Gut microbiota and metabolites of α-synuclein transgenic monkey models with early stage of Parkinson'sdisease

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Abstract

Background: Parkinson's disease（PD）is the second most prevalent neurodegenerative disease. Gut microbes are susceptible to various external factors (such as living environment, diet, antibiotic use), our research avoids these interferences very well. Gut microbiota affect the physiological processes of the host by regulating metabolites. However, it is unclear whether microbiota and metabolites have demonstrated changes at early stages of PD due to the difficulty to diagnose and identify early stage PD in clinical practice.

Methods: In a previous study, we constructed A53T transgenic monkeys with early Parkinson's symptoms. Here we analyzed the gut microbiota by metagenomic sequencing and metabolites by untargeted chromatography, which represent the first effort to identify the association between intestinal microbiota, metabolites and early stage of PD.

Results: Compared with control monkeys, the gut microbiota of A53T monkeys is more diverse. Sybergistetes and Eggerthella lenta were significantly elevated in A53T monkeys. In monkeys with early Parkinson's symptoms, Glyceric acid, L-Aspartic acid and p-Hydroxyphenylacetic acid were significantly elevated, but Myristic acid and 3-Methylindole was significantly decreased. ABC transporters are associated with two decreased metabolites. Metabolic pathways are associated with three elevated metabolites. We found KO0131 and KO2147 from metabolic pathways are related to Glycolysis.

Conclusion: We identified differential gut microbiota coincides with the microbiota of the currently reported PD patients to some extent. We found these differential metabolites and KOs suggest that A53T monkeys may have Glycolysis problem, and Glycolysis problem may be associated with mitochondrial dysfunction. Our results may be a sign of early Parkinson's screening and diagnosis.

Full Text

This preprint is available for download as a PDF.

