ORIGINAL ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

# Fecal Microbiota Transplantation's Positive Effects on Ulcerative Colitis

***Rasha Medhat El-Morsi[1], Magda Mourad[2], Bassant Nour[2], Yassmin Salama[2], Mostafa Hamed[2], Engy Derbala[2], Esraa Elsaeed Sobhy[1]****

*[1] Department of Microbiology, Faculty of Pharmacy, Delta University for Science and Technology, International Coastal Road, Gamasa, 11152, Egypt; [2] Faculty of Pharmacy, Delta University for Science and Technology, International Coastal Road, Gamasa, 11152, Egypt*

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*Correspondence Author:

E-mail: esraaelsaeed86@gmail.com

## Abstract

Ulcerative colitis (UC) is a severe disease caused by immune system abnormalities leading to inflammation and ulcers in the large intestine. Dysregulation of gut microbiota is a key factor in UC. Fecal microbial transplantation (FMT) involves transferring fecal matter from a healthy donor to a recipient to alter gut microbiota and improve health. This study explored the effects of FMT on gut microbiome abundance and virulence genes in UC patients. Thirty metagenomic samples were retrieved from the NCBI database published under the project PRJNA768409. In that project samples were collected from three groups of participants. The first group is “Before” which includes patients with UC before administering FMT. The second group is “After” which includes patients with UC after administering FMT, after FMT and from donor participants. The third group is “donor” which includes healthy participant that gives their healthy feces for the “before” group. Results showed that 50% of the samples had decreased virulence genes, with reduced Actinobacteria and Bacteroidetes and increased Firmicutes after FMT. FMT significantly impacts UC patients, potentially reshaping the gut microbiome. Pre-FMT metagenomic analysis of donor samples is recommended to ensure safety.

**Keywords:** *Ulcerative colitis, Fecal microbial transplantation, metagenomics, virulent genes*

**Abbreviations**

Fecal microbial transplantation, FMT; Inflammatory bowel disease, IBD; Ulcerative colitis, UC

## 1. Introduction:

Ulcerative colitis (UC), an autoimmune disease that is chronic, relapsing, and characterized by noninfectious inflammation and perforating ulcers of colorectal mucosa. Despite the disease's rising incidence rates globally, its cause is still unknown (Ghosh *et al.*, 2000). One of the main factors that is responsible for the development of chronic inflammatory bowel disease (IBD) is the dysregulation of the resident microbiota. The occurrence of intestinal inflammation might cause the production of a variety of several types of instant cell factors (Shen *et al.*, 2018). In UC

patients, both the function and composition of intestinal microbiota were altered. One of the most prevalent bacteria in the human gut microbiota, *Akkermansia muciniphila* (*A. muciniphila*), which makes up 1% to 5% of the human intestinal microbial population, has reduced. Numerous investigations have revealed a connection between UC and *A. muciniphila* (Bajer *et al.*, 2017). The permeability of the intestinal mucosa and intestinal microecology can both be improved by FMT. It can protect the intestinal mucosa by triggering the intestinal humoral immune response, which causes the production of IgA, IgG, and IgM through the TLR route. Additionally, it can lower the pH of the colon and raise bacterial adhesion while decreasing $H_2O_2$ levels to prevent pathogen adherence and translocation through competition (Yang *et al.*, 2014).

By increasing Th1 differentiation, T-cell activity, leukocyte adhesion, and immuno-stimulatory factors while suppressing the release of proinflammatory cytokines, FMT can cure immune diseases. FMT may successfully treat UC by increasing the likelihood that the donor's microbiota will have a long-lasting similarity in composition (Shen *et al.*, 2018). The present study aimed to analyze the microbiome contained in the gut environment before and after applying FMT by using metagenomics analysis to estimate the beneficial effect of FMT in the case of UC.

