News Release

Title

Improvement of intestinal bacteria may prevent dementia: Increased *Collinsella* and decreased *Bifidobacterium* in intestinal microbiota are associated with the development of dementia with Lewy bodies (DLB)

Key Points

- **By analyzing gut microbiota and fecal bile acids in 278 patients with Lewy body diseases, researchers identified gut bacteria that are associated with DLB.**
- **Some gut bacteria were shared in Lewy body diseases, and some were unique to DLB.**
- ***Bifidobacterium* was decreased in both Alzheimer's disease and DLB, suggesting the presence of a shared role of *Bifidobacterium*.**
- **Modulation of these bacteria and their metabolites may delay the onset and progression of neurodegenerative diseases, and improvement of the gut microbiota and administration of associated metabolites is a stepping stone in the treatment of dementia.**

Summary

A research group led by Associate Professor Masaaki Hirayama (Omics Medicine), Professor Kinji Ohno (Neurogenetics), and Assistant Professor Yutaka Nishiwaki (Neurogenetics) of Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura) together with Kenichi Kashihara, Director of Okayama Neurology Clinic, Tetsuya Maeda, Professor of Geriatrics and Neurology, Iwate Medical University, and Yoshio Tsuboi, Professor of Neurology, Fukuoka University (hereinafter referred to as the "research group") discovered that intestinal bacteria *Collinsella* and *Bifidobacterium* are associated with dementia with Lewy bodies (DLB).

DLB is the second most common form of dementia after Alzheimer's disease and is almost as common as Parkinson's disease (PD) in elderly people. In contrast to Alzheimer's disease, positive symptoms such as hallucinations cause a socioeconomic problem in DLB. DLB is caused by the accumulation of α-synuclein in the brain. Abnormal accumulation of α-synuclein due to changes in the enteric neural plexus has prion-like properties and progresses from the dorsal vagal nucleus to the substantia nigra, leading to rapid-eye-movement behavior disorder (RBD), PD, and DLB. The research group recently reported the involvement of gut microbiota in PD (*Movement Disorders* 35:1626, 2020; *mSystems* 5:e00797-20, 2020) and RBD (*npj Parkinson's Disease* 8:65, 2021).

In the present study, they analyzed gut microbiota and fecal bile acids of 278 patients with DLB, PD, and RBD. They found in both PD and DLB that the intestinal bacteria producing short-chain fatty acids (SCFA) were decreased and *Akkermansia*, which degrades the intestinal mucosa, were increased. In contrast, *Ruminococcus torques* and *Collinsella* were increased only in DLB but not in PD. Similarly, in a random forest model to distinguish DLB from PD with dementia (PDD), high *Ruminococcus torques*, high *Collinsella*, and low *Bifidobacterium* predicted DLB. Low *Bifidobacterium* is also observed in Alzheimer's disease. Increased *Ruminococcus torques* and *Collinsella* are expected to be protective against abnormal intestinal permeability.

As *Ruminococcus torques* and *Collinsella* are major secondary bile acid-producing bacteria, they quantified bile acids in feces and found high production of ursodeoxycholic acid (UDCA) in DLB. They assumed that anti-inflammatory effect of the secondary bile acids may be protective against the development of motor symptoms in DLB.

Research Background

Japan is confronted with a super-aging society. Prevention is the most important aspect of lifestyle-related diseases. Therapeutic management of diabetes and hypertension, and improvement of lifestyle habits such as diet and exercise can reduce the incidence of cerebrovascular disorders. Appropriate treatment methods are also being established for cancer diseases. However, neurodegenerative diseases, especially those related to cognition, are caused

by the accumulation of abnormal proteins and increase with aging, and there is no fundamental treatment for these diseases. DLB is the second most common form of dementia after Alzheimer's disease and is almost as common as Parkinson's disease (PD) in elderly people. In addition to dementia, the presence of positive symptoms such as hallucinations cause a socioeconomic problem. Braak and colleagues proposed the groundbreaking hypothesis that abnormal α-synuclein fibrils begin in the dorsal nucleus of the vagus nerve and gradually ascend into the substantia nigra, supports the notion that PD starts from the gastrointestinal tract. The research group recently reported the involvement of gut microbiota in this ascending pathologies in PD (*Movement Disorders* 35:1626, 2020; *mSystems* 5:e00797-20, 2020) and RBD (*npj Parkinson's Disease* 8:65, 2021). Both PD and DLB can develop dementia. In PD, psychiatric symptoms such as hallucinations, delusions, and dementia develop more than 10 years after the onset of motor symptoms (PD with dementia, PDD). In contrast, in DLB, the psychiatric symptoms are initial symptoms or develop in less than one year after the development of motor symptoms in PD. In addition, DLB and PDD are undisguisable at autopsy. Factors that differentiate DLB and PD, however, remain unknown. The research group examined whether intestinal bacteria and their metabolites account for the difference between DLB and PD.

