Bacterial strain displacement in inflammatory bowel diseases after fecal microbiota transplantation

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Abstract

BACKGROUND & AIMS: Fecal microbiota transplantation (FMT) has been proved to be efficient in treating Clostridium difficile infection disease, yet its efficacy in treating Inflammatory bowel disease including Crohn's Disease (CD) and Ulcerative Colitis (UC) at molecular level are blank.

METHODS: We performed a parallel study of patients with moderate to severe CD (Harvey-Bradshaw Index ≥ 7) and UC (Montreal classification, S2 and S3). Patients were treated with single FMT (via mid-gut, from healthy donors; n = 15). All participants had their fecal samples collected and shotgun sequenced before FMT and during their follow-up visits. The primary outcome was clinical remission and that of CD is defined as a decrease of Harvey-Bradshaw > 3, clinical remission of UC is defined as a decrease of Mayo score > 3. To describe and quantify the change of gut microbiota of IBD patients after FMT, we monitored strain populations in 44 fecal samples. Besides, we built a machine learning model to predict the existence and abundance of post-FMT patients' species compositions.

RESULTS: Of all 15 patients, 3 days after FMT treatment, 8 out of 11 CD patients were relieved, 3 out of 4 UC patients were relieved (Table S1).

We observed the transfer of donor strains to recipient was more abundant in UC than

in CD patients, persisting the follow-up time points. Besides, same-donor recipient differs in the degree of microbiota transfer. Furthermore, through building random forest classification and regression model, results showed that both the presence and abundance of some post-FMT patients' species were predicable, indicating a possibility of precision engineering of the recipients' gut microbiota under the FMT treatment.

CONCLUSIONS: FMT treatment efficiency differed in CD and UC patients and post-FMT patients' mOTU composition was predictable in our data set.

KEYWORDS：shotgun metagenomics; fecal microbial transplantation; Inflammatory bowel disease; strain-level analysis

Introduction

Fecal microbiota transplantation (FMT) is to transfer donor fecal suspension into a patient's gastrointestinal tract aiming at improving the recipient's gut microbial composition and confer a health benefit. Most of its prior applications were related to Clostridium difficile–associated disease (*1*). Recent years, FMT has been considered for Inflammatory bowel disease (IBD) treatment. The two main forms of IBD are CD and UC, which shares many clinical, epidemiologic, and immunologic features. In previous studies, gut dysbiosis has been well described in IBD patients, and UC and CD were found to be of two distinct subtypes of IBD at the microbial community level (*2*). However, while several studies have made progress to reveal the

composition and temporal stability of UC patients' microbiota after FMT (*3,4,5*), the same kind of investigations were lacking on CD patients. There were only a few case reports of CD patients treating with FMT (*6,7,8*).

Nowadays, in exploring the mechanism of FMT treatment, methods to track the bacteria engraftment from donor to recipient have come to at the strain level which followed the principle that strain-level differences had functional and clinically relevant consequences (*9,10*). In addition, towards the end of precision engineering, A recent study used machine learning methods to quantitively model bacterial engraftment in diverse metabolic syndrome human host and examined a series of factors that might promote the engraftment of individual strains (*10*). Combining these two state-of-art insights in investigating the differences and principles of bacterial engraftment among patients who under FMT treatment, we tended to uncover such rules in 15 IBD patients.

In our study, Shannon index of all samples were measured, and the extent of changes of the gut microbiome population structure after FMT were quantified at both species and strain level. Varied and highly individualized patterns were found even within patients who shared a donor, implying that personalized treatment may be of necessity. Besides, we identified some most important factors that contributed to donor bacteria engraftment and established relationships between post-FMT patients' species and patients' biochemical indexes. The composition of pre-FMT recipient flora along with its clinical phenotype made the greatest contribution to donor species transfer and

FMT therapeutic effect, implying the possibility of stratifying IBD patients to get better and more controllable FMT treatment effect.

Results

Bacteria diversity and abundance change at species level after treatment

In our study, two batches of data were included which corresponding to FMT and exclusive enteral nutrition (EEN) treatment of IBD respectively. In total, there were 72 fecal samples and for comparison, we separated them into 7 groups: 8 UC samples before and after FMT, 22 CD samples before and after FMT, 10 healthy people fecal samples, 28 CD samples before and after EEN.

Alpha-diversity was measured by Shannon index, and has been compared within and among groups (figure 1A). We found Shannon index was significantly lower in all CD patients than it was in healthy control (EEN CD patients P-value = 0.0021; FMT CD recipients P-value = 0.0035) while the difference between UC patients and healthy people were not significant (P-value = 0.57). Additionally, results showed that Shannon index was not significantly improved after either treatment (p-value> 0.01.), neither in CD nor in UC patients.

In terms of species abundance changes, we found that 3 days after FMT treatment, there was a universally obtain of Bacteroides, a lower level of which in the gut microbiota is associated with IBD in patients (*11*). And there were also some highly individualistic performances such like CD-9 gained an abundant amount of Lactobacillus which is considered to be probiotics while CD-1 had a great decrease in

Citrobacter which was considered to be pathogenic bacteria (figure1B). The amounts of species each recipient gained from their donor after FMT were showed in figure S1.

Bacterial engraftment evaluation at the species level

To investigate to what extent recipients' microbiome could be altered, we evaluated both its degree and direction of change after FMT. For clear clarification of the origins of post-FMT patients' microbiome, we divided their microbiome composition into four parts: donor-specific species, recipient-specific species, donor- and recipient-specific species (common species), and newly species. Results showed that microbial communities underwent large compositional changes after FMT and changes maintained throughout the follow-up time visits (figure 1B).

On average, 29.4% of the mOTUs came from the donor (n = 11, SD = 14.4%) in CD patients, while 28.2% of the mOTUs came from the donor (n = 4, SD= 20%) in UC patients. Species gained from donor in both types of IBD were not significantly differed (p = 0.89). Our results were very similar to previous study (35% of the mg-OTUs in the donor (n = 436, SD = 27%) (*9*). As for EEN treatment, on average, 48.6% of the mOTUs were newly gained (n = 14, SD = 24.1%) which instigated more variation at the species level compared with autologous FMT individuals from *Simone S. Li* paper (*9*).

Aiming at monitoring the direction of changes of IBD patients after FMT, we measured the distance across donor-recipient pairs using Euclidean distance (Figure 2A). Results varied between different donor-recipient pairs. With only 4 patients have

2 follow-up time points, we found that CD-9 and UC-2 tended to be closer to their donors and further from their pre-FMT status.CD-2 showed a slightly tendency to be back to its initial status, yet the disturbance can be ignored (from 10.628 to 10.57). Surprisingly, CD-1 showed an increased distance both from their donor and pre-FMT status. Though CD-1,2 and UC-2 shared the same donor, the direction of their gut flora change after FMT varied. Besides, we explored the consistency of the abundance of mOTUs in the patients before and after FMT (Figure 2B). As expectedly, mOTUs in post-FMT patients had high correlation with those in the pre-FMT patient (median cosine similarity of UC patient mOTUs = 0.93, that of CD patients = 0.95). More importantly, results showed that the mOTUs in the post-FMT patient were perfectly correlated those in the donor (median cosine similarity of UC patient mOTUs =0.95, that of CD patients = 0.91). Therefore, bacterial species in the post-FMT patient are shaped both by the host and donor.