## 2. Materials and methods

Raw data was retrieved from NCBI SRA using the SRA tool on the Galaxy server (Galaxy Community, 2022). We retrieved thirty samples from the PRJNA768409 project (ID 768409 - BioProject - NCBI (nih.gov). In that project samples were collected from three groups of participants. The first group is "Before" which includes patients with UC before administering FMT. The second group is "After" which includes patients with UC after administering FMT, after FMT and from donor participants. The third group is "Donor" which includes healthy participant that gives their healthy feces for the "Before" group. For sample IDs and their category, see Online Resource 1. SRA files were converted to FASTQ files by "fastq faster download and extract reads in FASTQ format from NCBI SRA" tool (0.73) (Leinonen *et al.*, 2010). Low-quality sequences were filtered by the PRINSQ Tool (Schmieder *et al.*, 2011). This tool was used to filter the sequences which have a quality score of less than 20. Then we used Metaphlan (3.0.14) (Beghini *et al.*, 2021) for taxonomic classification. Reads were assembled into contigs by the Megahit tool (1.2.9) (Li *et al.*, 2015). Contigs were used as input to the Abricate tool (1.0.1) (Seemann, 2016) to identify virulence genes by mapping against the virulence factor database (VFDB) database. The Run_lefse () function from microbiomeMarker R package (Cao *et al.*, 2022) was used perform LEfSe (Linear discriminant analysis Effect Size) to identify species that are statistically different between "Before", "After" and "Donor" groups and the LEfSe bar plot was visualizer by the ggplot2. The whole analysis was done on Galaxy server except for LEfSe and data visualization that were done on R.

## 3. Results and discussion

### *3.1. Relative abundance at the Phylum level*

Our study demonstrates the positive effects of FMT on UC patients. Bacteria were found to be less diverse before treatment with FMT. After FMT treatment, species turned to be more diverse and beneficial. Abdominal actinomycosis was found to be higher in "Before" (Fig. 1) but other studies reported no correlation with IBD. They found that abdominal actinomycosis can mimic IBD due to its indolent course and propensity to cause abscesses and fistulae (Garner *et al.*, 2007). Rarely, abdominal actinomycosis has been reported as an infectious complication in patients with IBD (Sevilla Chica *et al.*, 2001).

The abundance of *Firmicutes* is lower in UC "Before" group than "After" group (Fig. 1), this finding agrees with another study (Natividad *et al.*, 2015) that found that mice colonized with microbiota from patients with UC showing a low abundance of *Firmicutes* had increased sensitivity to colitis compared to mice colonized with fecal or synthetic ecosystems rich in *Firmicutes*. Microbiota low in *Firmicutes* increased expression of TH17-related genes and expansion of interleukin 17A expressing CD4+ cells in vivo. Supplementation with bacterial isolates belonging to the *Firmicutes* phylum abrogated the heightened TH17 responses invitro (Natividad *et al.*, 2015). We found that Bacteroides abundance is higher in UC before FMT (Fig. 1), this result agrees with another study (Lucke *et al.*, 2006) that revealed an abundance of sequences from *Bacteroides spp.* and *Prevotella spp.* in the mucosal tissue of patients with UC compared with individuals showing no signs of disease. The higher incidence of populations of members of the *Bacteroidetes* in UC suggests that these may influence the pathogenesis of the disease.