Research Results

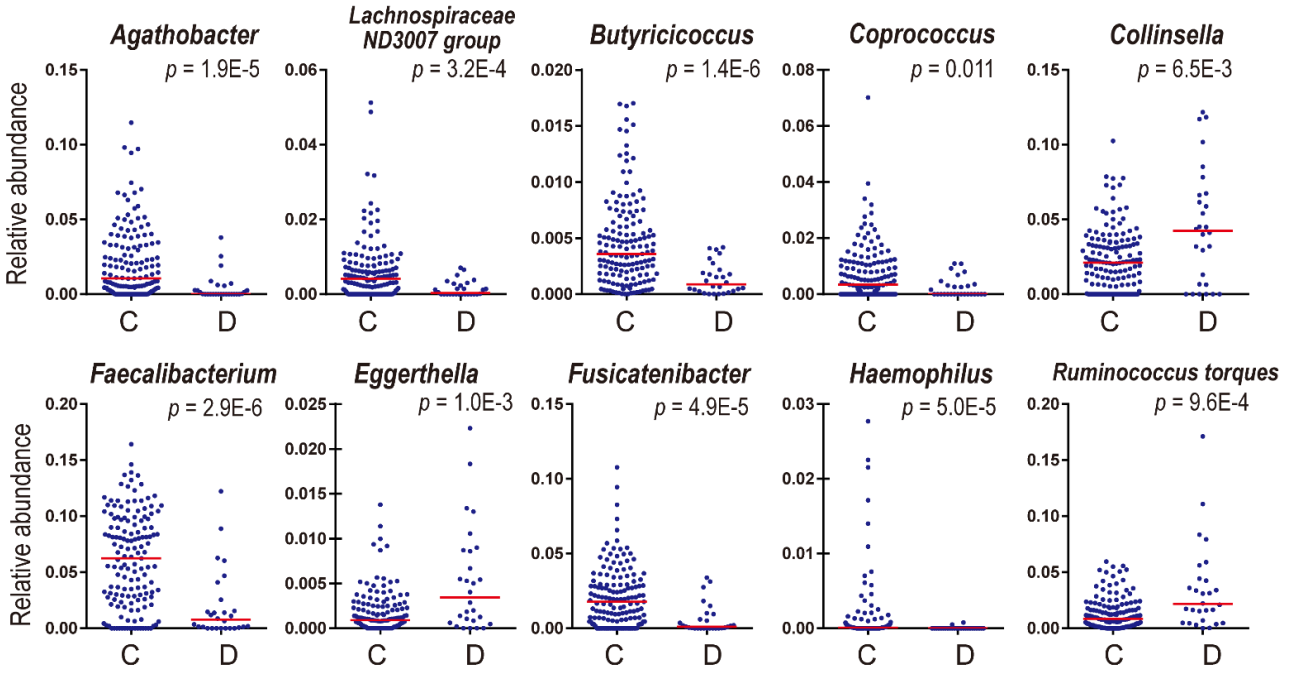


Figure 1. Ten intestinal bacteria at the genus level that were significantly altered in dementia with Lewy bodies (DLB, D) compared to healthy controls (C)

Fecal samples were provided by 224 PD patients, 26 RBD patients, 28 DLB patients, and 147 healthy controls. The decrease in SCFA-producing bacteria is also observed in PD, while increases in *Collinsella* and *Ruminococcus torques* were not observed in PD and were specific to DLB.