Figures

Figure 1

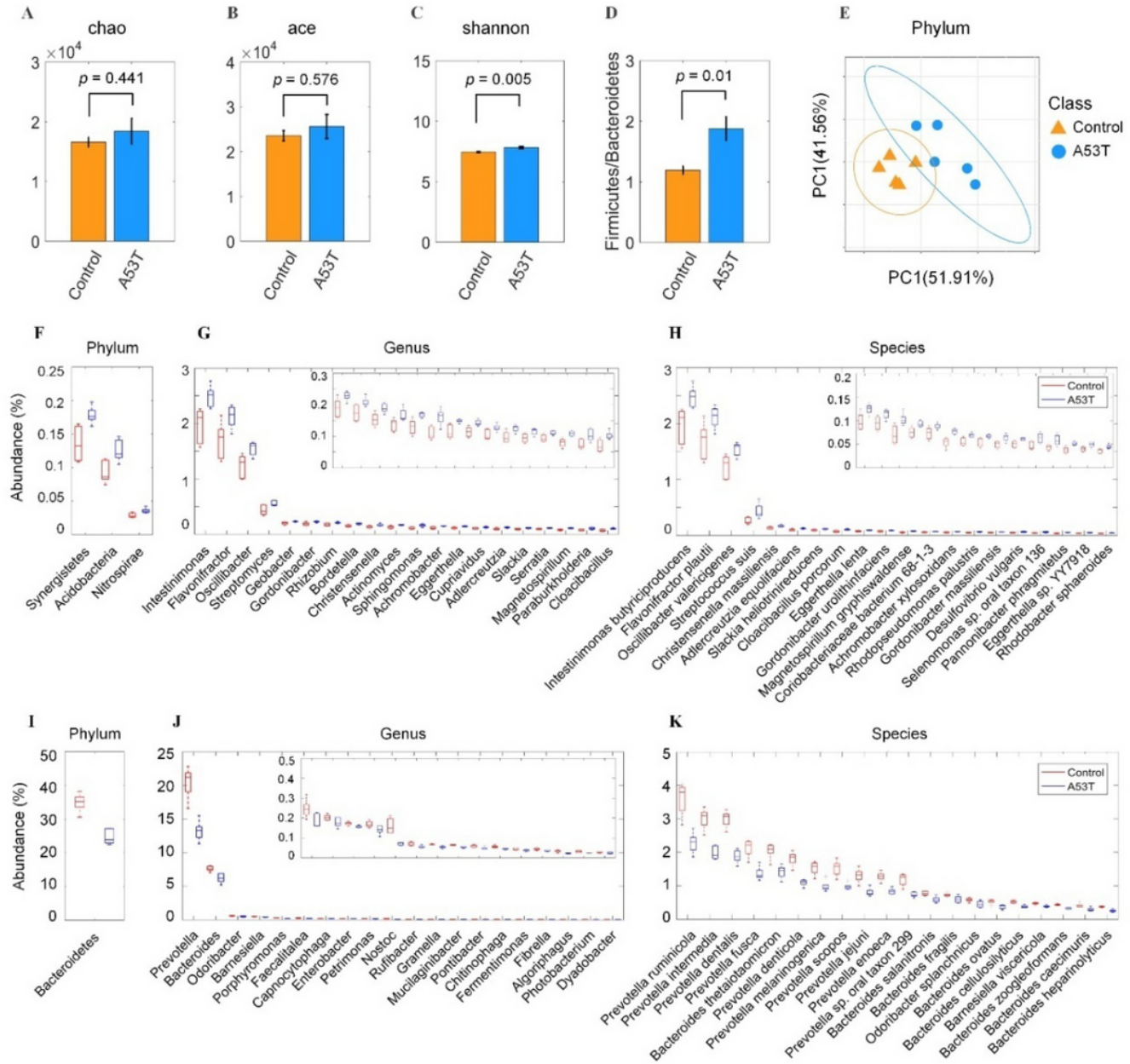

Figure 1

Phylogenetic profiles of gut microbes in A53T transgenic monkeys. (A, B, C) α diversity including Chao index, Ace index, Shannon index increased in A53T transgenic group compared to the control group, and Shannon index have significant difference ($p<0.005$). (D) The ratio of Firmicutes to Bacteroidetes increased in the A53T transgenic group. (E) An obvious separation between the A53T transgenic group and the control group was observed by β diversity analysis. The phylotypes significantly increased ($p<0.05$) in the A53T transgenic monkeys at the phylum (F), genus (G) and species (H) levels. The phylotypes significantly decreased in the A53T transgenic monkeys at the phylum (I), genus (J) and

species (K) levels. Red and blue represent controls group and A53T group, respectively. The phylotypes of the control and A53T group were compared with Welch's t-tests and the obtained p-values were corrected with the Benjamini Hochberg method.