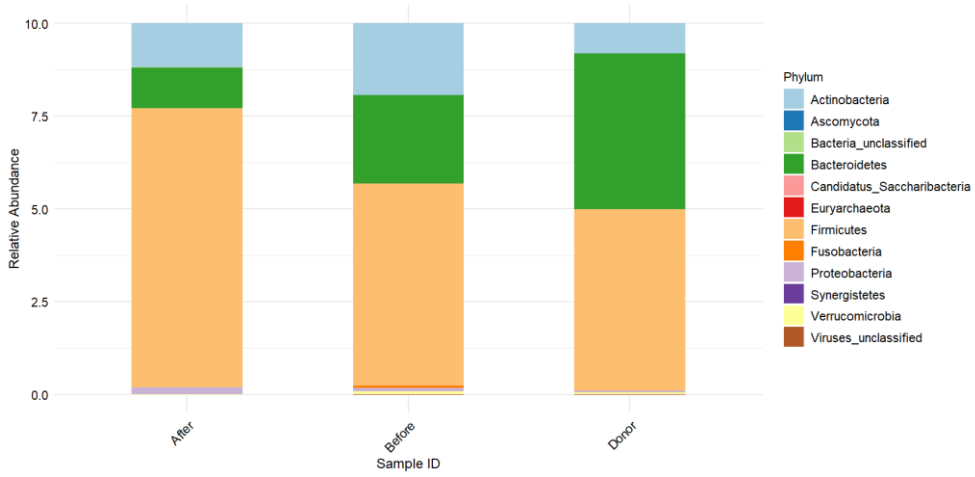


**Fig. 1: Relative abundance of Phyla in the "Before", "After". And "Donor" groups**

### *3.2. Differential analysis by LEfSe*

#### *3.2.1. Enriched species after FMT*

Fig. 2 shows enriched species in "Before", "After" and "Donor" groups. Some of these species were also detected to be in lower abundance in UC in other studies and some of them were detected to increase. The most apparent species as a marker for "After" group is *Faecalibacterium prausnitzii* as it has LDA = 5.02 (Fig. 2). A diminished presence of *F. prausnitzii* has been observed in conditions like inflammatory bowel disease (IBD) (Lopez-Siles *et al.*, 2015), Clostridium difficile infection (CDI) (Lu *et al.*, 2018) and viral infections including human immunodeficiency virus (HIV)(Pinto-Cardoso *et al.*, 2017). Studies suggest that enhancing the presence of *F. prausnitzii* through dietary changes, fecal microbiota transplantation, or cultivation techniques may shield both mice and humans from inflammatory diseases. Thus, *F. prausnitzii* might possess the potential to curb microbial translocation and inflammation, helping to prevent gastrointestinal complications, particularly in COVID-19 patients (He *et al.*, 2021). *E. rectale* is another marker species for the "After" group (LDA = 4.45). *E. rectale* is an anaerobic Gram-positive bacterium and ranks among the most prevalent bacterial species found in human fecal matter. Research indicates that *E. rectale* plays a critical role in butyrate production, a key energy source for colon cells that supports colon health (Pryde *et al.*, 2002). However, a significant reduction in *E. rectale* levels has been noted in patients with ulcerative colitis (UC), suggesting a potential link between decreased levels of this bacterium and the initiation of colitis (Pryde *et al.*, 2002). *R. intestinalis is another* marker species for the "After group" (LDA = 4.13). Pryde *et al.*, (2002) administered *R. intestinalis* via enema to rats and found a significant improvement in gut microbiota balance, aiding in the repair of the colon and enhancing gastrointestinal function in rats. This treatment alleviated colitis symptoms, improved stool consistency, and increased colon length. Restoration of gut epithelial integrity and the intestinal barrier was noted, highlighted by increased Zo-1 expression in colon tissues. Additionally, depressive-like behaviors in rats decreased, with corresponding reductions in IL-6, IL-7, and 5-HT levels in serum and brain tissue indicating the therapeutic impact of *R. intestinalis*. We found that *F. saccharivorans* enriched after treatment by FMT (LDA = 4.04) and this finding agrees with (Takeshita *et al.*, 2016) who said that *F. saccharivorans* decreased in correlation to UC activity and suppresses intestinal inflammation suggesting that *F. saccharivorans* could lead to novel UC treatment. In agreement with us, some researchers reported that clostridial groups were significantly less abundant in fecal samples from UC patients in relapse compared to UC patients in remission (Vigsnæs, 2011).

#### *3.2.2. Enriched species before FMT*

*Bacteroides vulgatus* was found to be enriched in the "Before" group (LDA= 5.023). This finding agrees with previous studies as numerous investigations revealed that *B. vulgatus* has a significant pathogenic function since it may cause experimental colitis in animal models. Proteases derived from *B. vulgatus* were overexpressed in the clinically active ulcerative colitis patients (Mills *et al.*, 2022; Vich Vila *et al.*, 2018; Zhou & Zhi, 2016). *Eubacterium hallii* was found to be enriched in the "Before" group (LDA = 4.83). In contrast to our results, *E. hallii* have a beneficial effect on the gut microbiota and demonstrated properties that enhancing a healthy gut environment (Vatn *et al.*, 2020; Engels *et al.*, 2016; Satokari, 2015). *Asaccharobacter celatus* was