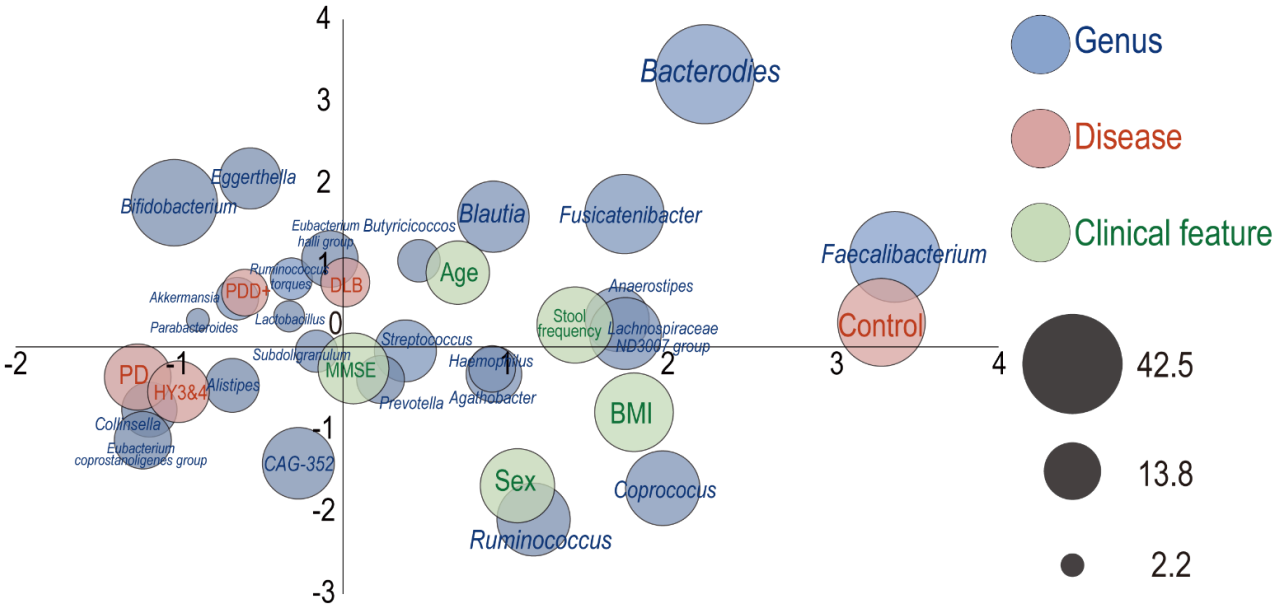


Figure 2. Integrated topology analysis by *tmap*

An integrated topology analysis, *tmap*, enables mapping of clinical symptoms, diseases, and intestinal bacteria on the same plane. The *tmap* analysis revealed that controls were closely located to short chain fatty acid (SCFA)-producing *Faecalibacterium* (Figure 2). Arbitrarily defined PD with dementia (PDD+) and HY3&4 (PD with Hoehn & Yahr stages 3 and 4, while 1 is the mildest stage and 5 is the severest stage) were also closely located (Figure 2). Principal coordinates analysis (PCoA) similarly shoed that PDD+ and HY3&4 were located in close proximity.