Bacterial engraftment evaluation at the strain level

To compare the extent of strain-level changes among the study groups, we monitored those identified SNVs in baseline samples over all available time points. A higher level of single-site allelic variation in UC FMT recipients was observed compared with autologous FMT recipients (P= 0.0056) from a previous paper (*9*), CD FMT recipients(P=0.070) and EEN treatment(P=0.059). Higher level of SNV was also observed in CD FMT recipients and EEN treatment than that in the autologous FMT recipients (P=0.148 and 0.234, respectively). And unexpectedly, EEN treatment had

153 equivalent level of single-site allelic variation compared with CD FMT recipients
154 (P=0.829) (figure 3).
155 To investigate whether the increased variation was due to the transfer and
156 establishment of donor microbiota or not, we followed methods defined in a
157 previously published paper (*9*). Across recipients, we observed the transfer of donor
158 strains (figure 4). Donor-specific SNVs were most highly retained 3 days after FMT
159 (UC: 62.8 ±25.3% of determinant positions across recipients, CD: 11 .4 ±10.3%) and
160 were still presented 1 months later (UC: 46.9%, CD: 19.99 ±10.1%). This contrasted
161 with much lower rates of variation observed at equivalent time points in autologous
162 FMT recipients (9.5 ± 1.8%) (figure S4) and showed that the increased variation in
163 post-FMT patients resulted from donor strain transfer instead of temporal variability
164 or abundance variation beyond detection thresholds.
165 Furthermore, marked differences in colonization success were observed between UC
166 or CD recipients who shared a donor (subjects CD-1,2,3,8, and UC-1,2). 3 days after
167 treatment, UC-1 ,2 retained a higher amount of donor-specific SNVs compared with
168 CD-1,2,3,8 (48.9%, 44.4%,11.9%, 3.4%,1.5% and 9.3%, respectively). Extensive
169 coexistence of donor and recipient strains (CD: in 44.1 ± 17.1% of shared species, UC:
170 21.3 ± 14.1%) were found in all other recipients, which persisted for at least one
171 months. This suggested that novel strains can colonize in the gut without replacing the
172 indigenous strain population of the recipient. It appeared that introduced strains were
173 more likely to establish in a new environment if the species was already present. We
174 sought to determine the extent of donor and recipient strain coexistence across species

and pattern of donor strains establishing alongside indigenous strains of the recipient was seen.

While CD FMT species showed more resistance to introduced strains compared with UC, durability of donor strains varied widely for most species. Donor strains of *Biffidobacterium longum, Citrobacter sp, Bacteroides vulgatus, Dorea longicatena, Eubacterium hallii* appeared to dominate recipient strains. In contrast, recipient strains like *Clostridium scindens, Coprococcus comes, Burkholdenriales bacterium, Alistipes putredinis* showed resistance to donor strains (figure 4). What amazed us was that EET treatment also presented the potential to change the recipient strains. *Bacteroides sp, Klebsiella pneumonia* presented newly SNPs up to 40%, while *Methanobrevibacter smithii* showed resistance to EEN treatment (figure 5).

Construction of a prediction model for post-FMT patients' mOTUs

We subsequently performed random forest analysis (RF analysis) to construct a classification model to predict the presence and absence of species in post-FMT patients and a regression model to predict the abundance of those species. Recipients' and the donors' mOTUs along with their clinical metadata before FMT were used as predictors to construct our model. As for classification, averaged across all predicted species, we got area under the curve (AUC) = 74.2%, SD = 16%; for regression model, we got rho = 0.478, $P < 2.2e-16$ (figure 6A). Results indicated that for some species of post-FMT patient both the existence and abundance were predictable. However, the AUC area is relatively lower than a similar study being conducted by *Christopher* S.Smillie *et al.* (*10*). Reasons may be that some other factors, such as diet,

bacterial species interactions, host genetics were not included in the construction of our model. (but in their model construction, taxonomy, abundance, clinical metadata, sequencing depth, Genome statistics, physiology, resource utilization are all included) The RF analysis assigned a variable importance score to each predictor to indicate their relative contribution to the model. Among the top 40 important variables we picked (see in methods part) (figure 6B). IgA score, T-cell and Th.cell.Induced of recipient were the top three clinical elements. *Streptococcus.anginosus*, *Bacteroides.plebeius*, *Clostridium.bolteae*, *Streptococcus.thermophilus* and *X.Ruminococcus..gnavus* were the top five species in the classification model. *Streptococcus.anginosus* was reported to be associated with colorectal cancer and *Ruminococcus..gnavus* was ever found to be associated with a certain kind of immunological rejection. Summarizing all those important variables, we found that species composition and clinic metadata of recipients took the prominent place. Thus, we suggested that in practice, people who fit the common healthy standards could be recruited as donor while patients may need to be stratified for better treatment effect. Our explanation for the importance of recipient phenotype, to some extent, was that it could reflect the gut healthy and immune status. To explain the biggest part of recipient mOTUs, we could assume that the engraftment of new species should have a competition process with those primitive microbiomes of recipient.

Relationships between mOTU change with clinical indexes change

Of all 15 patients, 3 days after FMT treatment, 8 out of 11 CD patients were relieved, 3 out of 4 UC patients were relieved (table S1). Clinical improvement was defined as

219 decrease of Harvey-Bradshaw Index > 3 for CD, and decrease of Mayo score > 3 for
220 UC (table S1).
221 To evaluate the diagnostic value of FMT, we built relationships between mOTU
222 change with clinical indexes change by conducting a three-step procedure. Firstly, we
223 tested whether the clinical indexed change before and after FMT were significantly
224 higher than 0 using Student's t-test (figure 7A). Results showed that Mental status
225 change, appetite change, tenesmus change, stool form change, bloody purulent change,
226 mucous stool change, defecation change and abdominal pain score change were
227 significant while all the detected change of Immune factors were not significant such
228 like CD4.CD8, NK cell, TSC, Th.cell.Induced, B cell. Secondly, we linked the
229 changes of clinical indices with the changes of relative abundance of recipients'
230 mOTUs before and after FMT using spearman's correlation (figure 7B). We found
231 that the defecation change was significantly positively correlated with
232 *Selenomonas.artemidis* and two other unclassified species, while negatively correlated
233 with *Enterococcus.casseliflavus* and *Prevotella.bivia*. The change of CD4.CD8. and
234 Th.cell.Induced both significantly positively with *Streptococcus.sp..C150*. Besides,
235 the change of CD4.CD8. was significantly positively correlated with
236 *Streptococcus.infantis*, *Streptococcus.parasanguinis*, *Streptococcus.australis* while
237 negatively correlated with *Lactobacillus.salivarius* and *Streptococcus.gordonii*. The
238 change of TSC was significantly positively correlated with the change of
239 *Bacteroides.fragilis*. Thirdly, we tended to examine the relationships of FMT-induced
240 changes in biochemical markers with some disease-associated characteristics such as

241 disease duration, patients' age and so on (table S2). Results showed that CD4.CD8
242 change, Th.cell.Induced change (counted by Flow cytometry) and Abdominal pain
243 score change were significantly negatively correlated with the start age of IBD disease
244 ($p < 0.05$). In addition, CD4.CD8. change and Th.cell.Induced change were also
245 significantly negatively correlated with Patients' age. Disease durance and age were
246 also discovered to act as important predictors in our random forest classification
247 model, we thus inferred that it may be profitable to have FMT at an early stage of IBD
248 and that the younger the patient, the better the treatment effect based on this selected
249 population.