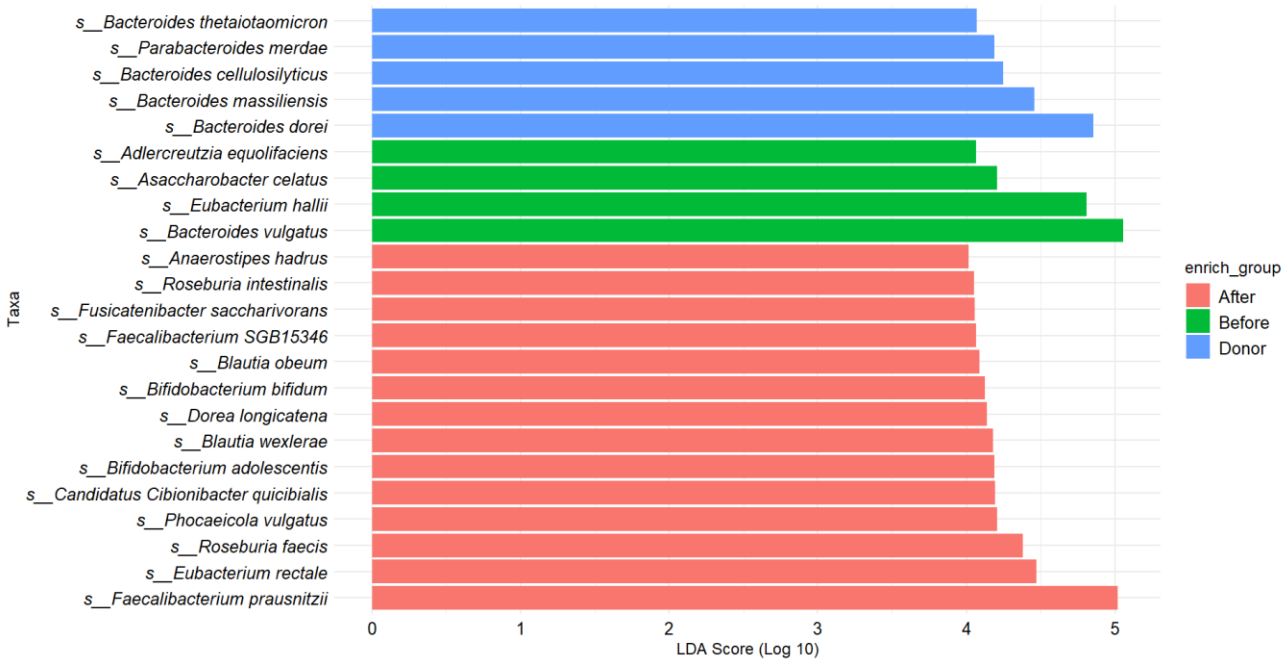


**Fig. 2: marker species (LDA ≥ 4 and *p*adj = 0.01) in "Before" and "Donor" groups. Species colored by green color are enriched in the "Before" group while species colored in red color are enriched in the "After" group and species colored in blue color are enriched in the "Donor" group**

found to be enriched in the "Before" group (LDA = 4.175). *A. celatus* is infrequently associated with IBD, by using cross-cohort integrative analysis (CCIA). Essential genes of the Two-component system pathway, which are connected to faecal calprotectin, have been associated to IBD, according to metagenomic functional analysis (Ning *et al.*, 2023). In this study *Adlercreutzia equolifaciens* is enriched in the UC (LDA = 4).

This finding disagrees with other studies, *A. equolifaciens* were detected to be in lower abundance in Crohn's disease (Choi *et al.*, 2019). Oñate *et al.*, (2023) reported that *A. equolifaciens* possesses anti-inflammatory effect, both in vitro and in vivo. Researchers showed that the human gut microbe *Eggerthella lenta* induces intestinal activation of Th17 cells. The bacterium is enriched in people with inflammatory bowel disease (LDA= 3.422), and it worsens colitis in mice (Alexander *et al.*, 2022).

### *3.3. Influence of FMT on Virulence genes in UC patients*

Following FMT, the "Before" group exhibited ~ 2.7 times more virulence genes compared to the "After" group, as depicted in Fig. 3. The variations in virulence gene counts across the "Before", "After", and "Donor" groups are categorized into three distinct patterns (Fig. 4): Firstly, a reduction in virulence genes post-FMT was observed in 50 % of samples (samples 5, 6, 7, 12, and 25). Secondly, only 2% of samples in the 'After' group show an increase in virulence compared to the 'Before' group after FMT. These samples seem strange like sample 1 and sample 4. Sample 4 in the 'Donor' group has only two virulence genes and sample 1 in the donor group only has a few virulence genes.