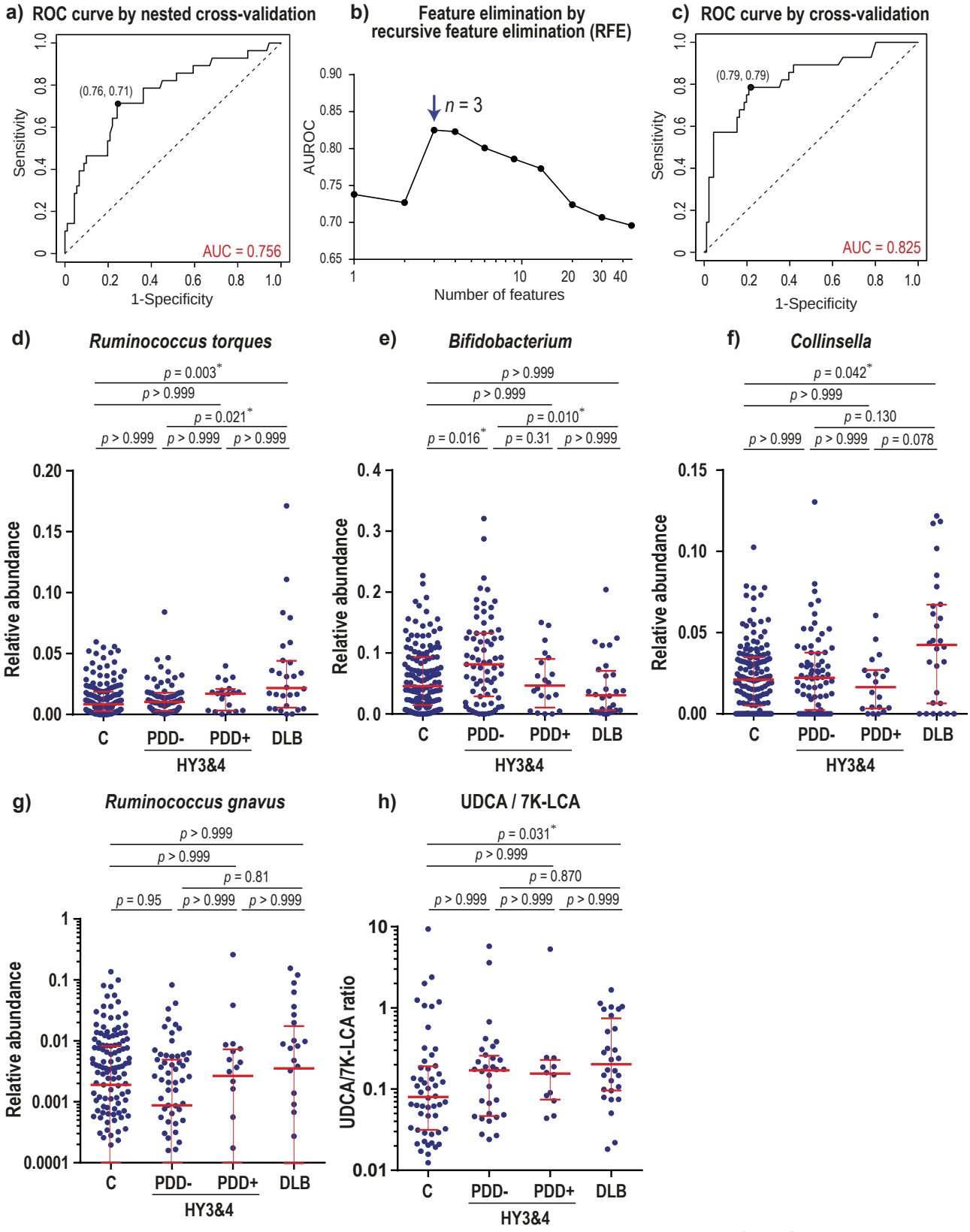
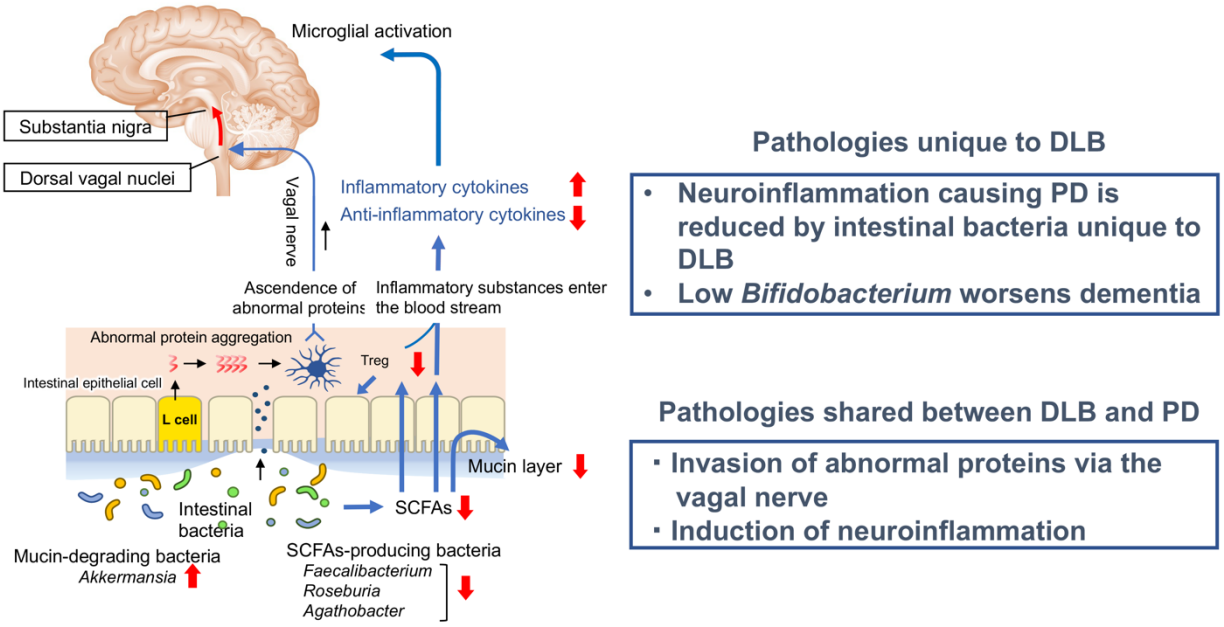