Figure 2

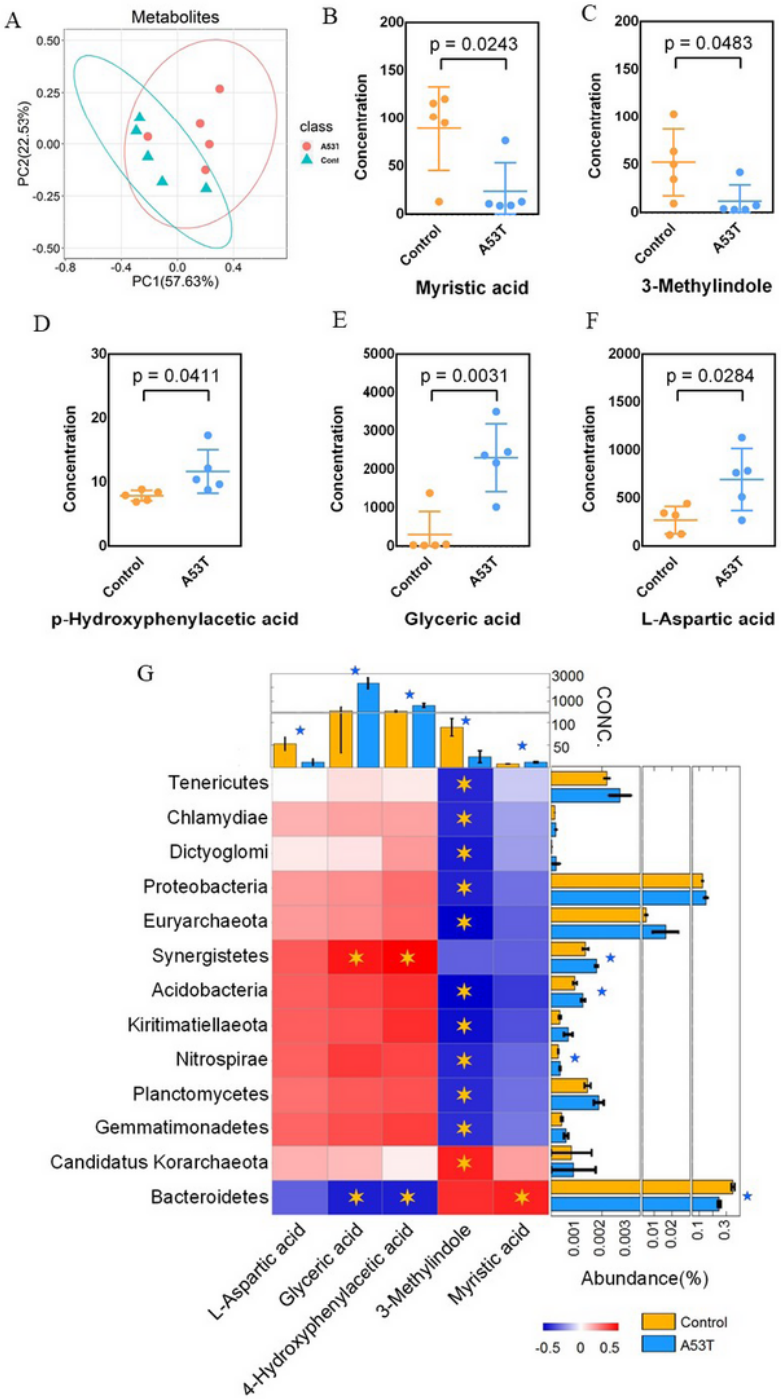

Figure 2

Microbiota from A53T transgenic and control monkeys produce discrete metabolite profiles and correlation analysis. (A) Metabolites had obviously divided between A53T transgenic group and control

group. (B-C) Myristic acid, 3-Methylindole significant decreased in A53T group. (D-F) p-Hydroxyphenylacetic acid, Glyceric acid and L-Aspartic acid significant increased in A53T transgenic group. The concentrations of different metabolites in the A53T transgenic and control groups were compared with Welch's t-tests and the obtained p-values were corrected with the Benjamini Hochberg method. (G) Analyze the correlation between bacteria and metabolites. Glyceric acid and p-Hydroxyphenylacetic is positively correlated with Sybergistetes. 634 Myristic acid and Bacteroidetes are significant positive correlated. Candidatus Korarchaeota and 3-Methylindole are positive correlated.