This may be due to any other factor or infection that happened besides UC in this patient and not reported by the patient. Also, sample 1 contains very few virulence genes before FMT but contains many virulence genes after FMT although the donor of sample 1 contains only 3 virulence which seems illogic. For details about virulence genes' names in the first and second states, see online resource 2. Thirdly, samples do not show any change in virulence genes in the "After" group like sample 11 which doesn't contain any virulence genes before FMT and also the donor of sample 11 doesn't contain any virulence genes.

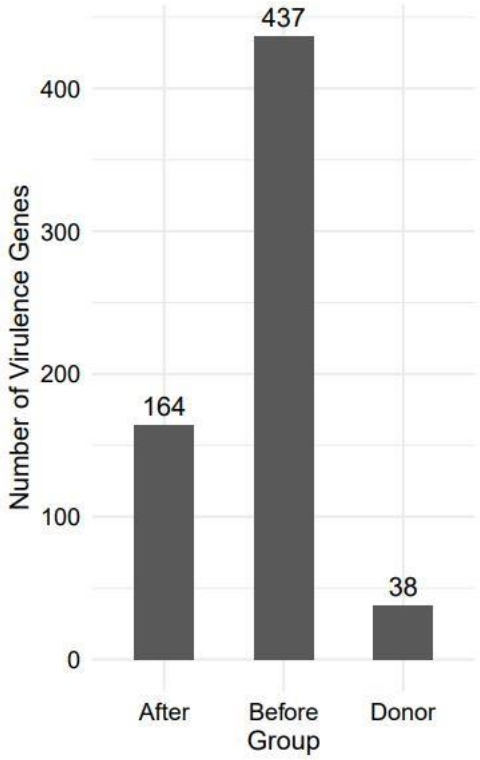


**Fig. 3: Number of virulence genes in the "Before", "After". And "Donor" groups**

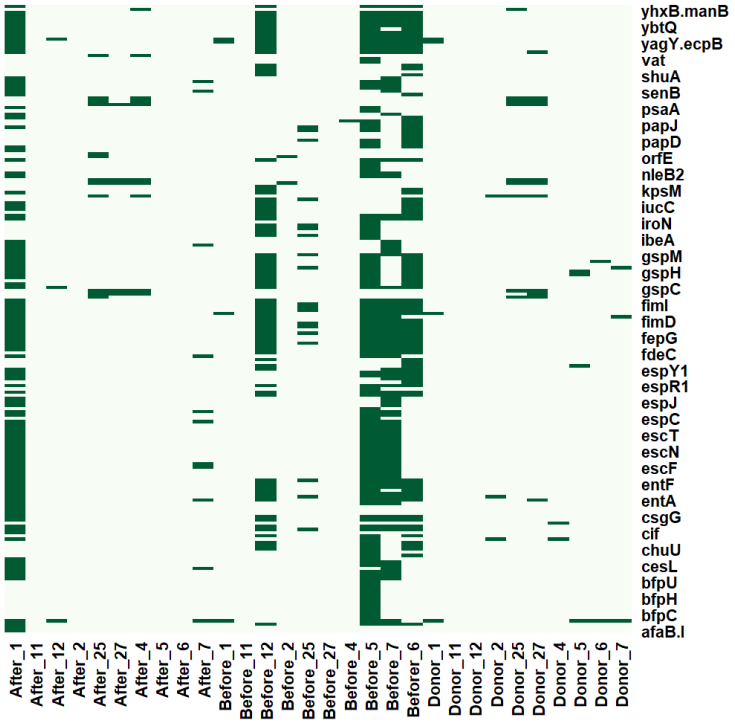


**Fig. 4: Heatmap shows presence and absence of virulence genes in the "Before", "After". And "Donor" groups**

## 4. Conclusion

Finally, we concluded that FMT has a great effect on UC patients and is capable of remodifying the bacterial community because harmful bacteria associated with UC disappeared after FMT. FMT may play an important role in the treatment of UC by decreasing percentage of virulence genes. Because some "Donor" samples were noticed to carry virulence genes, we recommend investigating donor samples before FMT in terms of which bacteria are there and the presence of virulence genes to ensure better safe colonization in the recipients' guts.