Figure 3 Random forest model to distinguish dementia with Lewy bodies (DLB) and Parkinson's disease with Hoehn & Yahr stages 3 and 4 (HY3&4)

To identify bacteria that were specifically altered in DLB, we created a random forest model that distinguished DLB and HY3&4. The area under the curve (AUC) of the receiver operating characteristic curve (ROC) under the conditions of no overfitting was 0.756 (Fig. 3a). When we gradually reduced the number of bacteria used for modeling, *Ruminococcus torques*, *Bifidobacterium*, and *Collinsella* made the highest ROC (Fig. 3b). In fact, when bacterial

differences between DLB and HY3&4 were sorted, *Ruminococcus torques*, *Bifidobacterium*, and *Collinsella* were ranked 1st, 3rd, and 7th, respectively. Plots of these bacteria in relation to the disease states showed that (i) *Ruminococcus torques* was increased in DLB compared to control and (ii) *Bifidobacterium* was decreased in DLB compared to PDD-, and (iii) *Collinsella* was increased in DLB compared to controls (Figure 3def). *Ruminococcus torques*, *Collinsella*, and *Ruminococcus gnavus* have 7ß-hydroxysteroid dehydrogenase (7BHD), which is the rate-limiting enzyme that produces the secondary bile acid, ursodeoxycholic acid (UDCA), from 7-ketolithocholic acid (7K-LCA). The research group established a new assay system to quantify UDCA and 7K-LCA in feces, and found that the UDCA/7K-LCA ratio was significantly increased in DLB compared to the controls (Figure 3h).



Abnormal intestinal bacteria in dementia with Lewy bodies (DLB) and Parkinson's disease (PD)

Intestinal bacteria that were significantly reduced in DLB were all SCFA-producing bacteria. Decreases of SCFA-producing bacteria have been repeatedly reported in PD, Alzheimer's disease, and ALS, and are likely to be a common feature in neurodegenerative diseases. SCFA increases the number of regulatory T cells (Tregs) by increasing the intestinal mucin layer and inhibiting histone deacetylases. SCFA also suppresses neuroinflammation without mediating Tregs, suggesting that the decrease in SCFA-producing bacteria in DLB exacerbates neuroinflammation. On the other hand, increased *Ruminococcus torques*, increased *Collinsella,* and decreased *Bifidobacterium* in DLB are essential gut bacteria that discriminate DLB from HY3&4. As secondary bile acids, especially UDCA, that are produced by *Ruminococcus torques* and *Collinsella* have antioxidant and anti-apoptotic properties, inflammation-exacerbated dopaminergic cell death may be alleviated in DLB. In other words, increased UDCA in DLB may delay the onset of motor symptoms due to the dopaminergic cell death at the substantia nigra. This may also explain the later age of onset of DLB compared to PD (see the graphical abstract above). *Bifidobacterium* is also decreased in Alzheimer's disease and its decrease predicts rapid worsening of PD. As *Bifidobacterium* increases the brain-derived neurotrophic factor (BDNF), its decrease in DLB, PDD, and Alzheimer's disease is likely to be associated with cognitive decline.

Research Summary and Future Perspectives

The uniqueness findings of the current study are that DLB, and PD share similar abnormalities in intestinal bacteria and that DLB has unique intestinal bacteria that produce secondary bile acids and suppress the development of PD. The presence of intestinal bacteria

unique to DLB may explain why some patients develop PD at first and the other DLB at first. However, the functions of most of the intestinal bacteria in PD and DLB remain unknown. Potential institution of intestinal bacteria unique to DLB may retard the development of PD, and normalization of abnormal bacteria shared between DLB and PD may regard the development of both PD and DLB. This may also pave the way for novel drug discovery that is completely different from currently available therapeutic modalities.

Publication

Hiroshi Nishiwaki, Jun Ueyama, Kenichi Kashihara, Mikako Ito, Tomonari Hamaguchi, Tetsuya Maeda, Yoshio Tsuboi, Masahisa Katsuno, Masaaki Hirayama, Kinji Ohno
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