Figure 3

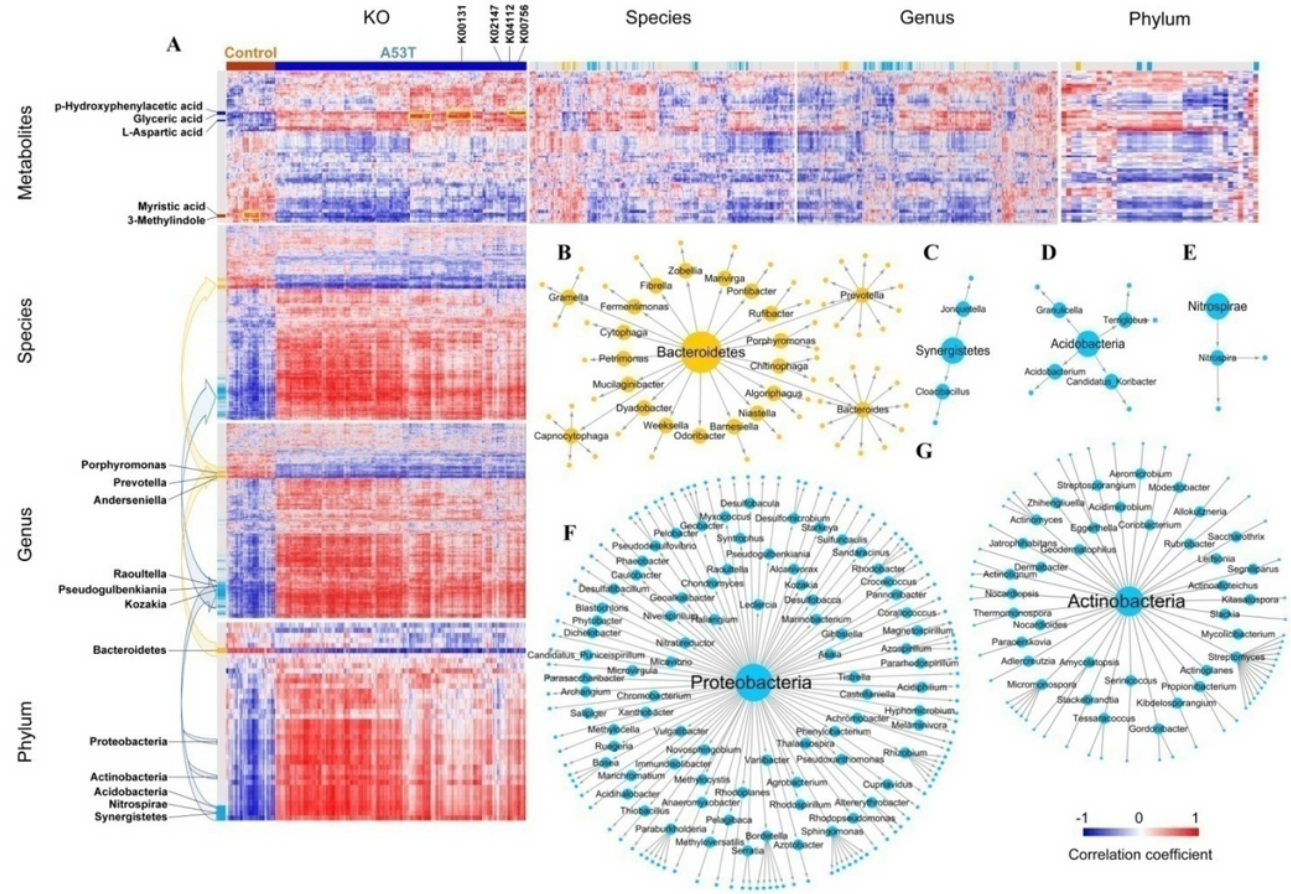

Figure 3

Integrated analysis of intestinal microbiota and metabolites. (A) The yellow/blue labels on the left side of the figure indicate that the microbe showed significantly different (t-test with p-value <0.05) enrichment in the control/A53T group. (B-G) This difference has a distinct transmission relationship in the classification

of part microbe (The direction of the phylum-genus-species is indicated by blue/yellow arrows). Yellow present increased in A53T group. Blue present increased in control group.