250 **Discussion**

251 Fecal microbiota transplantation has been utilized sporadically for over 50 years and it
252 is best known as a treatment for recurrent Clostridium difficile infection. However,
253 the mechanism by which it exerts its therapeutic effects have not yet been fully
254 elucidated.

255 Our results confirmed that CD patients were characterized with reduced diversity, all
256 15 IBD patients underwent significantly microbiota composition change 3 days after
257 FMT treatment and most of them showed a relief of clinical symptoms.

258 Both the existence and abundance of some post-FMT gut mOTUs were predictable
259 and correlated with recipients' and donors' mOTU and clinical indices such as IgM,
260 IgA and CD4.CD8. The recipient gut microbiome was altered and this phenomenon
261 could also be observed at the strain level. Our comprehensive survey of the gut
262 microbiomes of IBD patients after FMT supported the notion that IBD as a group of

inflammatory conditions of the colon and small intestine that could be triggered by a dysbiosis of gut flora and be relieved via an introduction of fecal flora from healthy people. These findings acted as a basis for future microbiome-based therapeutics and patient stratification in preclinical and clinical phase of IBD. The identified elements need to be validated in larger and independent cohorts with better experiments design. Functional analysis of the species and in vitro characterizations of the strains will be necessary to verify whether a few of the identified markers are “key species” or “key strains” for the relief of IBD patients after FMT treatment. With further investigation of the possible mechanisms of FMT, there will be a great promise for the development of microbiota-based precision treatments.

Methods

Patients recruitment and metagenomic sequencing

For FMT analysis, DNA of bacteria and associated metadata were collected from 44 fecal samples of 25 individuals. Descriptions of the trail design, patient selection, donor screening, sample collection, sample processing and sequencing strategy were also concisely described in *Cui B et al.* (*7*) paper. Our data set consisted of 10 samples from 10 healthy people among which 6 are donors, and 22 samples from 11 FMT recipients who had one follow-up time points collected at day 0 and day 3 and 12 samples from 4 FMT recipients who had two follow-up time points collected at day 0, day 3 and either day 7 or day 30. As for EEN analysis, DNA extracted from 28 fecal samples of 14 CD patients who underwent EEN treatment were from Qing He *et al.*

(*12*) study. Samples were collected at baseline and after 2-week EEN treatment and standards of recruitment and sequencing strategy were described in that paper. Additionally, DNA extracted from 25 fecal samples of 5 individuals were obtained from the *Vrieze et al.* (*13*) study. Those 25 samples of 5 autologous individuals were collected at day 0(pre-FMT) and days 2,14,42,84 after FMT.

In summary, 34 samples were used in analysis of the allogenic FMT group; 25 for the autologous; 10 for the healthy group; and 28 for the EEN group.

Microbiota taxonomic profiling.

Raw reads were quality controlled by trimming low quality bases and removing host-related reads using cOMG with default parameters (*13*).

Species level profiling was conducted using m-OTUS.pl to generate the mOTUs profiles which maps the high quality reads against the m-OTUS.v1.padded database and outputs metagenomic OUT linkage groups (m-OTUS) generating both taxa previously identified and those yet to be isolated and characterized, as described by *Sunagawa S et al.* (*14*). For strain-level profiling, high quality reads were mapped to over 5,000 bacterial species' representative genomes with default parameters using metaSNV (*15*).

Statistical analyses.

Statistical analyses were performed in R using the packages vegan, Hmcc, pROC, and randomForest. All statistical tests used were two-sided.

alpha-diversity. α-Diversity was calculated on the basis of the gene profile of each sample according to the Shannon index which is implemented in vegan.

Fecal microbiome derived features and visualization. Firstly, we departed its composition into 4 parts: donor- and recipient-specific species, newly gained species and species common to donor and recipient. After quantification of those 4 parts of patients, we averaged those across CD and UC patients separately. Microbiota variation between individuals was visualized using Bray-Curtis dissimilarity on the mOTUs -abundance matrix. And distance between the donor and the recipient after the transplantation and before and after the transplantation was compared.

A construction of the machine learning model. Clinic metadata of both recipient and donor along with mOTUs of both recipient and donor were used as predictors of our model to predict the existence and abundance of each mOTU of post-FMT patients. Firstly, we picked a mtry parameter with the lowest error using rfcv function with 5-folded cross validation. Then we use the randomForest function to do classification across all mOTUs. In total, we got 123 randomForest models and we computed auc for each. We chose important variables only from those models which had a good performance in prediction that means auc was bigger than 0.9. We extracted top 40 variables by ranking both their frequency and their contributions across those well performed classification models.

Correlations between mOTUs change with clinical index change. To investigate whether there is correlation between the clinical index change and some certain mOTU change, we used rcorr function in Hmisc package to compute spearman correlation of each motu-clinical index pair. And we used Benjamini-Hochberg to adjust p value. After that, we pick those pairs with q-value smaller than 0.05 to draw a

329 network using Cytoscape (*16*).

