News Release

Title Low short chain fatty acids (SCFA)-producing intestinal bacteria and high mucin-degrading intestinal bacterium drive the rapid progression of early Parkinson's disease (PD)

Key Points

- The research team made random forest models to predict the progression of Parkinson's disease (PD) in two years by gut microbiota in 165 PD patients.
- PD patients were divided into five established disease-severity categories. The progression of PD in two years in the earliest stage was predicted with accuracy of 79.2% by gut microbiota.
- PD patients with low SCFA-producing bacteria (*Fusicatenibacter, Faecalibacterium,* and *Blautia*) or high mucin degrading bacterium (*Akkermansia*) tend to progress faster.
- SCFA-producing bacteria (*Fusicatenibacter*, *Faecalibacterium*, and *Blautia*) were gradually decreased with disease progression. Mucin-degrading bacterium (*Akkermansia*) was gradually increased with disease progression. However, relative abundances of the four bacteria remained unchanged in two years. Thus, PD patients with abnormalities in the four bacteria were supposed to progress rapdily.
- The progression of an early stage of PD may be able to be slowed by normalizing gut microbiota or supplying deficient gut metabolites.

Summary

Professor Kinji Ohno (co-corresponding author), Associate Professor Masaaki Hirayama (co-corresponding author), Professor Masahisa Katsuno, and Assistant Professor 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 followed 165 PD patients in two years and made random forest models to predict the progression of PD in two years by gut microbiota. They found that early PD patients with low SCFA-producing bacteria (*Fusicatenibacter*, *Faecalibacterium*, and *Blautia*), or high mucin-degrading bacterium (*Akkermansia*) tend to progress faster.

Twenty studies in PD have been reported on gut microbiota. The research team showed in 2020 by meta-analysis of gut microbiota in five countries that mucin-degrading bacterium (*Akkermansia*) was increased and SCFA-producing bacteria (*Roseburia* and *Faecalibacterium*) were decreased in PD. In a Finnish study, intestinal bacterium (*Prevotella*) was decreased in PD, and PD patients with lower *Prevotella* tended to progress faster in two years. The research team made random forest models to predict the progression of PD in two years by gut microbiota in 165 PD patients. They divided PD patients into five established disease-severity categories. They predicted the progression of PD in two years in the earliest stage with accuracy of 79.2% by gut microbiota. PD patients with low SCFA-producing bacteria (*Fusicatenibacter, Faecalibacterium,* and *Blautia*), or high mucin-degrading bacteria (*Akkermansia*) tended to progress faster. SCFA-producing bacteria (*Fusicatenibacter*, *Faecalibacterium*, and *Blautia*) were gradually decreased with disease progression. On the other hand, mucin-degrading bacterium (*Akkermansia*) was gradually increased with disease progression. However, the four bacteria remained unchanged in two years in PD. This indicated

that the four bacteria were likely to have driven the progression of PD. We thus may be able to slow the progression of early stages of PD by normalizing gut microbiota or supplying deficient gut metabolites.

Research Background

PD is caused by abnormal accumulation of α-synuclein fibrils called Lewy bodies in the dopaminergic neurons in the midbrain. The following four observations indicate that abnormal accumulation of α-synuclein fibrils starts from the intestine and ascends to the midbrain. First, α-synuclein fibrils have the same nature as prions. Abnormally accumulated α-synuclein fibrils make normal α-synuclein accumulated abnormally, and drive a viscous cycle. 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 supports the ascending Lewy bodies in the brain stem. Third, total resection of the vagal nerve for treating duodenal ulcer in more than 30 years ago lowers the incidence of PD by 50%. Finally, abnormal accumulation of α-synuclein fibrils is frequently observed in the intestinal nerve network in PD.

Epidemiological studies indicate that older age, male, cognitive impairment, and postural instability/gait-dominant type of PD are predictive of rapid progression of PD.

A total of 20 studies in PD have been reported on gut microbiota. In 2020, the research team reported by meta-analysis of gut microbiota in five countries that mucin-degrading bacteria, *Akkermansia*, was increased and SCFA-producing bacteria, *Roseburia* and *Faecalibacterium*, were decreased in PD. In a Finnish study, intestinal bacterium, *Prevotella*, was decreased in PD, and PD patients with lower relative abundance of *Prevotella* tended to progress faster in two years. The research team made random forest models to predict the progression of 165 PD patients in two years using gut microbiota.

