News Release

Title Patients with Parkinson's disease share similar abnormalities in gut bacteria in five countries

Key Points

- The research team has developed a novel method to meta-analyze gut microbiota.
- They meta-analyzed gut microbiota in Parkinson's disease in Japan, USA, Finland, and Russia.
- Intestinal mucin layer-degrading *Akkermansia* was increased and short-chain fatty acid-producing *Roseburia* and *Faecalibacterium* were decreased in Parkinson's disease across countries.
- We hypothesized that degradation of the intestinal mucin layer increases permeability of the intestinal wall, and causes abnormal aggregation of α-synuclein in the intestinal neural plexus, which ascends to the brain.
- We also hypothesized that lowered short-chain fatty acids fail to suppress abnormal inflammation in the brain and worsens Parkinson's disease.

Summary

Professor Kinji Ohno (co-corresponding author), Associate Professor Masaaki Hirayama (co-corresponding author), Professor Masahisa Katsuno, and a graduate student Hiroshi Nishiwaki (first author) at Nagoya University Graduate School of Medicine; Professor Tetsuya Maeda at Iwate Medical University; Director Kenichi Kashihara at Okayama Neurology Clinic; and Professor Yoshio Tsuboi at Fukuoka University found that mucin layer-degrading *Akkermansia* is increased and short-chain fatty acid-producing *Roseburia* and *Faecalibacterium* are decreased in Parkinson's disease across countries.

Gut microbiota in Parkinson's disease has been reported by 17 groups. Compositions of intestinal bacteria, however, markedly differ from country to country even among normal individuals. This large difference makes it difficult to identify gut dysbiosis in Parkinson's disease across countries. The research team analyzed gut microbiota in 223 patients with Parkinson's disease. They developed a novel method for meta-analysis of gut microbiota, and meta-analyzed the Japanese, American, Finnish, Russian, and German datasets. They also developed a novel pathway analysis tool for gut microbiota, the Kyoto Encyclopedia of Genes and Genomes Orthology Set Enrichment Analysis (KOSEA). Meta-analysis revealed that intestinal mucin layer-degrading *Akkermansia* was increased and short-chain fatty acid-producing *Roseburia* and *Faecalibacterium* were decreased in Parkinson's disease across countries. The results suggest that in Parkinson's disease the increased intestinal permeability predisposes the intestinal neural plexus to oxidative stress and pesticides/herbicides, which leads to abnormal aggregation of α-synuclein fibrils in the intestine followed by the development of Parkinson's disease. The results also suggest that the decreased short-chain fatty acids fail to suppress inflammation in the central nervous system. This research is expected to lead to elucidation of the intestinal mechanisms of Parkinson's disease and to development of novel therapeutic strategies.

Research Background

Parkinson's disease is caused by abnormal accumulation of α-synuclein fibrils called Lewy bodies in the dopaminergic neurons in the substantia nigra in the midbrain. Abnormal accumulation of α-synuclein fibrils may start from the intestine and ascends to the midbrain. First, Lewy bodies are likely to ascend from the dorsal nucleus of the vagus nerve to the substantia nigra in the midbrain. Second, constipation, rapid eye movement sleep behavior disorder (RBD), and depression are frequently observed 20, 10, and 5 years before the onset of motor symptoms of Parkinson's disease. This is in accordance with the ascending Lewy bodies from the vagal nucleus to the locus coeruleus. Third, colon biopsies frequently show abnormal accumulation of α-synuclein fibrils in the submucosal neural plexus in Parkinson's disease. Fourth, we and others previously reported that intestinal permeability is abnormally increased in Parkinson's disease.

Gut microbiota in Parkinson's disease has been reported in 16 original articles and one abstract. Gut microbiota, however, differ from country to country in composition even among normal subjects. This

makes it difficult to compare Parkinson's disease and controls across countries. To identify gut dysbiosis in Parkinson's disease across countries, the research team analyzed gut microbiota in 223 patients with Parkinson's disease, which recorded the highest number of patients. They subsequently conducted meta-analysis of their dataset with those from USA, Finland, Russia, and Germany.

Research Results

After adjusting for confounding factors of body mass index, constipation, sex, age, and drugs, the research team identified that genera *Akkermansia* and *Catabacter* were increased, and genera *Roseburia*, *Faecalibacterium*, and *Lachnospiraceae ND3007 group* were decreased in Parkinson's disease (Fig. 1). Inspection of these bacteria in twelve datasets that could not be included in the meta-analysis revealed that increased genus *Akkermansia* and decreased genera *Roseburia* and *Faecalibacterium* were frequently observed across countries. The research team developed a novel metabolic pathway analysis tool, the Kyoto Encyclopedia of Genes and Genomes Orthology Set Enrichment Analysis (KOSEA), and observed changes in short-chain fatty acid metabolisms.