330

331 **Additional files**

332

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343

344 **Availability of supporting data**

345 The quality-controlled sequencing reads can be found in the database under the
346 BioProject number

347

348 **Competing interests**

349 The authors declare that they have no competing interests.

350

Consent for publication

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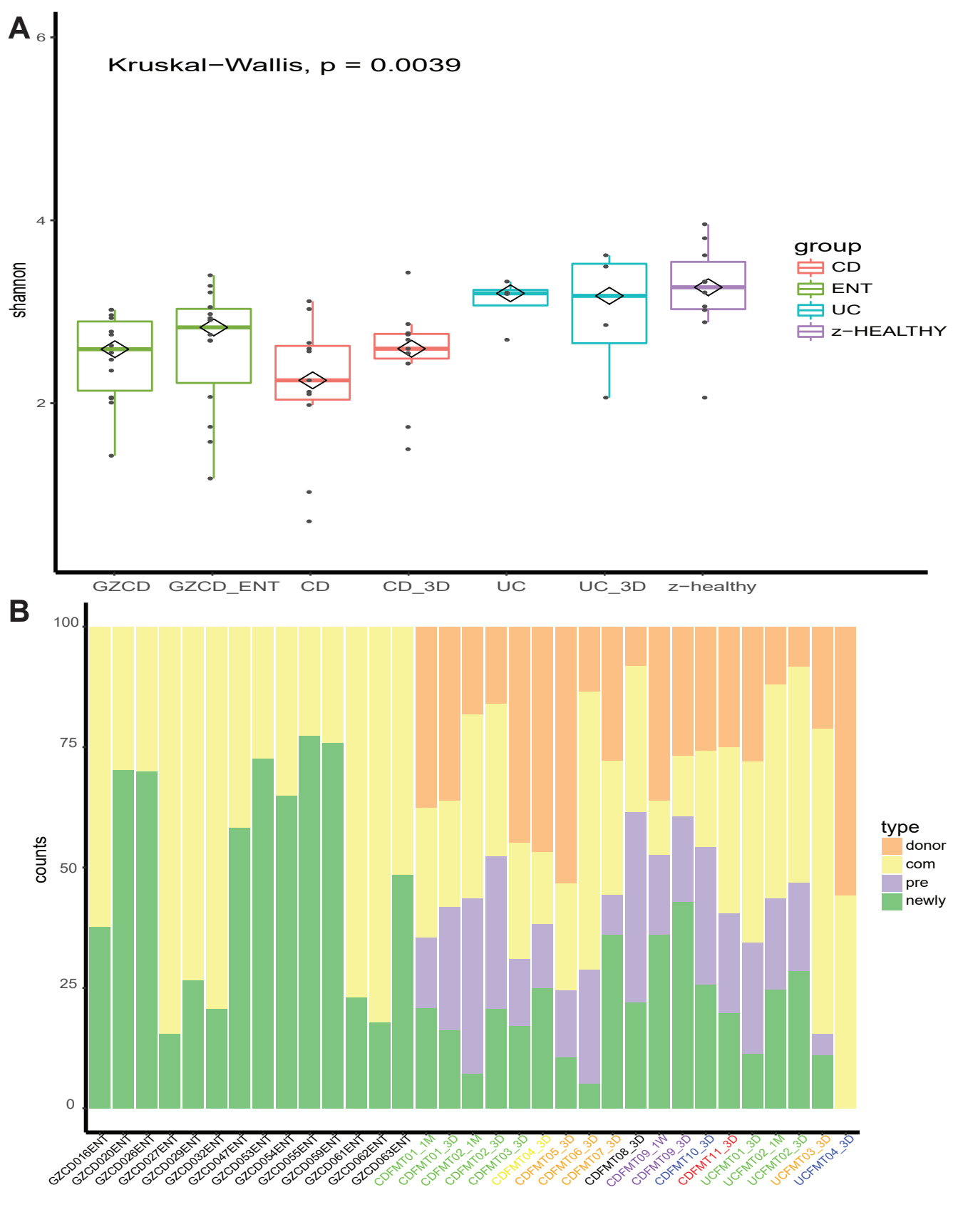
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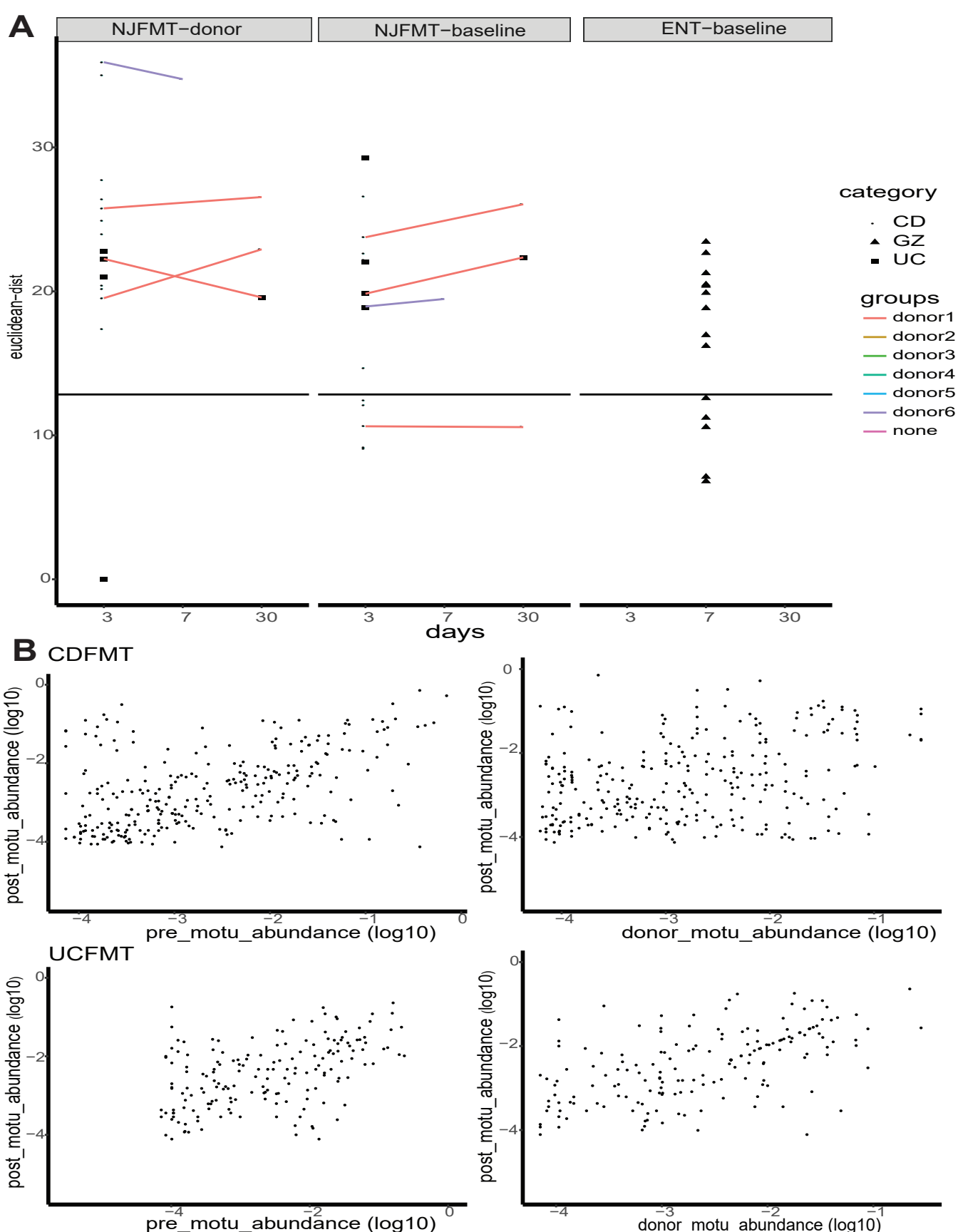
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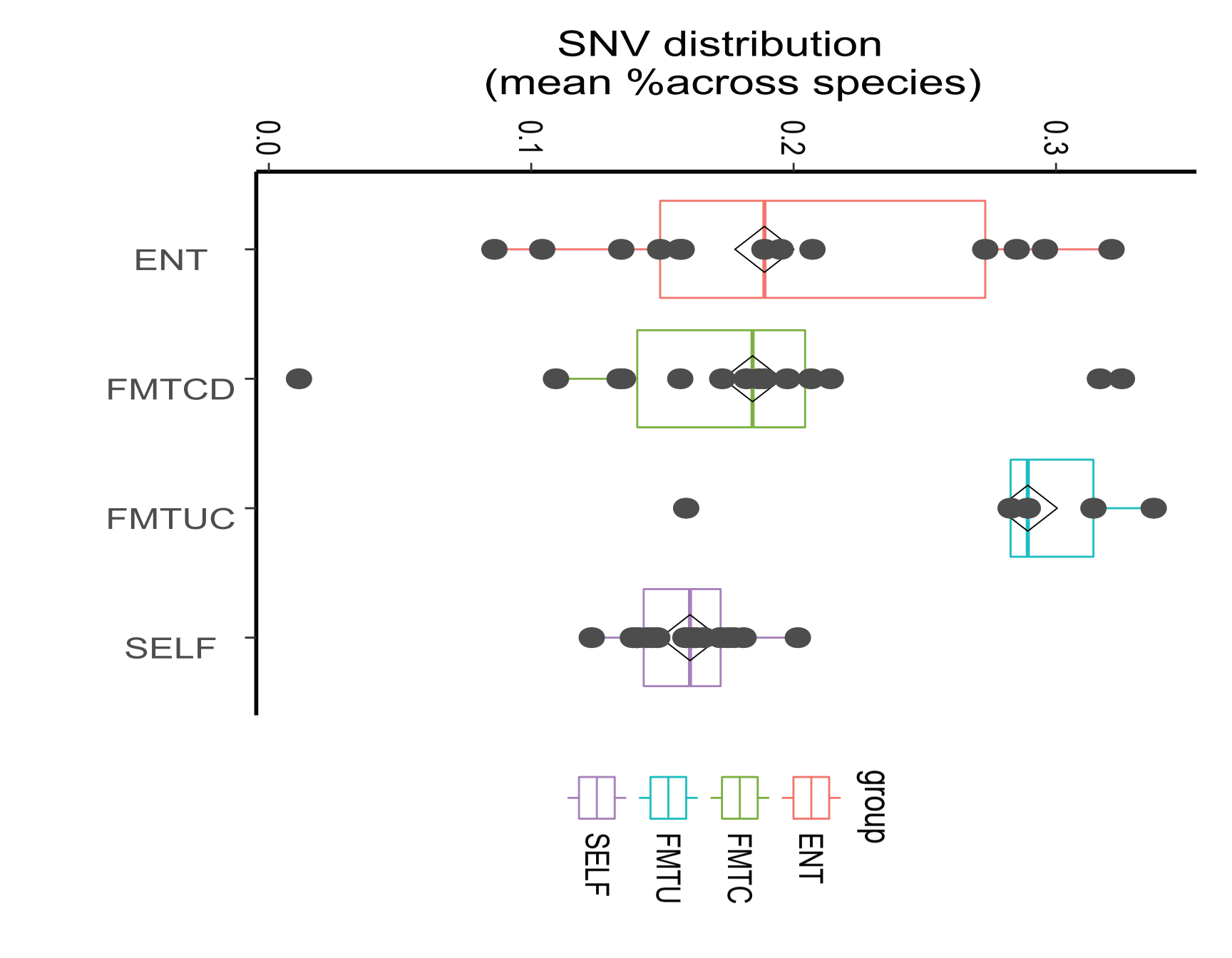
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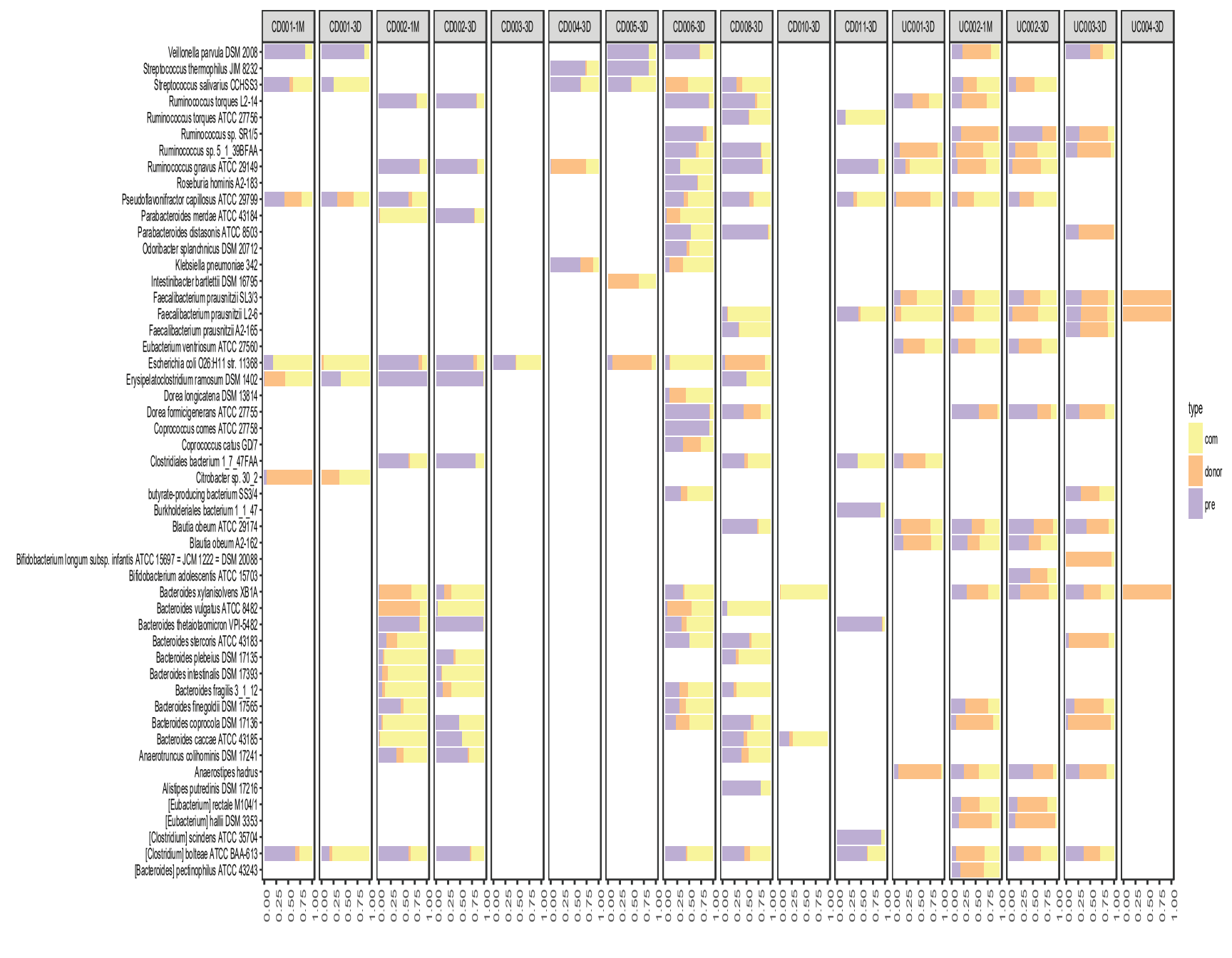
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Streptococcus salivarius CCHSS3
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Ruminococcus torques ATCC 27756
