1. **No.**

   FP01807091

2. **Title**

   Elucidation of causative association of intestinal microbiota in the reduced risk of Parkinson's disease in smokers

3. **Period**

   2017-2019

4. **Summary**

   A total of 63 epidemiological studies suggest that smoking reduces the risk of Parkinson's disease (PD) by ~40%. Abnormal aggregation of alpha-synuclein in the substantia nigra in PD starts from the intestinal neural plexus, and the effect of gut microbiota has been indicated by recent studies. Smoking potentially affects intestinal microbiota and subsequently reduces the risk of PD. Stool samples of 223 PD patients (10 current smokers, 34 past smokers, and 179 non-smokers) and 134 healthy cohabitants (10 current smokers, 34 past smokers, and 90 non-smokers) were collected. Intestinal microbiota was analyzed by 16S rRNA-seq and by shotgun metagenome sequencing. Current and past smokers were significantly lower in PD in our cohort. In our dataset, Faecalibacterium and Blautia were decreased in PD, whereas Akkermansia and Alistepes were increased in PD. Meta-analysis of Japanese, German, Russian, Finnish, and American cohorts similarly showed that Faecalibacterium was decreased in PD and Akkermansia was increased in PD. PERMANOVA analysis showed that PD, constipation, and smoking affected the gut microbiota profiles. Generalized linear modeling (GLM) analysis similarly revealed that PD affected 25 bacterial genera. We found that three confounding factors (catechol-O-methyltransferase inhibitor, constipation, and smoking) also affected some of the 25 genera. Among them, four genera were changed by smoking. Among them, two genera produce short chain fatty acids (SCFA), which activate regulatory T cells (Treg) and suppress inflammation. Changes in bacterially produced SCFA may account for a reduced risk of PD in smokers.