**Statements & Declarations**

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***Competing Interests***

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by All authors. The first draft of the manuscript was written by Esraa Elsaeed Sobhy and Rasha Medhat El-Morsi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

***Data Availability***

The datasets analyzed during the current study were retrieved from the NCBI repository and available under the PRJNA768409 project.

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# Supplementary Data

**Table 1:** Samples metadata

| Sample name | BioSample_ID | Run_accession | Group |
|---|---|---|---|
| After_1 | 22039207 | SRR16188884 | After |
| Before_1 | 22039206 | SRR16188895 | Before |
| Donor_1 | 22039205 | SRR16188896 | Donor |
| After_2 | 22039210 | SRR16188910 | After |
| Before_2 | 22039209 | SRR16188862 | Before |
| Donor_2 | 22039208 | SRR16188873 | Donor |
| After_4 | 22039216 | SRR16188893 | After |
| Beforer_4 | 22039215 | SRR16188894 | Before |
| Donor_4 | 22039214 | SRR16188897 | Donor |
| After_5 | 22039219 | SRR16188890 | After |
| Beforer_5 | 22039218 | SRR16188891 | Before |
| Donor_5 | 22039217 | SRR16188892 | Donor |
| After_6 | 22039222 | SRR16188887 | After |
| Before_6 | 22039221 | SRR16188888 | Before |
| Donor_6 | 22039220 | SRR16188889 | Donor |
| After_7 | 22039225 | SRR16188883 | After |
| Before_7 | 22039224 | SRR16188885 | Before |
| Donor_7 | 22039223 | SRR16188886 | Donor |
| After_11 | 22039231 | SRR16188877 | After |
| Before_11 | 22039230 | SRR16188878 | Before |
| Donor_11 | 22039229 | SRR16188879 | Donor |
| After_12 | 22039234 | SRR16188874 | After |
| Before_12 | 22039233 | SRR16188875 | Before |
| Donor_12 | 22039232 | SRR16188876 | Donor |
| After_25 | 22039246 | SRR16188919 | After |
| Before_25 | 22039245 | SRR16188861 | Before |
| Donor_25 | 22039244 | SRR16188863 | Donor |
| After_27 | 22039249 | SRR16188916 | After |
| Before_27 | 22039248 | SRR16188917 | Before |
| Donor_27 | 22039247 | SRR16188918 | Donor |

**Table 2:** Virulence genes name which increased or decreased in UC patients after FMT

| Sample name | State | Genes name |
|---|---|---|
| Sample 5 | Genes decreased after FMT | *-bfpB -bfpF -bfpI -cesAB -chuT -chuX -csgD -entA -entE -escD -escI -escO -escT -espB -espB -espG -espR4 -espY1 -fepC -fimA -fimE -fimI -fepF -gspJ -hLyA -iroE -iucA -nleB2 -pmpA -papG -papK -psaA -sepQ.escQ -wecA -yagY.ecpB -ybtP -ybtU* |
| Sample 6 | Genes decreased after FMT | *-bfbB -chuT -chuX -csgD -daaf -entE -escD -espL1 -espY1 -etgA -fepC -FimA -fimE -Fiml -gspF -gsPJ -glyA -iucA -iutA -KpsT -ompA -papG -papk -sat -shuT -wecA -yagY.ecpB -ybtP -ybtU* |
| Sample 7 | Genes decreased after FMT | *-bfpF - bfpI -cesAB -chuT -chuX -csgD -entE -cesL -escO -escT -espL1 -espR4 -espY1 -fepC -fimA -fimE -fimI -gspf -hLyA -iucA -nleB2 -ompA -papB -papk -psaA -wecA -yagy.ecpB -ybtU* |
| Sample 12 | Genes decreased after FMT | *-chux -csgD -daaF -entA -entE -espL1 -espR4 -etgA -fepC -fimA -fimE -fimI -gsPJ -hLyA -iroE -iucA -iutA -KPST -pmpA -shuT -wecA -ybtP -ybtU* |

| | | |
|---|---|---|
| Sample 4 | Genes increased after FMT | *-gmha –ipca -KpsT –iutA –sat –ybtU -- yagy.ecpB -papB* |
| Sample 27 | Genes increased after FMT | *-gmha –ipca -KpsT –iutA –sat - yagy.ecpB* |