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Ruminococcus sp. 5_1_39BFAA
Ruminococcus gnavus ATCC 29149
Roseburia hominis A2-183
Pseudoflavonifractor capillosus ATCC 29799
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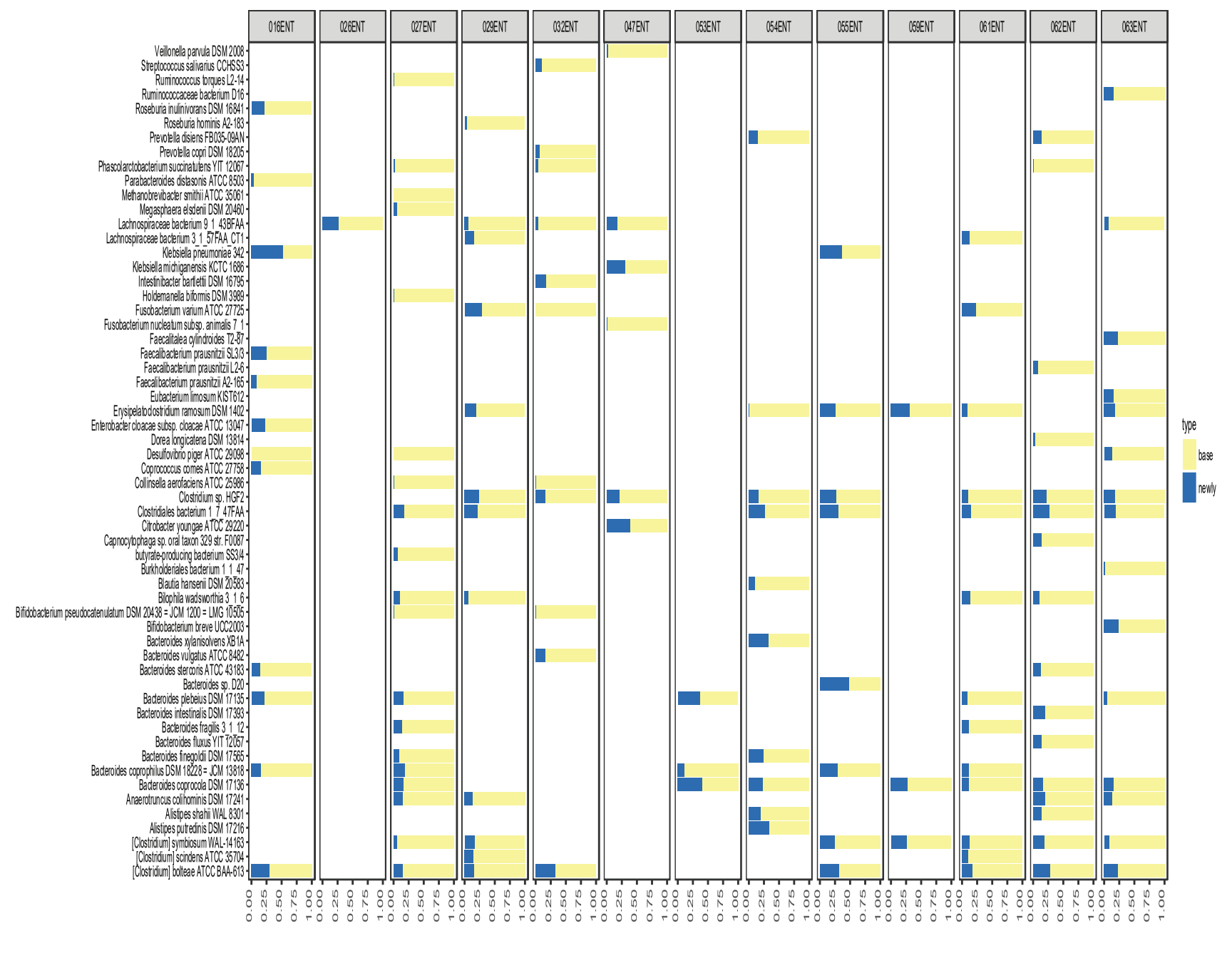
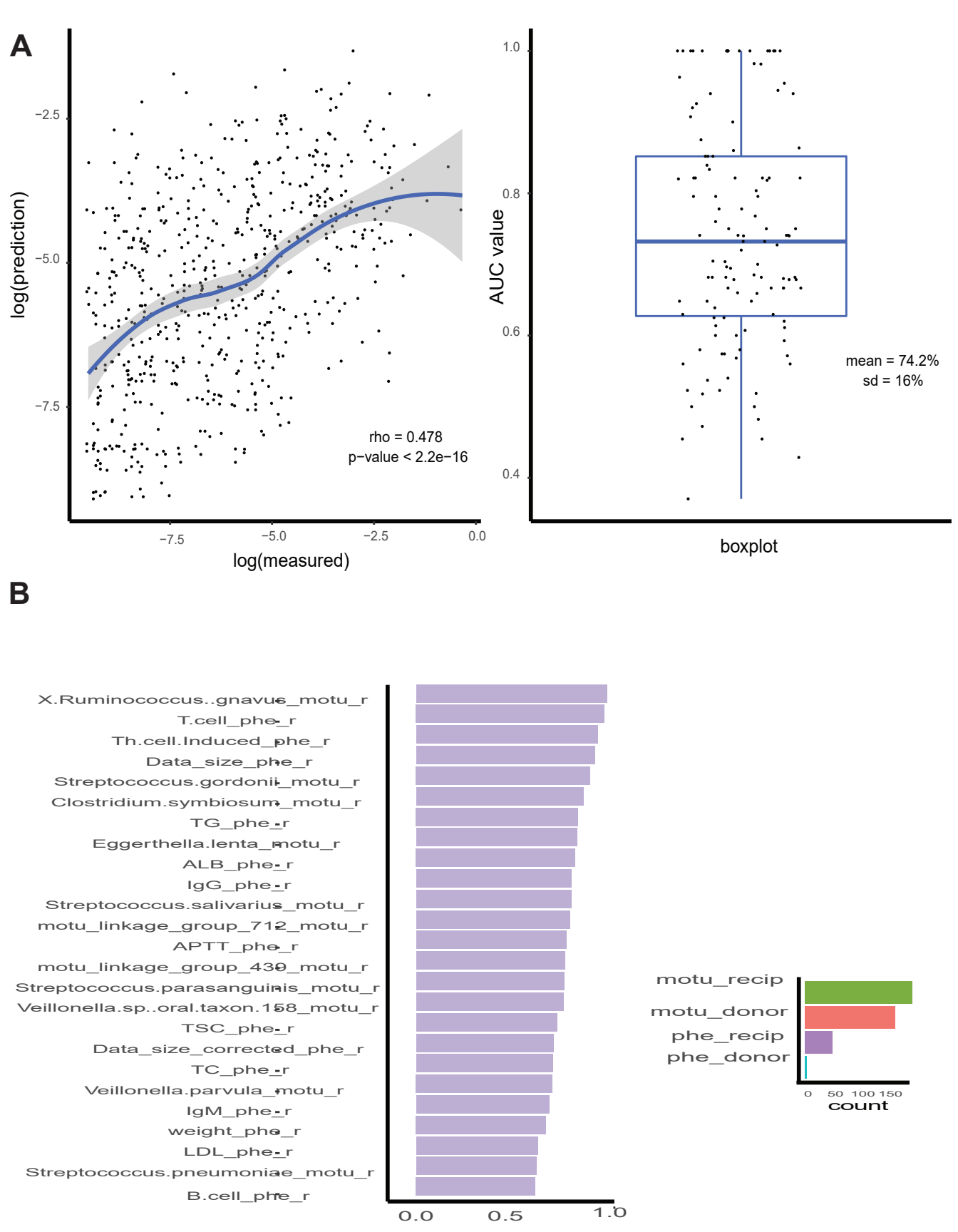
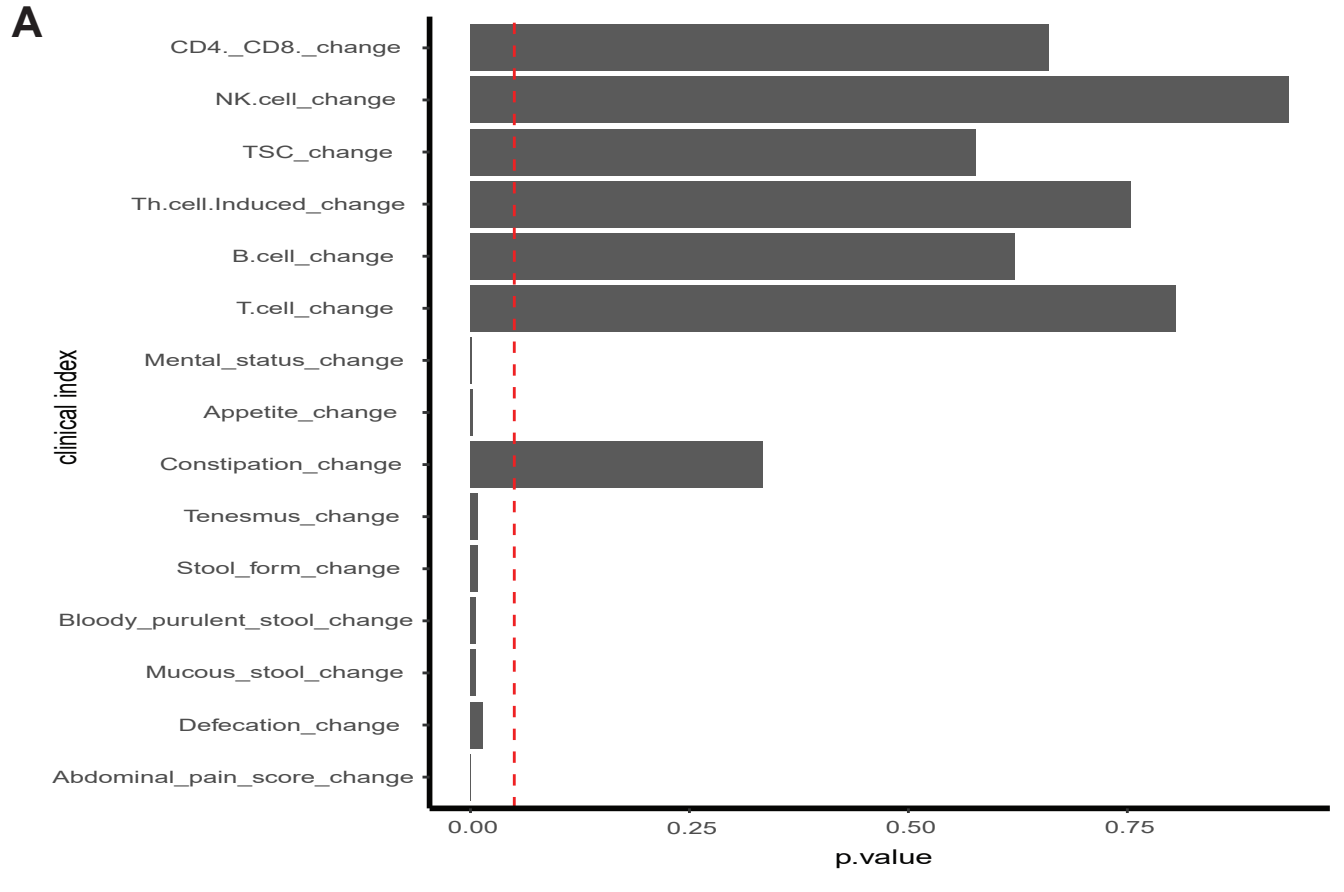
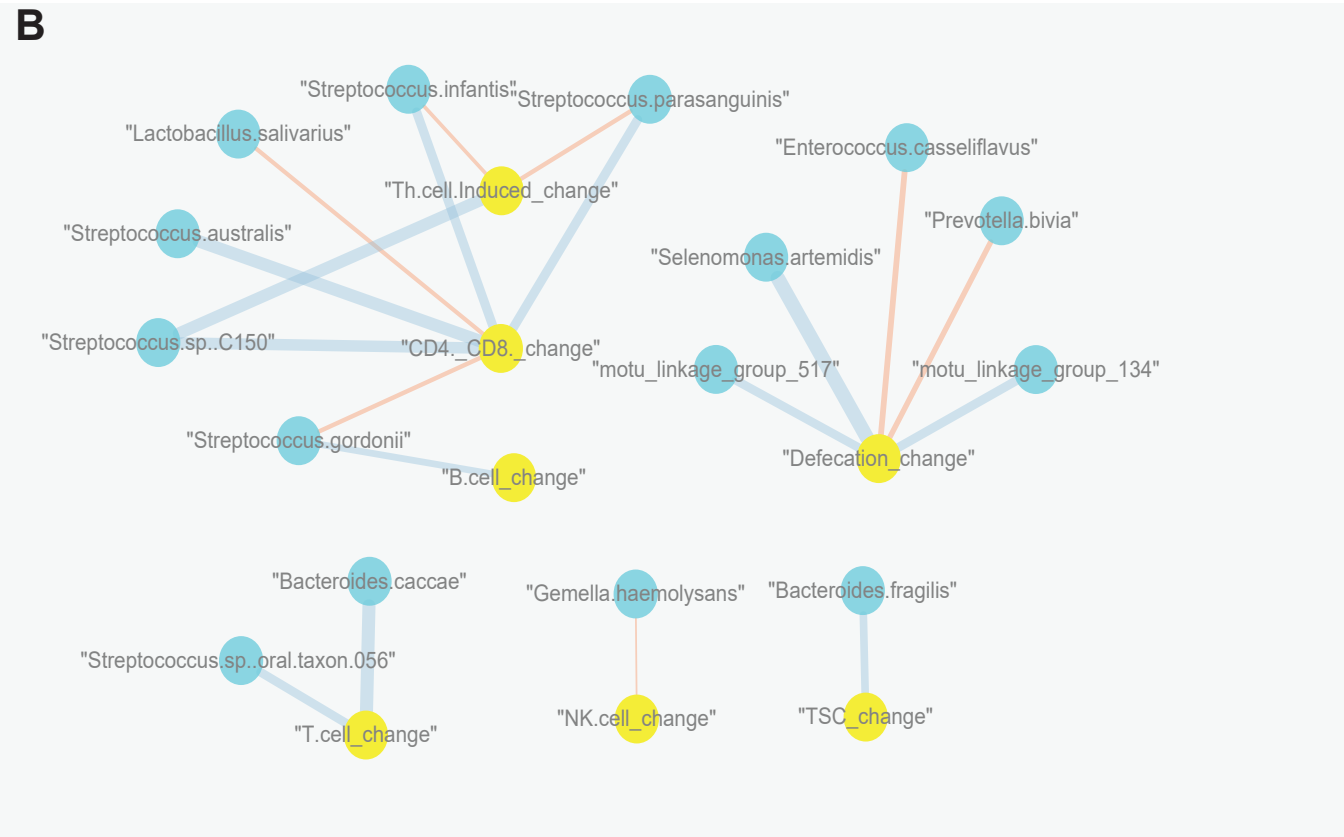
Parabacteroides distasonis ATCC 8503
Odoribacter splanchnicus DSM 20712
Klebsiella pneumoniae 342
Intestinibacter bartlettii DSM 16795
Faecalibacterium prausnitzii SL3/3
Faecalibacterium prausnitzii L2-6
Faecalibacterium prausnitzii A2-165
Eubacterium ventriosum ATCC 27560
Escherichia coli O26:H11 str. 11368
Erysipelatoclostridium ramosum DSM 1402
Dorea longicatena DSM 13814
Dorea formicigenerans ATCC 27755
Coprococcus comes ATCC 27758
Coprococcus catus GD/7
Clostridiales bacterium 1_7_47FAA
Citrobacter sp. 30_2
butyrate-producing bacterium SS3/4
Burkholderiales bacterium 1_1_47
Blautia obeum ATCC 29174
Blautia obeum A2-162
Bifidobacterium longum subsp. infantis ATCC 15697 = JCM 1222 = DSM 20088
Bifidobacterium adolescentis ATCC 15703
Bacteroides xylanisolvens XB1A
Bacteroides vulgatus ATCC 8482
Bacteroides thetaiotaomicron VPI-5482
Bacteroides stercoris ATCC 43183
Bacteroides plebeius DSM 17135
Bacteroides intestinalis DSM 17393
Bacteroides fragilis 3_1_12
Bacteroides finegoldii DSM 17565
Bacteroides coprocola DSM 17136
Bacteroides caccae ATCC 43185
Anaerotruncus colihominis DSM 17241
Anaerostipes hadrus
Alistipes putredinis DSM 17216
[Eubacterium] rectale M104/1
[Eubacterium] hallii DSM 3353
[Clostridium] scindens ATCC 35704
[Clostridium] bolteae ATCC BAA-613
[Bacteroides] pectinophilus ATCC 43243
0.00
0.25
0.50
0.75
1.00
type
com
donor
pre