Figure 4

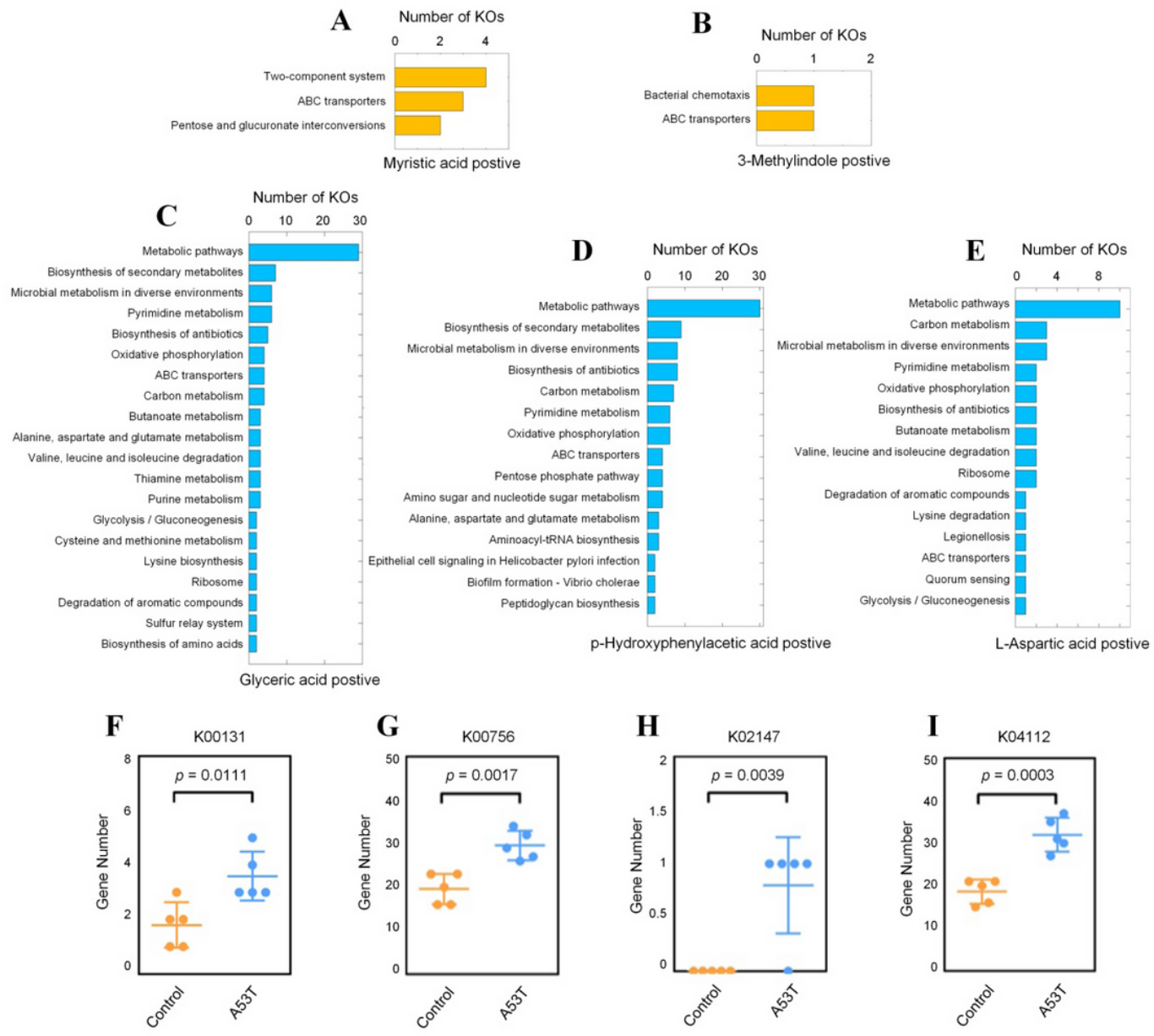

Figure 4

Analysis of enriched pathways for the five differential metabolites. (A-B) Metabolite- enriched pathways significantly associated with control monkeys. (C-E) Metabolite-enriched pathways significantly associated with A53T transgenic monkeys. (F-I) 4 KOs from metabolic pathways that are significantly elevated in the transgenic A53T monkeys.