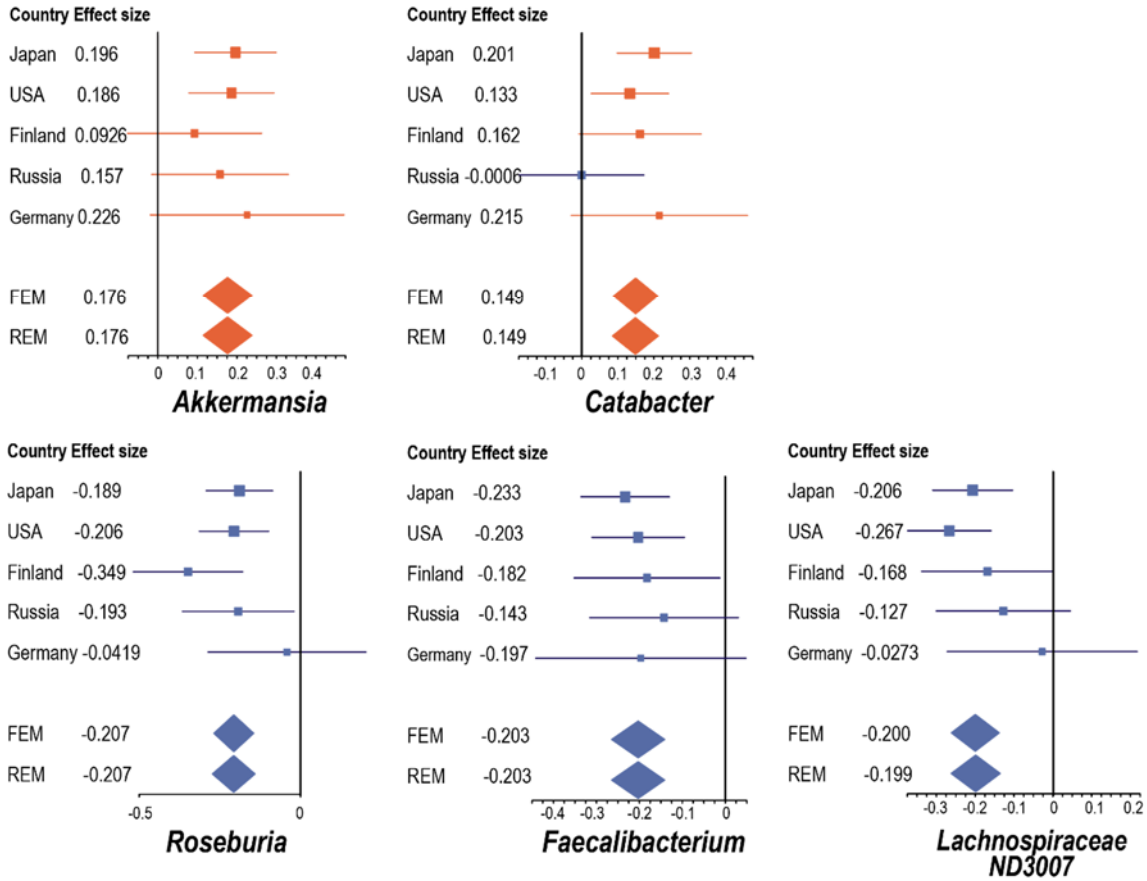

Fig. 1. Five bacterial genera that were commonly changed in Parkinson's disease across five countries. Genera increased in Parkinson's disease are shown in red symbols. Genera decreased in Parkinson's disease are shown in blue symbols. For plots of five countries, a mean is indicated by a box, and 95% confidence intervals are indicated by whiskers. FEM (fixed effect model) and REM (random effect model) are measures representing five countries. The mean and 95% confidence intervals are shown by a diamond.

Research Summary and Future Perspective

The research team identified that intestinal mucin layer-degrading *Akkermansia* is increased, and short-chain fatty acids-producing *Roseburia* and *Faecalibacterium* are decreased in Parkinson's disease. Increased intestinal permeability predisposes the intestinal neural plexus to oxidative stress and pesticides/herbicides, which leads to abnormal aggregation of α-synuclein fibrils in the intestine followed by the development of Parkinson's disease. Decreased intestinal short-chain fatty acids fail to suppress

inflammation in the central nervous system and the development and progression of Parkinson's disease. In addition, the KOSEA pathway analysis tool will disclose abnormalities in metabolic pathways mediated by gut microbiota in many other diseases. The research team is planning to dissect the precise molecular mechanisms of how gut dysbiosis leads to the development and progression of Parkinson's disease.

Publication

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Movement Disorders
Meta-Analysis of Gut Dysbiosis in Parkinson's Disease
DOI: 10.1002/mds.28119
https://onlinelibrary.wiley.com/doi/full/10.1002/mds.28119

Acknowledgements

This study was performed by Grants-in-Aid from the Japan Agency for Medical Research and Development and other funding agencies.

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