016ENT
026ENT
027ENT
029ENT
032ENT
047ENT
053ENT
054ENT
055ENT
059ENT
061ENT
062ENT
063ENT
Veillonella parvula DSM 2008
Streptococcus salivarius CCHSS3
Ruminococcus torques L2-14
Ruminococcaceae bacterium D16
Roseburia inulinivorans DSM 16841
Roseburia hominis A2-183
Prevotella disiens FB035-09AN
Prevotella copri DSM 18205
Phascolarctobacterium succinatutens YIT 12067
Parabacteroides distasonis ATCC 8503
Methanobrevibacter smithii ATCC 35061
Megasphaera elsdenii DSM 20460
Lachnospiraceae bacterium 9_1_43BFAA
Lachnospiraceae bacterium 3_1_57FAA_CT1
Klebsiella pneumoniae 342
Klebsiella michiganensis KCTC 1686
Intestinibacter bartlettii DSM 16795
Holdemanella biformis DSM 3989
Fusobacterium varium ATCC 27725
Fusobacterium nucleatum subsp. animalis 7_1
Faecalitalea cylindroides T2-87
Faecalibacterium prausnitzii SL3/3
Faecalibacterium prausnitzii L2-6
Faecalibacterium prausnitzii A2-165
Eubacterium limosum KIST612
Erysipelatoclostridium ramosum DSM 1402
Enterobacter cloacae subsp. cloacae ATCC 13047
Dorea longicatena DSM 13814
Desulfovibrio piger ATCC 29098
Coprococcus comes ATCC 27758
Collinsella aerofaciens ATCC 25986
Clostridium sp. HGF2
Clostridiales bacterium 1_7_47FAA
Citrobacter youngae ATCC 29220
Capnocytophaga sp. oral taxon 329 str. F0087
butyrate-producing bacterium SS3/4
Burkholderiales bacterium 1_1_47
Blautia hansenii DSM 20583
Bilophila wadsworthia 3_1_6
Bifidobacterium pseudocatenulatum DSM 20438 = JCM 1200 = LMG 10505
Bifidobacterium breve UCC2003
Bacteroides xylanisolvens XB1A
Bacteroides vulgatus ATCC 8482
Bacteroides stercoris ATCC 43183
Bacteroides sp. D20
Bacteroides plebeius DSM 17135
Bacteroides intestinalis DSM 17393
Bacteroides fragilis 3_1_12
Bacteroides fluxus YIT 12057
Bacteroides finegoldii DSM 17565
Bacteroides coprophilus DSM 18228 = JCM 13818
Bacteroides coprocola DSM 17136
Anaerotruncus colihominis DSM 17241
Alistipes shahii WAL 8301
Alistipes putredinis DSM 17216
[Clostridium] symbiosum WAL-14163
[Clostridium] scindens ATCC 35704
[Clostridium] bolteae ATCC BAA-613
0.00
0.25
0.50
0.75
1.00
type
base
newly