Figure 5

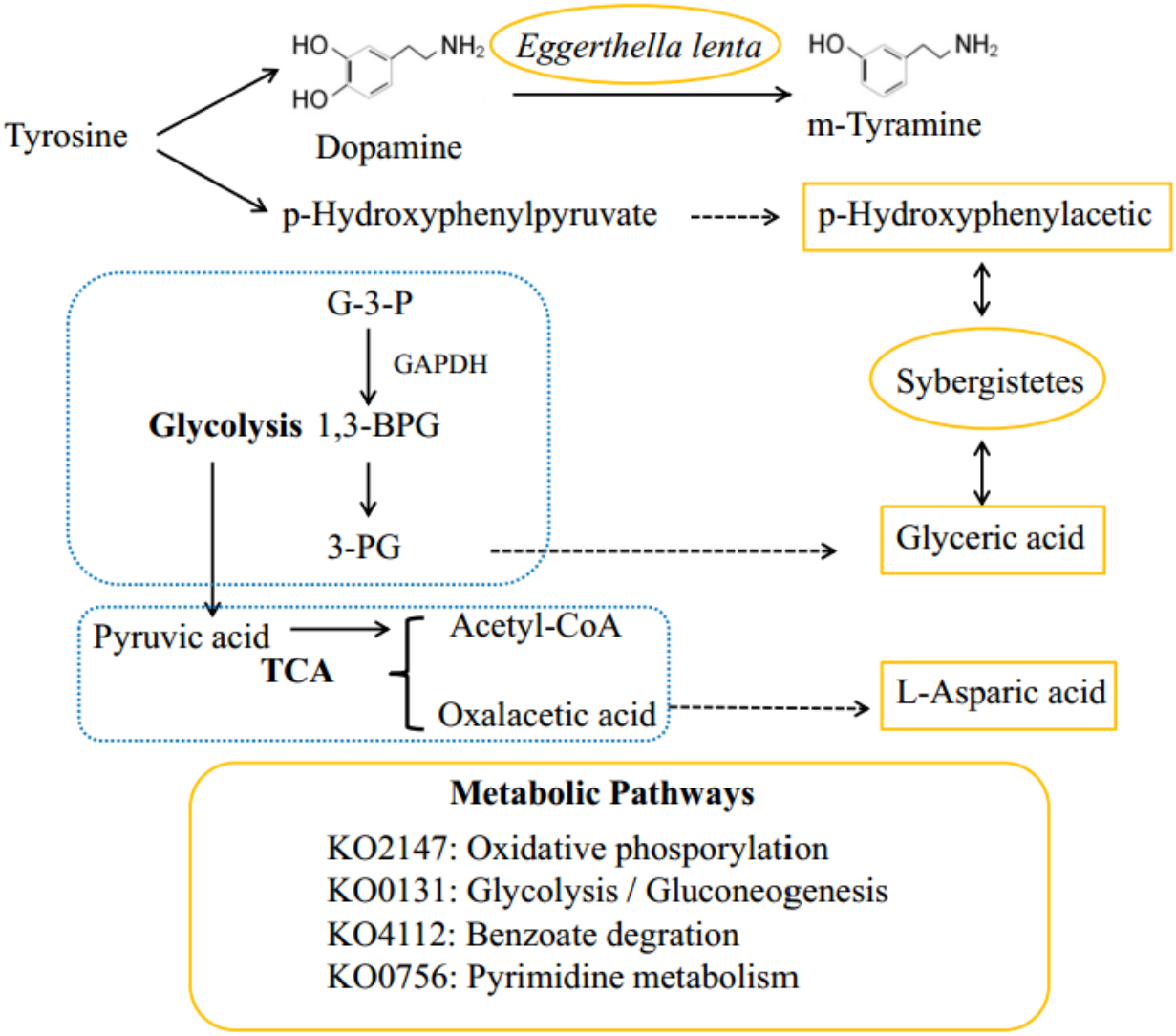

Figure 5

We speculate a possible metabolic response analysis of three differential metabolites, in which an increase of glyceric acid and L-aspartic acid may indicate an acceleration of glycolysis and TCA cycle, and functional analysis of differential metabolites also illustrates this speculated (KO2147, KO0131). In addition, tyrosine is decomposed into dopamine and p-hydroxyphenylpyruvate, Eggerthella lenta can convert dopamine to m-tyramine, p-hydroxyphenylpyruvate is oxidized to p-hydroxyphenylacetic. G-3-P: oxidation of plyeradehyde-3-phosphate; 1, 3-BPG: 1, 3-triglyceric acid diphosphate; 3-PG: 3-phosphoglycerate. Yellow: metabolites, microbiota, KO increased significantly in A53T monkeys.

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