and modulation of 5-HT. 5-HT signaling itself has been associated with USV. Given that the beneficial OTUs identified in this study are SCFA-producing species with the described properties, it is possible that these bacteria are capable of modulating 5-HT levels, thereby affecting USV.

Although further studies using human samples or germ-free mice conventionalized with the candidate of beneficial OTUs are required to confirm our results, the findings presented in this study suggest that beneficial OTUs which produce SCFAs, may enhance USV in the *15q dup* mouse model of ASD.