A
log(prediction)
−2.5
−5.0
−7.5
rho = 0.478
p−value < 2.2e−16
−7.5
−5.0
−2.5
0.0
log(measured)
AUC value
1.0
0.8
0.6
0.4
mean = 74.2%
sd = 16%
boxplot
B
X.Ruminococcus..gnavus_motu_r
T.cell_phe_r
Th.cell.Induced_phe_r
Data_size_phe_r
Streptococcus.gordonii_motu_r
Clostridium.symbiosum_motu_r
TG_phe_r
Eggerthella.lenta_motu_r
ALB_phe_r
IgG_phe_r
Streptococcus.salivarius_motu_r
motu_linkage_group_712_motu_r
APTT_phe_r
motu_linkage_group_439_motu_r
Streptococcus.parasanguinis_motu_r
Veillonella.sp..oral.taxon.158_motu_r
TSC_phe_r
Data_size_corrected_phe_r
TC_phe_r
Veillonella.parvula_motu_r
IgM_phe_r
weight_phe_r
LDL_phe_r
Streptococcus.pneumoniae_motu_r
B.cell_phe_r
0.0
0.5
1.0
motu_recip
motu_donor
phe_recip
phe_donor
0
50
100
150
count


A
CD4._CD8._change
NK.cell_change
TSC_change
Th.cell.Induced_change
B.cell_change
T.cell_change
Mental_status_change
Appetite_change
Constipation_change
Tenesmus_change
Stool_form_change
Bloody_purulent_stool_change
Mucous_stool_change
Defecation_change
Abdominal_pain_score_change
clinical index
0.00
0.25
0.50
0.75
p.value


B
"Streptococcus.infantis"
"Streptococcus.parasanguinis"
"Lactobacillus.salivarius"
"Th.cell.Induced_change"
"Streptococcus.australis"
"Streptococcus.sp..C150"
"CD4._CD8._change"
"Streptococcus.gordonii"
"B.cell_change"
"Enterococcus.casseliflavus"
"Prevotella.bivia"
"Selenomonas.artemidis"
"motu_linkage_group_517"
"motu_linkage_group_134"
"Defecation_change"
"Bacteroides.caccae"
"Streptococcus.sp..oral.taxon.056"
"T.cell_change"
"Gemella.haemolysans"
"NK.cell_change"
"Bacteroides.fragilis"
"TSC_change"