Research Results

The research team first confirmed that their modeling approach was appropriate by nested cross-validation. Nested cross-validation showed that the progression of PD patients in two years in the earliest stage was predicted by gut microbiota with an accuracy of 79.2%. The prediction efficiency, however, was decreased in the second and third stages of PD. In contrast to gut microbiota-based models, the progression of PD patients in two years in the third stage was predicted by 31 clinical features with an accuracy of 66.1%. The prediction efficiency, however, was decreased in the second and first stages of PD. Low SCFA-producing bacteria (*Fusicatenibacter*, *Faecalibacterium*, and *Blautia*), or high mucin-degrading bacterium (*Akkermansia*) predicted the progression of early PD. Decreased SCFAs are supposed to abnormally activate neuroinflammations in the brain and cause abnormal accumulations of α-synuclein fibrils. Increased *Akkermansia* is supposed to degrade mucin layers in the gut and increase the intestinal permeability, which facilitates the abnormal accumulations of α-synuclein fibrils. These four genera were significantly changed in their previous meta-analysis of PD patients in five countries. *Akkermansia* was gradually increased with the progression of PD, whereas *Fusicatenibacter*, *Faecalibacterium*, and *Blautia* were gradually decreased with the progression of PD. Because relative abundances of the four bacteria remained unchanged in two years, PD patients with these abnormal intestinal bacterial abundances were likely to be destined to progress rapidly.

Research Summary and Future Perspective

In early PD patients, increased mucin-degrading bacteria, *Akkermansia,* and decreased SCFA-producing bacteria, *Fusicatenibacter*, *Faecalibacterium*, and *Blautia,* accelerated the progression of PD. We thus may be able to slow the progression of an early stage of PD by normalizing gut microbiota or supplying deficient gut metabolites.

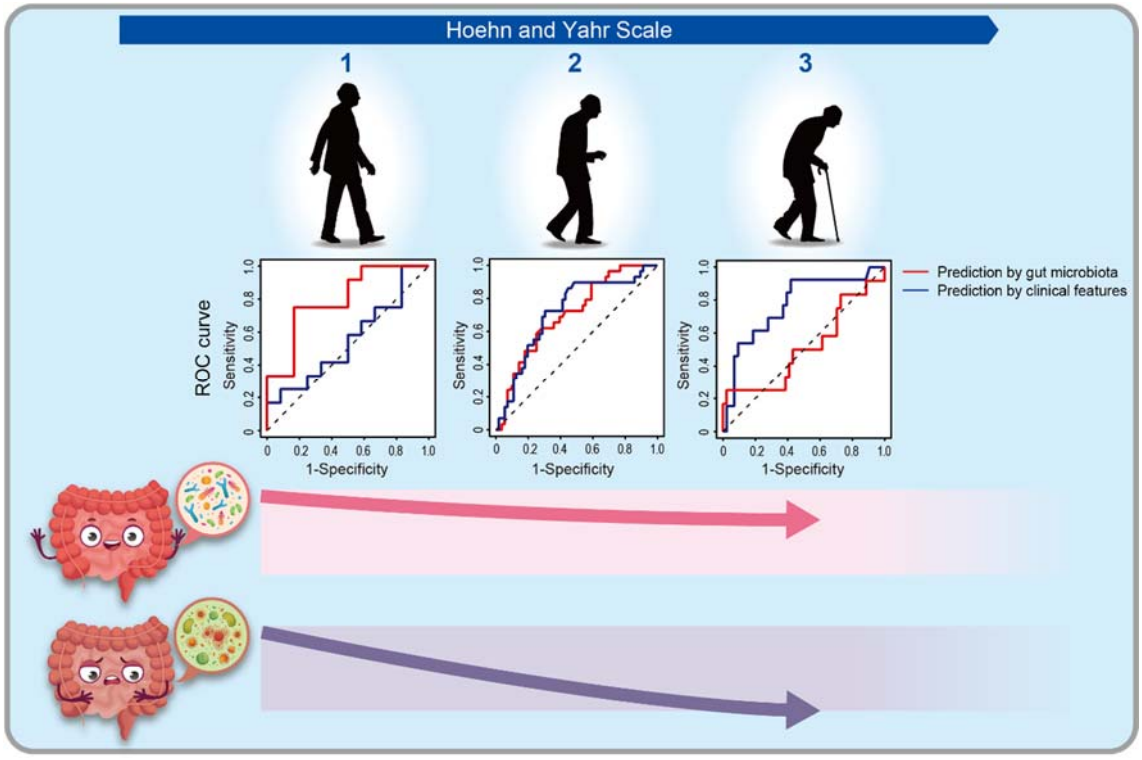

Fig. 1. Random forest models to predict the progression of Parkinson's disease in two years were generated using gut microbiota (red lines) and clinical features (blue lines) for stages 1 to 3 of five established disease stages of Parkinson's disease. Receiver-operating-characteristics curves by nested cross-validation are indicated. Gut microbiota (red lines) made dependable models to predict the progression of PD for the first stage of PD. In contrast, clinical features (blue lines) made dependable models to predict the progression of PD for the third stage. The research team showed that PD patients with abnormal gut microbiota tended to progress rapidly.

Publication

Nishiwaki H, Ito M, Hamaguchi T, Maeda T, Kashihara K, Tsuboi Y, Ueyama J, Yoshida T, Hanada H, Takeuchi I, Katsuno M, Hirayama M, Ohno K. Short chain fatty acids-producing and mucin-degrading intestinal bacteria predict the progression of early Parkinson's disease. *npj Parkinsons Dis* in press
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